...ural part in the prevention of complications. 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.

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Hyponatraemia and death or permanent brain damage in healthy children

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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 24 412 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 24 412 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.[1–8] Although the actual incidence of hyponatraemia seems to be similar among men and women,[8,9] 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 database[18] to obtain information on all paediatric surgical patients who had a postoperative serum sodium concentration of 128 mmol/l or less. There were 24412 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

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								
M 3·5	2·27	139	114	46	246	222	Fever, dysphagia, pharyngitis, tonsilitis	Antibiotics + fluids	Yes	154 mM sodium chloride	Vegetative, quadriplegia
F 5	18·0	141	123	14	96	33	Tonsillitis	Tonsillectomy	Yes	None	Died
F 4	18·2	139	115	21	114	NA	Tonsillitis	Tonsillectomy	Yes	None	Died
M 15	44·6	134	101	74	164	73	Fever, dysphagia, pharyngitis, tonsilltis	Antibiotics + fluids	Yes	154 and 514 mM sodium chloride	Aspiration pneumonia, sepsis, died
M 3·5	15·0	138	121	9	61	5	Tonsillitis	Tonsillectomy	Yes	None	Died
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
M 4	16·4	139	118	27	109	88	Elbow fracture from fall	Setting of fracture	Yes	None	Died
M 3	10·0	137	113	8	300	NA	Stricture of urethra; tonsillits	Urethral dilatation; tonsillectomy	Yes	None	Died
F 1·5	10·6	137	114	120	283	253	Hydrocephalus	Ventriculoperitoneal shunting	Yes	None	Vegetative
M 9	27·0	137	120	32	79	NA	Fractures from car accident	Operative setting of fractures	Yes	None	Vegetative
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
F 4	16·8	138	107	16	88	56	Tonsillitis	Tonsillectomy	Yes	None	Died
M 2	11·4	138	116	3	123	NA	Undescended testicle	Orchiopexy	Yes	None	Died
M 6	15·0	138	119	12	40	11	Severe epistaxis	Posterior packing	Yes	None	Died
M 12	42·0	137	123	19	34	9	Fever, appendicitis, ruptured appendix	Appendicectomy plus drainage	Yes	None	Died
F 12	28·5	134	116	66	113	72	Pneumonia	Antibiotics + fluids	Yes	None	Vegetative
7	23·8	138	115	37	125	74					
5	12·9	2	7	34	83	82					
1	3·2	1	2	9	21	24					

*Stools + gastric drainage + cerebrospinal fluid. NA = Not available.

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diagnosis of primary polydipsia and female subsequently developed the syndrome of central diabetes 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.[22] 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.[23] Thus brain weight was increased by more than 10% above control values for children of the age range studied.[24] 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 volume[4] 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.[5] 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.[20,25] 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 States[20] 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).

Discussion

These cases show that generally healthy children with symptomatic hyponatraemia (101-123 mmol/l) can abruptly develop respiratory arrest and either die 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.[1-4] The incidence of postoperative hyponatraemia in children (0·34%) was less than in adults (1-4%).[3,21] However, among paediatric patients who developed symptomatic hyponatraemia the incidence of permanent brain damage was substantially higher than in adults.[3] 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,[20] 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,[7,12-14,16,26] 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; $p < 0{\cdot}01$)[7] or diuretic induced loss of electrolytes.[7,16] 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.[3,5,6] Furthermore, the types of operations and the clinical conditions in this patient population were similar to those most common in the United States.[20] 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.[29-31] However, prepubescent children have only minimal to absent concentrations of either hormone, thus negating such effects.[32] Most adults suffering permanent brain damage from hyponatraemia are female,[3,5,6] but in the current series a minority of affected patients (43%) in both the prospective and retrospective studies were female. This, 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.[10,12,14,16]

EFFECTS OF PHYSICAL FACTORS

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

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.[13,14] In humans and laboratory animals brain water content is more than 2·5 times higher in the young, decreasing progressively with age.[36-38] 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.[21]

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.[15,40] As the percentage of cerebrospinal fluid in the brain increases with age[15,39] 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 adults[37] 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 cations[38] whereas adult animals with hyponatraemia can readily transport sodium out of the brain.[13,14]

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.[8] 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,[4,11,41] 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.

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Addendum

After submission of this paper a report appeared describing 34 paediatric patients with water intoxication.[42] 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.

