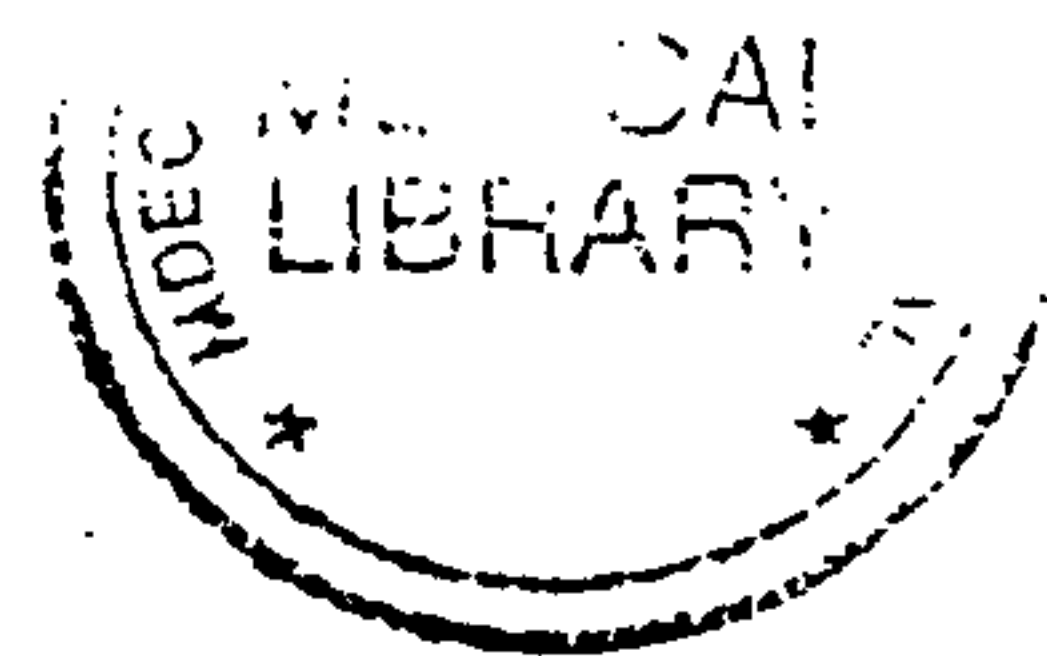


23 JUL 2001



ALTNAGELVIN HOSPITALS HEALTH AND SOCIAL SERVICES TRUST
ALTNAGELVIN AREA HOSPITAL

DEPARTMENT OF NURSING AND RISK MANAGEMENT

MEMORANDUM

TO: Mr Ciaran Cregan, Trust Librarian
FROM: Miss Irene Duddy, Director of Nursing
DATE: 20 July 2001
SUBJECT: ARTICLES

Ciaran,

I would be grateful if you could forward onto me copies of the following articles: -

- not
enc
1. Lane, N., Allen, K. Hyponatraemia After Orthopaedic Surgery ✓ ENC
BMJ 1999; 318: 1363-1364
- enc
2. Arieff, A.I., Ayus, J.C., Fraser, C.L. Hyponatraemia and Death or Permanent Brain Damage in Healthy Children BMJ 1992; 304: 1218-1222 ENC
- not
enc
3. Ayus, J.C., Wheeler, J.M., Arieff, A.I. Postoperative Hyponatraemic Encephalopathy in Menstruant Women Ann Intern Med 1992; 117: 891-897 ORDERED
- enc
4. Ayus, J.C., Arieff, A.I. Chronic Hyponatraemic Encephalopathy in Post Menopausal Women : Association of Therapies with Morbidity and Mortality JAMA 1999; 281: 2299-2304 ENC
- enc
5. Steele, A., Gowrishanker, M., Abrahamson, S., Mazer, C.D., Feldman, R.D., Halperin, M.L. Postoperative Hyponatraemia Despite Near-Isotonic Saline Infusion: A Phenomenon of Desalination Ann Intern Med 1997; 126: 20-25 ENC
- enc
6. Bussmann, C., Bast, T., Rating, D. Hyponatraemia in Children with Acute CNS Disease: Siadh or Cerebral Salt Washing Childs Nervous System 17 (1-2): 58-62 Discussion 63 2001 Jan ORDERED
- enc
7. Adroque, H.J., Madias, N.E. Primary Care Hyponathraemia New England Journal of Medicine 342 (21): 1581-9 2000 May 25 ENC

RB 9/3/05

- enc 8. Carlson, R.W., Keshanamurthy, L. Fluid and Electrolyte Emergencies: Some Signposts to Safe Management Journal of Critical Illness 14 (10): 554-62 1999 October ORDERED
- not enc 9. Rice, V. The Problem of Hyponatraemia: Recognition and Management Official Journal of the Canadian Nurses Association 2 (3): 9-11 1986 Summer ORDERED

BB 9/3/05

Many thanks for your co-operation in this matter.

A. J. Duddy

IRENE DUDDY (Miss)
Director of Nursing

diabetes. Most patients have control apart from the presence or absence of symptoms. Home monitoring of blood glucose concentrations is economically impracticable for most patients, but easier access to urine dipsticks would probably increase patients' interest and motivation in improved control and would not add greatly to total direct costs.

The need for inpatient admission should also be considered carefully, especially for newly presenting patients. Wherever possible admission is best avoided if the patient and family are able to receive initial daily outpatient education and supervision.¹⁵ Patients should be admitted only if they require nursing care or circumstances do not permit easy attendance at outpatient clinics. Admission rates for diabetic patients in Tanzania are six times higher than in the general population.¹⁶ When patients are admitted careful consideration should be given to the need for investigations. Testing urine four times or more daily for example, may be unnecessary if blood glucose concentrations are also being measured. Consideration should also be given to the period of admission since patients are often kept in the wards until most urine results are glucose free.

The small proportion of direct costs due to nurses' and doctors' services reflects the low rates of pay of medical staff in most sub-Saharan countries. A lecturer in medicine, for example, is paid \$60 monthly. The reasons for such low rate of remuneration are understood, but attention must also be paid to this problem since the motivation and interest of those caring for patients can have a significant impact on the quality of care.

University of Newcastle upon Tyne, the British Council; and the United Republic of Tanzania; the British Council; and the Overseas Development Administration.

- 1 Laing W, Williams R. *Diabetes: a model for health care management*. London: Office of Health Economics, 1989:32-49.
- 2 Fox NA, Jacobs J. *Direct and indirect costs of diabetes in the United States in 1987*. Alexandria, Virginia: American Diabetes Association, 1988.
- 3 Johnson B. Diabetes—the cost of illness and the cost of control. An estimate for Sweden 1978. *Acta Med Scand* 1983;671(suppl):19-27.
- 4 Triomphe A, Flori YA, Costagliola D, Eshchwege E. The cost of diabetes in France. *Health Policy* 1988;9:39-48.
- 5 Vaughan P, Gilson L, Mills A. Diabetes in developing countries: its importance for public health. *Health Policy and Planning* 1989;4:97-109.
- 6 World Bank. *United Republic of Tanzania: population, health and nutrition sector review*, 1989. Washington, DC: World Bank, 1989.
- 7 McLarty DG, Swai ABM, Kitange HM, Masuki G, Mutinangi BL, Kilima PM, et al. Prevalence of diabetes and impaired glucose tolerance in rural Tanzania. *Lancet* 1989;i:871-5.
- 8 World Health Organisation. World Health Organisation supports world diabetes day. *WHO Features* 1991;No 158 (June):1-4.
- 9 Swai ABM, Lutale J, McLarty DG. Diabetes in tropical Africa: a prospective study, 1981-7. Characteristics of newly presenting patients in Dar es Salaam, Tanzania. *BMJ* 1990;300:1103-6.
- 10 Aaron H, Schwartz WB. Rationing health care: the choice before us. *Science* 1990;247:418-22.
- 11 Enthoven A. Reforming US health care: the consumer choice health plan. In: Black N, Boswell D, Gray A, Murphy S, Popay J, eds. *Health and disease*. Milton Keynes: Open University Press, 1984: 335-40.
- 12 McLarty DG, Kinabo L, Sawi ABM. Diabetes in tropical Africa: a prospective study, 1981-7. II. Course and prognosis. *BMJ* 1990;300:1107-10.
- 13 Corrigan CB, Ahren B. Ten years' experience of a diabetes clinic in Northern Tanzania. *East Afr Med J* 1987;64:772-80.
- 14 Rolfe M, Armstrong JRM. Diabetes mellitus on the Zambian Copperbelt. *J R Coll Phys Lond* 1989;23:255-9.
- 15 Scott RS, Brown LJ, Clifford P. Use of health services by diabetic persons. II. Hospital admissions. *Diabetes Care* 1985;8:43-7.
- 16 Planning Commission. *Hali ya Uchumi wa taifa katika Muafaka* 1989. Dar es Salaam: Planning Commission, President's Office, 1990.

(Accepted 24 February 1992)

Hyponatraemia and death or permanent brain damage in healthy children

Allen I Arieff, J Carlos Ayus, Cosmo L Fraser

Abstract

Objective—To determine if hyponatraemia causes permanent brain damage in healthy children and, if so, if the disorder is primarily limited to females, as occurs in adults.

Design—Prospective clinical case study of 16 affected children and a review of 24412 consecutive surgical admissions at one medical centre.

Patients—16 children (nine male, seven female; age 7 (SD 5) years) with generally minor illness were electively hospitalised for primary care. Consultation was obtained for the combination of respiratory arrest with symptomatic hyponatraemia (serum sodium concentration ≤ 128 mmol/l).

Main outcome measures—Presence, gender distribution, and classification of permanent brain damage in children with symptomatic hyponatraemia in both prospective and retrospective studies.

Results—By retrospective evaluation the incidence of postoperative hyponatraemia among 24412 patients was 0.34% (83 cases) and mortality of those afflicted was 8.4% (seven deaths). In the prospective population the serum sodium concentration on admission was 138 (SD 2) mmol/l. From three to 120 inpatient hours after hypotonic fluid administration patients developed progressive lethargy, headache, nausea, and emesis with an explosive onset of respiratory arrest. At the time serum sodium concentration was 115 (7) mmol/l and arterial oxygen tension 6 (1.5) kPa. The hyponatraemia was primarily caused by extrarenal loss of electrolytes with replacement by hypotonic fluids. All 16 patients had

cerebral oedema detected at either radiological or postmortem examination. All 15 patients not treated for their hyponatraemia in a timely manner either died or were permanently incapacitated by brain damage. The only patient treated in a timely manner was alive but mentally retarded.

Conclusions—Symptomatic hyponatraemia can result in a high morbidity in children of both genders, which is due in large part to inadequate brain adaptation and lack of timely treatment.

Introduction

In previous studies from our laboratories we have described the symptomatology, clinical course, effects of treatment, and pathological findings in more than 225 adults (aged over 16) with symptomatic hyponatraemia.¹⁻⁴ Although the actual incidence of hyponatraemia seems to be similar among men and women,^{5,6} almost all adult patients suffering hyponatraemic brain damage are women. Although there are a number of reported paediatric cases of hyponatraemia,¹⁰⁻¹² there are few reported cases of death or permanent brain damage among children with this disorder,^{13,14} and most such children had pre-existing neurological disorders.¹⁵⁻¹⁷ Neither the gender distribution nor the incidence of brain damage among children with hyponatraemia is known.^{10-12,17} Among children suffering brain damage from hyponatraemia neither the type nor the gender distribution is known. We describe both a prospective and a retrospective analysis of generally healthy children who were elect-

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ively hospitalised. Sixteen children who developed severe symptomatic hyponatraemia either died or suffered permanent brain damage. Unlike the situation in adults, both males and females were adversely affected among these children.

Patients and methods

Prospective studies—Over a period of six years (1984-90) we were consulted about 16 previously healthy children (aged under 16) who had developed symptomatic hyponatraemia and either died or suffered permanent brain damage. These 16 patients were seen in consultation from five tertiary and nine community hospitals. The age of the children was 7 (SD 5) years (range 1.5 to 15 years), and the gender distribution was nine males and seven females. The mean weight was 23.8 (12.9) kg (range 10 to 52 kg). Symptomatic hyponatraemia developed within five days of admission to the hospital.

Epidemiological studies—We retrospectively studied all surgical admissions to a 456 bed tertiary paediatric university teaching hospital over three years (1989-91). The records of all paediatric (age under 16) surgical patients were evaluated for those who had postoperative hyponatraemia (serum sodium concentration 128 mmol/l or less) and the number who either died or suffered permanent brain damage as a result of the hyponatraemia. The epidemiological data were generated by computer search of the hospital records using the SAS database¹⁸ to obtain information on all paediatric surgical patients who had a postoperative serum sodium concentration of 128 mmol/l or less. There were 24 412 consecutive inpatient operations over the three years ended 31 December 1991. In addition, we calculated an approximation of the incidence of hyponatraemic brain damage in children in the United States from our epidemiological data plus a statistical database from the medical literature.^{19 20}

Results

STUDY PATIENTS

The table shows the clinical circumstances which resulted in hospitalisation of the 16 patients. All data

are presented as means (SD). Symptoms were not known in three patients, who were either too young (less than 18 months) or intubated and thus unable to vocalise any complaints. Of the remaining 13 patients, 11 had progressive lethargy, weakness, nausea, and emesis and 12 had headache. All patients suffered respiratory arrest after a mean of 37 hours (range three to 120 hours) from the start of intravenous fluid administration.

CLINICAL COURSE

At admission the serum sodium concentration was 138 (2) mmol/l. As early as two hours after starting hypotonic fluid administration those patients able to communicate became progressively more lethargic and complained of headache and nausea, with subsequent emesis. All such symptoms were generally unresponsive to conventional agents (phenothiazines and narcotics). After a mean of 37 hours all 16 patients suffered respiratory arrest, at which time the serum sodium concentration was 115 (7) mmol/l and urine osmolality 676 (66) mmol/kg. This level of urine hypertonicity in the presence of hyponatraemia suggests that the plasma antidiuretic hormone concentration was raised.²¹ The onset of respiratory arrest was, often explosive in nature, and hyponatraemia was generally not considered as a possible cause.

Immediately after respiratory arrest but before oxygen administration or intubation the arterial oxygen tension was evaluated in 11 patients and was 6.0 (1.5) kPa. During the 37 hours between the time of admission and onset of respiratory arrest the patients had received a mean of 125 (83) ml hypotonic intravenous fluids per kg daily. Urine output was 34 (34) ml/kg per day and other fluid losses averaged 28 (25) ml/kg per day (nasogastric suction, n=2; emesis, n=10; cerebrospinal fluid drainage, n=1; not charted, n=3) with mean net output of 74 (82) ml/kg daily and net positive fluid balance of only 27 (14) ml/kg per day. Hyponatraemia in these children was thus largely due to extensive extrarenal loss of electrolyte containing fluids with replacement by hypotonic fluids. Most of the intravenous fluids were administered as 280 mmol glucose per litre either in water or in sodium chloride 38 mmol/l, but the plasma glucose concentration was

Clinical characteristics of 16 children with symptomatic hyponatraemia

C N	Gender and age (years)	Weight (kg)	Serum sodium (mmol/l)		Duration of intravenous fluid treatment (hours)	Net fluid intake (ml/kg)	Net fluid output (ml/kg)*	Clinical history	Hospital procedures	Respiratory arrest	Treatment after respiratory arrest	Clinical outcome
			Initial	Lowest								
1	M 3.5	2.27	139	114	46	246	222	Fever, dysphagia, pharyngitis, tonsillitis	Antibiotics+fluids	Yes	154 mM sodium chloride	Vegetative, quadriplegia
2	F 5	18.0	141	123	14	96	33	Tonsillitis	Tonsillectomy	Yes	None	Died
3	F 4	18.2	139	115	21	114	NA	Tonsillitis	Tonsillectomy	Yes	None	Died
4	M 15	44.6	134	101	74	164	73	Fever, dysphagia, pharyngitis, tonsillitis	Antibiotics+fluids	Yes	154 and 514 mM sodium chloride	Aspiration pneumonia, sepsis, died
5	M 3.5	15.0	138	121	9	61	5	Tonsillitis	Tonsillectomy	Yes	None	Died
6	F 12	31.8	137	120	33	57	11	Elbow fracture from car accident	Setting of fracture	Yes	514 mM sodium chloride; intubation	Ambulatory, mental retardation
7	M 4	16.4	139	118	27	109	88	Elbow fracture from fall	Setting of fracture	Yes	None	Died
8	M 3	10.0	137	113	8	300	NA	Stricture of urethra; tonsillitis	Urethral dilatation; tonsillectomy	Yes	None	Died
9	F 1.5	10.6	137	114	120	283	253	Hydrocephalus	Ventriculoperitoneal shunting	Yes	None	Vegetative
10	M 9	27.0	137	120	32	79	NA	Fractures from car accident	Operative setting of fractures	Yes	None	Vegetative
11	F 15	52.0	138	102	94	87	57	Fractures from car accident	Operative setting of fractures	Yes	154 mM sodium chloride; intubation	Vegetative and blind
12	F 4	16.8	138	107	16	88	56	Tonsillitis	Tonsillectomy	Yes	None	Died
13	M 2	11.4	138	116	3	123	NA	Undescended testicle	Orchiopexy	Yes	None	Died
14	M 6	15.0	138	119	12	40	11	Severe epistaxis	Posterior packing	Yes	None	Died
15	M 12	42.0	137	123	19	34	9	Fever, appendicitis, ruptured appendix	Appendicectomy plus drainage	Yes	None	Died
16	F 12	28.5	134	116	66	113	72	Pneumonia	Antibiotics+fluids	Yes	None	Vegetative
Mean	7	23.8	138	115	37	125	74					
SD	5	12.9	2	7	34	83	82					
SE	1	3.2	1	2	9	21	24					

*Urine+emesis+gastric drainage+cerebrospinal fluid. NA=Not available.

subsequently developed the syndrome of central diabetes insipidus with betes mellitus and central diabetes insipidus with hypotonic polyuria. In these four patients the mean serum sodium concentration rose (without treatment) from 114 (6) mmol/l to 164 mmol/l and the glucose concentration to 31.1 mmol/l. None of these patients had been treated for their hyponatraemia.

OUTCOME

All 16 patients either died or suffered permanent brain damage (table): one was mentally retarded, 10 died, and five were in a persistent vegetative state which persisted for follow up intervals of at least two years. Twelve patients received no specific treatment for their hyponatraemia. Of these, nine died and three remained in a persistent vegetative state.²¹ Four patients were eventually treated with intravenous sodium chloride 154 and 514 mmol/l (table) such that the serum sodium concentration was increased from 108 (9) to 138 (4) mmol/l in 44 hours. The average delay from respiratory arrest to start of treatment was eight hours, all four patients were comatose, apnoeic, and intubated at the time treatment was begun, and none awoke either during treatment or for three days thereafter. Only one patient (case 6), who survived mentally retarded, was treated within 10 minutes of respiratory arrest.

NECROPSY FINDINGS

Postmortem examination of the brain was performed in 10 patients (three girls, seven boys). In nine patients who had received no treatment and died in less than 48 hours there was cerebral oedema and herniation on gross examination of the brain. The brain weight (unfixed) in six patients (three male, three female) whose mean age was 3.8 years was 1354 (95) g. For comparison, the normal brain weight in men is 1450 g; in women 1250 g, in 4-5 year old boys 1300 g, and in 4-5 year old girls 1150 g.²² Thus brain weight was increased by more than 10% above control values for children of the age range studied.²³ That transtentorial herniation was present in all nine patients subjected to postmortem evaluation correlates well with the observation that the human brain can expand by only about 5-7% of its normal volume²⁴ before herniation occurs. We have shown that men's brains can usually adapt to hyponatraemia within a few hours whereas women's brains may not adapt within several days.⁸ In all 16 children presented here the brains were unable adequately to adapt to hyponatraemia.

EPIDEMIOLOGICAL FINDINGS

Among 24 412 paediatric surgical admissions to a 456 bed university paediatric hospital there were 83 (0.34%) patients who developed hyponatraemia. Among these, seven (8.4%) died of complications of the hyponatraemia. Among the seven deaths, four were in boys and three in girls. Hence the incidence was 340 cases of paediatric postoperative hyponatraemia and 29 hyponatraemic deaths per 100 000 inpatient operations on children. There are 2.02 million paediatric inpatient operations a year in the United States.^{19,25} The estimated yearly incidence in the United States is 7448 cases of paediatric postoperative hyponatraemia, with 626 such hyponatraemic deaths in children. The most common inpatient operations on children in the United States²⁶ are to the nose, mouth, and pharynx (17%); digestive system (17%); musculoskeletal system (15%); and nervous system (13%), of which 43% are performed in girls. This was essentially the distribution in our series, in which 92% of operations were in these four groups and 44% of the patients were female (table).

can abruptly develop or develop permanent brain damage. The permanent or develop permanent brain damage. The permanent brain damage can include pituitary infarction with resultant central diabetes insipidus and mellitus, a syndrome not previously described in children.³ The incidence of postoperative hyponatraemia in children (0.34%) was less than in adults (1.4%).²¹ However, among paediatric patients who developed symptomatic hyponatraemia the incidence of permanent brain damage was substantially higher than in adults.²¹ Both the types of surgery and gender distribution among our 16 patients (table) were the same as the most common operations and gender distribution in the United States as a whole,²⁶ and thus our 16 patients were representative of the spectrum of elective paediatric surgical patients.

The hyponatraemia in these children seems to have been caused by extensive extrarenal loss of electrolyte containing fluids and intravenous replacement with hypotonic fluids (table) in the presence of antidiuretic hormone activity. Increased plasma concentrations of antidiuretic hormone are usually found in both children and adults with hyponatraemia,^{9,12-14,16,26} and the hormone has multiple cerebral and vascular effects which can impair the ability of the brain to adapt to hyponatraemia.^{27,28} However, the genesis of hyponatraemia in children is usually different from that in adults. In adults there has often been administration of very large quantities of intravenous fluid (net retention 63 ml/kg per day in adults v 28 ml/kg per day in children; $p < 0.01$)³³ or diuretic induced loss of cations.^{34,35} It is important to recognise that in children, when there is substantial extrarenal loss of electrolytes, a minimal positive balance of hypotonic fluid can lead to fatal hyponatraemia. Another major factor which may have contributed to the high morbidity among these children was the virtual absence of timely treatment in the presence of obvious symptoms.^{10,11,16,17} Furthermore, the types of operations and the clinical conditions in this patient population were similar to those most common in the United States.²⁶ Thus the index of suspicion for electrolyte disorders in generally healthy children undergoing elective surgery may be quite low.

BRAIN ADAPTATION TO HYPONATRAEMIA IN CHILDREN

In adults oestrogens seem to impair the ability of the brain to adapt to hyponatraemia and androgens may augment such adaptation.^{30,33} However, prepubescent children have only minimal to absent concentrations of either hormone, thus negating such effects. Most adults suffering permanent brain damage from hyponatraemia are female,^{33,37} but in the current series a minority of affected patients (43%) in both the prospective and retrospective studies were female. Thus unlike the marked gender differential in adults, male and female children seem to be at similar risk of developing hyponatraemia encephalopathy (NS (χ^2 test)). Furthermore, neither the actual concentration of serum sodium nor the rapidity of development of hyponatraemia seemed to predict the ultimate outcome in these 16 children (table). Hyponatraemia developed over a mean of 37 hours and the range of serum sodium values was 101-123 mmol/l, values quite similar to those previously reported in children with symptomatic hyponatraemia who did not develop brain damage.^{10,12,13,16}

EFFECTS OF PHYSICAL FACTORS

When hyponatraemia was present all 16 children had radiological evidence (computed tomography, magnetic resonance imaging) of cerebral oedema

whereas at necropsy nine of 10 evaluated had cerebral oedema with herniation. These findings show that adequate adaptation of the brain to hyponatraemia had not occurred. There are several unique characteristics of the paediatric central nervous system which may impair the ability to adapt to hyponatraemia. Such characteristics may include physical factors resulting from differences in the ratio of intracranial capacity to brain size, cerebrospinal fluid volume, and brain water and electrolyte content.

The early adaptation of brain to hyponatraemia involves a loss of blood and cerebrospinal fluid followed by extrusion of sodium from brain cells.^{34,35} Later adaptation includes loss of potassium and possibly amino acids, which act further to decrease brain cell osmolality and limit the gain of water.^{1,34} In humans and laboratory animals brain water content is more than 2.5 times higher in the young, decreasing progressively with age.^{34,35} In children the ratio of brain to skull size is such that there is less room for expansion of the paediatric brain in the skull than there is in adults.³⁹ As adults age there is a progressive decline in the brain volume whereas skull size remains constant.³⁹ Hence anatomically there is decreased room for expansion of the brain within the skull in children as compared with adults.²³

Adult brain size is reached at about age 6 whereas full skull size is not reached until age 16. Additionally, the intracerebral volume of cerebrospinal fluid is more than 10% greater in adults than in the young.³⁹ When brain swelling occurs the intracerebral loss of cerebrospinal fluid increases the available volume in which the brain can expand.^{34,35} As the percentage of cerebrospinal fluid in the brain increases with age³⁹ adults of both genders have more room in the rigid skull for the brain to expand than do children.³⁹ Furthermore, the brain intracellular concentration of sodium is about 27% higher in children than in adults³⁷ and may reflect a relative decreased ability to pump sodium out of the brain in children. In the presence of hyponatraemia this will result in a greater osmolar gap between brain and plasma in the young. It has been shown that in newborn puppies with hyponatraemia the brain is unable to extrude cations³⁸ whereas adult animals with hyponatraemia can readily transport sodium out of the brain.^{1,31,34}

PREVENTION AND TREATMENT OF HYPONATRAEMIC ENCEPHALOPATHY

Symptomatic hyponatraemia can best be prevented by not infusing hypotonic fluids to hospitalised children unless there is a clear cut indication for their use. Headache, nausea, emesis, weakness, and lethargy are consistent symptoms of hyponatraemia in children. If the condition is allowed to go untreated there can follow an explosive onset of respiratory arrest, coma, and transtentorial cerebral herniation. At present there is no way to predict which children may suffer respiratory arrest. As found recently in adults neither the magnitude of hyponatraemia nor its duration is the major determinant of brain damage.⁴ Recent studies show that recovery from symptomatic hyponatraemia in children, even after the onset of seizures and apnoea, may be possible if appropriate treatment is instituted in a timely manner.¹¹

When a paediatric patient receiving hypotonic fluids begins to have headache, emesis, nausea, or lethargy the serum sodium concentration must be measured. Although these symptoms are somewhat non-specific, the diagnosis is easily established at minimal cost and with virtually no risk to the patient by evaluating plasma electrolyte values. When symptomatic hyponatraemia is diagnosed the patient should be moved to a location where constant monitoring can be provided, such as the intensive therapy unit. Hypertonic sodium

chloride (514 mmol/l) should be infused as described,^{41,42} such that the serum sodium concentration is increased to 125-130 mmol/l but by no more than 25 mmol in the initial 48 hours. In addition to hypertonic sodium chloride, treatment may include intubation and assisted mechanical ventilation when required.

This work was supported by grant RO1 08575-01A2 from the National Institute on Aging, National Institutes of Health, Bethesda, Maryland, and by the research service of the Veterans Affairs Medical Center, San Francisco, California. We thank Anne Ludvik and Trish Sullivan, of the library service at the San Francisco Veterans Affairs Medical Center, for help in preparing the database and the medical records department of the Children's Hospital, Houston, Texas, for help in preparing the statistical data.

Addendum

After submission of this paper a report appeared describing 34 paediatric patients with water intoxication.⁴³ Two of the patients became hyponatraemic secondary to intravenous hypotonic fluid administration (serum sodium concentrations 112 and 114 mmol/l). Both suffered respiratory arrest and died, and at necropsy both had cerebral oedema. These two patients had a clinical course similar to the 16 in our series. The other 32 patients had oral water intoxication, and all survived because of timely and appropriate treatment.

- 1 Arieff AI, Llach F, Massry SG, Kerian A. Neurological manifestations, morbidity of hyponatremia: correlation with brain water and electrolytes. *Medicine (Baltimore)* 1976;55:121-9.
- 2 Ayus JC, Olivero JJ, Frommer JP. Rapid correction of severe hyponatremia with intravenous hypertonic saline solution. *Am J Med* 1982;72:43-8.
- 3 Arieff AI. Hyponatremia, convulsions, respiratory arrest, and permanent brain damage after elective surgery in healthy women. *N Engl J Med* 1986;314:1529-35.
- 4 Ayus JC, Krothapalli RK, Arieff AI. Treatment of symptomatic hyponatremia and its relation to brain damage. A prospective study. *N Engl J Med* 1987;317:1190-5.
- 5 Fraser CL, Arieff AI. Fatal central diabetes mellitus and insipidus resulting from untreated hyponatremia: a new syndrome. *Ann Intern Med* 1990;112:113-9.
- 6 Ashraf N, Locksley R, Arieff AI. Thiazide-induced hyponatremia associated with death or neurologic damage in outpatients. *Am J Med* 1981;70:1163-8.
- 7 Tien R, Arieff AI, Kucharczyk W, Wasik A, Kucharczyk J. Hyponatremic brain damage: is central pontine myelinolysis common? *Am J Med* (in press).
- 8 Ayus JC, Arieff AI. Effects of age and gender on outcome in patients with postoperative hyponatremia. *J Am Soc Nephrol* 1991;2:278.
- 9 Gross PA, Pehrish H, Rascher W, Schömig A, Hackenthal E, Ritz E. Pathogenesis of clinical hyponatremia: observations of vasopressin and fluid intake in 100 hyponatremic medical patients. *Eur J Clin Invest* 1987;17:123-9.
- 10 Crumacker RW, Kriel RL. Voluntary water intoxication in normal infants. *Neurology* 1973;23:1251-5.
- 11 Sarnaik AP, Meert K, Hackbarth R, Fleischmann L. Management of hyponatremic seizures in children with hypertonic saline: a safe and effective strategy. *Crit Care Med* 1991;19:758-62.
- 12 David R, Ellis D, Gartner JC. Water intoxication in normal infants: role of antidiuretic hormone in pathogenesis. *Pediatrics* 1981;68:349-53.
- 13 Judd BA, Haycock GB, Dalton N, Chantler C. Hyponatremia in premar babies and following surgery in older children. *Acta Paediatr Scand* 1987;76:385-93.
- 14 Cowley DM, Pabari M, Sinton TJ, Johnson S, Carroll G, Ryan J. Pathogenesis of postoperative hyponatremia following correction of scoliosis in children. *Aust N Z J Surg* 1988;58:485-9.
- 15 Crawford JD, Dodge PR. Complications of fluid therapy in neurologic disease. *Pediatr Clin North Am* 1964;11:1029-52.
- 16 Burrows FA, Shattuck JG, Crone RK. Inappropriate secretion of antidiuretic hormone in a postsurgical pediatric population. *Crit Care Med* 1983;11:527-31.
- 17 Varavithya W, Hellerstein S. Acute symptomatic hyponatremia. *J Pediatr* 1967;71:269-83.
- 18 SAS Institute I. *SAS user's guide: basics. Version 5 edition*. Cary, North Carolina: SAS Institute, 1985.
- 19 American Hospital Association. 1989 Annual survey of hospitals. Utilization, personnel and finances in US registered hospitals. In: *American Hospital Association hospital statistics*. Chicago: American Hospital Association, 1991:20 (table 5A).
- 20 US Department of Commerce. Population. In: *Statistical abstracts of the United States, 1990*. 110th ed. Washington, DC: Bureau of the Census, 1990: 16-8.
- 21 Chung HM, Kluge R, Schrier RW, Anderson RJ. Postoperative hyponatremia: a prospective study. *Arch Intern Med* 1986;146:333-6.
- 22 Jennett B, Plum F. Persistent vegetative state after brain damage. *Lancet* 1972;ii:734-7.
- 23 Dekaban AS, Sadowsky D. Changes in brain weights during the span of human life: relation of brain weights to body heights and body weights. *Ann Neurol* 1978;4:345-56.
- 24 Garcia JH, Conger KA, Morawetz R, Halsey JH Jr. Postischemic brain edema: quantitation and evolution. In: Cervós-Navarro J, Ferszt R, ed. *Brain edema. Pathology, diagnosis, and therapy*. New York: Raven Press, 1980: 147-69.
- 25 US Department of Commerce. Health and nutrition. In: *Statistical abstracts of the United States, 1990*. 110th ed. Washington, DC: Bureau of the Census, 1990:110-1.
- 26 Anderson RJ, Chung HM, Kluge R, Schrier RW. Hyponatremia: a prospec-

- mediated by ...
- 28 Faraci FM, Mayhan WG, Heistad DD. Effect of vasopressin on production of cerebrospinal fluid: possible role of vasopressin (V1)-receptors. *Am J Physiol* 1990;258:R94-8.
 - 29 Abramow M, Cogan E. Clinical aspects and pathophysiology of diuretic-induced hyponatremia. *Adv Nephrol (Paris)* 1984;13:1-28.
 - 30 Guerra M, del Castillo AR, Battaner E, Mas M. Androgens stimulate preoptic area Na⁺, K⁺-ATPase activity in male rats. *Neurosci Lett* 1987;78:97-100.
 - 31 Fraser CL, Sarnacki P. Na⁺-K⁺ ATPase pump function in male rat brain synaptosomes is different from that of females. *Am J Physiol* 1989;257:E284-9.
 - 32 Fraser CL, Kucharczyk J, Arief AI, Rollin C, Sarnacki P, Norman D. Sex differences result in increased morbidity from hyponatremia in female rats. *Am J Physiol* 1989;256:R880-5.
 - 33 Del Castillo AR, Battaner E, Guerra M, Alonso T, Mas M. Regional changes of brain Na⁺, K⁺-transporting adenosine triphosphate related to ovarian function. *Brain Res* 1987;416:113-8.
 - 34 Melton JE, Patlak CS, Pettigrew KD, Cserr HF. Volume regulatory loss of

- chemical composition of ...
- 37 Katzman R, Pappius HM, eds. Brain ions. In: *Brain electrolytes and fluid metabolism*. Baltimore: Williams and Wilkins, 1973:111-34.
- 38 Nattie EE, Edwards WH. Brain and CSF water in newborn puppies during acute hypo- and hypernatremia. *J Appl Physiol* 1981;51:1086-91.
- 39 Gur RC, Mozley PD, Resnick SM, Gottlieb GL, Kohn M, Zimmerman R, et al. Gender differences in age effect on brain atrophy measured by magnetic resonance imaging. *Proc Natl Acad Sci USA* 1991;88:2845-9.
- 40 Rosomoff HL, Zugibe FT. Distribution of intracranial contents in experimental edema. *Arch Neurol* 1963;9:36-44.
- 41 Worthley LIG, Thomas PD. Treatment of hyponatraemic seizures with intravenous 29.2% saline. *BMJ* 1986;292:168-70.
- 42 Keating JP, Schears GJ, Dodge PR. Oral water intoxication in infants. *Am J Dis Child* 1991;145:985-90.