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

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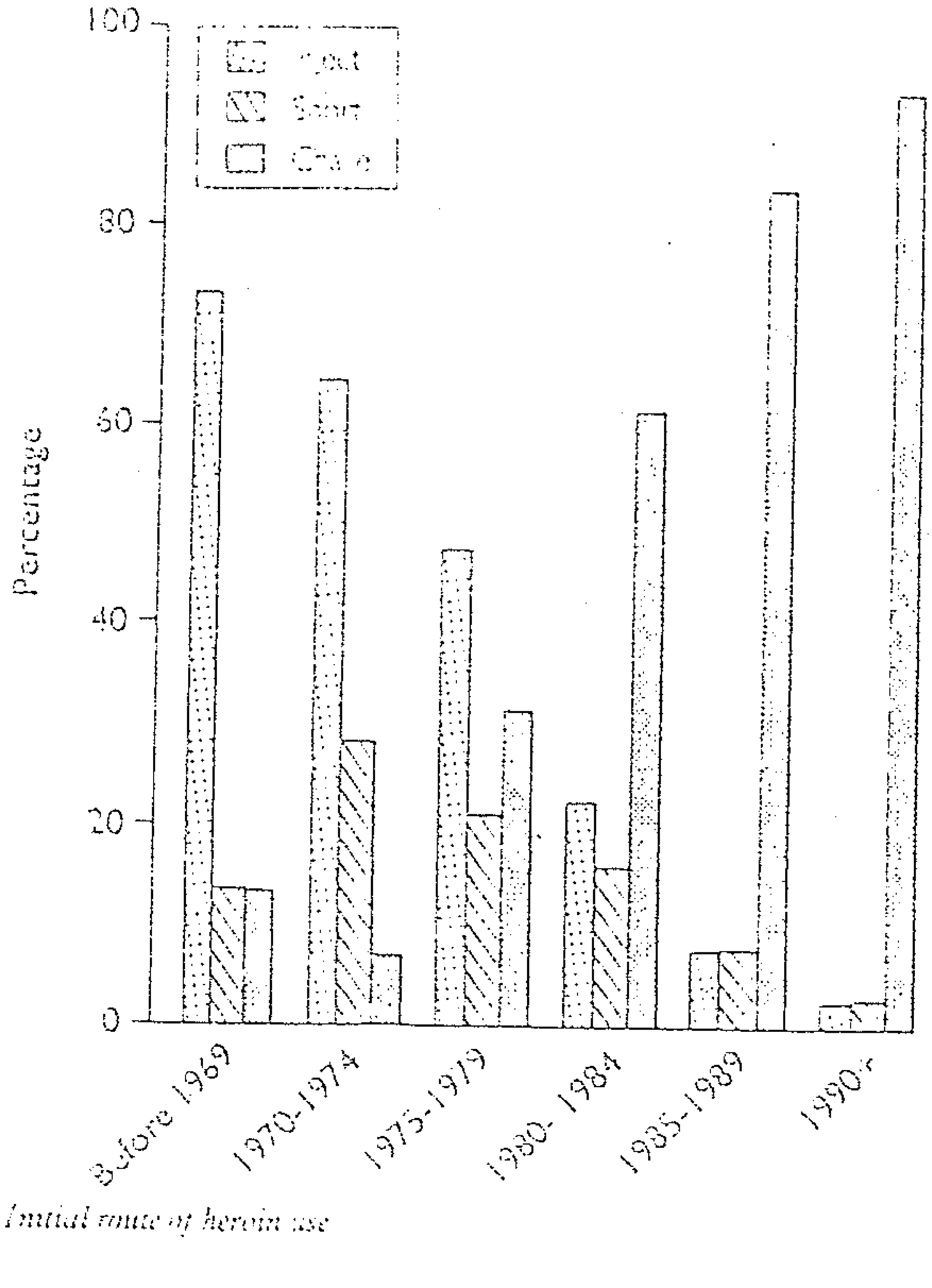
AIDS and drug misuse are linked mainly by the injection of many drugs. Major changes in the methods of heroin use, however, have fundamentally altered the importance of heroin use in the transmission of HIV. Recent reports describe the extent of "chasing the dragon" (inhaling sublimated heroin after heating it on tinfoil) as a new route of heroin use but give no information on the emergence of this pattern.[1] During the 1960s heroin use was by injecting.[2] 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 ... 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.



Initial route of heroin use

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[1] 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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DEBATE
Maintenance fluid therapy

Pouring salt on troubled waters

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The case for isotonic parenteral maintenance solution

Keywords: hyponatraemia; fluid maintenance; caloric expenditure; 0.9% saline; isotonic

Intravenous fluid and electrolyte therapy for acutely ill children has been a cornerstone of medical practice for well over 50 years. The scientific methodology behind fluid regimens generated much debate in the early 1950s following the pioneering work of Darrow, Talbot, Gamble and others who recognised the important relation between caloric expenditure and requirements for water.[1–3]

Caloric expenditure was originally calculated according to body surface area, which at the bedside required either tables or nomograms.[1] In 1957 Holliday and Segar simplified this approach, relating energy expenditure to one of three weight based categories (<10 kg, 10–20 kg, >20 kg).[4] Electrolyte requirements were also calculated on a weight basis, producing an "ideal", hypotonic solution comprising 0.2% saline in 5% dextrose water (0.18% saline in 4% dextrose in the United Kingdom). This simple regime was subsequently adopted on a global scale and is recommended in current paediatric and medical textbooks.

Advances in our understanding of water and electrolyte handling in health and disease have called into question the validity of the Holliday and Segar approach. Specifically, many authors have reported how hypotonic maintenance fluid may result in iatrogenic hyponatraemia in hospitalised patients, often with devastating consequences.[5–10] In this article we re-evaluate each of the concepts on which this traditional regime is based (energy expenditure, and water and electrolytes requirements) and use this to make the case for an alternative, namely isotonic fluid.

PITFALLS OF THE WEIGHT BASED HOLLIDAY AND SEGAR APPROACH

Energy expenditure

Talbot originally estimated basal metabolic rate in children based on water loss.[11] Crawford extended this concept, by presenting *total* energy requirements (basal metabolic rate plus growth and activity) using this data in relation to body surface area (fig 1). Holliday and Segar further advanced this by indexing energy expenditure to body weight rather than surface area, assuming 1 ml of water loss was associated with the fixed consumption of 1 kilocalorie.[4] The typical fluid losses for children (table 1) thus equate with an energy requirement of 120 kcal/kg/day for a 10 kg child.[12]

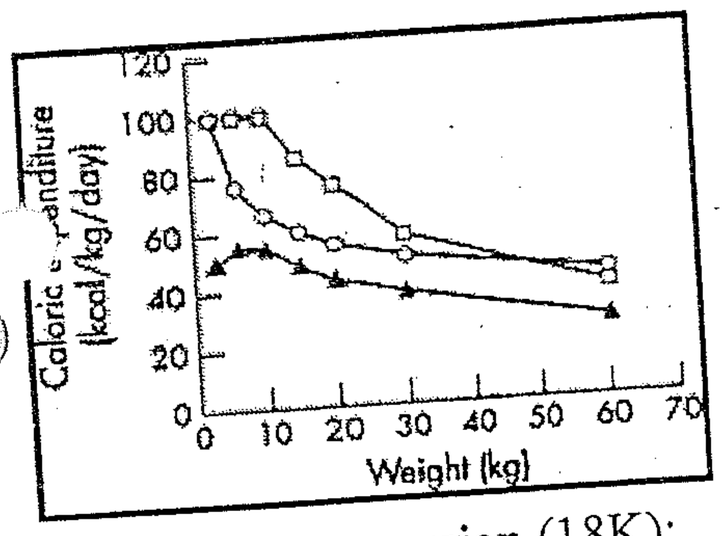

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Figure 1 Daily caloric expenditure according to the weight based method of Holliday and Segar and by surface area method of Crawford, and basal metabolic rate. Comparison of two different methods for calculating caloric expenditure across weight ranges (open squares = Holliday and Segar's weight based method; open circles = Crawford's surface area method*; referenced against basal metabolic rate**).

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Table 1 Typical water losses per 100 kilocalories (kcal) of energy expended for a healthy 10 kg child

There are two main flaws with this approach. First, it is now known that resting energy expenditure is closely related to *fat free mass* which includes muscle and the four major metabolic organs (heart, liver, kidneys, and brain).[13] Eighty per cent of the resting energy expenditure is accounted for by these four organs which comprise only 7% of total body mass. As a result, the use of weight alone to calculate energy expenditure may significantly overestimate caloric requirements. On average, the weight based method overestimates energy requirements in infants by 14% compared to the surface area method (fig 1).[4] Second, energy expenditure in healthy children, on whom historic models are based, is vastly different in acute disease or following surgery. Using calorimetric methods, energy expenditure in these patients is closer to the basal metabolic rate proposed by Talbot, averaging 50–60 kcal/kg/day.[14–16] This overestimate is multifactorial: ill patients are catabolic, often relatively inactive, and, in the intensive care environment may be pharmacologically sedated or muscle relaxed.[14–17] Almost half of the caloric intake suggested by Holliday and Segar is designated for growth, an unrealistic goal in acute disease.[16] Although fever and sepsis per se may increase metabolic rate this is usually limited to less than 1.5 times the basal metabolic rate, burns being an exception.

Water requirements

Historically water requirements have been based on crude estimates of both insensible (skin,

espiratory tract) and sensible (urine and stool) water losses.

nsensible water loss

This was generously estimated at 930 ml/m^2/day (27 ml/kg/day).[18] Recent data suggest the true figure may be only half of this, with basal insensible losses from the skin being 250 ml/m^2/day (7 ml/kg/day) and via the respiratory tract 170 ml/m^2/day (5 ml/kg/day).[19] Additionally many other risk factors may reduce insensible water loss such as use of humidifiers in ventilated patients (80% reduction in respiratory water loss) or a thermo neutral environment.[17] Bluemle *et al* have shown insensible water losses of as little as 330 ml/m^2/day (10 ml/kg/day) in catabolic acute renal failure patients.[20]

Urinary loss of water

According to Holliday and Segar, urinary water losses for healthy children amount to 50–60 ml/k[illegible]/day[4] based on the work of Pickering and Winters (table 1[illegible]).[12] The basis of this fluid regime w[illegible]ue observation that 15/28 infants and 20/25 children (unspecified diagnoses) who were given [illegible]avenous dextrose produced urine with an "acceptable" urine osmolarity between 150 and 600 mosm/l H_2O.[4] They presumed patients with dilute urine received too much water and conversely those with concentrated urine too little water.

Today we recognise this does not take into account the overriding influence of antidiuretic hormone (ADH) on urine flow rate.[21] When ADH is present, the renal solute load is effectively excreted in a smaller urine volume producing concentrated urine. Under these conditions urine output is often less than half the values observed in healthy children (approximately 25 ml/kg/day).[22] An increase in ADH is common during many childhood diseases, in response to stress (pain, fever, surgery) or secondary to use of opiates and non-steroidal anti-inflammatory drugs.[23–25] Under these conditions the administration of free water frequently leads to hyponatraemia because the kidneys are unable to excrete the water load.[5,6,26] Interestingly, the type of fluid administered may influence ADH levels. J[illegible]d *et al* showed that 0.9% saline but not 5% dextrose reduced ADH concentrations postoperatively.[21]

Thus the total fluid loss (sensible plus insensible) during acutely illness or following surgery may amount to approximately half that suggested by Holliday and Segar (50–60 ml/kg/day).[5,6] Also, the often overlooked production of endogenous water from tissue catabolism (water of oxidation) may be increased in acute disease.[20] In healthy children, this has been estimated to be 15 ml/100 kcal burnt.[4] Thus, all these factors need consideration when assessing overall water balance.

Electrolyte requirements

In healthy breast fed infants Holliday and Segar computed a dietary sodium intake of 1 mEq/100 calories per day.[4] Darrow recommended 3 mEq of sodium per 100 calories of energy expended per day.[4] This is based on urinary excretion rates of sodium in healthy, milk fed infants. However, daily electrolyte requirements in disease may differ considerably from this. For example, large urinary losses of sodium and potassium may occur through the phenomenon of desalination.[27,28] Furthermore, Al-Dahhan *et al* showed a beneficial effect on neurodevelopmental outcome from doubling the daily sodium intake (4 to 5 mmol/kg) in neonates.[26] This refutes the assumption that the neonatal kidney is incapable of "handling" a high sodium load. The recent discovery of the most potent natriuretic hormones, urodilatin and gut-related natriuretic peptide has also shed new light on

odium regulation.