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First use of heroin: changes in route of administration over time

John Strang, Paul Griffiths, Beverly Powis, Michael Gossop

AIDS and drug misuse are linked mainly by the injection of many drugs. Major changes in the methods of heroin use, however, have fundamentally altered the importance of heroin use in the transmission of HIV. Recent reports describe the extent of "chasing the dragon" (inhaling sublimated heroin after heating it on tinfoil) as a new route of heroin use but give no information on the emergence of this pattern.^{1,2} During the 1960s heroin use was by injecting.³ What events occurred (and when) to account for this substantial change in the nature and the link with HIV of the heroin epidemic?

Subjects, methods, and results

Four hundred heroin users were contacted and interviewed by trained peer group interviewers through a structured and tape recorded interview. A total of 204 (51%) were currently out of contact with any treatment service, 100 (25%) were currently attending a drug

clinic, and 124 (31%) were currently attending a needle exchange scheme. A total of 136 (34%) had never had contact with either treatment services or an exchange scheme. Their ages ranged from 17 to 53 (mean (SD) 27.6 (6.3) years); 248 (62%) were male; 96 (24%) were in current employment. There was wide variation in first year of use of heroin use (1954 to 1991): 16 (4%) started during the '60s, 28 (7%) during the early '70s, 76 (19%) during the late '70s, 124 (31%) during the early '80s, 120 (30%) during the late '80s, and 36 (9%) during the '90s.

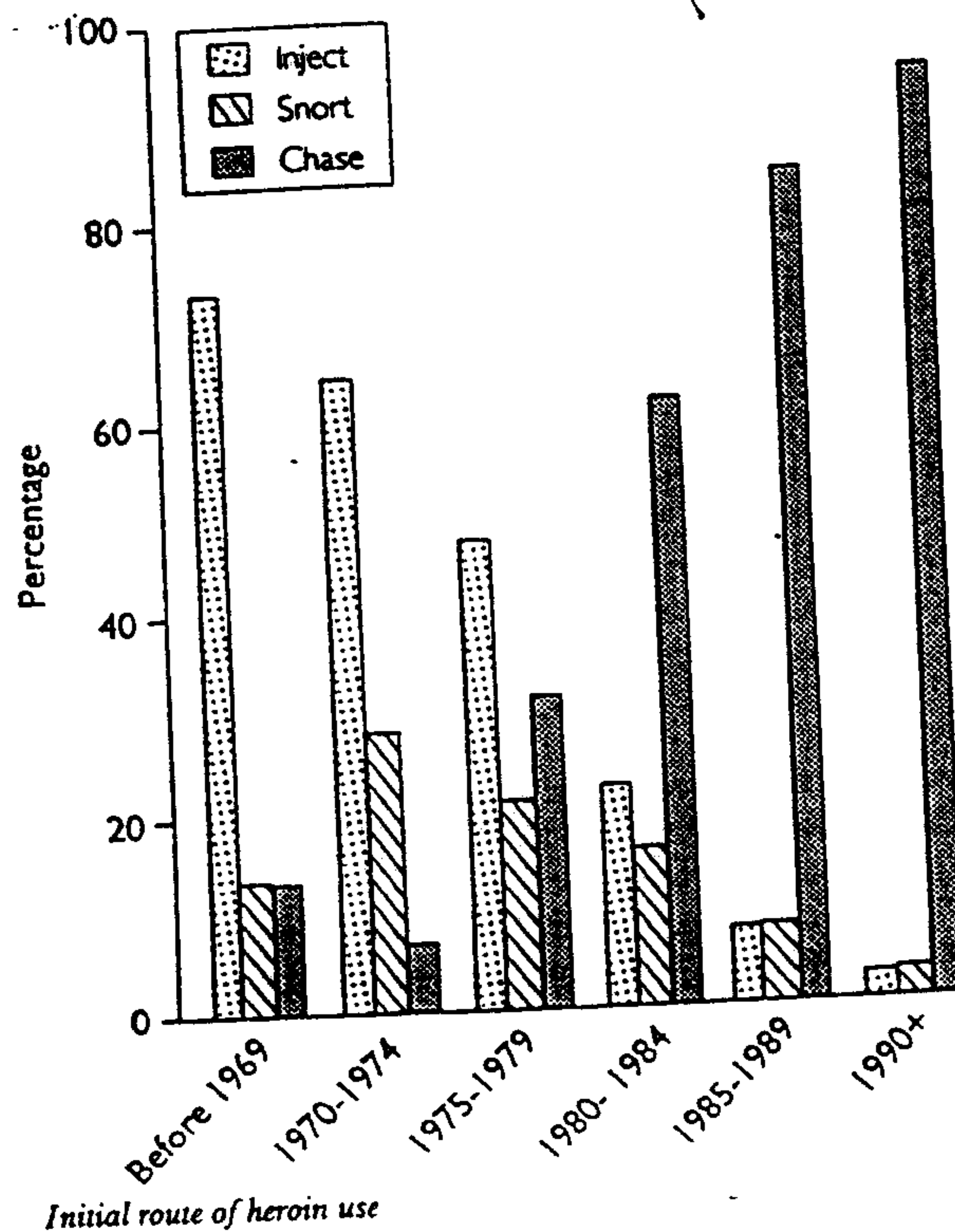
Three different routes of initial drug use were identified: injecting, snorting, and "chasing the dragon." Analysis of these data by year revealed a major change in the annual proportion who were initiated by either injecting or chasing (figure).

"Chasing" was a route of initiation for a minority of users up to the late 1970s but has become an increasingly common route of initiation since 1975. By 1979 there were as many initiations by chasing as by injecting, and by 1981 more than half of the initiations into heroin use were by chasing (with the annual proportion remaining above half since 1981). By 1985 more than three quarters of initiations were by chasing, and since 1988, 87 out of 93 initiations (94%) were by chasing. During most years, a tenth to a quarter of users were initiated by snorting.

Comment

Heroin use today is not what it was yesterday. Initiation no longer occurs by injecting but by the new route of "chasing the dragon." The emergence of new non-injecting routes of heroin use may partly explain not only the major heroin epidemic in the United Kingdom during the 1980s but also its apparent continuation despite the addition of AIDS as a potential consequence. Perhaps the protective societal taboo against injecting was circumvented and a less fettered epidemic has developed. In the 1990s virtually all initiations into heroin use in our London sample were by "chasing the dragon," even though heroin use in other countries (for example, the United States) and even in other British cities (for example, Edinburgh) continues to be by injection. Should the change in London be regarded as an isolated development in a few "chasing" cities, or is it an indication of likely future changes on a wider scale? And what is the significance for tomorrow's prevention and treatment programmes?

Our level of ignorance about changing routes of drug administration is not only scientifically disturbing but also interferes with the development of prevention and treatment programmes. Effective primary prevention strategies depend greatly on the adequacy of knowledge about the gateways into drug use, and yet our understanding of the phenomenon is informed largely by



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Chronic Hyponatremic Encephalopathy in Postmenopausal Women

Association of Therapies With Morbidity and Mortality

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CHRONIC HYPONATREMIA IS A common clinical problem in the elderly, particularly among women.¹ Although the mortality among such patients is substantial,²⁻⁵ it is unclear if these patients die of hyponatremia, the effects of therapy, or associated medical conditions. It is now well accepted that acute symptomatic hyponatremia (hyponatremic encephalopathy) in menstruant women can result in death or permanent brain damage.⁶⁻⁹ While failure to institute active therapy (intravenous [IV] sodium chloride) in such patients may lead to increased morbidity, IV hypertonic sodium chloride therapy is both safe and effective in preventing hyponatremic brain damage.¹⁰⁻¹³ However, for the past decade it has been suggested that there are important clinical distinctions between acute and chronic hyponatremia in regard to indications for active therapy and propensity for permanent brain damage.^{2,7,14} Furthermore, it has been suggested that much of the brain damage associated with chronic hyponatremia may be a consequence of improper therapy rather than hyponatremic encephalopathy.^{2,3,15} In general, studies of patients with chronic hyponatremia usually have not included information on whether the patients were symptomatic.¹⁻⁵ In the vast

Context Chronic hyponatremia in postmenopausal women is a common clinical problem often viewed as benign. Fluid restriction is usually the recommended therapy, largely because the extent of morbidity is unknown and because it has been postulated that intravenous (IV) sodium chloride may cause brain damage.

Objective To compare IV sodium chloride with fluid restriction in the treatment of postmenopausal women with chronic symptomatic hyponatremia.

Design Nonrandomized prospective study.

Setting Two university medical centers and affiliated community hospitals.

Patients A total of 53 postmenopausal women with chronic symptomatic hyponatremia (chronic plasma sodium <130 mmol/L in the presence of central nervous system manifestations) treated consecutively from 1988-1997 and followed up for 1 year. The mean (SD) age of the patients was 62 (11) years.

Interventions The therapeutic interventions were IV sodium chloride before respiratory insufficiency (n = 17), IV sodium chloride after respiratory insufficiency (n = 22), and fluid restriction only (n = 14).

Main Outcome Measures Morbidity and neurological outcome at 4 months or longer as assessed by cerebral performance category (CPC) in relation to the therapy, initial plasma sodium level, and rate of correction.

Results Chronic symptomatic hyponatremia (mean [SD] sodium level 111 [12] mmol/L) was present for 5.2 [4.5] days. Death or major morbidity occurred in 44 (83%) of 53 patients, including 10 with orthopedic injury. Twelve patients had hypoxemia (PO₂ = 63 [25] mm Hg) and cerebral edema. Among patients who received IV sodium chloride before respiratory insufficiency, plasma sodium levels were increased by 22 (10) mmol/L in 35 hours and patients had a CPC of 1.0 (normal or slight disability). Among patients who received IV sodium chloride after respiratory insufficiency, plasma sodium levels were increased by 30 (6) mmol/L in 41 hours and patients had a CPC of 3.0 (1.2) (severe disability). Among patients who had fluid restriction only, plasma sodium levels were increased by 3 (2) mmol/L in 41 hours and patients had a CPC of 4.6 (0.7) (4 = persistent vegetative state; 5 = death). The outcomes did not correlate with either the initial plasma sodium level ($r = 0.05$, $P > .12$) or the rate of correction ($r = 0.31$, $P > .10$).

Conclusions Chronic symptomatic hyponatremia in postmenopausal women can be associated with major morbidity and mortality. Therapy with IV sodium chloride was associated with significantly better outcomes than fluid restriction.

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majority of instances, chronic hyponatremia occurs in postmenopausal women, often in association with thiazide therapy or the syndrome of inappropriate secretion of antidiuretic hor-

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Table 1. Demographics and Laboratory Values*

Demographics (n = 53)	
Age, y	62 (11)
Weight, kg	62 (11)
Duration of hyponatremia, d	5.2 (4.2)
Arterial parameters (n = 12)	
pH	7.42 (0.13)
Arterial PO ₂ , mm Hg	63 (25)
Arterial PCO ₂ , mm Hg	31 (7)
Arterial bicarbonate, mmol/L	25.1 (3.1)
Plasma parameters (n = 53)	
Sodium, mmol/L	111 (12)
Potassium, mmol/L	3.2 (0.9)
Glucose	
mmol/L	9.1 (5.4)
mg/dL	164 (97)
Urea nitrogen	
mmol/L	3.9 (1.2)
mg/dL	11 (3)
Creatinine	
μmol/L	71 (26)
mg/dL	0.8 (0.3)
Urine parameters (n = 9)	
Sodium, mmol/L	78 (36)
Potassium, mmol/L	38 (29)
Osmolality, mmol/kg H ₂ O	426 (41)

*All data are mean (SD) unless otherwise noted.

mone.^{2,4,5,16} As a result, it is widely believed that postmenopausal women are in little danger of morbidity associated with chronic hyponatremia, and that initiation of therapy with IV sodium chloride is potentially hazardous.^{2,3}

Recent studies have demonstrated that the major criterion for use of IV sodium chloride therapy in patients with acute symptomatic hyponatremia is the presence of central nervous system symptoms, regardless of the level of plasma sodium.^{9,10,12} It has been suggested that therapy with sodium chloride might be appropriate in patients with chronic symptomatic hyponatremia.^{7,14} However, little if any actual data are available to support this contention, and fluid restriction is frequently suggested as the appropriate therapy.^{3-5,15,17} We have found no studies in which therapy with IV sodium chloride was compared with fluid restriction in patients with chronic symptomatic hyponatremia.

METHODS

We performed a prospective study of the outcomes and effects of interventional therapy in postmenopausal women with chronic symptomatic hyponatremia. The study group consisted of 53 consecutive patients about

whom 1 of the authors was consulted during the interval 1988-1997. No patients were omitted from the study. Other aspects of 5 of the 53 patients have been published in another context.¹⁸ Symptomatic hyponatremia (hyponatremic encephalopathy) was defined as a plasma sodium level below 130 mmol/L in the presence of central nervous system manifestations.^{7,19} Chronic hyponatremia was documented by 2 different modalities: (1) a documented duration of at least 48 hours,⁷ and (2) a rate of decrease in plasma sodium levels of less than 0.5 mmol/L per hour over at least 48 hours.²⁰ Fifty of 53 patients had a decrease in plasma sodium level of 0.5 mmol/L per hour or less for at least 48 hours. In all 53 patients there were at least 2 values for plasma sodium levels below 130 mmol/L separated by 48 or more hours, while in 44 patients there were more than 2 such values. The hyponatremic values were obtained either following surgery or during initial and subsequent visits to an emergency department or physician's office. None of the 53 patients had either edematous disorders (eg, heart failure, hepatic cirrhosis, or nephrotic syndrome) or acquired immunodeficiency syndrome.

The 53 postmenopausal women were divided into 3 groups based on the therapeutic regimen as follows: (1) 17 patients who were treated with IV sodium chloride before the onset of respiratory insufficiency; (2) 22 patients who had not been treated with sodium chloride prior to the onset of respiratory insufficiency, but received IV sodium chloride after respiratory insufficiency, as well as intubation and assisted ventilation; (3) 14 patients who were treated with fluid restriction only. The authors were directly involved in the therapy of the patients in group 1. The authors were consulted about the patients in group 2 only after the patients had experienced respiratory insufficiency and were intubated and receiving assisted ventilation. The authors were consulted about patients in group 3 only after the patients had experi-

enced respiratory insufficiency. For all patients in group 3, the managing physician(s) had made the decision to treat the hyponatremia with fluid restriction rather than IV sodium chloride. The major reason given by the managing physicians for therapy with fluid restriction was the fear of iatrogenic illness related to sodium chloride infusion, particularly cerebral demyelinating lesions.^{2,3} Respiratory insufficiency was defined as a state characterized by impaired respiration such that there was either respiratory arrest or arterial PO₂ below 50 mm Hg.

Cerebral edema was assessed by standard neuroradiological criteria.²¹ The functional outcome was assessed by cerebral performance category (CPC) based on the Glasgow outcome performance categories.^{22,23} Based on functional outcome after 4 months or longer, patients were classified in 1 of the 5 following groups: (1) normal function or only slight disability; (2) conscious and alert with moderate disability but able to care for self and live independently; (3) severe disability such that the subject was unable to care for self and usually required institutional care; (4) persistent vegetative state; and (5) death. In all patients, therapy with sodium chloride was considered to be complete after 48 hours, or earlier when any of the 3 following conditions were met¹³: (1) the patient became asymptomatic; (2) plasma sodium level increased by 25 mmol/L; (3) plasma sodium level increased to 132 mmol/L.

All values are presented as mean (SD). Significance was determined using analysis of variance or coefficient of correlation (*r*) using regression analysis.

RESULTS

Demographics

The mean (SD) age of the 53 women was 62 (11) years (range, 45-89 years) and all were postmenopausal (5 had surgically induced menopause). The duration of the hyponatremia was 5.2 (4.5) days. The laboratory values for all patients at the time hyponatremia was diagnosed are shown in TABLE 1. The

etiologies for the hyponatremia were similar among the 3 groups and included polydipsia ($n = 21$), use of thiazide diuretics ($n = 17$), postoperative complications ($n = 15$), and syndrome of inappropriate secretion of antidiuretic hormone ($n = 5$). Ten of the 53 patients were taking hormone replacement therapy (estrogens).

Clinical Presentation

Orthopedic injury was a prominent presenting feature in this series. The orthopedic injury was the initial clinical manifestation that led to the discovery of hyponatremia in 10 patients (FIGURE 1). The orthopedic injuries were hip fracture ($n = 3$), fractured vertebral processes ($n = 1$), tibia fracture ($n = 1$), shoulder dislocation ($n = 1$), knee dislocation ($n = 2$), and skull fracture ($n = 2$). The mean plasma sodium level when the orthopedic injury was discovered was 117 (11) mmol/L. All 10 orthopedic injuries followed seizures that were a consequence of the hyponatremia. In addition to orthopedic injury, the most common presenting clinical manifestations were headache ($n = 16$), nausea ($n = 14$), emesis ($n = 15$), generalized weakness ($n = 24$), and grand mal seizures ($n = 12$). The 12 patients (groups 1 and 2) whose blood gases were measured before initiation of therapy had severe hypoxemia, with arterial $PO_2 = 63$ (25) mm Hg.

Associated Medical and Surgical Conditions

Associated comorbid conditions included 10 patients with psychiatric disorders (schizophrenia [$n = 2$], bipolar disorder [$n = 3$], depressive illness [$n = 3$], posttraumatic stress disorder [$n = 1$], and beer potomania [$n = 1$]). There were 36 patients with the following medical conditions: coronary artery disease ($n = 1$), pneumonia ($n = 1$), survivable malignancy ($n = 4$), hypertension treated with thiazides ($n = 17$), irritable bowel syndrome ($n = 1$), military tuberculosis ($n = 1$), alcoholism ($n = 2$), febrile illness with polydipsia ($n = 5$), diabetes mellitus ($n = 3$), and cholecystitis ($n = 1$). There were 26 pa-

tients with associated surgical conditions, of whom 16 were postoperative: orthopedic ($n = 6$), plastic ($n = 1$), gynecological ($n = 4$), vascular ($n = 2$), neurosurgical ($n = 1$), gastrointestinal ($n = 2$), and primary orthopedic injury ($n = 10$).

Effects of Therapy

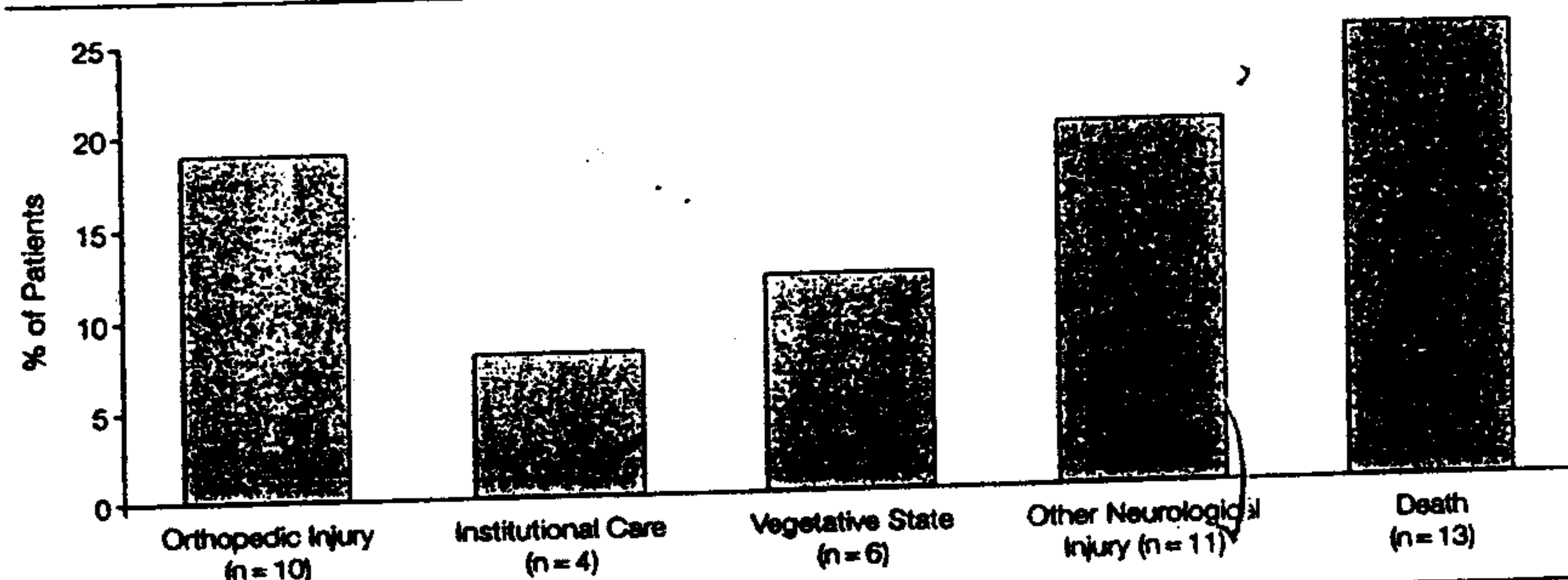
A summary of the effects of therapy for all 3 groups of patients is shown in TABLE 2. Prior to the episode of hyponatremia, all 53 patients were living independently (CPC = 1).

Group 1

The rate of decrease in plasma sodium levels for the group 1 patients was 0.27 (0.14) mmol/L per hour. All 17 group

1 patients were treated with IV sodium chloride (12 with 514 mmol/L and 2 with 154 mmol/L), 7 also received furosemide. The absolute change in plasma sodium levels after 12, 24, and 35 hours, the rate of correction (mmol/L per hour) and the initial plasma sodium level are shown relative to the outcome (CPC = 1 to 5) in Table 2 and FIGURE 2. All 17 recovered without neurological impairment or other complications (CPC = 1). Follow-up examination was done after at least 1 year for 9 of the 17 group 1 patients. All 9 were leading lives comparable to that before the episode of hyponatremic encephalopathy, without evidence of disability (CPC = 1). The other 8 were lost to follow-up.

Figure 1. Sequelae of Chronic Hyponatremic Encephalopathy in 53 Postmenopausal Women



Forty-four of the 53 experienced neurological or orthopedic injury or died.

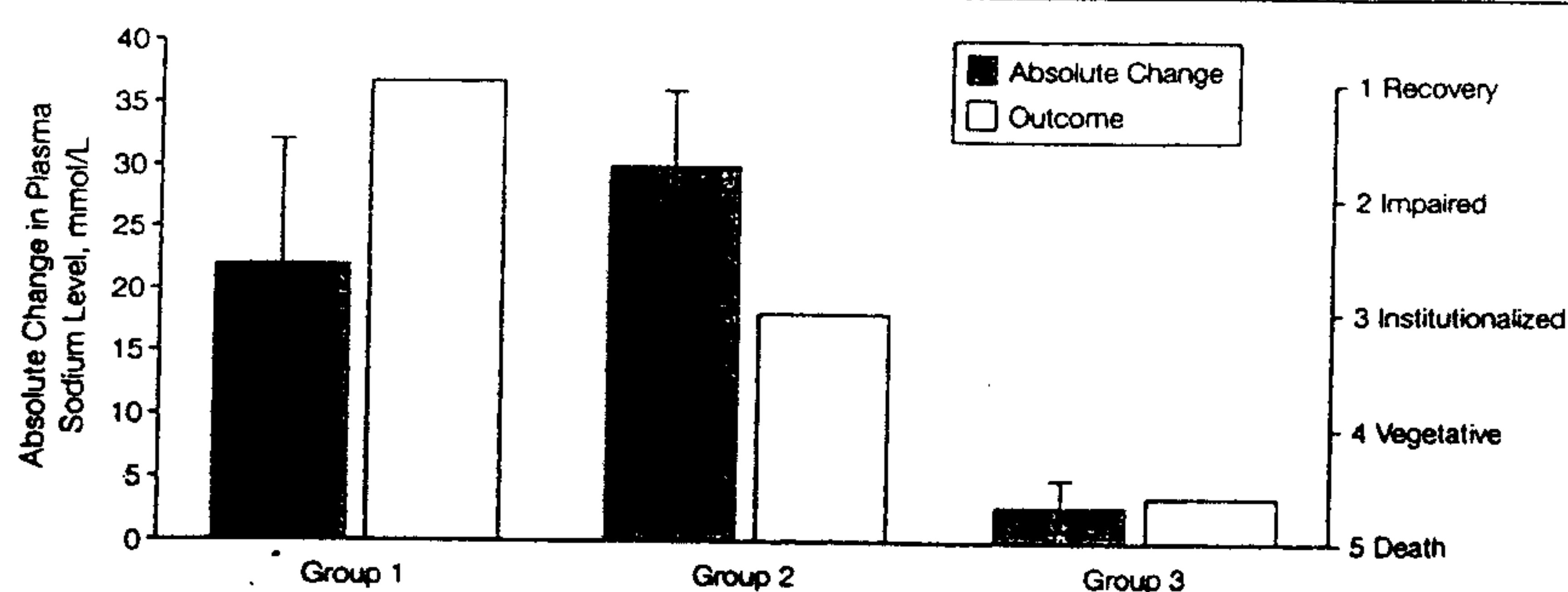
Table 2. Effects of 3 Different Therapies on Outcome in Elderly Women With Chronic Hyponatremic Encephalopathy*

	Group 1† (n = 17)	Group 2† (n = 22)	Group 3† (n = 14)
Age, y	71 (12)	55 (7)	64 (8)
Initial plasma sodium, mmol/L	111 (10)	103 (7)	109 (12)
Plasma sodium at 12 h, mmol/L	119 (4)	113 (9)	111 (10)
Plasma sodium at 24 h, mmol/L	125 (4)	125 (10)	112 (11)
Final plasma sodium, mmol/L	133 (5)	132 (4)	112 (11)
Absolute change in plasma sodium, mmol/L	22 (10)	30 (6)	3 (2)
Time of correction, h	35 (11)	41 (13)	10 Patients died within 24 h; 3 patients institutionalized or vegetative; 1 patient died after 70 d
Rate of correction, mmol/L per h	0.7 (0.3)	0.8 (7.0)	0.1 (0.1)
Outcome, CPC‡	1 (0)	3.0 (1.2)	4.6 (0.7)

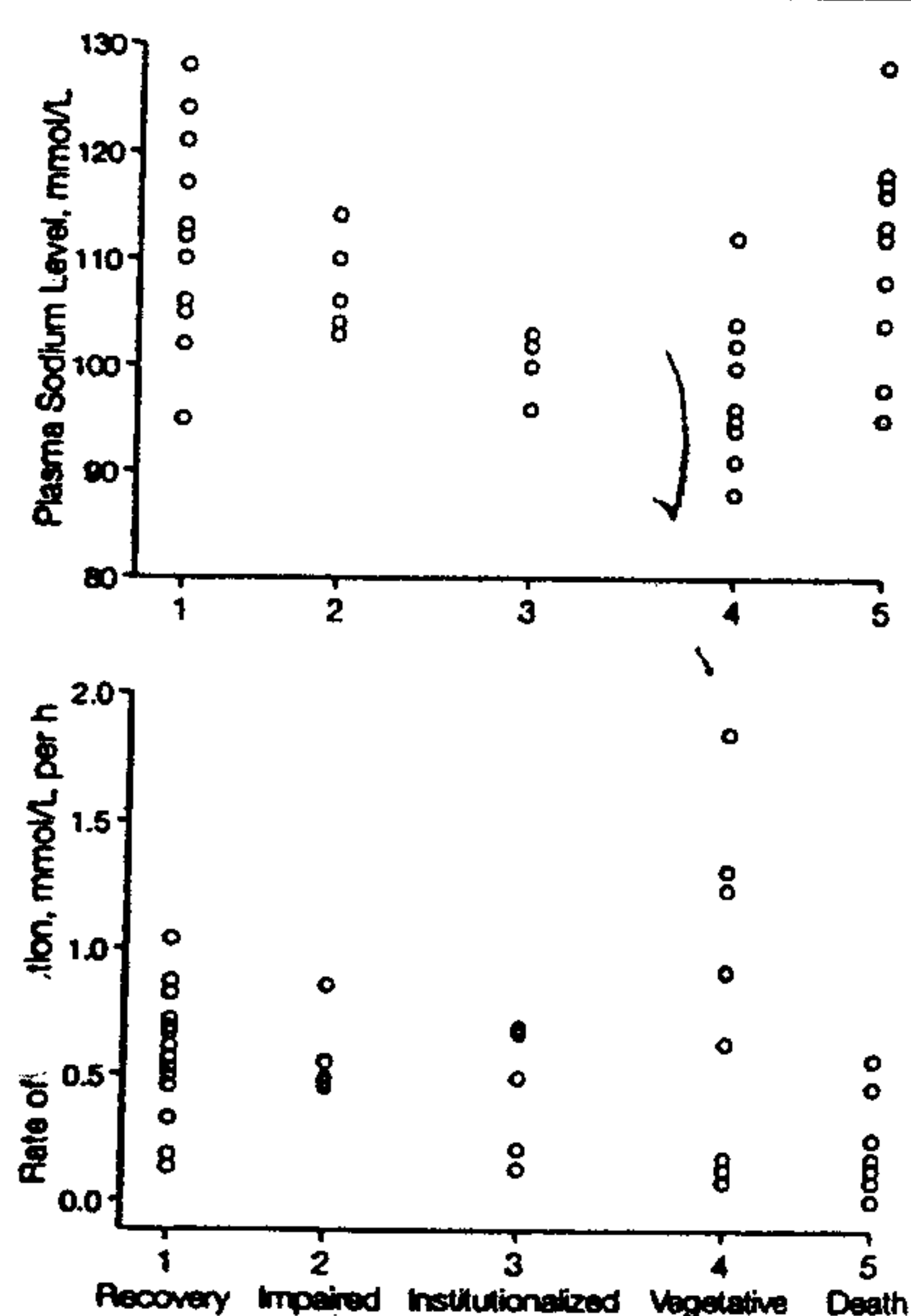
*All data are mean (SD) unless otherwise noted.

†Group 1 was given intravenous sodium chloride before respiratory insufficiency, group 2 was given sodium chloride after respiratory insufficiency, and group 3 was treated with fluid restriction only.

‡CPC indicates cerebral performance category: (1) normal function or only slight disability; (2) conscious and alert with moderate disability but able to care for self and live independently; (3) severe disability such that subject is unable to care for self; (4) persistent vegetative state; and (5) death.

Figure 2. Effects of Therapy on Outcome (Cerebral Performance Category) in 53 Postmenopausal Women With Chronic Hyponatremic Encephalopathy

The absolute change in plasma sodium level over the initial 2 days of therapy was significantly less in group 3 patients than in either group 1 or 2 patients ($P < .01$). The absolute change in group 2 patients was significantly larger than the absolute change in group 1 patients ($P < .05$). The outcome in both group 1 and 2 patients, who were treated with intravenous sodium chloride therapy, was significantly better ($P < .01$) than that in group 3 patients, who were treated with fluid restriction. Error bars represent SD. Group 1 outcomes 1 in all cases.

Figure 3. Relationship Between Patient Outcome (Cerebral Performance Category) and Initial Plasma Sodium Level Before Therapy and Rate of Correction of Plasma Sodium

There is no significant correlation between the outcome and either the initial plasma sodium level ($r = 0.05$; $P = .10$) (top) or the rate of correction ($r = 0.31$; $P = .12$) (bottom).

Group 2

The rate of decrease in plasma sodium levels for the group 2 patients was 0.33 (0.15) mmol/L per hour. All 22 patients experienced respiratory insuffi-

ciency and were intubated with assisted ventilation before therapy with sodium chloride was initiated. The absolute change in plasma sodium levels after 12, 24, and 41 hours, the rate of correction, and the initial plasma sodium levels are shown relative to the outcome in Figure 2 and Table 2. Two patients recovered completely and another 6 recovered so that they were able to live independently (CPC = 2). The remaining 14 either died or developed neurological impairment such that institutionalization was necessary (CPC = 3 to 5) (Figure 1). None of these 14 patients had any other associated medical condition that could have accounted for their morbidity. Follow-up examination was performed after at least 1 year in the 6 group 2 patients who were able to live independently. All 6 continued to live independently.

Group 3

The rate of decrease in plasma sodium levels for the group 3 patients was 0.26 (0.12) mmol/L per hour. The 14 patients were treated with fluid restriction only, and all 14 experienced respiratory insufficiency within 24 hours of the diagnosis of hyponatremia. Therapy with sodium chloride was never provided. The plasma sodium levels after 12 and 24 hours, the rate of correction, and the initial plasma sodium level are shown relative to the out-

come (CPC 1-5) in Figure 2 and Table 2. All 14 patients were eventually intubated and received assisted ventilation, but not until at least 15 minutes after respiratory insufficiency was diagnosed. Despite eventual intubation and ventilation, all 14 patients died or experienced permanent brain damage. None of these 14 patients had other associated medical conditions that accounted for their morbidity. Eleven patients died, 10 within the initial 24 hours, and 1 after 70 days. Three survived in an institutionalized or vegetative state for more than 6 months (CPC = 3 to 5).