The rationale behind the traditional approach is to balance sodium intake to match sodium loss. However, this fails to appreciate the *single* most important role of sodium in acute illness, namely maintenance of plasma tonicity.[25,29] There is a strong inverse relation between plasma sodium concentration and intracellular volume.[30] Cell membranes are permeable to water but not electrolytes. As sodium is the major extracellular cation (and hence osmole), it regulates the movement of water across cells along an osmotic concentration gradient, thus explaining cellular swelling in the presence of hyponatraemia.

It is also important to recognise the role of potassium in the regulation of tonicity balance. Potassium is a major intracellular osmole, and may directly influence extracellular sodium concentration by altering the distribution of water between fluid compartments.[25] Potassium loss, both urinary and stoo[illegible]ıay be significant in disease; yet its direct influence on serum sodium concentration is often not considered.[25,28]

Tonicity of intravenous fluids

It is crucial that clinicians appreciate the difference between osmolarity and tonicity. The osmolarity of a solution is the number of osmoles of solute per litre of solution. The tonicity of a solution refers to the total concentration of solutes that exert an osmotic force across a membrane in vivo. For example, 5% dextrose has the same osmolarity as plasma (286 mosm/l H_2O) but is rapidly metabolised in blood to water. Thus its *in vivo tonicity* is equal to that of electrolyte free water, as it contains no salt or other active osmole (zero tonicity). Every litre of 5% dextrose infused results in the expansion of the intracellular and extracellular fluid space by one litre (two thirds of this distributes to the intracellular space and one third to the extracellular space). Similarly, for every litre of 0.18% saline in 4% dextrose water infused, only 1/5th (200 ml) is isotonic to plasma (table 2). The remaining 800 ml is electrolyte free water, which will expand the intracellular fluid c[illegible]partment. This is particularly relevant if excretion of water is limited by ADH.[5–7,21,28,31] This fluid shift may even occur in the absence of hyponatraemia.[32] Small increases in tissue water through the use of hypotonic fluids may be harmful in conditions such as cerebral oedema where minor increases in cerebral water may lead to disproportionately large increases in intracranial pressure.

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Table 2 Approximate sodium concentration, in vitro osmolarity, in vivo tonicity, and theoretical volume of electrolyte free water (EFW) provided by commonly used intravenous solutions

The incidence and neurological complications of acute hyponatraemia

Hyponatraemia is a common biochemical finding in hospitalised children and is most commonly due to excess water intake rather than salt loss.[9,22,23] Shann and Germer showed an incidence of hyponatraemia (Na <134 mmol/l) as high as 45% in hospitalised children with pneumonia and 50% in bacterial meningitis.[8] Hanna *et al* recently reported a 30% incidence of admission hyponatraemia in infants with bronchiolitis requiring intensive care admission in the United Kingdom. 13% of which had seizures.[9] Halberthal *et al* was able to show a direct link between hyponatraemia and the use of hypotonic maintenance fluid.[7] The neurological complications of acute hyponatraemia include

ncephalopathy with seizures, irreversible brain damage, or brain death from cerebral herniation.[5–10] hildren are also among the most susceptible to hyponatraemic brain injury.[5,6] Fatal hyponatraemia an occur within hours of hypotonic fluid administration, particularly if standard fluid maintenance ates are used (100–120 ml/kg/day).[10]

THE RATIONALE FOR ISOTONIC MAINTENANCE FLUID

The paramount consideration in the choice of intravenous fluid is the requirement to maintain serum sodium at a normal level. The use of isotonic solutions such as 0.9% saline is more appropriate in acutely sick children as they do not theoretically expand the intracellular fluid space. Isotonic solutions preserve intracellular function and integrity, by minimising changes in plasma sodium concentration and tonicity.

Use of 0.9% saline as maintenance fluid, if combined with appropriate fluid restriction, will result in a two to threefold increase in daily sodium intake compared to the traditional regime. However, the ncern that this may cause severe hypernatraemia is without foundation because the sodium concentration and tonicity of 0.9% saline is similar to plasma. Andersen *et al* showed a rise in plasma sodium only after intravenous administration of hypertonic 3% saline but not 0.9% saline, despite a temporary positive sodium balance.[33] Heer *et al* showed chronic sodium loading in volunteers does not produce an increase in plasma sodium, body water, or weight as previously suggested.[34] Many of the historical assumptions concerning sodium handling are based on salt depleted subjects. Indeed massive sodium loads from large volume resuscitation of infants and children with sepsis (80–180 ml/kg/day) using 0.9% saline did not produce hypernatraemia.[35] Additionally an epidemic of hypernatraemia has not been documented in hospitalised adults where isotonic maintenance fluids are routine. When present, the aetiology of hypernatraemia in this scenario is frequently due to well recognised factors such diabetis insipidus or over-use of loop diuretics.[36]

The debate as to the optimal isotonic fluid is ongoing. For example, Hartman's solution has a more physiological concentration of chloride than 0.9% saline and hence does not cause hyperchloraemia. The benefit of Hartman's solution versus 0.9% saline is not currently known. It is important to stress that dextrose may be added to these isotonic solutions (commonly in concentration of 5–10%), when clinically indicated to avoid hypoglycaemia without changing the solution's in vivo *tonicity* (table 2 ⊞). Recent evidence suggests that a 1% dextrose solution following uncomplicated paediatric surgery may be adequate.[37] A suitable solution for neonates and infants is 0.9% saline in 5% dextrose water, which is commercially available. We advocate 0.9% saline (with or without added dextrose) as a safe maintenance solution, both perioperatively and in the acute phase of most childhood illnesses requiring hospitalisation (for example, pneumonia, bronchiolitis, and meningitis). Here, the water retaining effect of antidiuretic hormone may necessitate a moderate degree of fluid restriction (50–60%) to prevent fluid overload. The concept of fluid maintenance should not be confused with replacement therapy where abnormal or excessive quantities of water and electrolytes may be lost. In this instance the biochemical composition and tonicity of the replacement solution should approximate that which is lost.

CONCLUSION

We have shown a number of pitfalls in the Holliday and Segar approach to parenteral therapy.

namely that it focuses on fluid and electrolyte requirements for healthy children. In acute disease or following surgery, caloric expenditure, insensible water losses, and urine output are frequently much less than in health (often 50–60% of the reference values). Furthermore, this approach fails to recognise the importance of tonicity with its central role in the distribution of water between fluid compartments (intracellular and extracellular space).

We therefore agree with Moritz and Ayus who advocate isotonic solutions such as 0.9% saline for routine fluid maintenance in children.[38] Hypotonic solutions, such as 0.18% or even 0.45% saline, are potentially dangerous when renal water excretion is limited by ADH. This raises a significant ethical barrier to conducting a randomised control study as most acutely ill or postoperative patients have increased ADH levels. There are few occasions in medicine where mortality could be reduced by a task as simple as changing from a hypotonic maintenance solution to an isotonic one.

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FOOTNOTES

* Crawford calculated caloric expenditure based on the calories utilised per surface area of the body. The calculated caloric expenditure at each body surface area increment can be converted to weight by cross-referencing surface area to weight using standard growth charts. The ratio of weight to surface area rapidly declines from birth to 10 kg. The Holliday and Segar method does not take this into account.

** From the data of Talbot.

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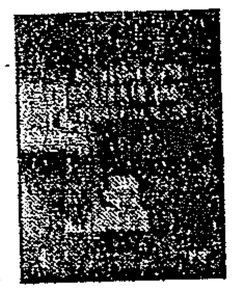

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BMJ

Hyponatraemia after orthopaedic surgery

Ignorance of the effects of hyponatraemia after surgery is widespread—and damaging

Iatrogenic injury is an unfortunate reversal of the physician's role. To cause the death or brain damage of a patient has to be the physician's worst transgression, particularly if the causes are well known, simple, and reversible. Each is true of acute postoperative hyponatraemia, but, despite repeated warnings, the condition remains common. According to a recent estimate based on prospective and retrospective studies, 20% of women who develop symptomatic hyponatraemia die or suffer serious brain damage, totalling 10 000-15 0000 cases every year in the United States and Western Europe.[1]

An elderly female friend of ours is a classic example. Some months ago she underwent a routine knee replacement operation. Before the operation her blood sodium concentration was 134 mmol/l—borderline hyponatraemia—attributable to her long term use of thiazide diuretics. After the operation she vomited frequently and received 6 litres of 5% dextrose saline over two days before passing into a coma. Her blood sodium concentration measured on the second day after surgery was 115 mmol/l, but electrolyte disturbance was disregarded by the orthopaedic doctors as a potential cause of coma until the medical team were called the next day. Sodium concentrations were restored to 134 mmol/l over five days, leaving our friend with mild—but permanent—cognitive impairment. The hospital concerned "apologises unreservedly" but confessed ignorance about the risks of hyponatraemia after joint replacement surgery.

Although the literature is full of similar examples, too many orthopaedic surgeons seem unaware of the dangers of hyponatraemia or its characteristic neurological symptoms. Perhaps the reason lies partly in the scatter of relevant publications: most of the articles are published in journals dedicated to neurology, urology, and acute care; only a handful of reports refer specifically to orthopaedic surgery[2–4]; and neither the Royal College of Surgeons nor the British Orthopaedic Association publishes guidelines. Many articles focus on tightly defined issues, such as the association between thiazide diuretics and hyponatraemia,[2] to the exclusion of a more general overview. As a result, four fundamental problems have arisen: clinicians fail to recognise patients at high risk of hyponatraemia; disregard the dangers of routine infusions of hypotonic fluids; confuse early symptoms of hyponatraemia with postoperative sequelae; and attribute the serious neurological symptoms of hyponatraemic encephalopathy to other conditions such as stroke.

Postoperative hyponatraemia is provoked by surgical stress, which causes a syndrome of inappropriate antidiuretic hormone in almost everyone, often promoting water retention for several days.[5,6] Women are more affected than men, as a result of their smaller fluid volume and other sex related hormonal factors.[5] Premenopausal women and children are prone to brain damage at sodium concentrations as high as 128 mmol/l. Postmenopausal women do not usually become symptomatic until sodium concentrations have fallen below 120 mmol/l, although normal symptoms can occur at higher levels if the rate of change is rapid.[5–7] Importantly, normal ageing impairs fluid homoeostasis and therefore increases the risk of major perturbations in sodium and water balance, especially severe hyponatraemia.[7] The risk of hyponatraemia among elderly people is compounded by chronic diseases and long term medications. In particular, many women requiring orthopaedic surgery also take thiazide diuretics to control hypertension.[2] Thiazides are well known to induce mild hyponatraemia and have been linked to the rapid onset of serious postoperative complications.[2,3]

Women at risk of hyponatraemia are imperilled by routine infusions of isotonic dextrose. Patients recovering from surgery metabolise glucose almost immediately, so "isotonic" dextrose infusions are in effect hypotonic. Since the 1950s numerous reports have linked hypotonic infusions with death or permanent brain damage in postoperative patients.[1] Recent authoritative reviews warn against routine infusions of dextrose,[1,6,8] even stating explicitly: "the rationale for using hypotonic fluids in postoperative patients is difficult to discern and has no place in the modern practice of medicine."[1] Volumes as low as 3-4 litres over two days may cause convulsions, respiratory arrest, permanent brain damage, and death in women who were healthy before admission.[5,8] Most of these cases go unrecognised and are ascribed to conditions such as stroke, arteriovenous malformation, subarachnoid haemorrhage, or herpes encephalopathy, even when blood sodium concentrations are known.[8]