Effects of Initial Plasma Sodium Level, Rate of Correction, and Absolute Correction on Patient Outcome

There was not a significant correlation between either the rate of correction of plasma sodium ($r = 0.31$, $P = .10$) or the initial plasma sodium level ($r = 0.05$, $P = .12$) for any of the 53 patients (Figure 3). The absolute change in plasma sodium level during correction for group 1 patients was 22 (10) mmol/L; for group 2 patients, 30 (6) mmol/L; and for group 3 patients, 3 (2) mmol/L. The absolute change for both group 1 and group 2 was significantly greater than that for group 3 patients ($P < .01$ by analysis of variance) and group 1 patients had significantly less than group 2 patients ($P < .05$). The outcome in group 1 patients was 1.0 (all recovered), while it was 3.0 (1.2) in group 2 patients and 4.6 (0.7) in group 3 patients (Figure 2).

Autopsy Findings

Postmortem examination was performed for 5 patients. Three patients from group 3, who had died within 24 hours of respiratory arrest, had generalized cerebral edema, with evidence of tentorial herniation (uncal notching) in 1. In 4 of the 5 patients, the pons was normal. In 2 patients from group 2, there were focal infarctions of the basal ganglia, thalamus, hypothalamus, cortical gray matter, subcortical white mat-

ter, putamen, lateral pons, and corpus striatum. There was no evidence of central pontine myelinolysis in any of the 5 patients.

Neuroradiological Evaluation

Eleven patients (2 in group 2, 9 in group 1) had neuroradiological evaluation of the brain (either computed tomographic scan or magnetic resonance imaging) before the initiation of therapy with sodium chloride. In 6 of these 11 patients, the neuroradiological evaluation revealed evidence of cerebral edema. Follow-up magnetic resonance imaging of the brain was done at least 4 months after recovery from hyponatremic encephalopathy in the 10 patients in group 1 and the 8 patients in group 2 who recovered to the point where they could live independently. All 18 patients evaluated had no evidence of central pontine myelinolysis; 1 patient in group 2 had a lateral pontine lesion.

COMMENT

This study demonstrates that chronic symptomatic hyponatremia (hyponatremic encephalopathy) in postmenopausal women is not a benign condition, as has been previously suggested.^{2,3} There is substantial morbidity and mortality among such patients, with sequelae ranging from primary orthopedic injury to neurologic impairment and death (Figure 1). The morbidity and mortality associated with chronic symptomatic hyponatremia were caused primarily by consequences of the hyponatremia itself, in conjunction with failure to initiate therapy with IV sodium chloride in a timely manner. None of the patients who were treated with sodium chloride¹³ before the onset of respiratory insufficiency (group 1) showed any evidence of brain damage after 1 year of follow-up. The 2 patients in group 2 who were treated with IV sodium chloride after respiratory insufficiency and recovered also showed no evidence of brain damage after 1 year of follow-up. The 22 group 2 patients had a maximum correction of 30 (6) mmol/L over the initial 48 hours, and

this probably contributed to the brain damage, particularly in the 14 whose absolute correction exceeded 25 mmol/L in the initial 48 hours.¹³ Thus, central nervous system symptoms would appear to be an indicator of the need for initiation of therapy with hypertonic sodium chloride.

There are at least 2 distinct mechanisms that can induce brain injury in hyponatremic patients.²⁴ The first is hyponatremic encephalopathy, which is the result of brain edema and increased intracranial pressure. In group 1 patients, who had brain edema before therapy was initiated, this was most likely the mechanism of the neurological dysfunction. When therapy is begun before respiratory insufficiency, patient outcome is generally favorable, both in the current study (Figure 2) and among patients with acute hyponatremia.^{9,10,12,24} The second mechanism is improper therapy for hyponatremia (defined as an increase of more than 25 mmol/L in the initial 48 hours), which can be associated with brain damage.^{2,13,25,26}

Among 158 patients with hyponatremic encephalopathy, less than 4% of the brain damage was associated with improper therapy.²⁴ Among our group 2 patients, 14 had an outcome of CPC of 3 or higher (ie, disabled, vegetative, or dead) and in these, the absolute change in plasma sodium levels following respiratory insufficiency was 30 (6) mmol/L in the initial 48 hours. A change in plasma sodium in excess of 25 mmol/L in 48 hours has been associated with brain damage in hyponatremic patients,^{13,25} and these conditions in our group 2 patients probably contributed to their brain damage. Data from the current study strongly suggest that, in addition, fluid restriction, resulting in only a small change in plasma sodium (3 [2] mmol/L per day) in symptomatic patients, is often associated with respiratory insufficiency, leading to death or permanent brain damage (Figure 2). While our study was not designed to determine the appropriate therapy for chronic hyponatremic encephalopathy, it suggests that either overcorrection¹³ or undercorrec-

tion (Figure 2) can lead to an adverse outcome. The use of normal (154 mmol/L of sodium chloride) vs hypertonic (514 mmol/L of sodium chloride) sodium chloride solution deserves comment. If the patient has seizures and/or respiratory distress, it is prudent to increase plasma sodium levels by about 8 mmol/L within the initial hour,¹⁰ and this can only be accomplished with IV hypertonic sodium chloride or sodium bicarbonate. If the patient has volume contraction, plasma sodium levels can be best increased with IV isotonic (normal) sodium chloride.

In addition to overcorrection or undercorrection of hyponatremia, hypoxia has been found to play a major role in the genesis of hyponatremic brain damage in both humans¹⁸ and laboratory animals.²⁷ Twelve group 1 and 2 patients in whom blood gases were evaluated prior to therapy were found to have arterial PO₂ of 63 (25) mm Hg when they had chronic hyponatremic encephalopathy. This level of hypoxia has also been reported in animals with chronic hyponatremia.²⁸ It has been suggested that chronic hyponatremia is usually not accompanied by cerebral edema because the brain has had time to adapt.^{26,29} In the current study, 6 of the 11 group 1 patients with chronic hyponatremic encephalopathy had evidence of cerebral edema on neuroradiological evaluation, which indicates that the adaptive process was impaired. Hypoxia impairs brain adaptation to hyponatremia,²⁷ and it is quite possible that in our patients with hypoxia, the failure to adapt to hyponatremia, despite a duration of more than 48 hours, was in part the result of associated hypoxemia. Our study also indicates that in postmenopausal women with hyponatremic encephalopathy who have seizures, orthopedic injury, such as hip fracture, can be the initial clinical manifestation, as well as a major cause of morbidity (Figure 1). Similar orthopedic injuries have been reported following hyponatremia with convulsive activity.³⁰ Patients with chronic hyponatremia may also have brain atrophy of the temporal lobe.³¹

The plasma potassium level was low (3.2 [0.9] mmol/L) in these 53 hyponatremic patients. This hypokalemia may have contributed to the hyponatremia by a number of mechanisms, including stimulation of thirst, polydipsia, and impaired urinary concentrating ability.³²

There are several limitations to the present study. Men and younger women were not evaluated, and these data apply only to postmenopausal women. There was no attempt at epidemiological evaluation, and we have provided no information on the incidence or prevalence of any of the conditions associated with hyponatremia, which include orthopedic injury, respiratory insufficiency, and brain dam-

age. Furthermore, our findings only apply to patients with chronic hyponatremia and central nervous system symptoms. Unlike patients with hyponatremic encephalopathy, elderly patients with asymptomatic hyponatremia often will do well when treated with fluid restriction.⁵ Elderly patients with chronic hyponatremia have a very high mortality rate: among 295 such patients, the mortality rate was 25%.^{2,5} Of these, neither the percentage with encephalopathy or that died of hyponatremia can be ascertained, but at least part of this total appears to be associated with reluctance to treat chronic hyponatremic patients with IV sodium chloride.^{2,5} Among postmenopausal women with chronic hyponatremic en-

cephalopathy, neither the initial plasma sodium level nor the rate of correction are correlated with patient outcome (Figure 3).

In conclusion, chronic hyponatremic encephalopathy in postmenopausal women is associated with substantial morbidity and mortality (Figure 1). Active therapy with IV sodium chloride is both safe and effective. Fluid restriction, on the other hand, is inadequate therapy for such patients (Figure 2).

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REFERENCES

1. Miller M, Hecker MS, Friedlander DA, Carter JM. Apparent idiopathic hyponatremia in an ambulatory geriatric population. *J Am Geriatr Soc*. 1996;44:404-408.
2. Sterns RH. Severe symptomatic hyponatremia: treatment and outcome: a study of 64 cases. *Ann Intern Med*. 1987;107:656-664.
3. Ellis SJ. Severe hyponatraemia: complications and treatment. *QJM*. 1995;88:905-909.
4. Hochman I, Cabili S, Peer G. Hyponatremia in internal medicine ward patients: causes, treatment and prognosis. *Isr J Med Sci*. 1989;25:73-76.
5. Hirshberg B, Ben-Yehuda A. The syndrome of inappropriate antidiuretic hormone secretion in the elderly. *Am J Med*. 1997;103:270-273.
6. Steele A, Gowrishankar M, Abrahamson S, Mazar CD, Feldman RD, Halperin ML. Postoperative hyponatremia despite near-isotonic saline infusion: a phenomenon of desalination. *Ann Intern Med*. 1997;126:20-25.
7. Lauriat S, Berl T. The hyponatremic patient: practical focus on therapy. *J Am Soc Nephrol*. 1997;8:1599-1607.
8. Arieff AI. Hyponatremia, convulsions, respiratory arrest, and permanent brain damage after elective surgery in healthy women. *N Engl J Med*. 1986;314:129-135.
9. Ayus JC, Wheeler JM, Arieff AI. Postoperative hyponatremic encephalopathy in menstruant women. *Ann Intern Med*. 1992;117:891-897.
10. Worthley LIG, Thomas PD. Treatment of hyponatremic seizures with intravenous 29.2% saline. *BMJ*. 1986;292:168-170.
11. Cheng JC, Zikos D, Skopicki HA, Peterson DR, Fisher KA. Long term neurologic outcome in psychogenic water drinkers with severe symptomatic hyponatremia: the effect of rapid correction. *Am J Med*. 1990;88:561-566.
12. Sarnaik AP, Meert K, Hackbarth R, Fleischmann L. Management of hyponatremic seizures in children with hypertonic saline: a safe and effective strategy. *Crit Care Med*. 1991;19:758-762.
13. Ayus JC, Krothapalli RK, Arieff AI. Treatment of symptomatic hyponatremia and its relation to brain damage: a prospective study. *N Engl J Med*. 1987;317:1190-1195.
14. Verbalis JG. The syndrome of inappropriate antidiuretic hormone secretion and other hyposmolar disorders. In: Schrier RW, Gottschalk CW, eds. *Diseases of the Kidney*. Boston, Mass: Little Brown & Co; 1997:2393-2427.
15. Harris CP, Townsend JJ, Baringer JR. Symptomatic hyponatremia: can myelinolysis be prevented by treatment? *J Neurol Neurosurg Psychiatry*. 1993;56:626-632.
16. Sonnenblick M, Friedlander Y, Rosin AJ. Diuretic-induced severe hyponatremia: review and analysis of 129 reported patients. *Chest*. 1993;103:601-606.
17. Kokko JP. Disorders of fluid volume, electrolytes and acid-base balance: osmolality disturbances. In: Bennett JC, Plum F, eds. *Cecil Textbook of Medicine*. Philadelphia, Pa: WB Saunders Co; 1996:532-538.
18. Ayus JC, Arieff AI. Pulmonary complications of hyponatremic encephalopathy: noncardiogenic pulmonary edema and hypercapnic respiratory failure. *Chest*. 1995;107:517-521.
19. Fraser CL, Arieff AI. Epidemiology, pathophysiology and management of hyponatremic encephalopathy. *Am J Med*. 1997;102:67-77.
20. Cluitmans FHM, Meinders AE. Management of severe hyponatremia: rapid or slow correction. *Am J Med*. 1990;88:161-166.
21. Arieff AI, Fraser CL, Rowley H, Truwit C, Kucharczyk J. Metabolic encephalopathy. In: Kucharczyk J, Moseley M, Barkovich AJ, eds. *Magnetic Resonance Neuroimaging*. Boca Raton, Fla: CRC Press; 1994:319-349.
22. Jennett B, Plum F. Persistent vegetative state after brain damage. *Lancet*. 1972;1:734-737.
23. Behringer W, Kittler H, Sterz F, et al. Cumulative epinephrine dose during cardiopulmonary resuscitation and neurologic outcome. *Ann Intern Med*. 1998;129:450-456.
24. Ayus JC, Arieff AI. Brain damage and postoperative hyponatremia: role of gender. *Neurology*. 1996;46:323-328.
25. Ayus JC, Krothapalli R, Armstrong DL, Norton HJ. Symptomatic hyponatremia in rats: effect of treatment on mortality and brain lesions. *Am J Physiol*. 1989;257:F18-F22.
26. Verbalis JG. Hyponatremia: epidemiology, pathophysiology, and therapy. *Curr Opin Nephrol Hypertens*. 1993;2:636-652.
27. Vexler ZS, Ayus JC, Roberts TPL, Kucharczyk J, Fraser CL, Arieff AI. Ischemic or hypoxic hypoxia exacerbates brain injury associated with metabolic encephalopathy in laboratory animals. *J Clin Invest*. 1994;93:256-264.
28. Soupart A, Penninckx R, Stenuit A, Perier O, De-caux G. Lack of major hypoxia and significant brain damage in rats despite dramatic hyponatremic encephalopathy. *J Lab Clin Med*. 1997;130:226-231.
29. Videen JS, Michaelis T, Pinto P, Ross BD. Human cerebral osmolites during chronic hyponatremia: a proton magnetic resonance spectroscopy study. *J Clin Invest*. 1995;95:788-793.
30. Remec PT, Everts CM. Bilateral central dislocation of the hip. *Clin Orthop*. 1983;181:118-120.
31. Luchins DJ, Nettles KW, Goldman MB. Anterior medial temporal lobe volumes in polydipsic schizophrenic patients with and without hypo-osmolemia: a pilot study. *Biol Psychiatry*. 1997;42:767-770.
32. Smith JD, Perazella M, DeFronzo RA. Hypokalemia. In: Arieff AI, DeFronzo RA, eds. *Fluid, Electrolyte and Acid-Base Disorders*. New York, NY: Churchill Livingstone; 1995:387-426.

Annals of Internal Medicine

Postoperative Hyponatremia despite Near-Isotonic Saline Infusion: A Phenomenon of Desalination

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Background: It is widely presumed that the development of postoperative hyponatremia (which may be severe) results from administration of hypotonic fluids while antidiuretic hormone is acting.

Objective: To show that hyponatremia would occur in patients 24 hours after surgery if only near-isotonic solutions are given and to evaluate the mechanisms responsible for hyponatremia in this setting.

Design: Prospective cohort study.

Setting: University medical center.

Patients: 22 women who were having uncomplicated gynecologic surgery with infusion of near-isotonic solutions only (sodium chloride, 154 mmol/L, or Ringer lactate [sodium, 130 mmol/L, and potassium, 4 mmol/L]).

Measurements: Plasma electrolyte levels were measured at the time of induction of anesthesia and 24 hours later. Data on the balance of water and electrolytes were obtained for the same 24-hour period.

Results: At the time of induction of anesthesia, the plasma sodium concentration was 140 ± 1 mmol/L; 24 hours later, it decreased in 21 of 22 patients (mean decrease, 4.2 ± 0.4 mmol/L [$P < 0.001$]; lowest level, 131 mmol/L in 2 patients). The urine remained hypertonic (peak sodium plus potassium concentration in urine, 294 ± 9 mmol/L) in all patients for the first 16 hours after induction of anesthesia.

Conclusions: Postoperative hyponatremia occurred within 24 hours of induction of anesthesia when only near-isotonic fluids were infused. Hyponatremia was generally caused by generation of electrolyte-free water during excretion of hypertonic urine—a desalination process. This electrolyte-free water was retained in the body because of the actions of antidiuretic hormone. If the pathophysiology of this hyponatremic state is understood, recommendations for its prevention and treatment can be

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deduced.

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Postoperative hyponatremia, which is especially important in young women, is a preventable cause of illness and death (1-3). When hyponatremia is associated with death, the plasma sodium concentration is usually far less than 120 mmol/L, but values as high as 128 mmol/L have been infrequently seen in patients who died of hyponatremia (2). Postoperative hyponatremia is usually attributed to two factors: first, the infusion of excessive amounts of electrolyte-free water (5% dextrose in water or hypotonic saline) and second, actions of antidiuretic hormone to prevent excretion of this electrolyte-free water. Administration of electrolyte-free water has been considered essential for causing hyponatremia in this setting. However, we reviewed the medical records of five patients who died of severe hyponatremia 1 to 3 days after surgery and found that they did not receive the amount of electrolyte-free water needed to cause this degree of hyponatremia.

To establish the basis for hyponatremia, data on the balance of water and electrolytes (sodium and potassium) are needed. Therefore, we did a prospective study of 22 women who had elective gynecologic surgery. Plasma sodium concentration was measured when anesthesia was induced and 24 hours later, and data on the balance of water and electrolytes were obtained for the same 24-hour period.

Methods

Patients with Acute, Fatal Postoperative Hyponatremia

We evaluated the medical records of five patients who died in hospitals in Canada ($n = 3$) and the United States ($n = 2$) to discover why severe hyponatremia occurred after surgery. We used data from these patients to define the problem rather than rigorously document the mechanism of postoperative hyponatremia. The volume and composition of intravenous and oral fluid intake, the plasma sodium and glucose concentrations at the time of cardiac arrest (4), and body weight had been measured in all patients. Urine had not been analyzed for electrolytes in any patient. We calculated the positive balance for electrolyte-free water that was necessary to induce the degree of hyponatremia that was seen using the following assumptions: 1) Preoperative total body water was 50% of body weight, and intracellular fluid volume was two thirds of body water (5) and 2) the number of particles in the intracellular fluid did not change in this acute setting. According to these assumptions, a woman weighing 70 kg would have 35 L of total body water before surgery and 9800 "effective" millio smoles in her body ($2 \times 140 \times 35$). If the plasma sodium concentration was 120 mmol/L after surgery, total body water

would be 40.8 L [$9800/(2 \times 120)$], or a gain of 5.8 L of electrolyte-free water.

Patients Who Received Only Near-Isotonic Saline

Because fatal hyponatremia after surgery occurs predominantly in young women (1-3), we studied 22 randomly selected women (weight, 70 ± 4 kg; age, 42 ± 1 years) who had gynecologic (uterine) surgery (duration, 2.2 ± 0.7 hours) under general anesthesia. Management of each patient was determined by the patient's anesthesiologist and surgeon. The study protocol was approved by the ethics committee for studies in human subjects at St. Michael's Hospital (Toronto, Ontario), and informed consent was obtained from each patient. Patients had no significant medical illness aside from the condition requiring surgery (fibroids, menorrhagia, or pelvic inflammatory disease) and were not given a diuretic. All patients received only intravenous near-isotonic fluid (half as isotonic saline [sodium chloride, 154 mmol/L] and half as Ringer lactate [sodium, 130 mmol/L; potassium, 4 mmol/L]). Patients did not ingest any fluids orally; each patient had an indwelling Foley catheter that remained in place for the 24 hours of observation (which is routine practice at our hospital). Samples of venous blood were obtained at the time of induction of anesthesia and 24 hours later. Urine samples were collected every 2 to 4 hours for the first 24 hours after surgery. All volumes of ingested and excreted fluids were carefully recorded. The surgeons estimated that less than 0.5 L of blood was lost.

Analytic Techniques

Urine and plasma osmolality and concentrations of sodium, potassium, chloride, creatinine, urea, and glucose were measured as described elsewhere (6).

Statistical Analysis

Results are reported as the mean $\pm$ SE. Statistical analysis was done on group mean values using the Student *t*-test. A *P* value less than 0.01 was considered to be statistically significant.

Results

Patients with Acute, Fatal Postoperative Hyponatremia

Data on all patients whose medical and nursing records were examined are reported in Table 1. Patients in whom electrolyte-free water gain was the only cause of hyponatremia received considerably less electrolyte-free water than would be required to induce the degree of hyponatremia that was seen. Rather than postulate errors that may have occurred in the documentation of each case, we surmised that hypertonic urinary losses could also be an important reason for developing such a severe degree of hyponatremia. However, pertinent data (that is, urinary electrolyte levels) were not available to test this hypothesis in any of these patients.

Patients Who Received Only Near-Isotonic Saline

022-086-241

Plasma sodium concentration decreased in 21 of the 22 patients (average decrease, 4.2 ± 0.4 mmol/L) ([Table 2](#)); the lowest plasma sodium concentration was 131 mmol/L (in 2 patients). The average volume of isotonic saline (2.6 ± 0.3 L) and Ringer lactate (2.8 ± 0.3 L) that were infused for 24 hours was 5.3 ± 0.2 L (3 L during surgery plus 100 to 125 mL of isotonic saline per hour thereafter). The average urine volume was 2.5 ± 0.3 L, resulting in a net water gain of 2.9 ± 0.3 L; however, the entire retained volume did not represent electrolyte-free water ([Table 3](#)). Almost every urine sample from these patients was hypertonic (defined as a combined sodium and potassium concentration greater than 150 mmol/L) for the first 1000 minutes after surgery ([Figure 1](#)). During this time, the maximum sodium plus potassium concentration in urine was 294 ± 9 mmol/L. In the subsequent 8 hours, the degree of hypertonicity of urine samples remained the same in some patients but decreased (sodium plus potassium concentration as low as 30 mmol/L) in others.

The balance was positive for sodium (367 ± 50 mmol) and negative for potassium (90 ± 7 mmol) ([Table 3](#)), yielding a gain of 277 ± 50 mmol of sodium plus potassium for the 24-hour period of observation. The balance for water during this period was positive (2.9 L) ([Table 3](#)). Subdividing the gain of water and electrolytes into isotonic and electrolyte-free water results in a net gain of 1.8 L of isotonic saline (which expanded the extracellular fluid volume) and a gain of 1.1 L of electrolyte-free water (which caused the hyponatremia) ([Figure 2](#) and [Table 3](#)).

Discussion

The physiologic principles that explain the development of hyponatremia after surgery are well characterized in the literature. A source of electrolyte-free water must be added to the extracellular fluid, and antidiuretic hormone must act to prevent excretion of this electrolyte-free water ([7](#)). The usual source of electrolyte-free water is administration from exogenous sources (5% dextrose in water or hypotonic saline intravenously or orally). It is also possible, however, for the kidney to generate electrolyte-free water. For this to occur, the urine must have high concentrations of sodium plus potassium. For the kidney to generate a large volume of electrolyte-free water in body fluids, there must be a high rate of excretion of a sodium salt, potassium salt, or both in hypertonic urine. However, it is not always obvious why some patients have a greater degree of natriuresis than others. Several possibilities are considered below.

Our study was unique because it showed that administration of electrolyte-free water retained in the body (0.36 L in Ringer lactate) is only partly responsible for acute postoperative hyponatremia. Most of the electrolyte-free water (0.74 L) was generated by the kidney. Excretion of this electrolyte-free water was prevented by action of antidiuretic hormone, as evidenced by the elaboration of hypertonic urine ([Figure 1](#) and [Table 3](#)). Our patients had a positive balance for fluid (2.9 L) and electrolytes (276 mmol of cations) that resulted from partial desalination (that is, excretion of much of the sodium chloride that was administered with disproportionately less water than was infused) of the near-isotonic saline that was administered ([Figure 2](#)). In quantitative terms, these

balances represent a net gain of approximately 1.8 L of isotonic saline (which would expand the extracellular fluid volume but not change the plasma sodium concentration) plus a gain of approximately 1.1 L of electrolyte-free water (which would lead to hyponatremia and cell swelling). This amount of electrolyte-free water represents approximately 3.0% of the total body water and accounts for the decline in plasma sodium concentration that we saw ([Table 3](#)).

At the same time, antidiuretic hormone must be present to prevent excretion of electrolyte-free water. Release of antidiuretic hormone was not triggered by the physiologic stimuli of hypertonicity or a low effective circulating volume but could represent a response to any combination of pain, drugs, stress, or nausea. The duration of action of antidiuretic hormone is important. Some patients (8 of 22) began to excrete electrolyte-free urine after 16 hours, whereas others (14 of 22) continued to excrete hypertonic urine for the entire observation period ([Figure 2](#)). Hyponatremia is being corrected in the former set of patients, but the latter group is generating more electrolyte-free water and is in danger of developing more severe hyponatremia.

The degree of postoperative hyponatremia in our patients resulted from the large volume of hypertonic urine that was excreted. One factor that contributed to the high rate of excretion of electrolytes was the amount of saline that was infused to maintain adequate blood pressure after induction of anesthesia. In our patients, 2 to 3 L of Ringer lactate was infused during surgery with the expectation that retained near-isotonic saline would not change tonicity; however, tonicity decreased because of the excretion of hypertonic urine. The most important stimulus for excretion of sodium was overexpansion of the extracellular fluid volume. The ratio of infused isotonic saline to extracellular fluid volume also affects the severity of hyponatremia. Hence, a smaller volume should be given to smaller patients because their risk for hyponatremia and desalination increases with each liter infused. Whether isotonic fluid is retained in extracellular fluid before anesthesia, as may occur premenstrually in some women or in anyone who has consumed a high-salt diet, should also be taken into account. Such retention could make a larger volume available for desalination without causing a low effective in extracellular fluid volume.

It follows from the above reasoning that a "good urine output" is no longer reassuring but rather a potential worry with respect to postoperative hyponatremia if such output is hypertonic. The degree of natriuresis and hyponatremia could be exaggerated further if natriuretic factors, either endogenous (such as in cerebral salt wasting [8, 9]) or pharmacologic (such as when thiazide diuretics are given) are present. Loop diuretics, in contrast, can compromise the concentration process and thereby help to prevent excretion of hypertonic urine. In quantitative terms, a urinary loss of 300 mmol of sodium plus potassium in 1 L of urine would be equivalent to the desalination of 2 L of isotonic saline, yielding a positive balance of 1 L of electrolyte-free water in the body. In a patient who weighs 70 kg, this occurrence would cause an almost 4-mmol/L decrease in plasma sodium concentration if all such water is retained in the body.

Another point that merits emphasis is potassium excretion (5, 10-12). It is

well known that potassium in the urine is important for tonicity (13). As with sodium excretion, excretion of potassium without water represents a loss of particles, which leads to a decrease in the concentration of sodium in plasma. Nevertheless, the effect of potassium loss on the intracellular fluid volume may differ from that of sodium loss (14). If potassium is lost with chloride and the potassium is replaced in the intracellular fluid with sodium, it represents a net loss of 2 particles from the extracellular fluid (the same as with loss of sodium chloride). This loss is associated with expansion of intracellular fluid volume and contraction of extracellular fluid volume. If potassium is lost with phosphate, however, water is shifted out of cells (that is, intracellular particles are lost) because both particles are ultimately of intracellular origin. In such cases, hyponatremia is accompanied by contraction of global intracellular fluid volume and expansion of extracellular fluid volume (5, 11, 12, 14, 15). However, potassium represented only 20% of the major cations excreted in our patients, which makes loss of potassium unlikely to have contributed substantially to the hyponatremia.

Another factor to consider is the ability of the renal medulla to increase the sodium concentration in urine under the influence of antidiuretic hormone. For example, if the urine has an inadequate concentration of sodium because of recent obstructive uropathy or administration of a loop diuretic, the patient would be expected to excrete a large volume of urine in which the sum of the concentration of sodium and potassium is almost 150 mmol/L, even when antidiuretic hormone is acting. In this situation, hyponatremia would not be anticipated to occur despite natriuresis if only isotonic fluids were being administered.

Most articles that describe postoperative hyponatremia (1, 3, 16-19) imply that this derangement is primarily the result of administration of hypotonic intravenous solutions, but quantitative analysis could not be done from the data available in these studies. The fatal postoperative hyponatremia that developed in five patients we evaluated would have required a positive balance of 4.1 L of electrolyte-free water if the condition developed on the basis of the administration of electrolyte-free water alone; in fact, these patients received only 2.7 L of electrolyte-free water intravenously (Table 1).

Four studies (20-23) that evaluated the influence of administration of isotonic fluid on the incidence of postoperative hyponatremia 24 hours after a surgical procedure are pertinent here. Only one (20) showed a substantial decline in natremia. Unfortunately, no data on urinary electrolytes were reported to help establish the mechanism that was involved in this decline. A second study (21) reported mean urine outputs and sodium excretion rates, but not values for potassium excretion (plasma osmolality did not change in the 24-hour period, but this measure is not sensitive enough to evaluate whether there was a small decline in the plasma sodium concentration). In two other studies (22, 23), the plasma sodium concentration did not decline during a 24-hour period. Nevertheless, such key data as the sodium plus potassium concentration in the urine were not reported. The urine output of the patients in these two studies was much lower than that of our patients. It is important to recognize that lower volumes of hypertonic urine yield lower volumes of electrolyte-free water (Figure 1). To explain why our patients had a high urine output is difficult without more information. Our patients were

young, had elective surgery, and received a large infusion of fluid (5.3 L in 24 hours); therefore, extensive natriuresis might be anticipated. Moreover, the same quantity of electrolyte-free water generated in a small patient causes a greater degree of hyponatremia because of the smaller volume of total body water, as noted.

Our study findings should not be misinterpreted as suggesting that infusing hypotonic solutions has a risk similar to that of infusing isotonic solutions; in fact, the risk is larger with hypotonic infusions. For example, if 2 L of isotonic saline were infused and 1 L of urine with a sodium plus potassium concentration of 300 mmol/L was excreted, the positive electrolyte-free water balance would be 1 L. In contrast, if 2 L of half-normal saline (77 mmol/L) were infused, all the sodium infused would now be excreted in 0.5 L with a concentration of sodium plus potassium of 300 mmol/L and lead to a positive electrolyte-free water balance of 1.5 L.

Our results suggest that standard clinical perioperative fluid and electrolytic management should change. Hypotonic intravenous fluids should not be given during or immediately after surgery; they should only be given if a patient is hypernatremic. The minimum volume of isotonic fluid needed during and after surgery to maintain hemodynamics should be infused. Plasma sodium concentration should be checked if more than 2 to 3 L of hypertonic urine (specific gravity > 1.020) has been excreted in the first 24 hours after surgery in a person weighing 70 kg. If hyponatremia is present and a large volume of hypertonic urine continues to be excreted, two therapeutic options are available to prevent a further decrease in the plasma sodium concentration. One option is to infuse a saline solution with the same tonicity and at the same flow rate as the urine; this requires that a hypertonic solution be infused until the concentration of sodium plus potassium in the urine decreases. The second option is to decrease the concentration of sodium plus potassium in the urine by administering a loop diuretic (24, 25) or an osmotic diuretic (such as urea) (26). A greater degree of hyponatremia can be anticipated if the patient has also consumed water, received hypotonic solutions, or retained saline before surgery (high salt intake); if a natriuretic agent (nonloop diuretic) has been acting; or if antidiuretic hormone actions (that is, pain, nausea, drugs, and stress) persist longer than 24 hours after surgery.

In summary, postoperative hyponatremia occurred in patients infused with isotonic saline. The degree of hyponatremia depends largely on the volume of intravenous fluid given relative to body size. Postoperative hyponatremia is the result of two factors: 1) addition of electrolyte-free water by infusion, renal generation, or both and 2) the presence of antidiuretic hormone to prevent excretion of electrolyte-free water. Many factors may explain the degree of desalination in an individual patient. With a better understanding of the mechanisms involved and more rational management, such tragedies as those described in Table 1 can be prevented.

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References

1. Arieff AI. Hyponatremia, convulsions, respiratory arrest, and permanent brain damage after elective surgery in healthy women. *N Engl J Med.* 1986;314:1529-35.
2. Ayus JC, Wheeler JM, Arieff AI. Postoperative hyponatremic encephalopathy in menstruant women. *Ann Intern Med.* 1992;117:891-7.
3. Ayus JC, Arieff AI. Brain damage and postoperative hyponatremia: the role of gender. *Neurology.* 1996;46:323-8.
4. Roscoe JM, Halperin ML, Rolleston FS, Goldstein MB. Hyperglycemia-induced hyponatremia: metabolic considerations in calculation of serum sodium depression. *Can Med Assoc J.* 1975;112:452-3.
5. Oh MS, Carroll HJ. Regulation of extra- and intracellular fluid composition and content. In: Arieff AI, DeFronzo RA, eds. *Fluid, Electrolyte, and Acid-Base Disorders.* 2d ed. New York: Churchill Livingstone; 1995:1-28.
6. Halperin ML, Vinay P, Gougoux A, Pichette C, Jungas RL. Regulation of the maximum rate of renal ammoniogenesis in the acidotic dog. *Am J Physiol.* 1985;248(4 Pt 2):F607-15.
7. Robertson GL. Regulation of vasopressin secretion. In: Seldin DW, Giebisch GH, eds. *Clinical Disturbances of Water Metabolism.* New York: Raven Pr; 1993:99-118.
8. Harrigan MR. Cerebral salt wasting syndrome: a review. *Neurosurgery.* 1996;38:152-60.
9. Nelson PB, Seif SM, Maroon JC, Robinson AG. Hyponatremia in intracranial disease: perhaps not the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). *J Neurosurg.* 1981;55:938-41.
10. Goldberg M. Hyponatremia. *Med Clin North Am.* 1981;65:251-69.
11. Halperin ML, Skorecki KL. Interpretation of the urine electrolytes and osmolality in the regulation of body fluid tonicity. *Am J Nephrol.* 1986;6:241-5.
12. Rose BD. New approach to disturbances in the plasma sodium concentration. *Am J Med.* 1986;81:1033-40.
13. Edelman IS, Leibman J, O'Meara MP, Birkenfeld LW. Interrelations between serum sodium concentration, serum osmolality and total exchangeable sodium, total exchangeable potassium and total body water. *J Clin Invest.* 1958;37:1236-56.
14. Gowrishankar M, Chen CB, Mallie JP, Halperin ML. What is the impact of potassium excretion on the intracellular fluid volume: Importance of urine anions. *Kidney Int.* 1996;50:1490-5.
15. Gowrishankar M, Chen CB, Steele A, Halperin ML. Hyponatremia in the rat in the absence of positive water balance. *J Am Soc Nephrol.* 1997; [In press].