Early symptoms of hyponatraemia (such as weakness, nausea, vomiting, and headache) can be distinguished from postoperative sequelae on the basis of sodium concentrations. Timing also helps discrimination: many patients tolerate surgery without

complications, being able to talk, walk, and eat before symptoms of hyponatraemic encephalopathy develop.[1] Treatment is simple and should be prompt: the risk of not treating acute cerebral oedema far exceeds the small risk of osmotic demyelination from treatment.[1 6] Fluid infusions should be restricted to normal or hypertonic saline and sodium concentrations monitored every two hours.[1 5 6] The aim is to raise serum sodium by 1-2 mmol/l per hour (depending on the severity of neurological symptoms) until symptoms resolve.[1 6] A loop diuretic such as frusemide (furosemide) may be used to enhance free water excretion and hasten the restoration of normal sodium concentrations.[1 6] Iatrogenic hyponatraemia is inexcusable. It is time that doctors woke up to the risks.

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Dietary management of hepatic encephalopathy

Too many myths persist

Myths are difficult to dispel and may delay good evidence based clinical practice. This is illustrated well by a paper in this week's issue on the dietary management of hepatic encephalopathy in patients with cirrhosis (p 1391).[1] Protein restriction in symptomatic patients with hepatic encephalopathy has been the cornerstone of treatment since the 1950s,[2] yet there is no evidence that it has any clinical benefit.

Hepatic encephalopathy is a syndrome of impaired mental status and abnormal neuromuscular function which results from major failure of liver function. Important factors contributing to it are the degree of hepatocellular failure, portosystemic shunting, and exogenous factors such as sepsis and variceal bleeding.[3] The pathogenesis of the syndrome is still uncertain, although current hypotheses include impaired hepatic detoxification of ammonia absorbed from the gut[4] and an increase in aromatic amines, which are precursors for false transmitters in the brain—for example, octopamine—and which alter the balance between neuronal excitation and neuronal inhibition.[5] Furthermore, increased expression of benzodiazepine receptors in hepatocellular failure suggests that the γ-aminobutyric acid-benzodiazepine inhibitory neurotransmitter system may be implicated in the development of hepatic encephalopathy.[6]

Protein restriction as a treatment conveniently began with 20 g protein/day and, with clinical recovery, 10 g increments were introduced every 3-5 days, as tolerated by the patient, to a limit of 0.8-1.0 g/kg body weight[3]; this was considered sufficient to achieve a positive nitrogen balance. This practice continues despite evidence showing that patients with stable cirrhosis have a higher protein requirement than normal, around 1.2 g/kg dry body weight to remain in positive balance.[7]

Protein energy malnutrition, defined by anthropometric criteria, may occur in 20-60% of patients with cirrhosis depending on the severity of the liver disease.[8] It is a common finding, with causative factors which include anorexia, nausea, malabsorption, and a hypermetabolic state. Intake may be further reduced by use of unpalatable low protein diets, already restricted in sodium and fluid.

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In 1997 the European Society for Parenteral and Enteral Nutrition published consensus guidelines recommending that the daily protein intake in patients with liver disease should, if possible, be around 1.0-1.5 g/kg depending on the degree of hepatic decompensation.[7] The guidelines also recommended that in patients who were intolerant of dietary protein 0.5 g protein/kg should be used transiently and that the remainder of their requirements should be achieved by giving branched chain amino acids.[9] However, not all studies agree on the use of branched chain amino acids.[10] Furthermore, aggressive enteral nutritional support of patients with alcoholic liver disease accelerates improvement without exacerbating hepatic encephalopathy.[11] Taking smaller meals more often and eating a late evening meal also improve nitrogen balance without exacerbating hepatic encephalopathy.[12] This may also be achieved with vegetable protein as opposed to animal proteins.[13]

The dilemma for the clinician arises in patients with acute hepatic encephalopathy, where increasing protein intake may worsen the condition in 35% of patients.[4] Use of branched chain amino acids may improve nitrogen balance but without producing any clinical improvement in the encephalopathy.[9] However, there is no consensus about the rate at which dietary protein should be reintroduced and at what clinical stage this is appropriate—the key points for the clinician.

Soulsby and Morgan provide recent evidence of perpetuation of the myth of protein restriction in patients with encephalopathy and, perhaps more alarmingly, that this therapy is used in patients with cirrhosis who have no neuropsychiatric impairment.[1] We

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Hyponatremia and hypernatremia

A systematic approach to causes and their correction

Pamela J. Fall, MD

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CME learning objectives

- To learn an approach to patient evaluation for hyponatremia and hypernatremia
- To identify patients at risk of complications from hyponatremia and hypernatremia
- To understand how to safely and effectively treat hyponatremia and hypernatremia

This page is best viewed with a browser that supports tables

Preview: Disorders of sodium and water metabolism are common in hospitalized patients and are occasionally encountered in outpatients. Both hyponatremia and hypernatremia can cause substantial morbidity and mortality, and ironically, incorrect treatment can add to the problem. In this article, Dr Fall outlines a general approach to evaluation and management of both conditions, with recommendations on safe and effective therapy.
Fall PJ. Hyponatremia and hypernatremia: a systematic approach to causes and their correction. Postgrad Med 107 (5):75-82

Osmotic forces determine the distribution of water between body fluid compartments. Each compartment has one major solute. Sodium is primarily extracellular, whereas potassium is primarily intracellular (1). In general, cell membranes (except for the renal medulla) are freely permeable to water. Therefore, water moves across a cell membrane until osmotic pressure is equal in the two compartments. This property allows brain cells to swell in the face of hyponatremia or shrink with hypernatremia, and

it is responsible for the neurologic manifestations of acute sodium disorders.

The osmolality of a solution is defined by the number of solute particles per kilogram of water. The extracellular osmoles consist primarily of sodium salts, glucose, and urea. Serum osmolality is defined by the following equation:

Serum osmolality = (2 X Na) + (glucose ÷ 18) + (urea ÷ 2.8)

Under normal conditions, glucose and urea contribute minimally to serum osmolality. Osmolality is determined primarily by the serum sodium concentration. Serum osmolality is tightly regulated between 275 and 290 mOsm/kg, primarily through the influence of antidiuretic hormone (ADH). Osmoreceptors in the hypothalamus detect serum osmolality changes as small as 1%. An increase in serum osmolality or a decrease in the effective circulating volume can enhance the thirst mechanism. Likewise, water excretion is controlled by ADH, and an increase in serum osmolality or a decrease in circulating volume can stimulate ADH release. These changes in water intake and excretion maintain serum osmolality within the normal range.

Hyponatremia

Hyponatremia reflects an abnormal ratio of sodium to water and is defined as a serum sodium concentration of less than 135 mEq/L. It usually results from retention of water secondary to impairment in free water excretion. Occasionally, hyponatremia is due to sodium loss exceeding that of water (eg, thiazide-induced hyponatremia). Elderly women may be susceptible to this condition (2).

Excretion of free water has two general requirements: (1) generation of free water and dilute urine by reabsorption of sodium chloride without water in the ascending limb of the loop of Henle, and (2) excretion of this water by maintenance of impermeability to water (no ADH) in the collecting duct. ADH release is maximally suppressed at a serum osmolality of 275 mOsm/kg, as depicted in figure 1 (not shown) (3).

Because the capacity to excrete water is so great, water retention leading to hyponatremia occurs only when there is a defect in renal water excretion or when the system is overwhelmed (eg, in primary polydipsia). The normal daily osmolar load is about 10 mOsm/kg of body weight, and urine can be diluted as low as 50 mOsm/kg. Consequently, a 70-kg (154-lb) person can excrete up to 14 L (14.8 qt) of urine daily.

Clinical features

Signs and symptoms of hyponatremia are primarily related to the central nervous system. In hyponatremia, the osmotic pressure gradient favors movement of water into brain cells, resulting in cerebral edema. The brain has adaptive capabilities that serve to minimize cell swelling, but in patients with acute development of hyponatremia, this adaptation cannot occur (4).

Early manifestations of hyponatremia include anorexia,

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nausea, lethargy, and apathy. More advanced symptoms include disorientation, agitation, seizures, depressed reflexes, focal neurologic deficits and, eventually, Cheyne-Stokes respiration (5). Coma and seizures usually occur only with acute reduction of the serum sodium concentration to less than 120 mEq/L (6).

Hence, clinical manifestations of hyponatremia correlate with the serum sodium concentration and, more important, with how rapidly the condition developed. The mortality rate of hyponatremia has been cited as ranging from 5% to 50%, depending on severity and acuity of onset (7).

Diagnosis

The diagnostic process in hyponatremia involves performing thorough history taking and physical examination and obtaining three basic laboratory values: serum osmolality, urine osmolality, and urine sodium (5). This information is used to determine the cause of hyponatremia and help guide therapy. Common causes of hyponatremia include the syndrome of inappropriate ADH and depletion of effective circulating volume.

Important information to obtain in history taking includes use of medications (particularly thiazide diuretics), recent vomiting, diarrhea or excessive sweating with hypotonic fluid ingestion, recent surgery, and a history of psychiatric illness, congestive heart failure (CHF), cirrhosis, or nephrotic syndrome with renal failure. Physical examination should focus on assessment of volume status and include orthostatic vital signs, skin turgor, mucous membrane appearance, jugular venous distention, findings of edema, and wedge pressure and central venous pressure if available.

The initial laboratory measurement needed in evaluation of hyponatremia is serum osmolality. A common cause of hyperosmolar hyponatremia (ie, serum osmolality >290 mOsm/kg) is hyperglycemia; hypertonic infusion of mannitol (Osmitrol) is a less common cause. Isosmolar hyponatremia (ie, normal serum osmolality of 275 to 290 mOsm/kg) may, rarely, be caused by pseudohyponatremia from either severe hyperlipidemia or hyperproteinemia. The finding results from the method used to measure the serum sodium concentration and does not represent true hyponatremia. Hypo-osmolar hyponatremia (ie, serum osmolality <275 mOsm/kg) is the most common type. Causes are listed in table 1 and are the focus of the remaining discussion.

Table 1. Differential diagnosis of hypo-osmolar hyponatremia

Volume status and condition	Urine sodium concentration (mEq/L)
Hypovolemic	
Renal loss (through diuretic use, salt-wasting nephropathy, hypoaldosteronism)	>20
Gastrointestinal loss (through vomiting, diarrhea, tube drainage)	<10

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Skin loss (through sweating, burns, cystic fibrosis)	<10
Peritonitis	<10
Euvolemic	
Antidiuretic hormone (ADH) excess (through syndrome of inappropriate ADH, use of thiazide diuretics or oral hypoglycemic agents)	>30
Pain	>30
Postoperative state (including transurethral prostatic resection syndrome)	>30
Cortisol deficiency	>30
Hypothyroidism	>30
Decreased solute intake	Variable
Psychogenic polydipsia	Variable
Resetting of osmostat (pregnancy, psychiatric disorders)	Variable
Hypervolemic	
Congestive heart failure	<10
Cirrhosis	<10
Nephrotic syndrome	<10
Acute and chronic renal failure	>20

The next measurement needed in evaluation of hyponatremia is urine osmolality. This value indicates whether water excretion is impaired. Normally, when the body is faced with a water load, serum osmolality is decreased, ADH is suppressed, and excess free water is excreted in very dilute urine (osmolality as low as 50 mOsm/kg). Patients with hyponatremia and urine osmolality of less than 100 mOsm/kg are appropriately excreting very dilute urine, as occurs in primary polydipsia and resetting of the osmostat (ie, a form of the syndrome of inappropriate ADH in which serum osmolality is reset downward to a new threshold). In patients with resetting of the osmostat, a serum sodium concentration between 125 and 130 mEq/L is usually maintained, with appropriate excretion of dilute urine during water loading. However, most patients with hyponatremia have urine osmolality of more than 200 mOsm/kg, reflecting impairment in water excretion.