16. **Chung HM, Kluge R, Schrier RW, Anderson RJ.** Postoperative hyponatremia. A prospective study. *Arch Intern Med.* 1986;146:333-6.
17. **Cowley DM, Pabari M, Sinton TJ, Johnson S, Carroll G, Ryan WE.** Pathogenesis of postoperative hyponatremia following correction of scoliosis in children. *Aust N Z J Surg.* 1988;58:485-9.
18. **Mebust WK.** Transurethral prostatectomy: immediate and postoperative complications. A cooperative study of 13 participating institutions evaluating 3,885 patients. *J Urol.* 1989;141:243-7.
19. **Wright HK, Gann DS.** Severe postoperative hyponatremia without symptoms of water intoxication. *Surg Gynecol Obstet.* 1962;115:553-6.
20. **Guy AJ, Michaels JA, Flear CT.** Changes in the plasma sodium concentration after minor, moderate and major surgery. *Br J Surg.* 1987;74:1027-30.
21. **Irvin TT, Modgill VK, Hayter CJ, McDowall DG, Goligher JC.** Plasma-volume deficits and salt and water excretion after surgery. *Lancet.* 1972;2:1159-61.
22. **Thomas TH, Morgan DB.** Post-surgical hyponatraemia: the role of intravenous fluids and arginine vasopressin. *Br J Surg.* 1979;66:540-2.
23. **Tindall SF, Clark RG.** The influence of high and low sodium intakes on post-operative antidiuresis. *Br J Surg.* 1981;68:639-44.
24. **Decaux G, Waterlot Y, Genette F, Mockel J.** Treatment of the syndrome of inappropriate secretion of antidiuretic hormone with furosemide. *N Engl J Med.* 1981;304:329-30.
25. **Hantman D, Rossier B, Zohlman R, Schrier R.** Rapid correction of hyponatremia in the syndrome of inappropriate secretion of antidiuretic hormone. An alternative treatment to hypertonic saline. *Ann Intern Med.* 1973;78:870-5.
26. **Decaux G, Brimiouille S, Genette F, Mockel J.** Treatment of the syndrome of inappropriate secretion of antidiuretic hormone by urea. *Am J Med.* 1980;69:99-106.

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Hyponatraemia in children with acute CNS disease: SIADH or cerebral salt wasting?

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Abstract Hyponatraemia in patients with an acute central nervous system disease can be caused by two different mechanisms: (1) excretion of free water, i.e. the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and (2) excessive sodium excretion, i.e., the cerebral salt wasting syndrome (CSW). Although the concept of CSW is well known in adult medicine, it is still not established in child neurology. We conducted a retrospective analysis of electrolyte disturbances in 195 children with various acute CNS diseases. In 20 children (10.3%) hyponatraemia with plasma sodium below 130 mmol/l was identified. On the basis of clinical and laboratory data

7 of these 20 children were diagnosed as having SIADH, and the other 9 children, as having CSW. Our data suggest that hyponatraemia attributable to CSW is at least as frequent in children as SIADH. Because of their different pathophysiological mechanisms, which require diametrically opposed therapeutic regimens, early differential diagnosis is mandatory if the correct treatment is to be given.

Keywords CNS disease · Hyponatraemia · Syndrome of inappropriate secretion of antidiuretic hormone · Cerebral salt wasting syndrome

Introduction

The cerebral salt wasting syndrome (CSW) was first defined in 1950 as renal loss of sodium and dehydration in patients with CNS disease [14]. After recognition of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in 1957 [15], the concept of CSW was abandoned for a long time. In SIADH, increased renal water retention results in dilution hyponatraemia. It is defined as plasma sodium <130 mmol/l, plasma osmolality <280 mosmol/l, urine sodium >25 mmol/l, and urine osmolality higher than plasma osmolality in the absence of thyroid, adrenal, renal, liver or cardiac dysfunction.

In 1981, Nelson et al. reported on ten patients who met the criteria for SIADH but showed reduced plasma volume [13]. Hyponatraemia in these patients was the result of an inappropriate natriuresis with consequent hypovolaemia rather than of renal free water retention.

Because most patients with CSW and SIADH show similar changes in serum electrolytes, the two conditions are difficult to differentiate by means of routine laboratory data ascertained at the onset of hyponatraemia. For differential diagnosis the plasma volume and total blood volume need to be known [13, 16], but these data are often not routinely available. Therefore exact diagnosis can only be achieved if prospective clinical data i.e. body weight [4], fluid balance [11, 19], central venous pressure (CVP) [2, 16] and clinical signs of dehydration [19] have been monitored at short intervals (Table 1). Additional laboratory investigations are helpful to differentiate between CSW and SIADH (Table 1) [10], but levels of plasma hormones (ADH, natriuretic peptides, plasma renin activity, aldosterone) are hard to measure and are not immediately available. Moreover, the results may be misleading owing to short half-lives and mutual influences [3].

Table 1 Differential diagnosis of cerebral salt wasting (CSW) versus syndrome of inappropriate antidiuretic hormone secretion (SIADH). (CVP Central venous pressure, ADH antidiuretic hormone, ANP atrial natriuretic hormone, ↓ decrease, ↑ increase, ↓↓ marked decrease, ↑↑ marked increase)

	CSW	SIADH
Plasma volume	↓↓	↑↑
Fluid balance	Negative	Positive
Clinical evidence of volume depletion	Present	Absent
Body weight	↓↓	↑↑
CVP	↓↓	↑↑
Haematocrit	↑↑	↓↓
Plasma sodium concentration	↓↓	Normal/ ↓↓
Serum uric acid concentration	Normal	↓
Blood urea – creatinine-ratio	↑↑	Normal
Sodium balance	↓↓↓	↓
Urine sodium concentration	↑↑	↑↑
Plasma osmolality	↓↓	↓↓↓
Urine osmolality	↑↑ / normal	↑↑↑
Plasma renin activity	↓	↓
Plasma aldosterone concentration	↓	↑
Plasma ADH concentration	Normal, secondary ↓	↑
Plasma ANP concentration	↑	Normal, secondary ↑↑

Table 2 Frequency of SIADH and CSW in 195 children with CNS disease (*n* number of patients, *M* male, *F* female, age in years)

Diagnosis	<i>n</i>	<i>M</i>	<i>F</i>	Mean age (years) (Range)	Hyponatraemia				Mean age (years) (Range)
					SIADH	CSW	Unknown origin	Total	
Intracranial tumour (surgery)	47	26	21	9 (0.8–15)	2	6		8	8.7 (2–14)
Intracranial haemorrhage	21	14	7	6 (0.2–16)	2	2	2	6	5.8 (0.6–16)
Bacterial meningitis	22	12	10	2.8 (0.7–8)			1	1	2.2
Tuberculous meningitis	1	/	1	1.7	1			1	1.7
Intracranial abscess	9	6	3	7 (0.8–12)	1	1		2	1.3 (0.8–2)
Hydrocephalus with shunt implantation or revision	95	54	41	5.2 (0.1–16)	1		1	2	5 (0.1–10)
Total	195	112	83	6.0	7	9	4	20	6.0

Although CSW is widely accepted in adult neurology and neurosurgery as a cause of secondary hyponatraemia [5], it has not been established in paediatric practice [10, 17]. However, its inclusion in the differential diagnosis of hyponatraemia is essential for correct therapy.

The aim of this paper is to bring CSW, a poorly recognized syndrome, to the attention of paediatricians and adult neurologists. Based on our retrospective review, we have assessed the incidence and course of hyponatraemia in children with acute CNS disease and suggest guidelines for its differentiation from SIADH.

Patients and methods

A retrospective chart review was performed embracing all paediatric patients with an acute CNS disease who were admitted to the Children's Department of Heidelberg University Hospital from January 1993 to December 1997. Children with the following diagnoses were included: surgery for brain tumour or hydrocephalus, bacterial or tuberculous meningitis, intracerebral abscess and intracerebral haemorrhage. Preterm infants and patients over

16 years of age were excluded from the study. The study group consisted of 195 patients, 112 male and 83 female, with a mean age of 6 years. The frequency of each of the different diagnoses is shown in Table 2.

Hyponatraemia was defined as plasma sodium <130 mmol/l in at least two consecutive measurements. In all hyponatraemic patients, clinical (i.e. fluid balance, sodium supply, CVP and medication) and biochemical data (i.e. haematocrit, plasma potassium, plasma creatinine, urine and plasma osmolality, urine sodium and specific gravity) were analysed. On the basis of these findings, patients were categorised into a CSW group and a SIADH group. CSW was diagnosed in hyponatraemic children with a greater than 20% negative fluid balance and/or a rise of haematocrit without transfusion at the beginning of hyponatraemia. SIADH was diagnosed in hyponatraemic children with a greater than 20% positive fluid balance and/or a decline in haematocrit in the absence of haemorrhage at the beginning of hyponatraemia. The extent of hyponatraemia was defined by the lowest plasma sodium value found in the charts; the onset of hyponatraemia was defined as the time interval between the initial intracerebral event and the 1st day of hyponatraemia; and the number of days with plasma sodium values <130 mmol/l was defined as the duration of hyponatraemia, which is not identical with the duration of therapy.

Table 3 Clinical data of children with SIADH and CSW

No.	Diagnosis of SIADH through	Age/sex (years)	Weight	Onset (kg)	Duration (day)	Fluid (days)	Fluid input (ml/24 h) at onset	Minimal output (ml/24 h) at onset	Days ^a sodium (mmol/l)	Osmolality (mosmol/kg)		Urine sodium (mmol/l)
										Serum	Urine	
1	Intracerebral haemorrhage	0.6 / M	8.5	1	1	580	360	129	1			
2	Intracerebral abscess	0.8 / M	6	0	4	810	350	127	0			
3	Tuberculous meningitis with tuberculoma	1.7 / F	8.5	1	16	890	540	118	1	254	452	119
4	Astrocytoma 8 / M (postoperative)	33	2	3	1780	1410	128	2		770	219	
5	Tuberous sclerosis with hydrocephalus, shunt revisions (4x)	10 / F	28	2	32	1600	1200	124	3	260	383	78
6	Epidural haemorrhage with hydrocephalus, shunt revisions (4x)	11 / F	47	0	4	5980	4810	118	1	257	564	135
7	Clivus chordoma (postoperative) CSW	14 / F	57	1	1	4250	2980	125	1			
8	Medulloblastoma (postoperative)	2 / F	11	2	1	600	750	127	2			
9	Intracerebral abscess	2 / M	10	0	2	500	1050	126	0			
10	Medulloblastoma (postoperative)	6 / F	16.5	1	1	2800	4200	129	1			
11	Pontine glioma (postoperative)	7 / M	22	5	1	2790	3750	127	5	271		
12	Epidural haemorrhage	11 / M	50	1	2			115	1			
13	Cerebellar neurinoma (postoperative)	13 / M	49	2	1	1550	2400	126	2	264	280	
14	Postoperative after biopsy of germinoma	13 / M	30	3	1	1200	1470	128	3			
15	Angioblastoma (postoperative)	14 / F	50	1	3	1670	3400	121	1	270		163
16	Epidural haemorrhage	16 / M	43	2	3	4980	6180	125	2			

^aNo. of days after initial intracerebral event

Results

During the 5-year study period, 20 of 195 paediatric patients (10.3%) with acute CNS disease developed hyponatraemia. According to our diagnostic criteria, SIADH were diagnosed in 7 patients, and 9 patients showed evidence of CSW (Table 2). In 4 patients the data were insufficient for further classification. In 1 of these patients, hyponatraemia has to be considered iatrogenic, as the patient had a high fluid input (150 ml kg⁻¹ day⁻¹) but received insufficient sodium substitution (<0.7 mmol kg⁻¹ day⁻¹). The highest frequency of hyponatraemia was found in patients with intracranial haemorrhage (6 out of 21). Surgery for brain tumour had been performed in 47 patients, and 8 of these developed hyponatraemia, the majority with CSW (6 of 8).

Detailed data on the patients classified as having CSW or SIADH are shown in Table 3. Because of the retrospective character of our study, urine sodium concentration, plasma and urine osmolality, and specific gravity in the course of hyponatraemia were not available in all patients. ADH concentration was measured in only 1 patient in the SIADH group (patient 5, ADH = 5.2 ng/ml). Although the ADH level was within the normal range, it must be considered as inappropriately elevated because of the low serum osmolality.

Hyponatraemia developed within 5 days of the onset of CNS disease in all patients. In patients with SIADH, hyponatraemia lasted between 1 and 4 days in 5 cases, and 16 days in 1 patient with tuberculous meningitis (patient 3). In patient 5, hyponatraemia persisted for over 4 weeks. During this period, she underwent four crani-

otomies for shunt revision. In patients with CSW hyponatraemia persisted for only 1–3 days.

There was no difference in total protein and plasma potassium concentrations between the two groups. Except for patients with intracranial haemorrhage, haematocrit values ranged from 25.7% to 37.1% (median 31.1%, $n=5$) in the SIADH group and from 26.8% to 45.7% (median 35.7%, $n=7$) in the CSW group. CVP had been measured in 3 patients with SIADH (patients 1, 5, 7: +6, +2, +3 mmHg) and in 4 patients with CSW (patients 10, 11, 12, 16: -1, +7, 0, +5 mmHg) and showed no difference between groups. Plasma creatinine levels were normal in all patients (0.2–0.7 mg/dl). No patients showed signs of cardiac failure or adrenal and renal dysfunction, or received diuretics.

There was no difference between the groups in the plasma sodium levels, but hyponatraemia tended to persist longer in patients with SIADH than in the CSW group. In all patients with CSW, serum sodium levels normalised within 3 days.

Discussion

Hyponatraemia in children with an acute CNS disease is an extremely important feature, because it can cause seizures and worsen the neurological status. In our series, the frequency of hyponatraemia in children with acute CNS disease was 10.3% (20 of 195 patients). In the literature, the frequency ranges from 4% to 88%, depending on the underlying disease [4, 10, 11]. The high frequency of hyponatraemia in our series emphasises that hyponatraemia is a common complication in children with acute CNS disease and that accurate diagnosis is necessary for correct treatment.

One cause of centrally induced hyponatraemia is CSW, whose pathogenesis is still under controversial discussion. The existing evidence suggests that natriuretic peptides may play a major part in the development of hyponatraemia in CSW. Most studies have dealt with the atrial natriuretic peptides, the atrial natriuretic peptide (ANP) and the brain natriuretic peptide (BNP). ANP has been found to be released from the right and left cardiac atria in response to atrial stretch [3]. It produces natriuresis and vasodilatation and inhibits the release of aldosterone [3]. Furthermore, ANP-containing neurons have been identified in the brain of rats in areas regulating the cardiovascular system (hypothalamus and lamina terminalis) [7]. The concentration of ANP in the brain, however, is 1/10,000th that in the heart [11]. In some studies, a positive correlation between ANP and the development of CSW could be shown [8]; however, the ANP measured seemed to be cardiac rather than cerebral origin [12]. Several studies supported the hypothesis of a regulating function of cerebral ANP in the release of cardiac ANP [5].

Brain natriuretic peptide (BNP) was originally isolated from porcine brain [3]. In contrast to other studies, Berendes et al. found a significant increase of BNP but not of ANP in patients with subarachnoid haemorrhage (SAH) [1]. Another natriuretic peptide, C-type natriuretic peptide (CNP), is present in the brain and cerebrospinal fluid in far greater amounts than ANP and BNP [9]. In contrast to ANP and BNP, CNP seems to lack any natriuretic activity, but appears to have a systemic and cerebral vasodilating action [18]. It is not yet known which of these substances is crucial in CSW.

Because measurements of serum hormone concentrations (ANP, BNP, ADH, renin and aldosterone) are not rapidly available and may be difficult to interpret in routine clinical practice, clinicians do not determine them regularly. A major problem in this is the fact that some hormones have very short serum half-lives, e.g. 3 min for ANP [3].

In this study, a systematic differentiation between the two pathomechanisms of centrally induced hyponatraemia, i.e. SIADH and CSW, has been attempted for the first time in children. Stidham et al. examined 14 children who underwent hypothalamic or pituitary surgery for tumour, and found real salt wasting and polyuria in 4 of them [17]. Kappy and Ganong presented three patients with CSW [4, 10], two boys with severe head injury and one girl with hydrocephalus. Because of the small number of patients, the authors were not able to compare SIADH with CSW.

The criteria of diagnosis are based on what the current literature regards as underlying pathomechanisms [5, 13]. However, as the literature provides no detailed criteria of diagnosis, we determined them in a way we regard as appropriate. We considered a 20% *negative* fluid balance incompatible with the water retention seen in SIADH. Conversely, a 20% *positive* fluid balance made the diagnosis of CSW extremely unlikely, since CSW is characterised mainly by dehydration. The haematocrit values found in both groups supported our classification: the mean haematocrit concentration in the SIADH group was below the one in the CSW group (31.1% vs 35.7%). As intracranial haemorrhage may have had an effect on total blood volume, haematocrit levels of these children in both groups were not taken into account. Owing to the small number of patients, the difference in haematocrit concentration was not significant, but nevertheless reflects the dilution in SIADH and dehydration in CSW.

As SIADH and CSW need totally different management, early differential diagnosis is essential. Whereas the primary treatment of SIADH consists in fluid restriction, patients with CSW need early salt and water supplementation [5]. Fluid restriction in CSW will cause further deterioration of the pre-existing volume depletion, with the risk of cerebral ischaemia secondary to haemoconcentration and microthrombosis [6].

The analysis of treatment performed in our patients clearly demonstrates the difficulty of differentiating between the two syndromes. Only 4 of the 7 patients with SIADH were treated with fluid restriction. Serum sodium levels normalised quickly in 2 of them, and persisted over 16 and 32 days in the other 2. Of the remaining patients 2 received increased fluid replacement and in 1 patient hyponatraemia was not treated at all.

In the CSW group only 3 of the 9 patients initially received an adequate fluid and sodium substitution. In 4 patients, apparently wrongly classified as suffering from SIADH, hyponatraemia was treated with fluid restriction despite a negative fluid balance. There was no specific therapy of hyponatraemia in the remaining 2 pa-

tients. In summary, 2 out of 7 patients with SIADH, and 4 out of 9 patients with CSW were treated incorrectly. Although we were lucky to have a good outcome in all our patients, these results are disappointing.

In conclusion, hyponatraemia (plasma sodium levels <130 mmol/l) occurred in 10% of the children with an acute CNS disease. Based on clinical and laboratory data, we classified 7 of the 20 as suffering from SIADH and 9 of the 20 as suffering from CSW; the other 4 patients could not be categorised retrospectively. Our findings suggest that CSW develops at least as frequently as SIADH in children with an acute CNS disease. Early differential diagnosis of SIADH and CSW is essential for initiation of the correct treatment.

References

- Berendes E, Walter M, Cullen P (1997) Secretion of brain natriuretic peptide in patients with aneurysmal subarachnoid haemorrhage. *Lancet* 349:245-249
- Damaraju SC, Rajshekhar Y, Chandy MJ (1997) Validation study of a central venous pressure-based protocol for the management of neurosurgical patients with hyponatremia and natriuresis. *Neurosurgery* 40:312-316
- Espinger EA (1994) Physiology of natriuretic peptides. *J Intern Med* 235:527-541
- Ganong CA, Kappy MS (1993) Cerebral salt wasting in children, the need for recognition and treatment. *Am J Dis Child* 147:167-169
- Harrigan M (1996) Cerebral salt wasting syndrome: a review. *Neurosurgery* 38:152-160
- Hasan D, Wijndicks EFM, Vermwulen M (1990) Hyponatremia associated with cerebral ischemia in patients with aneurysmal subarachnoid hemorrhage. *Ann Neurol* 27:106-108
- Imura H, Nakao K, Itoh H (1992) The natriuretic peptide system in the brain: implications of the central control of cardiovascular and neuroendocrine functions. *Front Neuroendocrinol* 13:217-249
- Isotani E, Suzuki R, Tomita K (1994) Alterations in plasma concentrations of natriuretic peptides and antidiuretic hormone after subarachnoid hemorrhage. *Stroke* 25:2189-2203
- Kaneko T, Shirakami G, Nakao K (1993) C-type natriuretic peptide (CNP) is the major natriuretic peptide in human cerebrospinal fluid. *Brain Res* 612:104-109
- Kappy MS, Ganong CA (1996) Cerebral salt wasting in children: the role of atrial natriuretic hormone. *Adv Pediatr* 43:271-308
- Minamino M, Makino Y, Tateyama H, Kangawa K, Matsuo H (1991) Characterization of immunoreactive human C-type natriuretic peptide in brain and heart. *Biochem Biophys Res Commun* 179:535-542
- Narotam PK, Kemp M, Buck R (1994) Hyponatremic natriuretic syndrome in tuberculous meningitis: the probable role of atrial natriuretic peptide. *Neurosurgery* 34:982-988
- Nelson PB, Seif SM, Maroon JC (1981) Hyponatremia in intracranial disease: perhaps not the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). *Neurosurgery* 55:938-941
- Peters JP, Welt LG, Sims EAH (1950) A salt wasting syndrome associated with cerebral disease. *Trans Assoc Am Physicians* 63:57-64
- Schwartz WB, Bennett W, Curelop S (1957) A syndrome of renal sodium loss and hyponatremia probably resulting from inappropriate secretion of antidiuretic hormone. *Am J Med* 23:529-542
- Sivakumar V, Rajshekhar V, Chandy M (1994) Management of neurosurgical patients with hyponatremia and natriuresis. *Neurosurgery* 34:269-274
- Stidham GL, DiSclafani A, Sanford RA (1987) CSW in pediatric neurosurgical patients. *Pediatr Res* 21:207A
- Wei C, Aarhus LL, Miller VM (1993) Action of C-type natriuretic peptide in isolated canine arteries and veins. *Am J Physiol* 264:H71-H73
- Yamaki T, Tanooka A, Takahashi A (1992) Cerebral salt wasting syndrome distinct from the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). *Acta Neurochir (Wien)* 115:156-162

The article "Hyponatraemia in children with acute CNS disease: SIADH or cerebral salt wasting?" by C. Bussan et al. raises important matters of debate and implies very close cooperation between neurosurgeons and pediatric neuroanesthetists in dealing with neurosurgical pathology of childhood.

The cerebral pathology (with or without neurosurgical solution) obviously exposes the patient to major hydroelectrolytic imbalances, both as a consequence of the basic disease and also through the therapeutic measures (diuretic administration, treatment of vasospasm, perioperative maintenance of hemodynamic and volemic stability, etc.). It is now generally accepted that the impact of electrolyte disturbances may lead to the triggering of a positive feedback loop affecting the patient's outcome, which means that correct diagnosis and management are mandatory.

One of the most frequent dys-electrolytemias that occurs in neurosurgical pathology is hyponatremia, whose incidence varies widely according to the current literature, with a mean of 33% [6]. The deleterious effects of hyponatremia on cerebral function include seizures, osmotic cerebral edema and severe alterations of consciousness.

Central hyponatremia is the main element of two different physiopathological entities, the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and the cerebral salt-wasting syndrome (CSWS); these are often difficult to differentiate clinically in certain situations, so that a proper differential diagnosis is needed, since they have somewhat opposing implications for further treatment [3].

SIADH is characterized by an excess of neurohypophyseal ADH secretion, the inappropriate pattern being conferred by the coexistence of plas-matic hypotonia (due to hyponatremia) and of normo- or hypervolemia (factors that would normally restrain ADH output). In fact, SIADH has been described in a large array of pediatric conditions, including infections

of the CNS, trauma, and diffuse cerebrovascular diseases [5]. Malignant neoplasms that produce ADH-like peptides are seldom met in children. The essential criterion for a diagnosis of SIADH is hyponatremia associated with a paradoxical hypernatruresis. If not properly diagnosed and treated these conditions lead to the nonspecific clinical picture of water intoxication (agitation, obtundation, seizures, coma and even death) [4]. This syndrome also affects other metabolic lines, the isotopic hormonal individualization of the known four ADH-releasing modes not being able to establish a correlation with the involved etiological factor [1]. If plasmatic sodium is still higher than 120 mEq/l at the time of diagnosis, in most cases a hydric intake restriction to no more than 750–1000 ml per day is effective. The actual complex therapeutic algorithms set in place in more severe imbalances, which make use of urea, diuretics, demeclocycline, lithium carbonate, diphenylhydantoin, fludrocortisone, etc. will certainly be highly beneficial once the use of V2 receptors antagonists and the K-opioid agonists, which are central inhibitors of ADH release, have been well quantified for use in routine practice.

CSWS has been reanalyzed during the last two decades since the identification of atrial natriuretic factor and since the neurons of the hypothalamus and lamina terminalis that effect its release have been isolated and the high plasmatic levels of this neuropeptide after cerebral aneurysmal ruptures demonstrated [2]. It is now known that CSWS occurs in a wide range of neurosurgical pathologies, and study of it in pediatric cerebral diseases, where there is reason to believe that it can be found as frequently as can SIADH, will surely have a significant impact on the patients' outcome. Since a negative hydric balance is a major step in the physiopathological cycle of CSWS, the main therapeutic goal is achievement of a correct hydrosodic intake to restore a normal volemic status.

Therefore, it appears essential to differentiate at an early stage between the two major causes of "central neurogenic hyponatremia": SIADH, with excessive retention of water, and CSWS, with excessive loss of sodium, since their treatment is also essentially different, though there are many common defining features and overlapping forms. The integration of cerebral neurosurgical diseases into the wider picture of the entire organism's biological changes avoids the negative consequences of major imbalances that may worsen the quality of recovery. Such a holistic treatment must thus be applied to brain lesions of children in all age groups.

References

1. Grenier B, Boulard G, Ravussier P (1996) Actualité du syndrome de sécrétion inappropriée d'hormone antidiurétique en réanimation. In: Conférences d'actualisation de la Société Française d'Anesthésie et réanimation, 1996–1997. Elsevier, Paris, pp 447–462
2. Ickx B (1995) Métabolisme de sodium. (Physiologie en anesthésiologie) Pradel, Paris, pp 197–206
3. Mangos JA, Lobeck CC (1964) Studies of sustained hyponatremia due to central nervous system infection. *Pediatrics* 34:503–510
4. Mendoza S (1976) Syndrome of inappropriate antidiuretic hormone secretion. *Pediatr Clin North Am* 23:681–690
5. Samii K (1995) Syndrome de sécrétion inappropriée d'ADH en Pédiatrie. In: Pant O, Bel S le (eds) Anesthésie et réanimation chirurgicale. Flammarion, Paris, pp 1735–1739
6. Tommasino C (1999) Fluid management in neurosurgical patients. In: Norfield P, Cottrell JE (eds) Handbook of neuroanesthesia. Lippincott / Williams & Wilkins, Philadelphia, pp 381–382

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Review Article

Primary Care

HYPONATREMIA

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HYPONATREMIA is defined as a decrease in the serum sodium concentration to a level below 136 mmol per liter. Whereas hyponatremia always denotes hypertonicity, hyponatremia can be associated with low, normal, or high tonicity.^{1,2} Effective osmolality or tonicity refers to the contribution to osmolality of solutes, such as sodium and glucose, that cannot move freely across cell membranes, thereby inducing transcellular shifts in water.³ Dilutional hyponatremia, by far the most common form of the disorder, is caused by water retention. If water intake exceeds the capacity of the kidneys to excrete water, dilution of body solutes results, causing hypo-osmolality and hypotonicity (Fig. 1B, 1E, 1F, and 1G). Hypotonicity, in turn, can lead to cerebral edema, a potentially life-threatening complication.⁴ Hypotonic hyponatremia can be associated, however, with normal or even high serum osmolality if sufficient amounts of solutes that can permeate cell membranes (e.g., urea and ethanol) have been retained (Fig. 1C). Importantly, patients who have hypotonic hyponatremia but normal or high serum osmolality are as subject to the risks of hypotonicity as are patients with hypo-osmolar hyponatremia.

The nonhypotonic hyponatremias are hypertonic (or translocational) hyponatremia, isotonic hyponatremia, and pseudohyponatremia.^{1,2} Translocational hyponatremia results from a shift of water from cells to the extracellular fluid that is driven by solutes confined in the extracellular compartment (as occurs with hyperglycemia or retention of hypertonic mannitol); serum osmolality is increased, as is tonicity, the latter causing dehydration of cells (Fig. 1D). Re-

tention in the extracellular space of large volumes of isotonic fluids that do not contain sodium (e.g., mannitol) generates iso-osmolar and isotonic hyponatremia but no transcellular shifts of water. Pseudohyponatremia is a spurious form of iso-osmolar and isotonic hyponatremia identified when severe hypertriglyceridemia or paraproteinemia increases substantially the solid phase of plasma and the sodium concentration is measured by means of flame photometry.^{1,2} The increasing availability of direct measurement of serum sodium with the ion-specific electrode has all but eliminated this laboratory artifact.⁵

A common clinical problem, hyponatremia frequently develops in hospitalized patients.⁶ Although morbidity varies widely in severity, serious complications can arise from the disorder itself as well as from errors in management. In this article, we focus on the treatment of hyponatremia, emphasizing a quantitative approach to its correction.

CAUSES

Hypotonic (dilutional) hyponatremia represents an excess of water in relation to existing sodium stores, which can be decreased, essentially normal, or increased (Fig. 1). Retention of water most commonly reflects the presence of conditions that impair renal excretion of water^{1,7,8}; in a minority of cases, it is caused by excessive water intake, with a normal or nearly normal excretory capacity (Table 1).⁷

Conditions of impaired renal excretion of water are categorized according to the characteristics of the extracellular-fluid volume, as determined by clinical assessment (Table 1).⁹ With the exception of renal failure, these conditions are characterized by high plasma concentrations of arginine vasopressin despite the presence of hypotonicity.^{10,11} Depletion of potassium accompanies many of these disorders and contributes to hyponatremia, since the sodium concentration is determined by the ratio of the "exchangeable" (i.e., osmotically active) portions of the body's sodium and potassium content to total body water (Fig. 1G).¹²⁻¹⁴ Patients with hyponatremia induced by thiazides can present with variable hypovolemia or apparent euvolemia, depending on the magnitude of the sodium loss and water retention.^{1,15-17}

Excessive water intake can cause hyponatremia by overwhelming normal water excretory capacity (e.g., primary polydipsia) (Table 1). Frequently, however, psychiatric patients with excessive water intake have plasma arginine vasopressin concentrations that are not fully suppressed and urine that is not maximally dilute, thus contributing to water retention.^{18,19}

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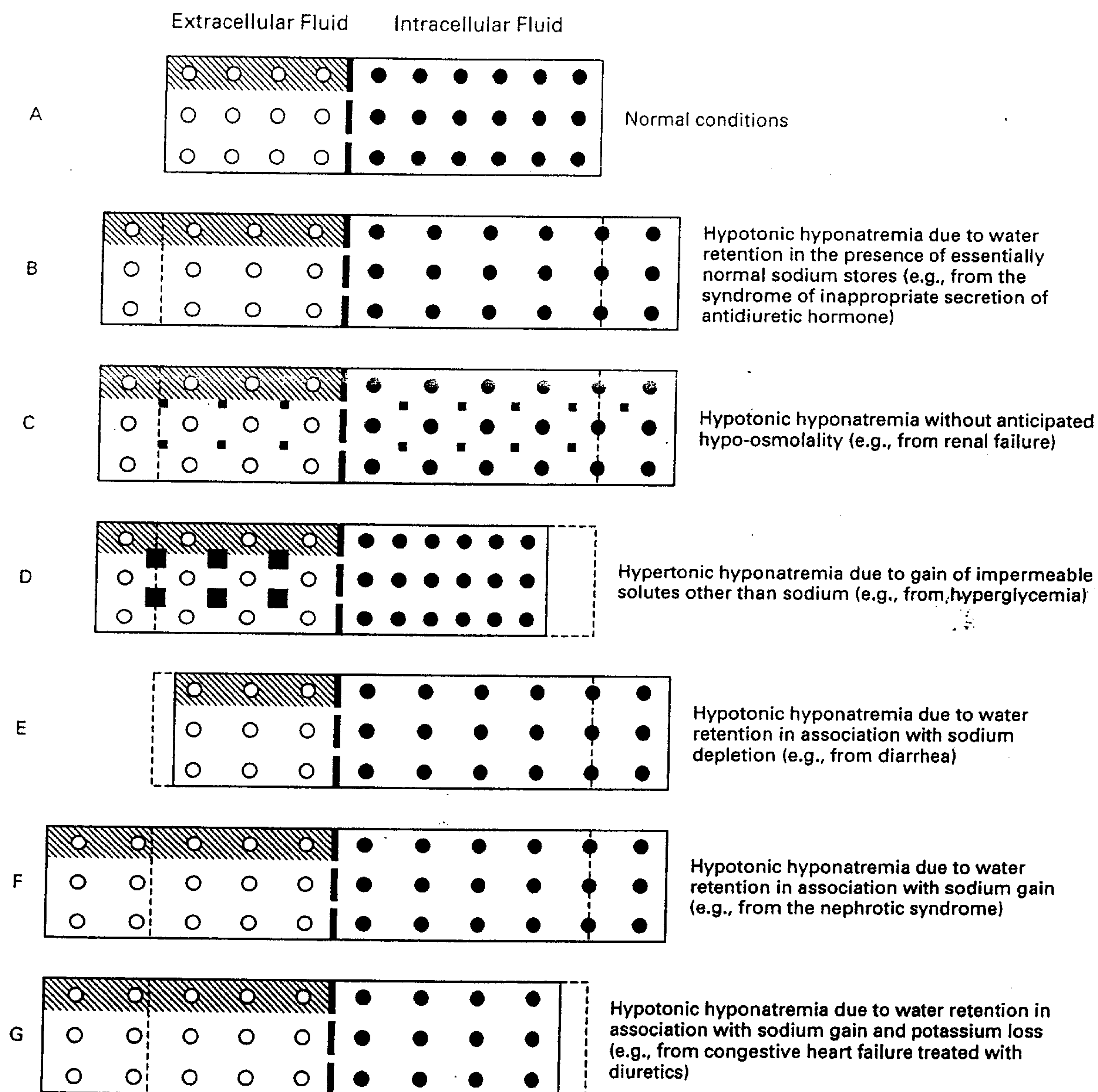


Figure 1. Extracellular-Fluid and Intracellular-Fluid Compartments under Normal Conditions and during States of Hyponatremia. Normally, the extracellular-fluid and intracellular-fluid compartments make up 40 percent and 60 percent of total body water, respectively (Panel A). With the syndrome of inappropriate secretion of antidiuretic hormone, the volumes of extracellular fluid and intracellular fluid expand (although a small element of sodium and potassium loss, not shown, occurs during inception of the syndrome) (Panel B). Water retention can lead to hypotonic hyponatremia without the anticipated hypo-osmolality in patients who have accumulated ineffective osmoles, such as urea (Panel C). A shift of water from the intracellular-fluid compartment to the extracellular-fluid compartment, driven by solutes confined in the extracellular fluid, results in hypertonic (translocational) hyponatremia (Panel D). Sodium depletion (and secondary water retention) usually contracts the volume of extracellular fluid but expands the intracellular-fluid compartment. At times, water retention can be sufficient to restore the volume of extracellular fluid to normal or even above-normal levels (Panel E). Hypotonic hyponatremia in sodium-retentive states involves expansion of both compartments, but predominantly the extracellular-fluid compartment (Panel F). Gain of sodium and loss of potassium in association with a defect of water excretion, as they occur in congestive heart failure treated with diuretics, lead to expansion of the extracellular-fluid compartment but contraction of the intracellular-fluid compartment (Panel G). In each panel, open circles denote sodium, solid circles potassium, large squares impermeable solutes other than sodium, and small squares permeable solutes; the broken line between the two compartments represents the cell membrane, and the shading indicates the intravascular volume.

TABLE 1. CAUSES OF HYPOTONIC HYPONATREMIA.

IMPAIRED CAPACITY OF RENAL WATER EXCRETION	
Decreased volume of extracellular fluid	Essentially normal volume of extracellular fluid
Renal sodium loss	Thiazide diuretics*
Diuretic agents	Hypothyroidism
Osmotic diuresis (glucose, urea, mannitol)	Adrenal insufficiency
Adrenal insufficiency	Syndrome of inappropriate secretion of antidiuretic hormone
Salt-wasting nephropathy	Cancer
Bicarbonaturia (renal tubular acidosis, disequilibrium stage of vomiting)	Pulmonary tumors
Ketonuria	Mediastinal tumors
Extrarenal sodium loss	Extrathoracic tumors
Diarrhea	Central nervous system disorders
Vomiting	Acute psychosis
Blood loss	Mass lesions
Excessive sweating (e.g., in marathon runners)	Inflammatory and demyelinating diseases
Fluid sequestration in "third space"	Stroke
Bowel obstruction	Hemorrhage
Peritonitis	Trauma
Pancreatitis	Drugs
Muscle trauma	Desmopressin
Burns	Oxytocin
Increased volume of extracellular fluid	Prostaglandin-synthesis inhibitors
Congestive heart failure	Nicotine
Cirrhosis	Phenothiazines
Nephrotic syndrome	Tricyclics
Renal failure (acute or chronic)	Serotonin-reuptake inhibitors
Pregnancy	Opiate derivatives
	Chlorpropamide
	Clofibrate
	Carbamazepine
	Cyclophosphamide
	Vincristine
	Pulmonary conditions
	Infections
	Acute respiratory failure
	Positive-pressure ventilation
	Miscellaneous
	Postoperative state
	Pain
	Severe nausea
	Infection with the human immunodeficiency virus
	Decreased intake of solutes
	Beer potomania
	Tea-and-toast diet

EXCESSIVE WATER INTAKE

Primary polydipsia†
 Dilute infant formula
 Sodium-free irrigant solutions (used in hysteroscopy, laparoscopy, or transurethral resection of the prostate)‡
 Accidental intake of large amounts of water (e.g., during swimming lessons)
 Multiple tap-water enemas

*Sodium depletion, potassium depletion, stimulation of thirst, and impaired urinary dilution are implicated.

†Often a mild reduction in the capacity for water excretion is also present.

‡Hyponatremia is not always hypotonic.

Hyperglycemia is the most common cause of translocational hyponatremia (Fig. 1D). An increase of 100 mg per deciliter (5.6 mmol per liter) in the serum glucose concentration decreases serum sodium by approximately 1.7 mmol per liter, with the end result a rise in serum osmolality of approximately 2.0 mOsm per kilogram of water.¹ Retention of hypertonic mannitol, which occurs in patients with re-

nal insufficiency, has the same effect. In both conditions, the resultant hypertonicity can be aggravated by osmotic diuresis; moderation of hyponatremia or frank hypernatremia can develop, since the total of the sodium and potassium concentrations in the urine falls short of that in serum.²⁰

Massive absorption of irrigant solutions that do not contain sodium (e.g., those used during transurethral

prostatectomy) can cause severe and symptomatic hyponatremia. Reflecting the composition of the irrigant, the resultant hyponatremia can be either hypotonic (with an irrigant containing 1.5 percent glycine or 3.3 percent sorbitol) or isotonic (with an irrigant containing 5 percent mannitol). Whether the symptoms derive from the presence of retained solutes, the metabolic products of such solutes, hypotonicity, or the low serum sodium concentration itself remains unclear.^{21,22}

The most common causes of severe hyponatremia in adults are therapy with thiazides, the postoperative state and other causes of the syndrome of inappropriate secretion of antidiuretic hormone, polydipsia

in psychiatric patients, and transurethral prostatectomy.^{1,17,23-25} Gastrointestinal fluid loss, ingestion of dilute formula, accidental ingestion of excessive water, and receipt of multiple tap-water enemas are the main causes of severe hyponatremia in infants and children.^{17,26}

CLINICAL MANIFESTATIONS

Just as in hypernatremia, the manifestations of hypotonic hyponatremia are largely related to dysfunction of the central nervous system, and they are more conspicuous when the decrease in the serum sodium concentration is large or rapid (i.e., occurring within a period of hours).²⁷ Headache, nausea, vomiting, mus-

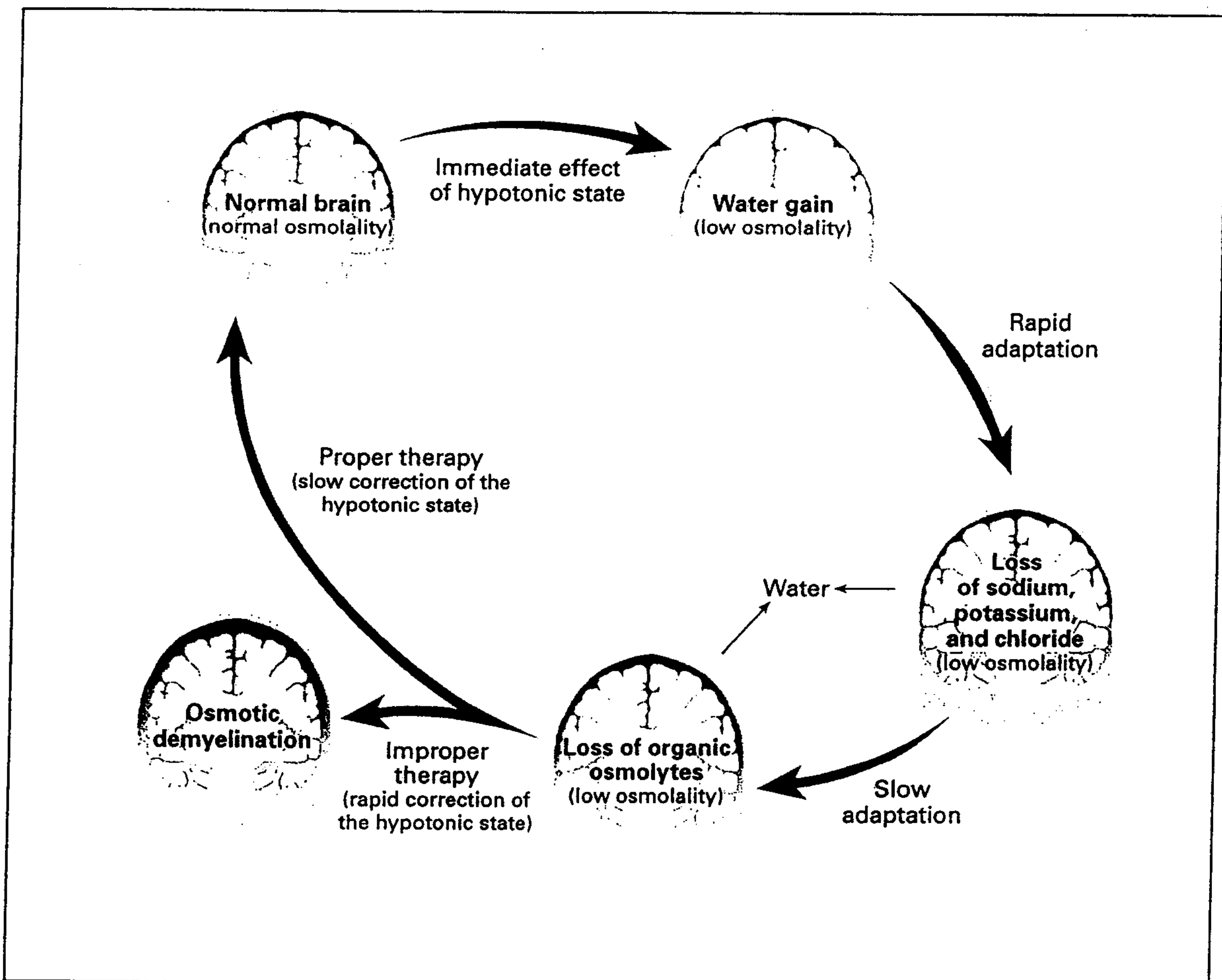


Figure 2. Effects of Hyponatremia on the Brain and Adaptive Responses.

Within minutes after the development of hypotonicity, water gain causes swelling of the brain and a decrease in osmolality of the brain. Partial restoration of brain volume occurs within a few hours as a result of cellular loss of electrolytes (rapid adaptation). The normalization of brain volume is completed within several days through loss of organic osmolytes from brain cells (slow adaptation). Low osmolality in the brain persists despite the normalization of brain volume. Proper correction of hypotonicity reestablishes normal osmolality without risking damage to the brain. Overly aggressive correction of hyponatremia can lead to irreversible brain damage.

cle cramps, lethargy, restlessness, disorientation, and depressed reflexes can be observed. Whereas most patients with a serum sodium concentration exceeding 125 mmol per liter are asymptomatic, those with lower values may have symptoms, especially if the disorder has developed rapidly.⁴ Complications of severe and rapidly evolving hyponatremia include seizures, coma, permanent brain damage, respiratory arrest, brain-stem herniation, and death. These complications often occur with excessive water retention in patients who are essentially euvoletic (e.g., those recovering from surgery or those with primary polydipsia); menstruating women appear to be at particular risk.^{23,28}

Hypotonic hyponatremia causes entry of water into the brain, resulting in cerebral edema (Fig. 2). Because the surrounding cranium limits expansion of the brain, intracranial hypertension develops, with a risk of brain injury. Fortunately, solutes leave brain tissues within hours, thereby inducing water loss and ameliorating brain swelling.^{29,30} This process of adaptation by the brain accounts for the relatively asymptomatic nature of even severe hyponatremia if it develops slowly. Nevertheless, brain adaptation is also the source of the risk of osmotic demyelination.³¹⁻³³ Although rare, osmotic demyelination is serious and can develop one to several days after aggressive treatment of hyponatremia by any method, including water restriction alone.³⁴⁻³⁶ Shrinkage of the brain

triggers demyelination of pontine and extrapontine neurons that can cause neurologic dysfunction, including quadriplegia, pseudobulbar palsy, seizures, coma, and even death. Hepatic failure, potassium depletion, and malnutrition increase the risk of this complication.^{1,37}

MANAGEMENT

The optimal treatment of hypotonic hyponatremia requires balancing the risks of hypotonicity against those of therapy.²⁸ The presence of symptoms and their severity largely determine the pace of correction.

Symptomatic Hypotonic Hyponatremia

Patients who have symptomatic hyponatremia with concentrated urine (osmolality, ≥ 200 mOsm per kilogram of water) and clinical euvoletic or hypervolemia require infusion of hypertonic saline (Table 2). This treatment can provide rapid but controlled correction of hyponatremia. Hypertonic saline is usually combined with furosemide to limit treatment-induced expansion of the extracellular-fluid volume. Because furosemide-induced diuresis is equivalent to a one-half isotonic saline solution, it aids in the correction of hyponatremia, as do ongoing dermal and respiratory fluid losses; anticipation of these losses should temper the pace of infusion of hypertonic saline. Obviously, electrolyte-free water intake must be withheld. In addition to hypertonic saline, hormone-

TABLE 2. FORMULAS FOR USE IN MANAGING HYPONATREMIA AND CHARACTERISTICS OF INFUSATES.

FORMULA*	CLINICAL USE	
1. Change in serum Na ⁺ = $\frac{\text{infusate Na}^+ - \text{serum Na}^+}{\text{total body water} + 1}$	Estimate the effect of 1 liter of any infusate on serum Na ⁺	
2. Change in serum Na ⁺ = $\frac{(\text{infusate Na}^+ + \text{infusate K}^+) - \text{serum Na}^+}{\text{total body water} + 1}$	Estimate the effect of 1 liter of any infusate containing Na ⁺ and K ⁺ on serum Na ⁺	
INFUSATE	INFUSATE Na ⁺ mmol per liter	EXTRACELLULAR-FLUID DISTRIBUTION %
5% Sodium chloride in water	855	100†
3% Sodium chloride in water	513	100†
0.9% Sodium chloride in water	154	100
Ringer's lactate solution	130	97
0.45% Sodium chloride in water	77	73
0.2% Sodium chloride in 5% dextrose in water	34	55
5% Dextrose in water	0	40

*The numerator in formula 1 is a simplification of the expression (infusate Na⁺ - serum Na⁺) × 1 liter, with the value yielded by the equation in millimoles per liter.³⁸ The estimated total body water (in liters) is calculated as a fraction of body weight. The fraction is 0.6 in children; 0.6 and 0.5 in nonelderly men and women, respectively; and 0.5 and 0.45 in elderly men and women, respectively.³⁹ Normally, extracellular and intracellular fluids account for 40 and 60 percent of total body water, respectively.³⁹

†In addition to its complete distribution in the extracellular compartment, this infusate induces osmotic removal of water from the intracellular compartment.

replacement therapy should be given to patients with suspected hypothyroidism or adrenal insufficiency after blood samples are obtained for diagnostic testing.^{7,17} On the other hand, most patients with hypovolemia can be treated successfully with isotonic saline. Patients with seizures also require immediate anticonvulsant-drug therapy and adequate ventilation.⁴⁰

Patients with symptomatic hyponatremia and dilute urine (osmolality, <200 mOsm per kilogram of water) but with less serious symptoms usually require only water restriction and close observation. Severe symptoms (e.g., seizures or coma) call for infusion of hypertonic saline.

There is no consensus about the optimal treatment of symptomatic hyponatremia.^{28,40-49} Nevertheless, correction should be of a sufficient pace and magnitude to reverse the manifestations of hypotonicity but not be so rapid and large as to pose a risk of the development of osmotic demyelination. Physiologic considerations indicate that a relatively small increase in the serum sodium concentration, on the order of 5 percent, should substantially reduce cerebral edema.^{9,50} Even seizures induced by hyponatremia can be stopped by rapid increases in the serum sodium concentration that average only 3 to 7 mmol per liter.^{51,52} Most reported cases of osmotic demyelination occurred after rates of correction that exceeded 12 mmol per liter per day were used, but isolated cases occurred after corrections of only 9 to 10 mmol per liter in 24 hours or 19 mmol per liter in 48 hours.^{34,35,40,48,53-56} After weighing the available evidence and the all-too-real risk of overshooting the mark, we recommend a targeted rate of correction that does not exceed 8 mmol per liter on any day of treatment. Remaining within this target, the initial rate of correction can still be 1 to 2 mmol per liter per hour for several hours in patients with severe symptoms. Should severe symptoms not respond to correction according to the specified target, we suggest that this limit be cautiously exceeded, since the imminent risks of hypotonicity override the potential risk of osmotic demyelination. Recommended indications for stopping the rapid correction of symptomatic hyponatremia (regardless of the method used) are the cessation of life-threatening manifestations, moderation of other symptoms, or the achievement of a serum sodium concentration of 125 to 130 mmol per liter (or even lower if the base-line serum sodium concentration is below 100 mmol per liter).^{28,40} Long-term management of hyponatremia (described below) should then be initiated. Although faster rates of correction can be tolerated safely by most patients with acute symptomatic hyponatremia, there is no evidence that such an approach is beneficial.^{40,57} Moreover, ascertaining the duration of hyponatremia is usually difficult.

How can the physician determine what the rate of infusion of the selected solution should be? This rate

can be derived expediently by applying formula 1 in Table 2, the same formula used for managing hypernatremia, which projects the change in serum sodium elicited by the retention of 1 liter of any infusate.³⁸ Dividing the change in serum sodium targeted for a given treatment period by the output of this formula determines the volume of infusate required, and hence the rate of infusion. Table 2 also presents the sodium concentrations of commonly used infusates, their fractional distribution in the extracellular fluid, and clinical estimates of total body water.³⁹ We do not recommend use of the conventional formula for the correction of hyponatremia, as follows:

$$\text{sodium requirement} = \text{total body water} \times (\text{desired serum sodium concentration} - \text{current sodium concentration}).$$

The conventional formula requires a complicated procedure to convert the amount of sodium required to raise the sodium concentration to an infusion rate for the selected solution.

The cases described below illustrate the various forms of symptomatic hyponatremia and their management.

Hyponatremia in the Postoperative State

A previously healthy 32-year-old woman has three grand mal seizures two days after an appendectomy. She receives 20 mg of diazepam and 250 mg of phenytoin intravenously and undergoes laryngeal intubation with mechanical ventilation. Three liters of 5 percent dextrose in water had been infused during the first day after surgery, and the patient subsequently drank an unknown but substantial amount of water. Clinically, she is euolemic, and she weighs 46 kg. She is stuporous and responds to pain but not to commands. The serum sodium concentration is 112 mmol per liter, the serum potassium concentration is 4.1 mmol per liter, serum osmolality is 228 mOsm per kilogram of water, and urine osmolality is 510 mOsm per kilogram of water. Hypotonic hyponatremia in this patient is a result of water retention caused by the impaired excretion of water that is associated with the postoperative state. Planned treatment includes the withholding of water, the infusion of 3 percent sodium chloride, and the intravenous administration of 20 mg of furosemide. The estimated volume of total body water is 23 liters (0.5×46).

According to formula 1 of Table 2, it is estimated that the retention of 1 liter of 3 percent sodium chloride will increase the serum sodium concentration by 16.7 mmol per liter ($[(513 - 112) \div (23 + 1)] = 16.7$). Given the seriousness of the patient's symptoms, the initial goal is to raise the serum sodium concentration by 3 mmol per liter over the next three hours; thus, 0.18 liter of hypertonic sodium chloride ($3 \div 16.7$), or 60 ml per hour, is required. Frequent monitoring of the serum sodium concentration, initially every two to three hours, is necessary in order

to make further adjustments in the amount of fluid administered. Although measuring urinary electrolytes can occasionally assist with management, it is generally unnecessary, and we do not recommend the routine use of this procedure.

Three hours later, the patient's serum sodium concentration is 115 mmol per liter. There have been no further seizures, but the level of responsiveness remains unchanged. The new goal is to increase the serum sodium concentration by an additional 3 mmol per liter over a period of six hours with the use of 3 percent sodium chloride; thus, the infusion rate is adjusted to 30 ml per hour. Nine hours after admission, the serum sodium concentration is 119 mmol per liter. There has been no seizure activity, and the patient now responds to simple commands. Hypertonic saline is discontinued, but close monitoring of the patient's clinical status and serum sodium concentration remains in effect. If the rate of correction is estimated to exceed the targeted rate, hypotonic solution should be administered.⁵⁸

Hyponatremia in an Essentially Euvolemic State

A 58-year-old man with small-cell lung carcinoma presents with severe confusion and lethargy. Clinically, he is euvolemic, and he weighs 60 kg. The serum sodium concentration is 108 mmol per liter, the serum potassium concentration is 3.9 mmol per liter, serum osmolality is 220 mOsm per kilogram of water, the serum urea nitrogen concentration is 5 mg per deciliter (1.8 mmol per liter), the serum creatinine concentration is 0.5 mg per deciliter (44.2 μ mol per liter), and urine osmolality is 600 mOsm per kilogram of water. The physician makes a provisional diagnosis of the tumor-induced syndrome of inappropriate secretion of antidiuretic hormone on the basis of the presence of hypotonic hyponatremia and concentrated urine in a euvolemic patient, the absence of a history of diuretic use, and the absence of clinical evidence of hypothyroidism or hypoadrenalism. The treatment plan includes water restriction, the infusion of 3 percent sodium chloride, and the intravenous administration of 20 mg of furosemide. The estimated volume of total body water is 36 liters (0.60×60).

According to formula 1 of Table 2, the retention of 1 liter of 3 percent sodium chloride is estimated to increase the serum sodium concentration by 10.9 mmol per liter ($[513 - 108] \div [36 + 1] = 10.9$). The initial goal is to increase the serum sodium concentration by 5 mmol per liter over the next 12 hours. Therefore, 0.46 liter of 3 percent sodium chloride ($5 \div 10.9$), or 38 ml per hour, is required.

Twelve hours after admission, the serum sodium concentration is 114 mmol per liter. The patient is mildly lethargic but easily arousable. Hypertonic saline is stopped, but fluid restriction and close monitoring continue. The new goal is to increase the se-

rum sodium concentration by 2 mmol per liter over the next 12 hours. Twenty-four hours after admission, the serum sodium concentration is 115 mmol per liter and the patient is alert. Long-term management of hyponatremia is instituted.

Hyponatremia in a Hypovolemic State

A 68-year-old woman is brought to the hospital because of progressive drowsiness and syncope. She is being treated with a low-sodium diet and 25 mg of hydrochlorothiazide daily for essential hypertension; she has had diarrhea for the past three days. She is lethargic but has no focal neurologic deficits. She weighs 60 kg. Her blood pressure while in a supine position is 96/56 mm Hg, and the pulse is 110 beats per minute. The jugular veins are flat, and skin turgor is decreased. The serum sodium concentration is 106 mmol per liter, the serum potassium concentration is 2.2 mmol per liter, the serum bicarbonate concentration is 26 mmol per liter, the serum urea nitrogen concentration is 46 mg per deciliter (16.4 mmol per liter), the serum creatinine concentration is 1.4 mg per deciliter (123.8 μ mol per liter), serum osmolality is 232 mOsm per kilogram of water, and urine osmolality is 650 mOsm per kilogram of water. Hypotonic hyponatremia caused by thiazide therapy, gastrointestinal losses of sodium, and an associated depletion of potassium are diagnosed. Hydrochlorothiazide and water are withheld, and infusion of a 0.9 percent sodium chloride solution containing 30 mmol of potassium chloride per liter is initiated. The estimated volume of total body water is 27 liters (0.45×60).

According to formula 2 of Table 2 (a simple derivative of formula 1), it is projected that the retention of 1 liter of this infusate will increase the serum sodium concentration by 2.8 mmol per liter ($[154 + 30] - 106 \div [27 + 1] = 2.8$). Considering the patient's hemodynamic status, the physician prescribes 1 liter of infusate per hour for the next two hours. At the end of this period, the blood pressure is 128/72 mm Hg, mental status is substantially improved, the serum sodium concentration is 112 mmol per liter, and the serum potassium concentration is 3.0 mmol per liter. The physician recognizes that as soon as the patient's extracellular-fluid volume nears restoration, the nonosmotic stimulus to arginine vasopressin release will cease, thereby fostering rapid excretion of dilute urine and correction of the hyponatremia at an overly rapid pace. Therefore, the prescription is switched to 0.45 percent sodium chloride containing 30 mmol of potassium chloride per liter infused at 100 ml per hour. Despite the estimate that retention of 1 liter of this infusate will have no measurable effect on the serum sodium concentration (i.e., $[77 + 30] - 112 \div [27 + 1] = -0.2$), the anticipated production of urine with lower sodium and potassium concentrations than those of the infusate will promote correc-

tion of the hyponatremia. Twelve hours after admission, the patient's condition continues to improve; the serum sodium concentration is 114 mmol per liter, and the serum potassium concentration is 3.2 mmol per liter. To slow down further correction over the next 12 hours, an infusion of 5 percent dextrose in water containing 30 mmol of potassium chloride per liter is started at a rate matching urinary output. Subsequently, long-term management of hyponatremia should be pursued.

Asymptomatic Hypotonic Hyponatremia

For certain patients with asymptomatic hyponatremia, the main risk of complications occurs during the correction phase. This is true of patients who stopped drinking large amounts of water³⁶ and those who underwent repair of a water-excretion defect (e.g., repletion of extracellular-fluid volume and discontinuation of drugs that cause the condition). If excessive diuresis occurs and the projected rate of spontaneous correction exceeds that recommended for patients with symptomatic hyponatremia, hypotonic fluids or desmopressin can be administered.⁴⁴

By contrast, there is no such risk associated with the asymptomatic hyponatremia that accompanies edematous states or the persistent syndrome of inappropriate secretion of antidiuretic hormone because of the prevailing defect of water excretion. Water restriction (to <800 ml per day) is the mainstay of long-term management, with the goal being induction of negative water balance.^{43,44} In severe cardiac failure, optimization of hemodynamics by several measures, including the use of angiotensin-converting-enzyme inhibitors, can increase excretion of electrolyte-free water and moderate hyponatremia. Loop, but not thiazide, diuretics reduce urine concentration and augment excretion of electrolyte-free water, thereby permitting relaxation of fluid restriction. In the syndrome of inappropriate secretion of antidiuretic hormone, but not in edematous disorders, loop diuretics should be combined with plentiful sodium intake (in the form of dietary sodium or salt tablets), a treatment that augments water loss. If these measures fail, 600 to 1200 mg of demeclocycline per day can help by inducing nephrogenic diabetes insipidus.⁴⁴ Monitoring of renal function is required, because demeclocycline has nephrotoxic effects, especially in patients with cirrhosis. Moreover, the drug imposes the risk of hypernatremia in patients who do not take in sufficient water. Management of chronic hyponatremia will be helped by the anticipated introduction of promising oral agents that antagonize the effect of arginine vasopressin on the V₂ receptor.^{59,60}

Nonhypotonic Hyponatremia

Corrective measures for nonhypotonic hyponatremia are directed at the underlying disorder rather than at the hyponatremia itself. Administration of

insulin is the basis of treatment for uncontrolled diabetes, but deficits of water, sodium, and potassium should also be corrected. Furosemide hastens the recovery of patients who absorb irrigant solutions; if renal function is impaired, hemodialysis is the preferred option.²²

Common Errors in Management

Although water restriction will ameliorate all forms of hyponatremia, it is not the optimal therapy in all cases. Hyponatremias associated with the depletion of extracellular-fluid volume (Table 1) require correction of the prevailing sodium deficit. On the other hand, isotonic saline is unsuitable for correcting the hyponatremia of the syndrome of inappropriate secretion of antidiuretic hormone; if administered, the resulting rise in serum sodium is both small and transient, with the infused salt being excreted in concentrated urine and thereby causing a net retention of water and worsening of the hyponatremia.³⁸ Although uncertainty about the diagnosis might occasionally justify a limited trial of isotonic saline, attentive follow-up is needed to confirm the diagnosis before substantial deterioration occurs. Great vigilance is required in order to recognize and diagnose hypothyroidism and adrenal insufficiency, since these disorders tend to masquerade as cases of the syndrome of inappropriate secretion of antidiuretic hormone. The presence of hyperkalemia should always alert the physician to the possibility of adrenal insufficiency.

Whereas patients with persistent asymptomatic hyponatremia require slow-paced management, those with symptomatic hyponatremia must receive rapid but controlled correction. Prudent use of hypertonic saline can be lifesaving, but failure to follow the recommendations for treatment can cause devastating and even lethal consequences.

Hyponatremia that is acquired in the hospital is largely preventable.⁶ A defect of water excretion can be present on admission, or it can worsen or develop during the course of hospitalization as a result of several antidiuretic influences (e.g., medications, organ failure, and the postoperative state). The presence of such a defect notwithstanding, hyponatremia will not develop as long as the intake of electrolyte-free water does not exceed the capacity for water excretion plus insensible losses. Thus, hypotonic fluids must be supplied carefully to hospitalized patients.

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REFERENCES

1. Gennari FJ. Hypo-hypernatraemia: disorders of water balance. In: Davison AM, Cameron JS, Grünfeld J-P, Kerr DNS, Ritz E, Winearls CG, eds. Oxford textbook of clinical nephrology. 2nd ed. Vol. 1. Oxford, England: Oxford University Press, 1998:175-200.

2. Hyponatremia and hypernatremia. In: Adrogué HJ, Wesson DE. Salt & water. Boston: Blackwell Scientific, 1994:205-84.
3. Gennari FJ. Serum osmolality: uses and limitations. *N Engl J Med* 1984;310:102-5.
4. Arieff AI, Llach F, Massry SG. Neurological manifestations and morbidity of hyponatremia: correlation with brain water and electrolytes. *Medicine (Baltimore)* 1976;55:121-9.
5. Maas AHJ, Siggaard-Andersen O, Weisberg HF, Zijlstra WG. Ion-selective electrodes for sodium and potassium: a new problem of what is measured and what should be reported. *Clin Chem* 1985;31:482-5.
6. Anderson RJ. Hospital-associated hyponatremia. *Kidney Int* 1986;29:1237-47.
7. Hypoosmolar states — hyponatremia. In: Rose BD. *Clinical physiology of acid-base and electrolyte disorders*. 4th ed. New York: McGraw-Hill, 1994:651-94.
8. Frizzell RT, Lang GH, Lowance DC, Lathan SR. Hyponatremia and ultramarathon running. *JAMA* 1986;255:772-4.
9. Sterns RH, Narins RG. Hypernatremia and hyponatremia: pathophysiology, diagnosis, and therapy. In: Adrogué HJ, ed. *Contemporary management in critical care*. Vol. 1. No. 2. Acid-base and electrolyte disorders. New York: Churchill Livingstone, 1991:161-91.
10. Anderson RJ, Chung H-M, Kluge R, Schrier RW. Hyponatremia: a prospective analysis of its epidemiology and the pathogenetic role of vasopressin. *Ann Intern Med* 1985;102:164-8.
11. Burrows FA, Shutack JG, Crone RK. Inappropriate secretion of antidiuretic hormone in a postsurgical pediatric population. *Crit Care Med* 1983;11:527-31.
12. Edelman IS, Leibman J, O'Meara MP, Birkenfeld LW. Interrelations between serum sodium concentration, serum osmolality and total exchangeable sodium, total exchangeable potassium and total body water. *J Clin Invest* 1958;37:1236-56.
13. Fichman MP, Vorherr H, Kleeman CR, Telfer N. Diuretic-induced hyponatremia. *Ann Intern Med* 1971;75:853-63.
14. Laragh JH. The effect of potassium chloride on hyponatremia. *J Clin Invest* 1954;33:807-18.
15. Sonnenblick M, Friedlander Y, Rosin AJ. Diuretic-induced severe hyponatremia: review and analysis of 129 reported patients. *Chest* 1993;103:601-6.
16. Ashraf N, Locksley R, Arieff AI. Thiazide-induced hyponatremia associated with death or neurologic damage in outpatients. *Am J Med* 1981;70:1163-8.
17. Sterns RH, Spital A, Clark EC. Disorders of water balance. In: Kokko JP, Tannen RL, eds. *Fluids and electrolytes*. 3rd ed. Philadelphia: W.B. Saunders, 1996:63-109.
18. Goldman MB, Luchins DJ, Robertson GL. Mechanisms of altered water metabolism in psychotic patients with polydipsia and hyponatremia. *N Engl J Med* 1988;318:397-403.
19. Kramer DS, Drake ME Jr. Acute psychosis, polydipsia, and inappropriate secretion of antidiuretic hormone. *Am J Med* 1983;75:712-4.
20. Gennari FJ, Kassirer JP. Osmotic diuresis. *N Engl J Med* 1974;291:714-20.
21. Gonzales R, Brensilver JM, Rovinsky JJ. Posthysteroscopic hyponatremia. *Am J Kidney Dis* 1994;23:735-8.
22. Agarwal R, Emmett M. The post-transurethral resection of prostate syndrome: therapeutic proposals. *Am J Kidney Dis* 1994;24:108-11.
23. Ayus JC, Wheeler JM, Arieff AI. Postoperative hyponatremic encephalopathy in menstruant women. *Ann Intern Med* 1992;117:891-7.
24. Arieff AI. Hyponatremia, convulsions, respiratory arrest, and permanent brain damage after elective surgery in healthy women. *N Engl J Med* 1986;314:1529-35.
25. Chung H-M, Kluge R, Schrier RW, Anderson RJ. Postoperative hyponatremia: a prospective study. *Arch Intern Med* 1986;146:333-6.
26. Adelman RD, Solhung MJ. Sodium. In: Behrman RE, Kliegman RM, Arvin AM, eds. *Nelson textbook of pediatrics*. 15th ed. Philadelphia: W.B. Saunders, 1996:189-93.
27. Arieff AI, Guisado R. Effects on the central nervous system of hypernatremic and hyponatremic states. *Kidney Int* 1976;10:104-16.
28. Berl T. Treating hyponatremia: damned if we do and damned if we don't. *Kidney Int* 1990;37:1006-18.
29. Verbalis JG, Gullans SR. Hyponatremia causes large sustained reductions in brain content of multiple organic osmolytes in rats. *Brain Res* 1991;567:274-82.
30. Gullans SR, Verbalis JG. Control of brain volume during hyperosmolar and hypoosmolar conditions. *Annu Rev Med* 1993;44:289-301.
31. Lien YH, Shapiro JJ, Chan L. Study of brain electrolytes and organic osmolytes during correction of chronic hyponatremia: implications for the pathogenesis of central pontine myelinolysis. *J Clin Invest* 1991;88:303-9.
32. Videen JS, Michaelis T, Pinto P, Ross BD. Human cerebral osmolytes during chronic hyponatremia: a proton magnetic resonance spectroscopy study. *J Clin Invest* 1995;95:788-93.
33. Laureno R, Karp BI. Myelinolysis after correction of hyponatremia. *Ann Intern Med* 1997;126:57-62.
34. Karp BI, Laureno R. Pontine and extrapontine myelinolysis: a neurologic disorder following rapid correction of hyponatremia. *Medicine (Baltimore)* 1993;72:359-73.
35. Sterns RH, Riggs JE, Schochet SS Jr. Osmotic demyelination syndrome following correction of hyponatremia. *N Engl J Med* 1986;314:1535-42.
36. Tanneau RS, Henry A, Rouhart F, et al. High incidence of neurologic complications following rapid correction of severe hyponatremia in polydipsic patients. *J Clin Psychiatry* 1994;55:349-54.
37. Kumar S, Berl T. Approach to the hyponatremic patient. In: Berl T, ed. *Disorders of water, electrolytes, and acid-base*. Part 1 of *Atlas of diseases of the kidney*. Vol. 1. Philadelphia: Blackwell Science, 1999:1.9-1.15.
38. Adrogué HJ, Madias NE. Aiding fluid prescription for the dysnatremias. *Intensive Care Med* 1997;23:309-16.
39. Oh MS, Carroll HJ. Regulation of intracellular and extracellular volume. In: Arieff AI, DeFronzo RA, eds. *Fluid, electrolyte, and acid-base disorders*. 2nd ed. New York: Churchill Livingstone, 1995:1-28.
40. Oh MS, Kim HJ, Carroll HJ. Recommendations for treatment of symptomatic hyponatremia. *Nephron* 1995;70:143-50.
41. Cluitmans FHM, Meinders AE. Management of severe hyponatremia: rapid or slow correction? *Am J Med* 1990;88:161-6.
42. Lauriat SM, Berl T. The hyponatremic patient: practical focus on therapy. *J Am Soc Nephrol* 1997;8:1599-607.
43. Gross P, Reimann D, Neidel J, et al. The treatment of severe hyponatremia. *Kidney Int Suppl* 1998;64:S6-S11.
44. Verbalis JG. Hyponatremia and hypoosmolar disorders. In: Greenberg A, ed. *Primer on kidney diseases*. 2nd ed. San Diego, Calif: Academic Press, 1998:57-63.
45. *Idem*. Hyponatremia: epidemiology, pathophysiology, and therapy. *Curr Opin Nephrol Hypertens* 1993;2:636-52.
46. Soupart A, Decaux G. Therapeutic recommendations for management of severe hyponatremia: current concepts on pathogenesis and prevention of neurologic complications. *Clin Nephrol* 1996;46:149-69.
47. Sterns RH. Severe symptomatic hyponatremia: treatment and outcome: a study of 64 cases. *Ann Intern Med* 1987;107:656-64.
48. Sterns RH, Cappuccio JD, Silver SM, Cohen EP. Neurologic sequelae after treatment of severe hyponatremia: a multicenter perspective. *J Am Soc Nephrol* 1994;4:1522-30.
49. Fraser CL, Arieff AI. Epidemiology, pathophysiology, and management of hyponatremic encephalopathy. *Am J Med* 1997;102:67-77.
50. Sterns RH. The treatment of hyponatremia: first, do no harm. *Am J Med* 1990;88:557-60.
51. Sarnaik AP, Meert K, Hackbarth R, Fleischmann L. Management of hyponatremic seizures in children with hypertonic saline: a safe and effective strategy. *Crit Care Med* 1991;19:758-62.
52. Worthley LIG, Thomas PD. Treatment of hyponatremic seizures with intravenous 29.2% saline. *BMJ* 1986;292:168-70.
53. DeWitt LD, Buonanno FS, Kistler JP, et al. Central pontine myelinolysis: demonstration by nuclear magnetic resonance. *Neurology* 1984;34:570-6.
54. Kleinschmidt-DeMasters BK, Norenberg MD. Rapid correction of hyponatremia causes demyelination: relation to central pontine myelinolysis. *Science* 1981;211:1068-70.
55. Sterns RH, Thomas DJ, Herndon RM. Brain dehydration and neurologic deterioration after rapid correction of hyponatremia. *Kidney Int* 1989;35:69-75.
56. Brunner JE, Redmond JM, Haggard AM, Kruger DF, Elias S. Central pontine myelinolysis and pontine lesions after rapid correction of hyponatremia: a prospective magnetic resonance imaging study. *Ann Neurol* 1990;27:61-6.
57. Cheng JC, Zikos D, Skopicki HA, Peterson DR, Fisher KA. Long-term neurologic outcome in psychogenic water drinkers with severe symptomatic hyponatremia: the effect of rapid correction. *Am J Med* 1990;88:561-6.
58. Oh MS, Uribarri J, Barrido D, Landman E, Choi K-C, Carroll HJ. Danger of central pontine myelinolysis in hypotonic dehydration and recommendation for treatment. *Am J Med Sci* 1989;298:41-3.
59. Serradeil-Le Gal C, Lacour C, Valette G, et al. Characterization of SR 121463A, a highly potent and selective, orally active vasopressin V2 receptor antagonist. *J Clin Invest* 1996;98:2729-38.
60. Saito T, Ishikawa S, Abe K, et al. Acute aquaresis by the nonpeptide arginine vasopressin (AVP) antagonist OPC-31260 improves hyponatremia in patients with syndrome of inappropriate secretion of antidiuretic hormone (SIADH). *J Clin Endocrinol Metab* 1997;82:1054-7.

Fluid and electrolyte emergencies: Some signposts to safe management

These facts will help you to anticipate problems and pitfalls

RICHARD W. CARLSON, MD, PhD and LAKSHMI KESHAVAMURTHY, MD

ABSTRACT: In treating a patient with hypernatremia or hyponatremia, be guided by measurements of serum sodium concentration and osmolality and estimates of extracellular fluid volume. Correct chronic hyponatremia cautiously, because too-rapid increases in the serum sodium concentration (at a rate above 10 mEq/L/d) heighten the risk of central pontine myelinolysis. Patients with postural hypotension and normal serum sodium levels are not dehydrated; they require infusion of sodium-containing fluids. The uncommon syndrome of cerebral salt wasting partly resembles but is distinct from the syndrome of inappropriate antidiuretic hormone, and the proper management of the two conditions differs. Hyperkalemia may develop with use of trimethoprim-sulfamethoxazole. Hypophosphatemia and hypocalcemia are common in critically ill patients; the former may aggravate cardiorespiratory crises, and the latter suggests a poor outcome. Calcium infusion is warranted for severe, symptomatic hypocalcemia but must be undertaken cautiously because it can produce serious complications. (*J Crit Illness*. 1999;14(10):554-562)

► When is it dangerous to correct electrolyte imbalances very quickly or aggressively?

► Which commonly used medications are known to produce electrolyte disturbances?

► What are the tip-offs to low phosphate levels?

► How are serum potassium levels related to pH?

The list of practical questions, obvious and not obvious, about disorders of fluid and electrolyte balance could be extended indefinitely. Distinct conditions, requiring different therapies, can have deceptively similar manifestations. Diagnostic signs

are not always in plain sight. You must recognize exceptions to trusted rules. The selected facts that we review in this article, though some may be relatively unfamiliar, have direct bearing on common diagnostic and therapeutic problems. They also show how important alertness and flexibility are in negotiating this territory.

Fact 1

Central pontine myelinolysis (CPM) is more likely to occur when chronic hyponatremia is rapidly corrected and the rate of increase in the serum sodium concentration exceeds 10 mEq/L in 24 hours.

CPM, the demyelination of neurons within the mid-base of the pons, can result from too-rapid reversal of hyponatremia. In contrast to other demyelinating conditions, such as multiple sclerosis, CPM is not characterized by a marked inflammatory response. Despite its name, this disorder may also affect extrapontine areas of the brain, including the thalamus and subcortical white matter. Although some patients recover from CPM, the damage it causes can be fatal or irreversible. CPM can usually be avoided in patients with hyponatremia by careful management of the serum sodium disturbance.

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Alcoholism, which is frequently associated with depression of serum sodium levels, is a strong risk factor for CPM. Liver transplant recipients are vulnerable to the condition for 1 to 2 weeks after the operation.^{1,2} Patients who have undergone aggressive diuresis, patients with gastroenteritis, and some women during pregnancy are also at risk.

Symptoms of CPM usually appear within several days to 2 weeks after hyponatremia has been corrected. They include upper motor neuron deficits, quadriparesis, and pseudobulbar palsy. Altered mentation may develop and is an especially ominous occurrence.

In managing severe hyponatremia, weigh the risk of illness or death posed by the untreated electrolyte imbalance against the risk of CPM.³ Patients with chronically depressed serum sodium levels are more susceptible to CPM than those with hyponatremia of recent onset.^{1,4} In either case, hypertonic saline infusion usually is not required when the patient is asymptomatic; it may be necessary when convulsions, agitation and confusion, or coma occurs.

The rate of correction of the serum sodium concentration should be less than 10 mEq/L in any 24-hour period.² Aim initially for a sodium level of about 125 mEq/L rather than "full" correction. Monitor sodium levels carefully during repletion because they may increase with unexpected speed; it may even become necessary to relower the serum sodium level to ensure that the overall rate of correction is kept below 10 mEq/L/d.³

Fact 2

Hyponatremia and hypernatremia reflect alterations of total body sodium or water content, or both. The serum sodium concentration can be regarded as the "water hematocrit."

Total body sodium content may

be high, low, or normal in patients with either hyponatremia or hypernatremia. Body fluid hypotonicity is always accompanied by hyponatremia, but the converse does not hold true. Hypertonic states and serum hyperosmolality may be associated with low, normal, or elevated serum sodium levels.

The relationship between total body sodium and water contents can be disturbed by an alteration of either or both. The serum sodium concentration reflects the ratio of sodium to water. In a comparable manner, the hematocrit relates the number of red cells to total blood volume; a high or low hematocrit does not necessarily represent an increase or decrease in red cell mass.

Likewise, a low sodium value may represent an absolute deficit of body sodium, as with renal salt wasting, or an excess of body water, as with polydipsia. Conversely, a high sodium concentration may be due to a high body sodium content or a deficit of water. To discover which is altered, sodium or water content, proceed as outlined below (Fact 3).

Fact 3

To determine how best to manage hypernatremia or hyponatremia, you

should first measure serum osmolality and then estimate extracellular fluid (ECF) volume.

Base treatment of hyponatremia, for example, on the severity of the sodium deficit, the clinical findings, and the magnitude of the ECF volume disturbance.

► **Step 1—Measure osmolality:** In hypotonic conditions, serum osmolality and serum sodium concentration are reduced in parallel. You must measure both to distinguish true from artifactual hyponatremia. In true (hypotonic) hyponatremia, sodium concentration and osmolality are both low (Table 1).

Isotonic hyponatremia (pseudohyponatremia) is a decrease of the measured serum sodium level with normal osmolality. It may be associated with hyperlipidemia or hyperproteinemia. In these conditions, the aqueous component of serum or plasma is reduced. Therefore, if the concentration of sodium in a sample is expressed in relationship to the total volume rather than to the aqueous component, the reported value of sodium will be low.

Pseudohyponatremia may compromise the measurement of serum sodium levels by flame photometry. It is not a problem with other tech-

Table 1 – Diagnostic approach to hyponatremia

Type of hyponatremia	Measured serum sodium level	Measured osmolality	Possible cause
Hypotonic	Low	Low	Numerous reasons; see article
Isotonic	Low	Normal	Hyperlipidemia hyperproteinemia
Hypertonic	Low	High	Alcohol methanol hypoglycemia mannitol administration

Fluid and electrolyte emergencies: Some signposts to safe management

niques, such as those that employ ion-selective membranes.

Hypertonic hyponatremia is a low serum sodium concentration with increased osmolality. This abnormality occurs when small solute molecules other than sodium (such as glucose, mannitol, or ethanol) are present in increased numbers in body water. Therefore, the serum sodium concentration is low, but osmolality is increased. In this case the clinician must evaluate both disturbances.

Step 2—Estimate ECF volume: Hypervolemic states associated with low serum sodium concentrations can occur in congestive heart failure, nephrotic syndrome, and hepatic disease. In these conditions, both total body water content and total body sodium content are high, but because water content is increased to a greater degree, the serum sodium concentration is low. Edema or other signs of excess fluid are usually present.

Euvolemic hyponatremia is characteristic of the syndrome of inappropriate antidiuretic hormone (SIADH), certain drugs, psychogenic polydipsia, and hypothyroidism and may occur with adrenal insufficiency. It is frequently difficult to differentiate be-

tween euvolemic and hypovolemic hyponatremia. Evaluation of urinary sodium excretion may be helpful.

Hypovolemic hyponatremia typically occurs with gastrointestinal disorders, mineralocorticoid deficiency, significant fluid loss through the skin, third-space sequestration, salt wasting in renal damage, and urinary obstruction. Patients with hypovolemic hyponatremia have decreases in both total body water and total body sodium contents, but sodium is more depleted. Such patients often have hemodynamic instability with hypotension, oliguria, and tachycardia.

► **Therapy:** The management of hyponatremia takes into account both osmolality and volume status (Figure). Treat hyponatremia in hypervolemic patients with diuretics and sodium restriction. For euvolemic patients, water restriction is indicated. Consider saline infusion for hypovolemic patients.

Fact 4

Patients with postural hypotension and low to normal serum sodium values are not dehydrated. The proper therapy is not water replacement but infusion of sodium-containing fluids.

As Mange and associates⁵ have pointed out, the term "dehydration" is inappropriate when hypotension is accompanied by normal serum sodium levels, because the disturbance then is a deficit of ECF volume rather than an isolated deficit of water. ECF volume depletion often warrants treatment with saline infusions, particularly when there is hemodynamic instability.

Use sodium-containing fluids for repletion of vascular volume when the patient has hypotension, regardless of the measured serum sodium level. The reason is that isotonic sodium-containing fluids expand plasma volume two to three times more than free water given as 5% dextrose in water (D₅W). For example, administering 1 L of normal saline (0.9% NaCl) produces 250 to 300 mL of plasma volume expansion, whereas 1 L of D₅W expands the plasma volume by less than 100 mL (Table 2). Virtually all of the fluid that is given as normal saline is distributed to the ECF compartment.

If the serum sodium level is already high, infusion of normal saline will not further elevate it. However, infusion of normal saline tends to raise an initially low serum sodium concentration.

Dehydration is an absolute deficit of total body water; it affects both intracellular and extracellular fluid volumes and increases the tonicity of plasma. This condition is best treated by infusion of free water (as D₅W).

Fact 5

SIADH and the cerebral salt wasting (CSW) syndrome may present with similar electrolyte disturbances but are managed differently.

Patients with hyponatremia and CNS dysfunction may have SIADH, but hyponatremia associated with acute CNS disorders can be part of a distinct CSW syndrome. The man-

Table 2 – Effects on fluid volume of infusing 1 L of free water or normal saline solution

Variable	Free water	Normal saline
Sodium content (mEq)	0	154 (and 154 mEq/L in 0.9% NaCl)
Water content (mL)	1000	1000
Increase in extracellular fluid volume (mL)	33	250
Increase in intracellular fluid volume (mL)	666	0
Increase in plasma volume (mL)	83	250

*5% dextrose in water.
Adapted from Mange K et al. *Ann Intern Med*. 1997;127:1-11.

agement of CSW differs in important ways from that of SIADH.

Hyponatremia associated with CSW has been described in patients who have undergone CNS surgery and in those with acute subarachnoid hemorrhage; brain trauma, tumor, or infection; and various diffuse CNS disorders. The CSW syndrome resembles SIADH; both are marked by hyponatremia and natriuresis. However, these are distinct conditions that you need to differentiate both clinically and with laboratory tests.

In SIADH, inappropriate secretion of ADH leads to "euvolemic" hyponatremia, in which the urine osmolality and sodium concentration are atypically high with respect to their counterparts in serum.

In the CSW syndrome, levels of brain natriuretic peptide and atrial natriuretic peptide are increased. The patient loses water and sodium and becomes volume-depleted; this is the key point. Patients with the CSW syndrome should receive infusions of sodium-containing fluids, whereas SIADH usually responds to restriction of water.

The serum uric acid level is another clinical clue that can separate the two conditions: in CSW it is usually elevated, whereas in SIADH it is normal or low.

Fact 6

The use of trimethoprim-sulfamethoxazole (TMP-SMX) is commonly associated with hyperkalemia in hospitalized patients.

In a prospective chart review at a community-based teaching hospital, hyperkalemia was found in more than 60% of patients treated with standard dosages of TMP-SMX (up to 320 mg/d of TMP and 1,600 mg/d of SMX).⁶ Hyperkalemia severe enough to warrant urgent correction occurred in more than 20% of patients who received TMP-SMX. A possible mecha-

nism is the chemical similarity of TMP to potassium-sparing diuretics. The risk of hyperkalemia was highest for patients with renal insufficiency.

Because TMP-SMX is commonly prescribed for a variety of infections, it is important to keep this association with hyperkalemia in mind. Other drugs that are linked with hyperkalemia in the ICU are pentamidine and succinylcholine.

Fact 7

Hyperkalemia is associated with acidemia. A 10% to 15% rise in the serum potassium level is noted for every 0.1 decrement in pH. This association is primarily with mineral acidosis, not respiratory or organic acidosis. Hypokalemia is also a common clinical problem.

As pH falls, potassium leaves cells and enters the ECF. This relationship is strongest in mineral acidosis (see "Case studies: Potassium-pH relationships in acidosis").

Table 3 – Potassium infusion guide

• Maximum infusion rate = 20 mEq/h
• Without cardiac monitoring: Administer through a peripheral vein at a concentration of not more than 40 mEq/L and a rate not to exceed 8–10 mEq/h
• With ECG monitoring: Infuse through a peripheral vein at a maximum concentration of 60 mEq/L and a rate no greater than 20 mEq/h
• Patients with severe hypokalemia: Administer with ECG monitoring through a central catheter at a concentration of 200 mEq/L and a rate up to 20 mEq/h
Adapted from Sise et al. J Trauma 1994

Many factors besides pH affect internal potassium balance. Some hormones, including insulin and aldosterone, drive potassium into cells, as do β -agonists and states of metabolic alkalosis. α -Agonists and β -antagonists inhibit normal potassium uptake into cells. Hypertonicity, exercise, and cell lysis cause potassium to be released into the ECF.

Typically, acidosis is associated with hyperkalemia and alkalosis with hypokalemia. In renal tubular acidosis, however, either hypokalemia or hyperkalemia can develop. Metabolic acid-base disorders have a greater effect on serum potassium levels than respiratory acid-base disorders.

Common causes of hypokalemia include excessive renal loss of potassium with diuretic use, other drugs (for example, carbenicillin, gentamicin, and amphotericin B), chronic metabolic alkalosis, renal tubular acidosis, and mineralocorticoid excess. Gastrointestinal loss of potassium

Table 4 – Chloride clues in the ICU

Finding	Possible Implications
Low chloride concentration	Metabolic alkalosis, respiratory acidosis, SIADH (if patient is hyponatremic)
High chloride concentration	Metabolic acidosis, respiratory alkalosis, dehydration (if patient is hypernatremic)
SIADH syndrome of inappropriate antidiuretic hormone	

through vomiting and diarrhea also can result in hypokalemia. Intracellular shifts of potassium occur with acute alkalosis, barium ingestion, insulin therapy, vitamin B₁₂ therapy, hypokalemic periodic paralysis and, uncommonly, thyrotoxicosis.

Potassium infusion without cardiac monitoring is safe if the rate of infusion and the concentration of the infused solution are low (Table 3).^{7,8} Many institutions have guidelines that address the circumstances in which ECG monitoring is necessary, whether the infusion should be given through a peripheral or a central vein, and whether the infusion must be administered in the ICU. In general, the rate of infusion of potassium should not exceed 20 mEq/h.

Fact 8

Hypochloremia is more common than hyperchloremia in the ICU, and the concentration of chloride usually changes reciprocally with that of bicarbonate.

Chloride is the principal serum anion and is regulated primarily by the kidney. The normal serum chloride concentration is 95 to 105 mEq/L. The total body concentration is approximately 40 mEq/kg.

As the serum concentration of bicarbonate rises, that of chloride usually falls; a typical instance is the hypochloremia that accompanies metabolic alkalosis caused by ECF volume contraction (Table 4). In contrast, as the serum bicarbonate concentration falls (in metabolic acidosis), the chloride concentration rises.

Other causes of hypochloremia include burns, Addison's disease, diuretic therapy, congestive heart failure, and overtreat-

Case studies: Potassium-pH relationships in acidosis

Potassium moves from cells into the fluid as pH falls, resulting in an association between hyperkalemia and acidosis. As the following case studies illustrate, this relationship is strongest for mineral acidosis.

Case 1: Mineral acidosis
Presentation: 20-year-old man with methanol intoxication, hyperosmolality. **Laboratory values:** Sodium, 140 mEq/L; pH, 6.9; bicarbonate, 3 mEq/L; potassium, 6.7 mEq/L.

Note the strong relationship between serum potassium and pH.

Case 2: Lactic acidosis
Presentation: 45-year-old man with a seizure disorder. **Laboratory values:** Sodium, 135 mEq/L; pH, 6.99; bicarbonate, 4 mEq/L; potassium, 5 mEq/L; chloride, 95 mEq/L; lactate, 14 mEq/L.

In lactic (organic) acidosis, the serum potassium-pH relationship is weak. See also Case 4, below, which involves an organic acidosis in which a serum potassium-pH relationship is not discernible.

Case 3: Respiratory acidosis
Presentation: 65-year-old man with chronic obstructive pulmonary disease. **Laboratory values:** pH, 7.1; potassium, 4.4 mEq/L; arterial carbon dioxide tension, 94 mm Hg.

In respiratory acidosis, as in organic acidosis, there is a weak, unpredictable relationship between the serum potassium and pH levels.

Case 4: Diabetic ketoacidosis
Presentation: 20-year-old woman with hyperglycemia and diabetic ketoacidosis. **Laboratory values:** Sodium, 130 mEq/L; pH, 6.99; bicarbonate, 3 mEq/L; potassium, 4.6 mEq/L; chloride, 96 mEq/L; glucose, 1,000 mg/dL.

In diabetic ketoacidosis—another common form of organic acidosis—changes in the serum potassium and pH levels do not correlate.

ment with hypotonic fluids. Hyperchloremia is commonly seen in association with acetazolamide therapy, severe diarrhea, or saline infusion. Hyperchloremic metabolic acidosis can result from renal tubular acidosis.

Evaluate abnormal serum chloride levels in relation to the value of serum sodium. In patients who have hypernatremia caused by dehydration, the chloride level is typically increased. In those with the hyponatremia of SIADH, the chloride level is decreased.

Also take the anion gap into account.⁹ The serum chloride level usually remains normal when the serum concentration of bicarbonate falls in anion-gap acidosis, and the change in the anion gap approximates the change in bicarbonate concentration. If the chloride concentration is disproportionately low and the bicarbonate level is high, suspect an additional process, such as metabolic alkalosis or respiratory acidosis, that is generating bicarbonate.

Examine the changes in the anion gap and the bicarbonate level. If the deviation of the anion gap from normal (ΔAG) is greater than the deviation of the bicarbonate concentration from normal (ΔHCO_3), a mixed acid-base disturbance exists—metabolic alkalosis as well as anion gap acidosis. A ΔAG that is smaller than the ΔHCO_3 implies metabolic acidosis or respiratory alkalosis.

Hyperchloremic acidosis can coexist with an anion gap acidosis such as diabetic ketoacidosis (DKA). The clinician needs to recognize this "double-defect" acidosis in a patient with DKA so that acid-base and electrolyte disturbances can be corrected ap-

Table 5 - The electrolyte panel in 'double-defect' acidosis

Variable	Normal value (mEq/L)	Value in hyperchloremic acidosis (mEq/L)	Value in DKA (mEq/L)	Value when both are present (mEq/L)
Sodium	140	141	140	141
Chloride	103	113	103	113
Bicarbonate	25	16	15	6
Anion gap	12	12	22	22
Change in bicarbonate concentration		9	10	20
Change in anion gap		0	10	10
Change in chloride concentration		10	0	10

DKA: diabetic ketoacidosis

appropriately. Electrolyte anomalies when DKA and hyperchloremic acidosis co-exist represent, more or less, a superimposition of the two conditions (Table 5).

Fact 9

Hypophosphatemia, which is common in the ICU and relatively easy to correct, may reflect depletion of total body stores of phosphorus or only a decreased concentration of phosphate in ECF. Critical hypophosphatemia is often self-induced or iatrogenic—as with phosphate-deficient diets and the use of phosphate binders, respectively—and may aggravate cardiorespiratory crises.

Hypophosphatemia is more common in the ICU than hyperphosphatemia. Causes include decreased intake or gastrointestinal absorption of phosphorus, redistribution of phosphate (as in respiratory alkalosis or catecholamine excess), renal or gastrointestinal losses, or a combination of these factors (Table 6). Respiratory alkalosis causes a greater intracellular shift of phosphate than metabolic alkalosis and may thereby induce hypophosphatemia. Manifestations of

severe hypophosphatemia include muscle weakness, rhabdomyolysis, proximal myopathy, respiratory failure, cardiac dysfunction, and altered mental status.

Alcoholism is associated with low serum phosphorus levels for many reasons. Alcohol may have a direct effect on phosphate; although a mechanism has not been identified.

Alcoholics often have a reduced dietary intake of phosphorus or may lose phosphorus through vomiting and diarrhea or through the phosphorus-binding effect of antacids that may be used to treat gastritis. In addition, refeeding with glucose lowers phosphorus levels, hypomagnesemia associated with alcoholism increases urinary phosphate loss and decreases

Table 6 - Fact check: Phosphate and hypophosphatemia

Phosphate • About 85% of total body phosphorus is in bone; of the remainder, 99% is in intracellular fluid and 1% in extracellular fluid. • Excess and deficits can pertain to total body phosphorus or serum concentration only. • Total body pools approximately 700 g. • Normal serum values 2.7-4.5 mg/dL.
Hypophosphatemia • It may reflect total body depletion or decreased extracellular fluid concentration. • It is common in critical illness, including diabetic ketoacidosis and alcoholism. • Renal loss of phosphate occurs in hyperparathyroidism, renal tubular acidosis, and acetazolamide use. • Gastrointestinal loss or malabsorption of phosphate occurs in vitamin D deficiency, vomiting, and diarrhea and with use of binders and nasogastric suction. • Signs and symptoms, such as muscle weakness, rhabdomyolysis, proximal myopathy, and cardiac dysfunction, are frequent and severe when the serum phosphate concentration is less than 1.5 mg/dL.

Fluid and electrolyte emergencies: Some signposts to safe management

es gastrointestinal absorption of phosphate, and respiratory alkalosis associated with cirrhosis or alcohol withdrawal leads to redistribution hypophosphatemia.

Therapy for hypophosphatemia is uncomplicated. Oral phosphate loading is usually successful. This can be done with skim milk (which contains 1 mg/mL of phosphorus) or commercial preparations of phosphorus. When the patient is incapable of oral intake or hypophosphatemia is severe, phosphorus can be replaced parenterally. A maximal repletion dose is 2 mg/kg of phosphorus over 6 hours, and no more than 1 g of phosphorus should be given in 24 hours.¹⁰

The most common causes of hyperphosphatemia are renal failure, vitamin D intoxication, and oral or parenteral phosphate administration.

Rhabdomyolysis, leukemia, lymphoma, cytotoxic therapy, and hyperthermic syndromes may be associated with hyperphosphatemia.

Fact 10

Hypomagnesemia, which is often observed in patients who are admitted to medical and surgical ICUs, is associated with increased morbidity and mortality. Treatment is usually straightforward.

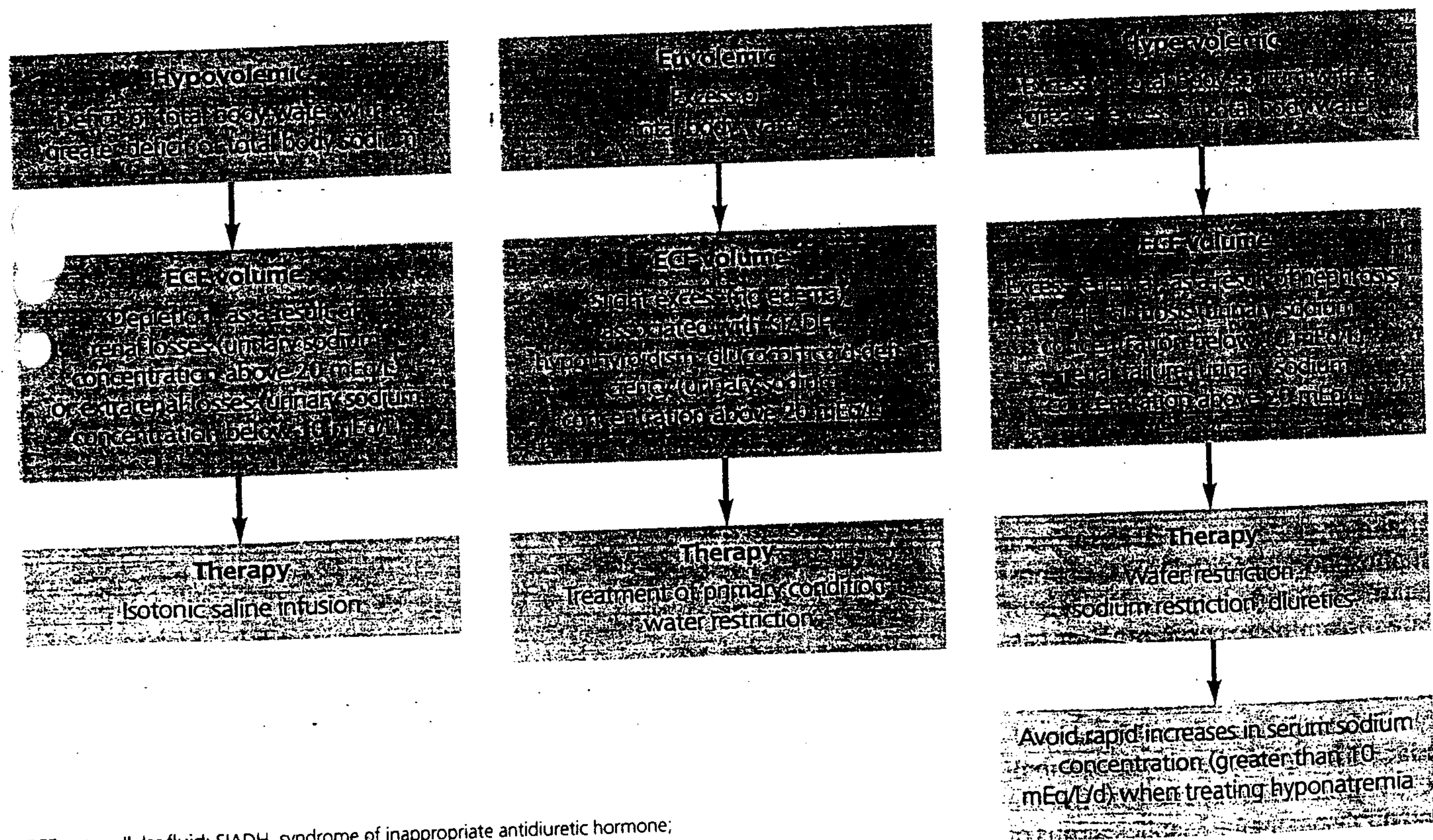
Up to two thirds of patients in ICUs may have hypomagnesemia, although low magnesium levels are not thought to be a direct cause of illness or death (Table 7).¹¹⁻¹³ (The association of hypomagnesemia with cardiac arrhythmias, such as torsades de pointes, may be the result of concomitant depletion of intracellular potassium.) Hypomagnesemia is es-

pecially common in alcoholics, burn patients, and lactating women and with the use of some drugs, such as aminoglycosides and cyclosporine. Restoration of normal magnesium levels is important because hypokalemia may be difficult to treat if hypomagnesemia is not corrected.

Hypomagnesemia often reflects total body magnesium depletion as well as decreases in the magnesium concentration in ECF. However, magnesium is primarily an intracellular ion, and measurement of serum magnesium is not a reliable indicator of body stores.

Gastrointestinal and renal losses and decreased intake of magnesium are the most frequent causes of hypomagnesemia. Serum magnesium concentrations below 1.7 mg/dL are correlated with increased morbidity,

Figure – Management of hyponatremia



ECF, extracellular fluid; SIADH, syndrome of inappropriate antidiuretic hormone;
CHF, congestive heart failure.

length of hospital stay, and mortality.

Magnesium therapy is usually safe and straightforward. For hypomagnesemic emergencies such as torsades de pointes or other life-threatening arrhythmias, eclampsia, or seizures, 2 g (16.2 mEq) of magnesium sulfate in 10 mL of D₅W (20% solution) may be given intravenously over 1 to 2 minutes, followed by 5 g (40.5 mEq) in 500 mL of solution over the next 5 to 6 hours.¹¹

For less severe hypomagnesemia, a variety of enteral magnesium preparations are available. Magnesium-containing antacids may be used. The common liquid antacids contain 10 mEq of magnesium/5 mL, of which 6% to 15% is absorbed. Giving 30 mL of the antacid four times a day will provide up to 36 mEq of absorbable magnesium a day.

Fact 11
Hypocalcemia, which is also common in critically ill patients and portends an unfavorable outcome, usually reflects a defect of internal regulation rather than depletion of body stores. Treatment with parenteral calcium should be undertaken cautiously but may be needed for severe hypocalcemia.

It is crucial to recall both how common hypocalcemia is in critical illness and how carefully it may have to be managed. Hypocalcemia—an abnormally low level of serum ionized calcium—may be seen in up to two thirds of patients in ICUs and is correlated with poor outcomes.¹⁴

The total serum calcium concentration does not accurately reflect the ionized calcium level; direct measurement of ionized calcium is preferred and is now widely available through ion-selective membrane technology. Ionized calcium is the biologically active fraction. Nearly all of the calcium in the body is found in teeth and bones; most of the remain-

Table 7 – Fact check: Magnesium
Magnesium • Is predominantly intracellular • Is a natural competitor of calcium; 20%–30% protein bound • May compete for slow-channel calcium receptors • May block calcium entry into vascular smooth muscle • Helps drive calcium into the sarcoplasmic reticulum
Effects of intravenous magnesium • Lowers systemic and pulmonary arterial blood pressure • Potentiates vasodilator effects • Inhibits vasoconstrictors • Inhibits platelet aggregation

der, which includes ionized calcium as well as chelated and protein-bound calcium, is in the ECF.

Hypocalcemia frequently ac-

companies sepsis and other inflammatory states. In contrast to hypomagnesemia, which is commonly associated with depletion of total body

CLINICAL CONCLUSIONS:

Managing fluid and electrolyte emergencies

1. Serum electrolyte levels are critical in patient care. Electrolyte abnormalities can lead to life-threatening complications. The most common electrolyte abnormalities are hyponatremia, hypokalemia, hypocalcemia, and hypomagnesemia. These abnormalities can be caused by a variety of factors, including fluid overload, renal failure, and endocrine disorders. Prompt recognition and treatment are essential to prevent complications.

2. Hyponatremia is a common electrolyte abnormality. It can be caused by a variety of factors, including fluid overload, renal failure, and endocrine disorders. Prompt recognition and treatment are essential to prevent complications.

3. Hypokalemia is a common electrolyte abnormality. It can be caused by a variety of factors, including fluid overload, renal failure, and endocrine disorders. Prompt recognition and treatment are essential to prevent complications.

4. Hypocalcemia is a common electrolyte abnormality. It can be caused by a variety of factors, including fluid overload, renal failure, and endocrine disorders. Prompt recognition and treatment are essential to prevent complications.

5. Hypomagnesemia is a common electrolyte abnormality. It can be caused by a variety of factors, including fluid overload, renal failure, and endocrine disorders. Prompt recognition and treatment are essential to prevent complications.

6. Hypomagnesemia and hypocalcemia are common in critically ill patients and are associated with poor outcomes. Magnesium replacement therapy, when oral or intravenous hypomagnesemic crises such as torsades de pointes, parenteral is generally straightforward. Parenteral calcium therapy can cause severe complications and must be undertaken cautiously.

CRITICAL CARE MEDICINE 1999

Fluid and electrolyte emergencies:
Some signposts to safe management

magnesium stores, hypocalcemia often results from defects of internal regulation.

Depression of the serum ionized calcium level has multiple causes, including defects of vitamin D metabolism, parathyroid gland function, or end-organ responsiveness. In sepsis, cytokines have been implicated in the causation of hypocalcemia.¹⁵

Other factors that contribute to hypocalcemia include hypomagnesemia, renal insufficiency, alkalemia, and acute pancreatitis. In some studies of hypocalcemia in acutely ill patients, the cause remained unknown in more than half the cases.

To correct hypocalcemia, treat the underlying cause. Administration of calcium for asymptomatic mild

hypocalcemia often is not warranted, but magnesium, phosphate, and potassium levels should be checked.

Patients whose hypocalcemia results from hypoparathyroidism are treated with calcium and vitamin D. Vitamin D administration increases both calcium absorption in the gut and bone mineralization.

Calcium infusion can be dangerous because of the risk of calcium overload and cell damage. It may also lead to hyperphosphatemia and tissue precipitation of calcium phosphate. Nevertheless, intravenous administration of calcium is appropriate for certain severe conditions, including:

► Severe, symptomatic hypocalcemia (serum ionized calcium level less than 0.7 mmol/L).

- Hypocalcemic seizures or tetany.
- Calcium channel blocker overdose.
- Massive chelation.
- Severe hyperkalemia (serum potassium concentration greater than 6.5 mEq/L) associated with heart block, ventricular arrest, widening QRS complex, or sine wave pattern.

In the most urgent settings, 10 to 20 mL of 10% calcium gluconate solution (which contains 10 mg/mL of elemental calcium) may be administered over 10 to 20 minutes. When speed is not of the essence, the dosage is based on body weight, and patients may receive 20 mg/kg of elemental calcium intravenously over 4 to 8 hours. Remember that extravasation of calcium salts can cause severe tissue damage.

SELECTED REFERENCES

1. Wszolek ZK, McComb RD, Pfeiffer RF, et al. Pontine and extrapontine myelinolysis following liver transplantation. Relationship to serum sodium. *Transplantation*. 1989;48:1006-1012.
2. Singh N, Yu VL, Gayowski T. Central nervous system lesions in adult liver transplant recipients: clinical review with implications for management. *Medicine (Baltimore)*. 1994;73:110-118.
3. Laureno R, Karp BI. Myelinolysis after correction of hyponatremia. *Ann Intern Med*. 1997;126:57-62.
4. Verbalis JG, Martinez AJ. Neurological and neuropathological sequelae of correction of chronic hyponatremia. *Kidney Int*. 1991;39:1274-1282.
5. Mange K, Matsuura D, Cizman B, et al. Language guiding therapy: the case of dehydration versus volume depletion. *Ann Intern Med*. 1997;127:848-853.
6. Alappan R, Perazella MA, Buller GK. Hyperkalemia in hospitalized patients treated with trimethoprim-sulfamethoxazole. *Ann Intern Med*. 1996;124:316-320.
7. Kruse JA, Clark VL, Carlson RW, Geheb MA. Concentrated potassium chloride infusions in critically ill patients with hypokalemia. *J Clin Pharmacol*. 1994;34:1077-1082.
8. Blumberg A, Weidman P, Shaw S, et al. Effect of various therapeutic approaches on plasma potassium and major regulating factors in terminal renal failure. *Am J Med*. 1988;85:507-512.
9. Gabow PA. Disorders associated with an altered anion gap. *Kidney Int*. 1985;27:472-483.
10. Lee DBN, Brauthar N, Kleeman CR. Disorders of phosphorus metabolism. In: Bronner F, Coburn JW, eds. *Disorders of Mineral Metabolism*. Vol. 3. New York: Academic Press; 1981:283-421.
11. Rubeiz GJ, Thill-Baharozian M, Hardie D, et al. Association of hypomagnesemia and mortality in acutely ill medical patients. *Crit Care Med*. 1993;21:203-209.
12. Salem M, Munoz R, Chernow B. Hypomagnesemia in critical illness. A common and clinically important problem. *Crit Care Clin*. 1991;7:225-252.
13. Whang R. Magnesium deficiency: pathogenesis, prevalence, and clinical implications. *Am J Med*. 1987;82:24-29.
14. Desai TK, Carlson RW, Geheb MA. Prevalence and clinical implications of hypocalcemia in acutely ill patients in a medical intensive care setting. *Am J Med*. 1988;84:209-214.
15. Zaloga GP. Hypocalcemia in critically ill patients. *Crit Care Med*. 1992;20:251-262.

CHAPTER 8

Fluid balance: all aspects

LUCINDA HUSKISSON

Fluid physiology	233	Blood and blood products	243
Maintenance crystalloid requirements	234	Conclusion	245
Colloids	238	References	246

This chapter aims to cover the basics of fluid balance. It is loosely divided into four sections. The first outlines fluid physiology. The use of crystalloid maintenance fluids is dealt with in the second. The third section deals with colloids and touches on the crystalloid:colloid debate for volume replacement. The final part covers the use of blood and its components in paediatric anaesthesia.

Body water is conventionally divided into three compartments: intracellular, extracellular and transcellular. In adults 60% of water is intracellular, 10% transcellular and 30% extracellular, of which 7.5% is intravascular. Although it is well recognized that disease states may affect the distribution of water in the body, it is less well known that age will also influence it. Extracellular water decreases from 60% in a 20-week fetus to 45% at term and falls a further 5% in the first 5 days of life.¹ Adult levels are reached by the end of the second year of life.

FLUID PHYSIOLOGY

THE STARLING EQUATION

TOTAL BODY WATER AND FLUID BALANCE

Total body water varies with degree of adiposity (90% of muscle weight is water vs 10% of fat), disease state and age. Ninety-four per cent of the body weight of a 12-week fetus is water and this falls to 80% by 32 weeks' gestation and 78% by term. There is a further reduction of about 5% in the first week of life, followed by a gradual fall to adult levels of 50–60% by 18 months of age.¹

The extracellular compartment is further subdivided into the interstitial and intravascular spaces, with the interstitial space being three and a half times larger than the intravascular.² Fluid flux between the two was first described by Starling, who noted that the rate of fluid movement into or out of a capillary was related to the net hydrostatic pressure minus the net osmotic pressure.³ The Starling equation:⁴

$$J_v = K_{fc}[(P_c - P_t) - \delta_c(\pi_c - \pi_t)],$$

where J_v = rate of fluid movement into/out of

capillary: K_{fc} = capillary filtration coefficient; P_c = capillary hydrostatic pressure; P_t = tissue fluid hydrostatic pressure; δ_c = reflection coefficient; π_c = capillary colloid osmotic pressure; π_t = tissue colloid osmotic pressure. has been further modified to incorporate coefficients which represent the permeability of the capillary membrane to small solutes (K_{fc}) and the reflection coefficient which describes the membrane's ability to prevent large molecules such as plasma proteins from crossing it: the Starling coefficient (sc).⁵ If sc is 1, then a fluid can realize its full osmotic pressure: if sc for a membrane is 0 then fluids will pass freely across it and no pressure will be exerted. The coefficients vary between different organs of the body and are altered by disease. Burns, sepsis and cardiopulmonary bypass, in particular, reduce sc, resulting in capillaries which are increasingly 'leaky'. This has two effects: it allows water to leak out causing tissue oedema and it allows osmotically active particles to escape into the interstitial space. If sc then increases again, these particles will remain in the interstitial space, increasing its osmotic pressure and altering the balance of the Starling equation until they can be removed by the lymphatic system.

Most of the components of the Starling equation can be measured only with difficulty in the laboratory but the intravascular osmotic pressure and the capillary hydrostatic pressure can be measured clinically.^{6,7} Guyton *et al.* describe certain 'oedema protection factors', such as increased lymphatic flow, which prevent the accumulation of oedema until the capillary hydrostatic pressure has increased by more than 15 mmHg.⁸ This is supported clinically by the observation that in the absence of pulmonary capillary damage, the left atrial pressure (equivalent to hydrostatic pressure) must be increased to 15–20 mmHg before pulmonary oedema is seen.

One of the main differences between the fluid balance of adults and infants is the relatively large water turnover in the infant. The water contained within the extracellular space of a 70 kg man is about 14 l. Just under 3 l day⁻¹ is lost in urine, faeces, sweat and during respiration (20%). In a 7 kg infant, the extracellular space contains about 1.6 l and obligatory losses are around 0.7 l day⁻¹ (44%).² Any relatively

small increase in losses will therefore have a much greater effect on a small child and this explains why diarrhoea remains such an important cause of infant mortality world-wide.

MAINTENANCE CRYSTALLOID REQUIREMENTS

MAINTENANCE WATER REQUIREMENTS

Although there are numerous formulae for calculating maintenance fluid requirements, it is important to stress that these are all guidelines only. They may be used as a starting point but the individual child's response to the fluid given must be monitored and appropriate adjustments made to the regimen.

The formulae available for calculating fluid requirement have as their basis body surface area (BSA), caloric requirement and the weight of the child.

Body surface area

Various nomograms are published which calculate BSA from height and weight. In older children the calculation of BSA is relatively easy and accurate because it is possible to obtain an accurate height. Measurements of the length of a neonate or small infant are not as reliable and errors of up to 20% in BSA are well recognized in babies less than 3 kg.⁹ Because the height-length measurement is inaccurate, most centres now use a formula based on weight alone to calculate fluid requirement and the use of BSA has fallen from favour.¹⁰

Calorie requirements

The metabolism of 1 calorie requires 1 ml of water because, although 0.2 ml of water is produced, a further 1.2 ml is consumed. Therefore, 100 calories will require 100 ml of water for metabolism and knowing the calorie requirement of a child will also reveal the water requirement.¹¹ In 1911 Howland calculated the calorie requirement of an infant from 3–10 kg

to be 100 cal kg^{-1} , with older children needing 75 and adults 35 cal kg^{-1} . The extra calories metabolized by the younger children are attributed to proportionally larger surface area and growth.¹² In infants of less than 10 kg body weight, 50 cal kg^{-1} will be needed for basal metabolic requirements and the rest for growth. Children of less than 20 kg body weight need 1000 calories for the first 10 kg but only 50 cal kg^{-1} for the next 10 kg because of slower growth rate, and larger children and adults need only three times the calories of a neonate (1500 calories for the first 20 kg and 20 cal kg^{-1} thereafter).¹¹

Normal maintenance fluid requirements calculated by weight

Whatever mechanism is used to calculate fluid requirements, it must be simple and foolproof because small miscalculations can result in significant errors in fluids administered. It has already been said that 100 calories requires 100 ml of water. A 25 kg child, therefore, requires 100 ml kg^{-1} for the first 10 kg (1000 ml), 50 ml kg^{-1} for the next 10 kg (500 ml) and 20 ml kg^{-1} thereafter (100 ml), making a total of 1600 ml per day or 66 ml h^{-1} . This can be simplified by assuming that there are 24 h in a day. The child then needs $4 \text{ ml kg}^{-1} \text{ h}^{-1}$ for the first 10 kg (40 ml), $2 \text{ ml kg}^{-1} \text{ h}^{-1}$ for the next 10 kg (20 ml) and $1 \text{ ml kg}^{-1} \text{ h}^{-1}$ thereafter (5 ml), giving an hourly total of 65 ml, which can be computed at the bedside without a calculator.

Neonates have greater fluid requirements than infants. As a general rule, most neonatal units allow 60 ml kg^{-1} for the first day, increasing by $30 \text{ ml kg}^{-1} \text{ day}^{-1}$ to 150 ml kg^{-1} for a term neonate and $180 \text{ ml kg}^{-1} \text{ day}^{-1}$ for a preterm. This requirement will be affected by

environment (overhead heaters increase water loss compared with incubators); by whether the baby is ventilated (when there will be a humidifier in the circuit) and by the general state of the neonate. A premature baby with a patent ductus arteriosus may close the duct in response to fluid restriction and this may avoid the need for more aggressive management.

Dextrose requirements

In the UK, intravenous dextrose infusions are usually supplied as 4%, 5%, 10% and 20% strengths. In addition, 50% dextrose is available for management of hypoglycaemia. Most infants and children require 4% or 5% dextrose. A recent study from Germany, however, suggests that when these infusions are given peroperatively, children may become hyperglycaemic with dextrose concentrations as low as 2.5% although these were administered at large volumes equivalent to $200 \text{ ml kg}^{-1} \text{ day}^{-1}$.¹³ Neonates have poor glycogen stores and require higher glucose infusions to maintain their blood glucose levels. The majority of neonates, therefore, are traditionally managed using infusions of 10% dextrose which can be given through a peripheral cannula. Sick neonates on the intensive care unit, particularly in the presence of sepsis, may require higher infusions than this. Such patients may also need fluid restriction and it is not uncommon for small septic babies to need 20% infusions of dextrose. A neonate who cannot be fed enterally for more than a couple of days will require parenteral hyperalimentation rather than simple dextrose saline solutions. Hyperglycaemia can develop in response to stress. Both hypoglycaemia and hyperglycaemia can occur and blood sugar levels should be regularly monitored.

Electrolyte requirements

Electrolyte requirements vary with prematurity, losses and disease states. There is some debate as to whether a neonate needs sodium on the first day of life. Some units use a dextrose solution without added electrolytes, whilst others add sodium, potassium and calcium, particularly for premature infants. Preterm breast milk contains higher concentrations of sodium, calcium and phosphorus for the first 2–

Table 8.1 Normal maintenance fluid requirements

Weight (kg)	Maintenance fluid requirement (cumulative values) ($\text{ml kg}^{-1} \text{ day}^{-1}$)
< 10	100
11–20	50
> 20	20

4 weeks of lactation, and meets the preterm infant's increased requirements for these elements. Preterm formulae with similar electrolyte composition are also available. As a guide for prescribing, most children require 2–3 mmol kg⁻¹ of sodium and 2 mmol kg⁻¹ of potassium. This means that a 10 kg infant who needs 1000 ml of fluid per day will also need around 30 mmol of sodium. In the UK, fluids are available as dextrose (4% or 10%) and 0.18% saline (i.e. containing 30 mmol l⁻¹). For most patients, a ready-made bag of fluid will provide their electrolyte needs. In some instances, additional sodium will be required. This can be added to a standard bag using a strong sodium (30%: 5000 mmol l⁻¹) solution, or Normal saline (0.9%: 150 mmol l⁻¹) or half Normal saline (0.45%: 75 mmol l⁻¹) can be used in its place.

The amount of sodium administered to neonates in the immediate postoperative period needs to be monitored. Krummel *et al.* studied 20 surgical newborns and found that hypernatraemia occurred in 64% of term babies and 67% of preterms. In all cases this appeared to be due predominantly to an administered sodium load of more than 400% of the estimated maintenance requirements. This was compounded by a slightly reduced ability to excrete sodium and a short period of post-operative sodium retention.¹⁴

SPECIAL REQUIREMENTS

Gastrointestinal losses

Gastrointestinal surgery is relatively common in small infants. Ileus may also occur in a sick child; therefore, gastrointestinal losses are of importance. Nasogastric aspirates should be replaced volume for volume with normal saline containing 10 mmol potassium chloride per 500 ml. This sodium load allows the patient's kidneys to correct the hydrogen deficit incurred by the loss of gastric secretions. Stoma losses may also need to be replaced. High stomas in particular may be associated with significant sodium losses leading to as much a 6-fold increase in sodium requirements. Losses of more than 40 ml kg⁻¹ day⁻¹ are likely to require parenteral replacement using the same solution of normal saline with 10 mmol potass-

ium per 500 ml. Usually, 0.5 ml is replaced for every 1 ml lost but, depending on the volume of losses and the site of the stoma, anything from one-third to three-quarter replacement may be required. Children who have ileus, either from gastrointestinal surgery and pathology or secondary to another cause, can secrete large amounts of fluid within the gut and peritoneal cavity. Babies with abdominal distension due to Hirschsprung's disease (colonic aganglionosis) may be intravascularly depleted in the presence of steady weight or even weight gain and such patients may need intravascular volume replacement despite normal indices.

Pyloric stenosis

Hypertrophic pyloric stenosis is a common condition with an incidence of about 1 : 200. All babies with this condition vomit and will require preoperative intravenous fluids. About 50% of patients will have a significant derangement of their electrolytes and acid: base status as a result of vomiting. The most useful electrolyte to gauge the seriousness of the metabolic upset is chloride, which can be used to calculate the chloride deficit and this must often be specifically requested as it is no longer performed routinely in most hospitals. While the serum chloride remains low, the infant will be alkalotic.¹⁵ The vomiting of HCl, together with the kidney's attempts to conserve sodium, results in a metabolic alkalosis and a depletion of total body potassium. Because potassium is an intracellular ion, the serum potassium is a poor guide to potassium requirements and will usually be within the normal range.

To correct the metabolic alkalosis, the infant must be given sufficient sodium and potassium so that the kidneys can conserve hydrogen ions and correct the acid: base status. Chloride is also given as the anion to both sodium and potassium. Most babies with mild derangement (sodium bicarbonate < 35 mmol) will be corrected within 24 h using a solution of 5% dextrose plus 0.45% saline with 15 mmol of potassium chloride per 500 ml bag at 150–180 ml kg⁻¹ day⁻¹. In extreme cases, normal saline (or 4.5% albumin which contains 150 mmol NaCl l⁻¹) may be required and 2–3 days of parenteral fluids may be needed preoperatively. It is also important to remember

that any gastric distension results in more gastric juices being secreted and lost. A wide-bore nasogastric tube should be left on free drainage with regular aspirations and any nasogastric losses should be replaced millilitre for millilitre with normal saline with added potassium (10 mmol in 500 ml).

Posterior urethral valves

Posterior urethral valves cause a congenital obstruction of the male posterior urethra and affected infants may also have a degree of renal dysplasia. Nowadays, the condition is increasingly diagnosed antenatally and most other children present within the first month of life. The initial management of a neonate with valves is to catheterize the patient and then confirm the diagnosis by cystogram and/or cystoscopy. Surgery consists of valve ablation via the cystoscope. A significant number of these children will have renal impairment which may be long-term, and almost all have a diuresis in response to catheterization and relief of the obstruction. Urine output must be closely monitored in these patients and their fluid intake will be based on their creatinine and their output. Most of these babies are well enough to receive oral feeds but will also require parenteral supplementary fluids to keep up with urinary losses. This diuretic phase can last for between 24 h and a couple of weeks, again emphasizing that strict criteria cannot be laid down for neonatal fluid infusions.

Congenital diaphragmatic hernia

The fluid handling of a neonate with congenital diaphragmatic hernia merits special mention. There appears to be only a narrow path between hypovolaemia and fluid overload, either of which may have catastrophic effects resulting in a worsening spiral of acidosis and hypoxia. *Olve et al.* studied the urine output and osmolality of both urine and serum in 22 infants with diaphragmatic hernia vs 12 control infants undergoing laparotomy for some other reason. They found that although all controls responded appropriately, 64% of the diaphragmatic hernia group inappropriately retained fluid in the first 16 h after surgery and one-third still had an inappropriate urine output

24 h after surgery.¹⁶ Fluid management of these children involves strict crystalloid restrictions ($30 \text{ ml kg}^{-1} \text{ day}^{-1}$ for the first 24 h) and colloid boluses to maintain normovolaemia. Close monitoring of urine output and serum and urine osmolality will help in the management.

Phototherapy

Neonatal 'physiological' jaundice is relatively common and is worsened by dehydration. Some neonates with a rising unconjugated hyperbilirubinaemia can be managed simply by liberalizing their fluids. This may need to be via a nasogastric tube or parenterally as the jaundice tends to make the baby sleepy and therefore less able to feed, which compounds the problem. If phototherapy is required, environmental water loss is increased significantly and an extra $25 \text{ ml kg}^{-1} \text{ day}^{-1}$ should be added to the fluids to compensate.

Effects of surgery

In 1968 Reid showed in adult patients that fluid accumulation occurred in the early postoperative phase and that this occurred entirely within the extravascular space. There was no change in the intravascular volume even when large fluid increases were seen extravascularly.¹⁷ Seven years earlier, *Shires et al.* had studied fluid shifts preoperatively and noted an acute contraction of the functional extracellular fluid which, in the absence of blood loss, they presumed to be due to internal redistribution. They noted that the magnitude of the internal redistribution was related to the degree of surgical trauma and particularly to the duration and degree of retraction. They concluded that this was a major stimulus to the fluid and sodium retention seen postoperatively.¹⁸ Certainly, after major abdominal surgery there is a fall in the serum sodium and evidence of fluid retention with periorbital and dependent oedema, which can be reduced by restricting fluids for the first 24-48 h following surgery. Following minor procedures patients are allowed their full maintenance fluids, but after any major surgery their intake is reduced to 50% of requirements for the first postoperative day, and if additional fluid is required it may be better to be given as colloid.

Sepsis

Hyponatraemia in sepsis is well recognized and is associated with a worse prognosis. Hannon and Boston looked at fluid and ion redistribution in an animal model of sepsis and found significant shifts of sodium, chloride and water into cells compared with sham controls.¹⁹ They found this trend to be exacerbated by infusing 5% dextrose compared with normal saline with fluid shifts occurring when the volume infused was less than the estimated fluid requirement. They suggested that the hyponatraemia and plasma hypo-osmolality were caused by a combination of intracellular shift of sodium and water, and a dilution of the extracellular space, probably caused by physiological antidiuretic hormone (ADH) secretion. Their conclusion was that, in the presence of sepsis, 4% dextrose + 0.18% sodium chloride is inappropriate, potentially dangerous and should be avoided.

Burns (see also Chapter 15)

Significant burns cause large fluid losses and burns patients require large volumes of fluid resuscitation. In addition to normal maintenance fluids, such patients need resuscitation fluid administered as Normal saline, Ringer's solution or Gelofusine[®] given over at least the first 36 h after injury. The 36 h are divided into six periods: three of 4 h, two of 6 h and one of 12 h. The timing starts from the moment of injury so that the first infusion is inevitably delayed. During each period the child needs an average of 0.5 ml kg^{-1} per % burn. The precise volume given is adjusted on the basis of urine output, urine and plasma osmolality, perfusion and the calculated plasma deficit. This can be calculated from the formula:

$$\begin{aligned} \text{plasma deficit} &= \text{blood volume} \\ &- \left(\text{blood volume} \right. \\ &\quad \times \left. \frac{\text{normal haematocrit}}{\text{observed haematocrit}} \right) \end{aligned}$$

Deep burns result in red cell destruction and the usual blood requirement is of 1% of normal blood volume per 1% burn for deep burns of more than 10% surface area. Because the

haematocrit is a useful guide to the plasma deficit, blood is usually best administered during the last 12 h of fluid resuscitation.²⁰

Clinical assessment of dehydration

Although thirst appears with the loss of approximately 2% of total body water, the state of the peripheral circulation is the most sensitive guide to more serious levels of clinical dehydration in children. Core-peripheral temperature difference becomes clinically detectable and mucous membranes dry at around 5% loss of total body water. With 10% dehydration the peripheries are cold and capillary refill, normally complete within 2 s, is delayed. Pulse and respiratory rates increase, consciousness may be clouded, and in the neonate the fontanelle is sunken. Blood pressure may fall, although because of the increased cardiac output caused by the tachycardia this is not an early or reliable sign. Urine output is decreased. At 15% dehydration capillary refill may be incomplete even after 10 s, the mouth is parched and the eyes are sunken. The pulse is rapid and thready and blood pressure low. The child is stuporose and oliguric, and may show signs of respiratory distress. Losses in excess of 20% may be fatal.

COLLOIDS

THE CRYSTALLOID VERSUS COLLOID DEBATE

The superiority of colloid over crystalloid for volume replacement remains controversial.^{21,22} Whilst crystalloids are generally more popular in the USA, colloids are preferred in Europe.²³ The debate centres on which fluid space needs replenishing and the importance or otherwise of colloid osmotic pressure.

Colloids theoretically remain within the intravascular space, therefore expanding the intravascular volume more efficiently, producing the same increase in cardiac output for a smaller volume of fluid. The proponents of crystalloid argue that the whole extracellular fluid space is reduced in hypovolaemia because of fluid movement from the interstitial compart-

undergone a circulating volume transfusion of red cells. In babies and infants, a transfusion of $5-10 \text{ ml kg}^{-1}$ is usually sufficient, whilst unit transfusions are appropriate in older patients.

FRESH-FROZEN PLASMA AND CRYOPRECIPITATE

FFP contains 1 unit of factor activity per millilitre of plasma. A decision to use FFP or cryoprecipitate should be based on a combination of clinical and laboratory findings. An INT of less than 1.4 or a partial thromboplastin time of less than 60 s is unlikely to cause significant bleeding problems and correction is not required. Laboratory values greater than these levels or significant bleeding will require correction. An empiric dose of $5-10 \text{ ml kg}^{-1}$ is usually adequate or the dose can be calculated by body weight, plasma volume and desired increment of clotting factors.

Cryoprecipitate is a poor source of factors II, V, IX, X, XI and XII but contains factors VIII, C, VIII-WF, XIII, fibrinogen and fibronectin. Indications for its use include haemophilia A, von Willebrand disease, fibrinogen deficiency, massive transfusion and anaemic platelet dysfunction. Its advantage over FFP is that it is concentrated and one bag (of 15–20 ml) is the dose per 10 kg body weight.

SPECIAL SITUATIONS

Jehovah's witnesses

The Royal College of Surgeons of England have produced a code of practice for the surgical management of Jehovah's Witnesses. This acknowledges that the children of Jehovah's Witnesses requiring blood transfusion present a most difficult management problem.⁸⁴ There are some mitigating factors, however. Either parent may sign a consent form permitting a transfusion. Most operations on children do not require or involve blood transfusion, but it is unethical to let a child die for want of a blood transfusion. The surgeon and anaesthetist must, however, respect the beliefs of the family and should make every effort to avoid the perioperative use of blood or blood products. For

children under 13 years of age who require or may require a transfusion but whose parents refuse to give consent, legal advice should be sought. Such children will normally be made a temporary ward of court. This subject is covered more fully in Chapter 2.

Sickle cell disease

Traditionally, patients with sickle cell disease have been routinely transfused before elective surgery. There has, however, been little consensus as to whether simple correction of the anaemia is sufficient or whether the level of HbS should be reduced to less than 30%. Vichinsky *et al.* compared a conservative regimen (transfusing to a haemoglobin level of around 10 g dl^{-1}) with an aggressive regimen (haemoglobin of around 10 g dl^{-1} and an HbS level of less than 30%). They found the conservative regimen to be as effective in preventing perioperative complications and this group had half as many transfusion-associated complications.⁸⁵ Similarly, immediately preoperative transfusion to a haematocrit of more than 36% was as efficacious as two-volume exchanges beginning 2 weeks prior to surgery, with less disruption to the family.⁸⁶ Patients with HbSS disease should receive transfusions to correct their anaemia. They should be given adequate perioperative hydration with crystalloid. Post-operatively, they should receive adequate analgesia in addition to oxygen and physiotherapy to prevent atelectasis. For more information, see Chapter 1.

CONCLUSION

Fluid management in paediatrics is an art as well as a science: clinicians need to monitor the response to therapy and change the regimen appropriately. This chapter contains guidelines and suggestions for safe fluid administration but cannot replace clinical experience.

REFERENCES

- 1 Rowe, M.I. A dynamic approach to fluid and electrolyte management of the newborn. *Zeitschrift für Kinderchirurgie* 1985; **40**: 270-7.
- 2 Lippold, O.C.J. and Winton, F.R. The distribution of body fluids. In: Lippold, O.C.J. and Winton, F.R. (eds). *Human Physiology*. Edinburgh: Churchill Livingstone, 1979: 118-21.
- 3 Starling, E.H. On the absorption of fluids from the connective tissue spaces. *Journal of Physiology* 1896; **19**: 312-26.
- 4 Bush, G.H. Intravenous fluid therapy in paediatrics. *Annals RCS* 1971; **49**: 92-101.
- 5 Bevan, D.R. Colloid osmotic pressure. *Anaesthesia* 1980; **35**: 263-70.
- 6 Morissette, M.P. Colloid osmotic pressure: its measurement and clinical value. *Canadian Medical Association Journal* 1977; **116**: 897-900.
- 7 Barclay, S.A. Colloid osmotic pressure: its measurement and role in clinical cardiovascular medicine. PhD Thesis. University of London, 1986.
- 8 Guyton, A.C., Granger, H.J. and Taylor, A.E. Interstitial fluid pressure. *Physiology Review* 1971; **51**: 527-63.
- 9 Boyd, E. *Growth of Surface Area of the Human Body*. Institute of Child Welfare, Monograph Series 10. Minneapolis, MN: University of Minnesota Press, 1935.
- 10 Oliver, W.L., Graham, B.D. and Wilson, J.L. Lack of scientific validity of body surface as a basis for parenteral fluid dosage. *Journal of the American Medical Association* 1958; **167**: 1211-18.
- 11 Siker, D. Pediatric fluids and electrolytes. In: Gregory, G.A. (ed.). *Pediatric Anaesthesia*. 2nd edn. New York: Churchill Livingstone, 1989: 581-617.
- 12 Howland, J. The fundamental requirements of an infant's nutrition. *American Journal of Diseases of Childhood* 1911; **2**: 49.
- 13 Fosel, T.H., Uth M., Wilhelm W., Gruness Z. Comparison of two solutions with different glucose concentrations for infusion therapy during laparotomies in infants. *Infusionstherapie und Transfusionsmedizin* 1996; **23**: 80-4.
- 14 Krummel, T.M., Lloyd, D.A. and Rowe, M.I. The postoperative response of the term and preterm newborn infant to sodium administration. *Journal of Pediatric Surgery* 1985; **20**: 803-9.
- 15 Gon, D.W., Hall, S.K., Gomall, P., Buick, R.G., Green, A. and Corkery, J.J. Plasma chloride and alkalaemia in pyloric stenosis. *British Journal of Surgery* 1990; **77**: 922-3.
- 16 Rowe, M.I., Smith, S.D. and Cheu, H. Inappropriate fluid response in congenital diaphragmatic hernia: first report of a frequent occurrence. *Journal of Pediatric Surgery* 1988; **23**: 1147-53.
- 17 Reid, D.J. Intracellular and extracellular fluid volume during surgery. *British Journal of Surgery* 1968; **55**: 594-6.
- 18 Shires, T., Williams, J. and Brown, F. Acute changes in extracellular fluids associated with major surgical procedures. *Annals of Surgery* 1961; **154**: 803-10.
- 19 Hannon, R.J. and Boston, V.E. Hyponatraemia and intracellular water in sepsis: an experimental comparison of the effect of fluid replacement with either 0.9% Normal saline or 5% dextrose. *Journal of Pediatric Surgery* 1990; **25**: 422-5.
- 20 Muir, I.F.K. and Barclay, T.L. Treatment of burn shock. In: *Burns and Their Treatment*. London: Lloyd-Luke, 1962.
- 21 Laks, H., O'Connor, N.E., Anderson, W., et al. Crystalloid versus colloid hemodilution in man. *Surgery, Gynecology and Obstetrics* 1970; **142**: 506-12.
- 22 Poole, G.A., Meredith, J.W., Pennell, T., et al. Comparisons of colloids and crystalloids in resuscitation from hemorrhagic shock. *Surgery, Gynecology and Obstetrics* 1982; **154**: 577-86.
- 23 Shoemaker, W.C. Hemodynamic and oxygen transport effects of crystalloids and colloids in critically ill patients. *Current Studies in Hematology and Blood Transfusion* 1986; **53**: 175-76.
- 24 Ross, A.D. and Angaran, D.M. Colloids versus crystalloids - a continuing controversy. *Drug Intelligence and Clinical Pharmacology* 1986; **18**: 202-12.
- 25 Hunt, T.K., Rabkin, E. and von Smitten, K. Effects of edema and anemia on wound healing and infection. *Current Studies in Hematology and Blood Transfusion* 1986; **53**: 107-11.
- 26 Chan, S.T.F., Kapadia, C.R., Johnson, A.W., et al. Extracellular fluid volume expansion and third space sequestration at the site of small bowel anastomoses. *British Journal of Surgery* 1983; **70**: 36-9.
- 27 Folk, J.L., Rackow, E.C., Aziz, M., et al. Fluid resuscitation in shock. *Journal of Cardiothoracic Anesthesia* 1988; **2** Suppl: 33-8.
- 28 Weil, M.H., Henning, R.J., Morissette, M.P., et al. Relationship between colloid osmotic pressure and pulmonary artery wedge pressure in patients with acute cardiorespiratory failure. *American Journal of Medicine* 1978; **64**: 643-50.
- 29 Virgilio, R.W., Rice, C.L., Smith, D.E., et al. Crystalloid versus colloid resuscitation: is one better? A randomized clinical study. *Surgery* 1979; **85**: 129-39.
- 30 Velanovich, V. Crystalloid versus colloid fluid resuscitation: a meta-analysis of mortality. *Surgery* 1989; **105**: 65-71.
- 31 Huskisson, L.J. Intravenous volume replacement - which fluid and why. *Archives of Disease in Childhood* 1992; **67**: 649-53.
- 32 Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. *British Medical Journal* 1998; **317**: 235-40.
- 33 APLS. Advanced Life Support Group. London: BMA Publishing 1997.
- 34 Ryan, C.A. and Soder, C.M. Relationship between core, peripheral temperature gradient and central hemodynamics in children after open heart surgery. *Critical Care Medicine* 1989; **17**: 638-40.
- 35 de Felipe, J., Timoner, J., Velasco, I.T., et al. Treatment of refractory hypovolaemic shock by 7.5% sodium chloride injections. *Lancet* 1980; **ii**: 1002-4.
- 36 Vincent, J.-L. Fluids for resuscitation. *British Journal of Anaesthesia* 1991; **67**: 185-93.
- 37 Wilkins, B.H. Renal function in sick very low birthweight infants: 3. Sodium, potassium and water excretion. *Archives of Disease in Childhood* 1992; **67**: 1154-61.

- 38 National Institute of Health Consensus Conference. Fresh frozen plasma. Indications and risks. *Journal of the American Medical Association* 1985; **253**: 551-3.
- 39 Messmer, K. Chapter 2. In: Lowe, K.C. (ed.). *Blood Substitutes, Preparation, Physiology and Medical Application*. Hemel Hempstead: Ellis Horwood Series in Biomedicine, 1988.
- 40 Ring, J. Anaphylactoid reactions to plasma substitutes. *International Anesthesiology Clinics* 1985; **23**: 67-95.
- 41 Quon, C.Y. Clinical pharmacokinetics and pharmacodynamics of colloidal plasma volume expanders. *Journal of Cardiothoracic Anesthesia* 1988; **2**: 13-23.
- 42 McClelland, D.B.L. Human albumin solutions. *British Medical Journal* 1990; **300**: 35-7.
- 43 Lewis, R.T. Albumin: role and discriminative use in surgery. *Canadian Journal of Surgery* 1980; **23**: 322-8.
- 44 Saddler, J.M. and Horsey, P.J. The new generation gelatins. *Anaesthesia* 1987; **42**: 998-1004.
- 45 Webb, A.R., Barclay, S.A. and Bennett, E.D. *In vitro* colloid osmotic pressure of commonly used plasma expanders and substitutes: a study of the diffusibility of colloid molecules. *Intensive Care Medicine* 1989; **15**: 116-20.
- 46 Edwards, M.P., Clark, D.J., Mark, L.S. *et al.* Compound sodium lactate (Hartmann's solution). Caution: risk of clotting. *Anaesthesia* 1986; **41**: 1053-4.
- 47 Hulse, J.D. and Yacobi, A. Hetastarch: an overview of the colloid and its metabolism. *Drug Intelligence and Clinical Pharmacology* 1983; **17**: 134-41.
- 48 Mishler, I.M. Synthetic plasma volume expanders - their pharmacology, safety and clinical efficacy. *Clinics in Hematology* 1984; **13**: 75-92.
- 49 Klotz, U. and Kroemer, H. Clinical pharmacological considerations in the use of plasma expanders. *Clinical pharmacokinetics* 1987; **12**: 123-35.
- 50 Waxman, K., Holmes, R., Tennant, G. *et al.* Hemodynamics and oxygen transport effects of pentastarch in burn resuscitation. *Annals of Surgery* 1989; **209**: 341-5.
- 51 Thompson, W., Fukushima, T. and Rutherford, R.B. Intravascular persistence, tissue storage and excretion of hydroxyethyl starch. *Surgery, Gynecology and Obstetrics* 1970; **131**: 663-72.
- 52 Lawrence, D.A. and Scheil, R.E. Influence of hydroxyethyl starch on humoral and cell-mediated immune response in mice. *Transfusion* 1985; **25**: 213-9.
- 53 Ring, J. and Messmer, K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. *Lancet* 1977; **i**: 466-9.
- 54 Adeimann-Grill, B. and Schoning, B. Lack of evidence for immunological reactions to gelatin. *Developmental Biological Standards* 1981; **48**: 237-40.
- 55 Watkins, J., Wild, G., Appleyard, T.N. *et al.* Complement activation by polystarch and gelatin volume expanders. *Lancet* 1990; **335**: 213.
- 56 Lorenz, W., Duda, D., Dick, W. *et al.* Incidence and clinical importance of perioperative histamine release: randomised study of omne-100 and antihistamines after induction of anaesthesia. *Lancet* 1994; **343**: 933-40.
- 57 Watkins, J. Allergic and pseudo-allergic reactions to colloid plasma substitutes: which colloid? *Care of the Critically Ill* 1991; **7**: 213-17.
- 58 Johnson, S.D., Lucas, C.E., Gerrick, S.J. *et al.* Altered coagulation after albumin supplements for treatment of oligoemic shock. *Archives of Surgery* 1979; **114**: 379-83.
- 59 Tullis, J.L. Albumin 1. Background and use. *Journal of the American Medical Association* 1977; **237**: 355-9.
- 60 Strauss, R.G. Volume replacement and coagulation: a comparative review. *Journal of Cardiothoracic Anesthesia* 1988; **2**: 24-32.
- 61 Macintyre, E., Mackie, I.J., Ho, D. *et al.* The haemostatic effects of hydroxyethyl starch used as a volume expander. *Intensive Care Medicine* 1985; **11**: 300-3.
- 62 Diehl, J.T., Lester, J.L. III and Cosgrove, D.M. Clinical comparison of hetastarch and albumin in postoperative cardiac patients. *Annals of Thoracic Surgery* 1982; **34**: 674-9.
- 63 Falk, J.L., Rackow, E.C., Astiz, M. *et al.* Effects of hetastarch and albumin on coagulation in patients with septic shock. *Journal of Clinical Pharmacology* 1988; **28**: 412-15.
- 64 Cully, M.C., Larson, C.P. and Silverberg, G.D. Hetastarch coagulopathy in a neurosurgical patient. *Anesthesiology* 1987; **66**: 706-7.
- 65 Lockwood, D.N.J., Bullen, C. and Machin, S.I. A severe coagulopathy following volume replacement with hydroxyethyl starch in a Jehovah's Witness. *Anaesthesia* 1988; **43**: 391-3.
- 66 Stump, D.C., Strauss, R.G. and Henriksen, R.A. Effects of hydroxyethyl starch on blood coagulation, particularly Factor VIII. *Transfusion* 1985; **25**: 349-54.
- 67 Alexander, B., Odake, K., Lawlor, D. *et al.* Coagulation, hemostasis and plasma expanders: a quarter century enigma. *Federation Proceedings* 1975; **34**: 1429-40.
- 68 Fujii, K., Kaneko, K., Iwahori, Y. *et al.* The influence of Gelofusine on the blood coagulating function. *Japanese Gelofusine Symposium* 1967.
- 69 Haskisson, L.I. Evaluation of synthetic colloids in paediatric surgical practice. MS Thesis, 1994. University of London.
- 70 Mercante, W., Papadopoulos, A., Tufaro, R. *et al.* A clinical physiologic study of hydroxyethyl starch. *Surgery, Gynecology and Obstetrics* 1970; **131**: 255-67.
- 71 Killian, L., Spiker, D. and Borst, R. The effect of 6% HES, 4.5% Dextran and 5.5% Oxygel Gel on blood volume and circulation in human volunteers. *Anaesthesist* 1975; **24**: 193-7.
- 72 Lamke, L.-O. and Liljedahl, S.-O. Plasma volume changes after infusion of various plasma expanders. *Resuscitation* 1976; **5**: 93-102.
- 73 Lazrove, S., Waxman, K., Shippy, C. *et al.* Hemodynamic, blood volume and oxygen transport responses to albumin and HES infusions in critically ill postoperative patients. *Critical Care Medicine* 1980; **8**: 302-6.
- 74 Edwards, J.D., Nightingale, P., Wilkins, R.G. *et al.* Hemodynamic and oxygen transport response to modified fluid gelatin in critically ill patients. *Critical Care Medicine* 1989; **17**: 996-8.
- 75 Sudhindran, S. Perioperative blood transfusion: a plea for guidelines. *Annals of the Royal College of Surgeons of England* 1997; **79**: 299-302.
- 76 Spence, R.S., Carson, J.A., Posos, R. *et al.* Elective surgery without transfusion: influence of preoperative hemoglobin level and blood loss on mortality. *American Journal of Surgery* 1990; **159**: 320-4.
- 77 James, L., Greenough, A. and Naik, S. The effect of blood transfusion on oxygenation in premature venti-

- lated neonates. *European Journal of Pediatrics* 1997; 156: 139-41.
- 78 Welch, H.G., Meehan, K.R. and Greenough, L.T. Prudent strategies for elective red blood cell transfusion. *Annals of Internal Medicine* 1992; 116: 393-402.
- 79 Contreras, M. and Chapman, C.E. Autologous transfusion and reducing allogenic blood exposure. *Archives of Disease in Childhood* 1994; 71: 105-7.
- 80 Jensen, L.S., Anderson, A.J., Christiansen, P.M., et al. Postoperative infection and natural killer cell function following blood transfusion in patients undergoing elective colorectal surgery. *British Journal of Surgery* 1992; 79: 513-16.
- 81 Nielsen, H.J. Detrimental effects of perioperative blood transfusion. *British Journal of Surgery* 1995; 82: 582-7.
- 82 Blumberg, N., Agarwal, M.M. and Chuang, C. Relation between recurrence of cancer of the colon and blood transfusion. *British Medical Journal* 1985; 290: 1037-9.
- 83 Kaplan, J., Sarnaik, S., Gitlin, J., et al. Diminished helper/suppressor lymphocyte ratios and natural killer activity in recipients of repeated blood transfusions. *Blood* 1984; 64: 305-10.
- 84 The Royal College of Surgeons of England. Code of practice for the surgical management of Jehovah's - Witnesses. 1996.
- 85 Vichinsky, E.P., Haberkern, C.M., Neuav, L., et al. A comparison of conservative and aggressive transfusion regimens in the perioperative management of sickle cell disease. *New England Journal of Medicine* 1995; 333: 206-13.
- 86 Janik, J. and Seeler, R.A. Perioperative management of children with sickle hemoglobinopathy. *Journal of Pediatric Surgery* 1980; 15: 117-20.

Editorial

Postoperative hyponatraemic encephalopathy following elective surgery in children

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Introduction

In the United States, there are an estimated 15 000 deaths per year as a consequence of postoperative hyponatraemia (1) (Figure 1). There have been a number of recent studies which have described postoperative hyponatraemic encephalopathy with death or permanent brain damage (2-6). From these studies, it appears that brain damage associated with postoperative hyponatraemic encephalopathy primarily affects menstruant women (1) and prepubertal children (6).

Postoperative hyponatraemic encephalopathy in prepubertal children

There are multiple reports of prepubertal children suffering brain damage from postoperative hyponatraemic encephalopathy (6-9). The aetiology of the hyponatraemia usually involves a combination of: a) intravenous hyponatraemic fluids; b) elevated plasma antidiuretic hormone (ADH); c) respiratory insufficiency secondary to hyponatraemic encephalopathy. It has been demonstrated in several series that plasma levels of ADH (vasopressin, antidiuretic hormone) are elevated in virtually every postoperative child (7,10-13). If such patients are given intravenous free water (any solution with a sodium concentration below 140 mmol L⁻¹), there will always be a tendency towards postoperative hyponatraemia (14). When compared with other groups, prepubertal children are far more susceptible to brain damage from hyponatraemia than are adults (6), and recent experimental evidence demonstrates why this may be the case.

Effects of hyponatraemia on the paediatric central nervous system

Nattie & Edwards (15) studied the effects of acute hyponatraemia on the brain of puppies. They found that acute lowering of plasma sodium from 140 to 120 mmol L⁻¹ resulted in severe hypoxaemia (arterial PO_2 fell from 11.4-6.9 kPa (88 to 53 mmHg)) and cerebral oedema. In contrast to adults, the brains of paediatric animals (three day old puppies and neonatal rats) were unable to adapt to hypo-osmotic stress by extrusion of cation (15,16).

Adaptation of the brain to hyponatraemia occurs as a consequence of the following sequence of events. First, hyponatraemia leads to a movement of water into brain cells as a result of osmotic forces. In addition, vasopressin which is usually elevated in the plasma of hyponatraemic patients (17) may lead to a direct movement of water into brain cells independent of the effects of hyponatraemia (18). The early response of the brain to this hyponatraemia-mediated oedema is the loss of blood and cerebrospinal fluid, followed by extrusion of sodium from brain cells by several pathways (19). Loss of potassium and possibly organic osmolytes follows later, in an attempt to decrease brain cell osmolality without a gain of water (20).

Effects of hormones and physical factors on brain adaptation to hyponatraemia

There is a significantly higher intracellular brain water content in prepubertal rats in comparison with adult rats, suggesting that the brain occupies a greater percent of the available intracranial volume in young rats (16). Such physical factors may be important determinants of outcome in hyponatraemic rats. As individuals age, there is a progressive decline in the volume of brain, while skull size remains constant in adult life (21). Thus, elderly individuals of both

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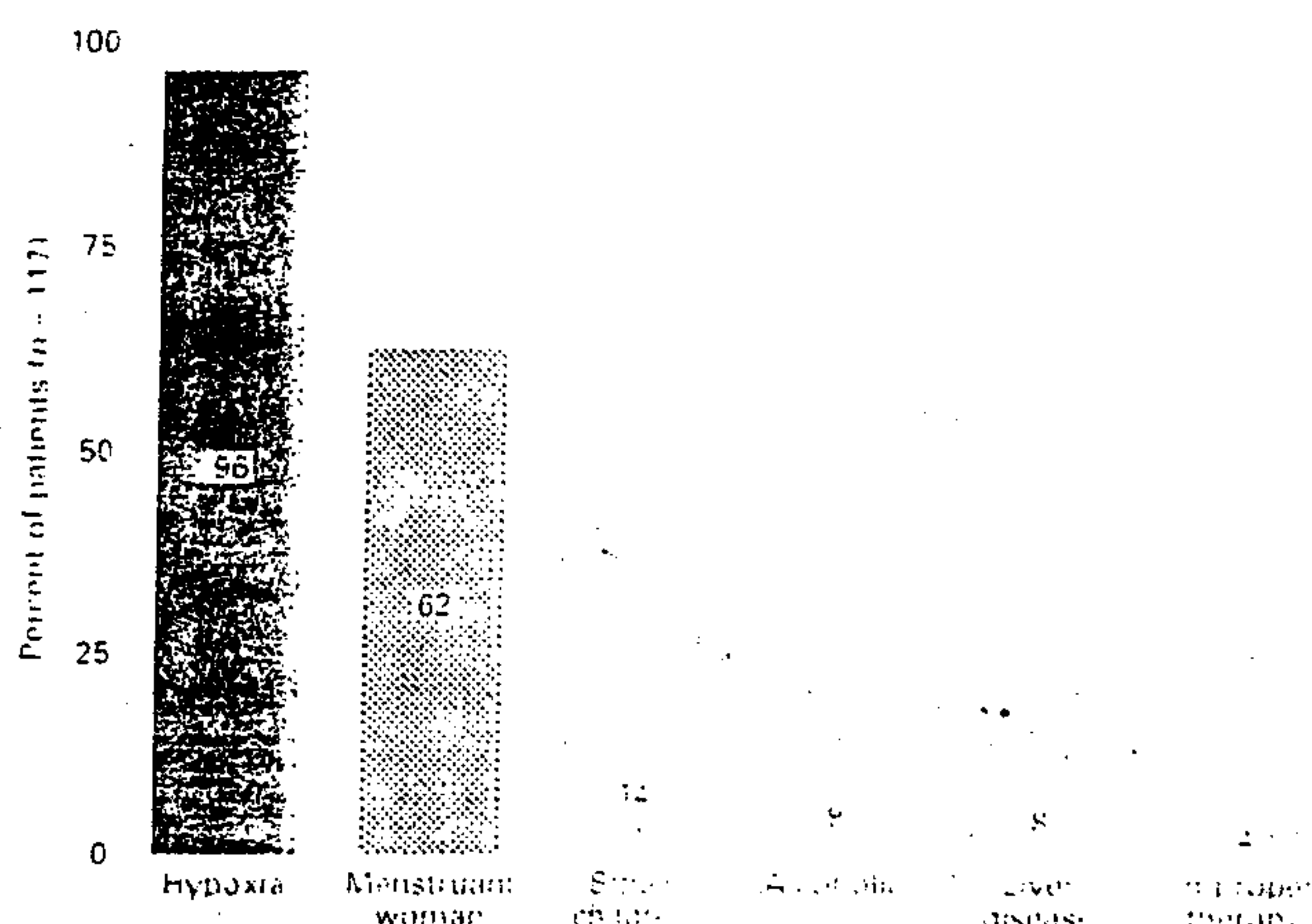


Figure 1

In nine published series from our laboratory comprising 847 hospitalized patients with postoperative hyponatraemia, 19% (158/847) developed hyponatraemic encephalopathy and 11% developed permanent brain damage or died. The major risk factors associated with permanent brain damage in these 11% patients with hyponatraemic encephalopathy are shown. Most patients (96%) suffered an hypoxic episode because of failure to initiate active therapy in a timely manner. In 4% of patients suffering permanent brain damage, improper therapy for hyponatraemia was implicated in the outcome.

genders have more room in the rigid skull for the brain to expand than do younger ones. This finding is more marked in males (21).

If adaptation of the brain is not adequate, pressure of the swollen brain on the rigid skull leads to a decrease in cerebral blood flow (22) and cerebrospinal fluid production (23). If the ability of the brain to adapt is impaired, there will be increasing oedema, with eventual tentorial herniation and secondary cerebral ischaemia (24). This often leads to respiratory insufficiency (4), with reduced delivery of oxygen to brain because of the further decrease of cerebral blood flow, thereby exacerbating the existing cerebral ischaemia (22).

Sex steroid and certain neuropeptide hormones may influence brain adaptation to hyponatraemia. Male rabbits and cats are more efficient than females in extruding sodium to decrease brain cell osmolality during hyponatraemia, resulting in significantly less brain swelling in male than in female hyponatraemic animals (16,25). Oestrogens have also been reported to stimulate, and androgens to suppress, vasopressin release (26,27). Virtually all hyponatraemic patients have increased plasma levels of vasopressin (17,28), a neuropeptide which may exert multiple potentially deleterious cerebral effects. In normonatraemic animals vasopressin results in water accumulation in

the brain (18), a significant decline in brain synthesis of ATP (29), and a decline of brain pH (29,30). Vasopressin also impairs the function of several important adaptive pathways to hyponatraemia (31,32).

Recent studies have demonstrated that the brains of prepubertal rats are unable to adapt to hyponatraemia (16). The greater mortality with hyponatraemia in prepubertal rats is associated with a greater accumulation of water in the intracellular space of the brain than in rats belonging to other age groups, as well as an inability of the prepubertal brain to extrude sodium from brain cells. The baseline intracellular sodium content in the prepubertal rats was greater by almost 50% than in control adult rats, a finding consistent with previous studies in newborn dogs (15,33).

Biochemical differences in paediatric vs adult brain with hyponatraemia

There are several possible reasons for the increased brain intracellular sodium in prepubertal rats. The Na^+/K^+ ATPase system appears to be the major early adaptive pathway for extrusion of sodium from brain cells during hyponatraemia (19,34) and its impairment results in decreased ability to pump sodium out of the brain. In prepubertal rats, the brain Na^+/K^+ ATPase activity is significantly lower than that observed in adults, both *in vitro* (35) and *in vivo* (36). Coupled with the higher brain sodium, these differences may reflect a limited ability to pump sodium out of the prepubertal brain. The increased intracellular sodium content may be a consequence of limited cerebral Na^+/K^+ ATPase function in young rats compared to adults. The decreased cerebral Na^+/K^+ ATPase activity may be responsible for the impaired adaptation to hyponatraemia in prepubertal rats. Testosterone stimulates Na^+/K^+ ATPase activity in rat brain (37,38). Pretreatment of prepubertal rats with testosterone resulted in a significant decrease in the brain intracellular content of both sodium and water while also reducing the mortality associated with acute hyponatraemia from 84% to zero (16).

Clinical effects of hyponatraemia in children vs adults

If one can extrapolate the above experimental findings to paediatric patients, then the implications would be that children are more susceptible to brain damage from postoperative hyponatraemia than are adults. The reasons include: a) decreased available

room for swelling of the paediatric brain in the rigid skull, leading to a propensity for brain herniation with what might appear to be a small decrement of plasma sodium (39); b) impaired ability of the paediatric brain to adapt to hyponatraemia when compared with adults (15,37); c) severe systemic hypoxaemia secondary to respiratory insufficiency frequently occurs in children with only modest hyponatraemia (6,15,39). The respiratory insufficiency is a consequence of increased intracranial pressure (3).

Gomola *et al.* have described a prepubertal (10 years old) female child with middle face hypoplasia who underwent elective maxillary reconstruction (40). The surgery went well and postoperatively, she was given primarily free water intravenously (280 mM glucose in 51 mM NaCl) at a rate of 2 l per day. The child weighed 30 kg with estimated total body water of 18.5 l. On the first postoperative day, the child became confused and developed headache and vomiting. Renal function was apparently normal on the basis of normal plasma urea and creatinine. The plasma sodium was found to be 117 mmol·l⁻¹. She was initially treated with sodium supplementation, but on the second post-operative day, the plasma sodium was still low at 120 mmol·l⁻¹. The urine and plasma osmolalities were 342 and 255 mOsm·kg⁻¹. An MRI of the brain was normal. The authors proposed three possible explanations for the hyponatraemia: a) dilutional hyponatraemia secondary to IV hypotonic fluid; b) pituitary insufficiency; c) inappropriate secretion of ADH. Pituitary insufficiency was ruled out by normal values for ACTH, cortisol, thyroid hormone and growth hormone. The ADH was 4 to 5 pg·ml⁻¹, which is 'normal' but inappropriately high for the extracellular hypoosmolality (41) and is essentially a universal finding in both paediatric and adult postoperative patients (7–13). The child received 2 l per day of hypotonic IV fluid in the presence of elevated plasma ADH. Although neither initial plasma sodium, urine output or total volume of IV fluids are provided, given the child's weight and rate of infusion, the plasma sodium of 117 mmol·l⁻¹ appears very likely to have been the consequence of retention of about 3 l of IV hypotonic fluid over two days (6). The expression inappropriate secretion of ADH (SIADH) was originally used for elevated plasma ADH related to lung cancer (42) and has become a catch all term for virtually any patient with elevated plasma ADH. In particular, postoperative patients as well as those with heart failure or hepatic

cirrhosis have elevated plasma ADH levels but are functionally hypovolaemic as well (41). Postoperative subjects are functionally hypovolaemic, so that the term SIADH may not be appropriate in this patient (11). There is also a perception that ADH, and by association SIADH, can somehow lower the plasma sodium. Although ADH leads to increased retention of ingested or infused water, in the absence of increased water intake, ADH by itself will have no effect upon the plasma sodium. Thus, the most likely explanation for the hyponatraemia in this patient is infusion of hypotonic fluid (51 mM NaCl/280 mM glucose) in the presence of the expected postoperative increase in plasma ADH. Adrenal insufficiency is ruled out by the normal plasma cortisol and the fact that she remained normal for six months without any steroid replacement therapy. Exactly why the plasma sodium rose following IV hydrocortisone is uncertain, but may have been related to the expected decline of ADH values to normal after four to five postoperative days. Pituitary insufficiency is ruled out by normal values for ACTH, IGF1 and growth hormone.

Symptomatic postoperative hyponatraemia carries a mortality of at least 15% (43), particularly in children and respiratory arrest is a frequent occurrence, but once this complication occurs, the morbidity is substantial (6,7). There is no obvious rationale for the administration of hypotonic fluid to a postoperative patient, unless the individual is hypernatraemic (14). If the patient becomes symptomatic, therapy with hypertonic NaCl is indicated (39). The syndrome can be prevented by administration of primarily isotonic fluids to postoperative patients.

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References

- 1 Ayus JC, Arieff AI. Brain damage and postoperative hyponatremia: Role of gender. *Anesthesiology* 1996; 46: 323–328.
- 2 Ayus JC, Wheeler IM, Arieff AI. Postoperative hyponatremic encephalopathy in menstruant women. *Ann Intern Med* 1992; 117: 891–897.
- 3 Ayus JC, Arieff AI. Pulmonary complications of hyponatremic encephalopathy: Noncardiogenic pulmonary edema and hypercapnic respiratory failure. *Chest* 1995; 107: 517–521.
- 4 Arieff AI. Hyponatremia, convulsions, respiratory arrest, and permanent brain damage after elective surgery in healthy women. *New Engl J Med* 1986; 314: 1529–1535.

- 5 Steele A, Gowrishankar M, Abrahamson S *et al*. Postoperative hyponatremia despite near-isotonic saline infusion: A phenomenon of desalination. *Ann Intern Med* 1997; 126: 20-25.
- 6 Arieff AJ, Ayus JC, Fraser CL. Hyponatraemia and death or permanent brain damage in healthy children. *Brit Med J* 1992; 304: 1218-1222.
- 7 Cowley DM, Pahari M, Sinton TJ *et al*. Pathogenesis of postoperative hyponatraemia following correction of scoliosis in children. *Aust NZ J Surg* 1988; 58: 485-489.
- 8 Varavithya W, Hellerstein S. Acute symptomatic hyponatremia. *J Pediatrics* 1967; 71: 269-283.
- 9 Grushkin AB, Sarnaik A. Hyponatremia: Pathophysiology and treatment, a pediatric perspective. *Pediatr Nephrol* 1992; 6: 280-286.
- 10 Burrows FA, Shatack JC, Crone RK. Inappropriate secretion of antidiuretic hormone in a postsurgical pediatric population. *Crit Care Med* 1983; 11: 527-531.
- 11 Judd BA, Haycock GB, Dalton N *et al*. Hyponatraemia in premature babies and following surgery in older children. *Acta Paediatr Scand* 1987; 76: 385-393.
- 12 Judd BA, Haycock GB, Dalton N *et al*. Antidiuretic hormone following surgery in children. *Acta Paediatr Scand* 1990; 79: 461-466.
- 13 Brazel PW, McPhee IB. Inappropriate secretion of antidiuretic hormone in postoperative scoliosis patients: The role of fluid management. *Spine* 1996; 21: 724-727.
- 14 Rosenthal MH, Arieff AJ. Fluid and electrolyte therapy in surgical and postoperative patients. *Curr Opin Crit Care* 1995; 1: 469-477.
- 15 Nattie EE, Edwards WH. Brain and CSF water in newborn puppies during acute hypo- and hypernatremia. *J Appl Physiol* 1981; 51: 1086-1091.
- 16 Arieff AJ, Kozniowska E, Roberts T *et al*. Age, gender and vasopressin affect survival and brain adaptation in rats with metabolic encephalopathy. *Am J Physiol* 1995; 268 (Reg Integr Comp Physiol 37) (5): R1143-R1152.
- 17 Anderson RJ, Chung HM, Kluge R *et al*. Hyponatremia: A prospective analysis of its epidemiology and the pathogenetic role of vasopressin. *Ann Intern Med* 1985; 102: 164-168.
- 18 Rosenberg GA, Estrada E, Kyner WT. Vasopressin-induced brain edema is mediated by the V1 receptor. *Advan Neurol* 1990; 52: 149-154.
- 19 Vexler ZS, Ayus JC, Roberts TPL *et al*. Ischemic or hypoxic hypoxia exacerbates brain injury associated with metabolic encephalopathy in laboratory animals. *J Clin Invest* 1994; 93: 256-264.
- 20 Melton JE, Patlak CS, Pettigrew KD *et al*. Volume regulatory loss of Na, Cl, and K from rat brain during acute hyponatremia. *Am J Physiol* 1987; 252 (Renal Fluid Electrolyte Physiol 21): F661-F669.
- 21 Gur RC, Mozley PD, Resnick SSM *et al*. Gender differences in age effect on brain atrophy measured by magnetic resonance imaging. *Proc Natl Acad Sci USA* 1991; 88: 2845-2849.
- 22 Kozniowska E, Roberts TPL, Vexler ZS *et al*. Hormonal dependence of the effects of metabolic encephalopathy on cerebral perfusion and oxygen utilization in the rat. *Circ Res* 1995; 76: 551-558.
- 23 Faraci FM, Mayhan WG, Heistad DD. Effect of vasopressin on production of cerebrospinal fluid: Possible role of vasopressin (V1)-receptors. *Amer J Physiol* 1990; 258 (Reg Integr Comp Physiol 27): R94-R98.
- 24 Fraser CL, Arieff AJ. Fatal central diabetes mellitus and insipidus resulting from untreated hyponatremia: A new syndrome. *Ann Intern Med* 1990; 112: 113-119.
- 25 Vexler ZS, Roberts T, Derugin N *et al*. Adaptation of the brain to hyponatraemia in two different species: Effects of gender. *Abstracts Soc Neurosci* 1994; 24: (in press).
- 26 Akaishi T, Sakuma Y. Estrogen-induced modulation of hypothalamic osmoregulation in female rats. *Amer J Physiol* 1990; 258 (Reg Integr Comp Physiol 27): R924-R929.
- 27 Stone JD, Crofton JT, Share L. Sex differences in central adrenergic control of vasopressin release. *Amer J Physiol* 1989; 257: R1040-R1045.
- 28 Gross PA, Pehrish H, Rascher W *et al*. Pathogenesis of clinical hyponatremia: Observations of vasopressin and fluid intake in 100 hyponatremic medical patients. *Eur J Clin Invest* 1987; 17: 123-129.
- 29 Fraser CL, Kucharczyk J, Arieff AJ *et al*. Sex differences result in increased morbidity from hyponatremia in female rats. *Am J Physiol* 1989; 256 (Reg Integr Comp Physiol 25): R880-R885.
- 30 Adler S, Simplaceanu V. Effect of acute hyponatremia on rat brain pH and rat brain buffering. *Amer J Physiol* 1989; 256 (Renal Electrolyte Physiol 25): F113-F119.
- 31 Kanda F, Arieff AJ. Vasopressin inhibits calcium-coupled sodium efflux system in rat brain synaptosomes. *Amer J Physiol* 1994; 266 (Reg Integr Comp Physiol 35): R1169-R1175.
- 32 Kanda F, Sarnaik P, Arieff AJ. Atrial natriuretic peptide inhibits the amiloride-sensitive sodium-hydrogen exchanger in rat brain. *Amer J Physiol* 1992; 263 (Reg Integr Comp Physiol 32): R279-R283.
- 33 Widdowson EM, Dickerson JWT. The effect of growth and function on the chemical composition of soft tissues. *Biochem J* 1960; 77: 30-43.
- 34 Fraser CL, Sarnaik P. Na⁺-K⁺ ATPase pump function in male rat brain synaptosomes is different from that of females. *Am J Physiol* 1989; 257 (Endocr Metab 20): E284-E289.
- 35 Matsuda T, Shimizu I, Baba A. Postnatal change in a Ca²⁺-mediated decrease in (Na⁺ + K⁺)-ATPase activity in rat brain slices. *Brain Res* 1992; 572: 349-351.
- 36 Jinna RR, Uzodinma JE, Desai D. Age-related changes in rat brain ATPases during treatment with chlordecone. *J Toxicol Environ Health* 1989; 27: 199-208.
- 37 Guerra M, del Castillo AR, Battaner E *et al*. Androgens stimulate preoptic area Na⁺ + K⁺ ATPase activity in male rats. *Neurosci Lett* 1987; 78: 97-100.
- 38 Fraser CL, Swanson RA. Female sex hormones inhibit volume regulation in rat brain astrocyte culture. *Am J Physiol (Cell Physiol 36)* 1994; 267: C909-C914.
- 39 Sarnaik AP, Meert K, Hackbarth R *et al*. Management of hyponatremic seizures in children with hypertonic saline. A safe and effective strategy. *Crit Care Med* 1991; 19: 758-762.
- 40 Gomola A, Cabrol S, Murat I. Severe hyponatraemia after plastic surgery in a girl with cleft palate, medial facial hypoplasia and growth retardation (case report). *Paediatr Anaesth* 1998; 8: 69-71.
- 41 Schrier RW. Pathogenesis of sodium and water retention in high-output and low-output cardiac failure, nephrotic syndrome, cirrhosis, and pregnancy. Parts 1 and 2. *New Engl J Med* 1988; 319(16): 1065-1072 and 1127-1134.
- 42 Bartter FE, Schwartz WB. The syndrome of inappropriate secretion of antidiuretic hormone. *Am J Med* 1967; 42: 790-806.
- 43 Fraser CL, Arieff AJ. Epidemiology, pathophysiology and management of hyponatremic encephalopathy. *Am J Med* 1997; 102: 67-77.