The final step in evaluation of hyponatremia is to measure the urine sodium concentration and use this finding in conjunction with volume status to determine the cause of hyponatremia and help guide therapy. In general, a spot test showing urine sodium concentration of less than 30 mEq/L differentiates patients with hypovolemic hyponatremia from patients with euvolemic hyponatremia (who have urine sodium concentration greater than 30 mEq/L on spot testing) (table 1) (8). (Spot testing of urine

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sodium concentration can also be helpful in identifying hypervolemic hyponatremia.)

In interpreting urine sodium concentration, the following caveats should be considered: A high urine sodium concentration may be found in patients with volume depletion secondary to a renal cause of salt wasting (eg, adrenal insufficiency, thiazidediuretic use), metabolic alkalosis, or osmotic diuresis (eg, from hyperglycemia). The so-called sodium-avid states of CHF, cirrhosis, and nephrotic syndrome all typically have a low urine sodium concentration unless patients are taking a diuretic, whereas renal failure tends to cause a high urine sodium concentration (table 1).

Treatment

Much has been written about treatment of hyponatremia and the potential adverse outcome of central pontine myelinolysis (9,10). This condition is demyelination of the pons, which can lead to mutism, dysphasia, spastic quadriparesis, pseudobulbar palsy, delirium, coma, and even death.

On the basis of observations in both animals and humans, it appears that aggressive treatment of hyponatremia that has been present for longer than 24 to 48 hours is responsible for development of central pontine myelinolysis. Raising the serum sodium concentration more than 25 mEq/L or to a normal or above-normal level in the first 48 hours increases the likelihood of central pontine myelinolysis. In addition, certain patients have a greater propensity for the disorder (eg, alcoholics, elderly women taking thiazide diuretics, patients who are malnourished or hypokalemic, burn patients) (11).

Treatment of hyponatremia varies depending on whether symptoms are present (11-14).

In asymptomatic patients: When symptoms are absent, the focus of therapy should be on identifying and correcting the underlying cause of hyponatremia. If a patient is judged to be hypovolemic on the basis of clinical assessment and urine sodium concentration, normal saline solution should be administered initially to correct the extracellular fluid volume deficit. If a patient is hypervolemic, salt and water restriction is key.

Most patients with CHF or nephrotic syndrome maintain a serum sodium concentration of more than 125 mEq/L, even with marked increase in ADH levels. Patients with CHF can be treated with inotropes, afterload reduction, and loop diuretics in addition to salt and water restriction. Loop diuretics are the mainstay of therapy in patients with nephrotic syndrome, and if these agents are unsuccessful, dialysis may be warranted.

For patients who are euvolemic and hyponatremic, therapy consists primarily of water restriction. Again, treating the underlying cause is important (eg, withdrawing a thiazide diuretic, initiating hormone therapy for hypothyroidism or adrenal insufficiency) and may correct the hyponatremia. When the cause of the syndrome of inappropriate ADH is unknown or not treatable, other methods can be used, including increased dietary protein and salt and use of urea, loop diuretics and, rarely, demeclocycline hydrochloride

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(Declomycin).

In symptomatic patients: Patients with acute symptomatic hyponatremia are candidates for aggressive treatment (11,14). In this condition, acute hyponatremia develops so quickly (within 48 hours) that the brain has little time for adaptation. It most commonly occurs in hospitalized patients who receive hypotonic fluids postoperatively. Young menstruating women seem to be particularly susceptible to hyponatremic encephalopathy (15).

Hyponatremia can be corrected with administration of hypertonic saline solution (3%) at a rate of about 1 mL/kg per hour. A loop diuretic may be added to enhance water excretion if urine osmolality is greater than 300 mOsm/kg. With use of this combination therapy, sodium lost in the urine is replaced with an equal amount of sodium in a smaller volume. The serum sodium concentration should be raised no more than 25 mEq/L in the first 48 hours, at a rate of no more than 2 mEq/L per hour, and the target goal should be 120 to 125 mEq/L. Treatment with hypertonic saline solution is advocated only for patients with severe hyponatremia who have profound neurologic symptoms.

The main controversy in the literature surrounds treatment of chronic symptomatic hyponatremia because, as mentioned, central pontine myelinolysis may result if the condition is corrected too rapidly (11,14). Therefore, although treatment in these patients is similar to that just described, the rate of correction should be slower (0.5 to 1 mEq/L per hour). Aggressive therapy should be discontinued when the serum sodium concentration is raised 10% or symptoms abate.

Regardless of whether a symptomatic patient presents with acute or chronic hyponatremia, the key to successful management is frequent monitoring of serum electrolytes to ensure adherence to the guidelines outlined. In general, the serum sodium concentration should be reassessed every 2 to 4 hours during active intervention.

Hypernatremia

Hypernatremia, like hyponatremia, reflects an abnormal ratio of sodium and water. It is defined as a serum sodium concentration exceeding 145 mEq/L. Unlike hyponatremia, hypernatremia always represents a hyperosmolar state. Hypernatremia results from water loss or sodium retention, although sodium retention occurs in only a few circumstances (eg, administration of hypertonic sodium bicarbonate during cardiopulmonary resuscitation). Thus, the underlying cause of hypernatremia in the vast majority of patients is water loss in excess of solute (table 2) (1).

Table 2. Differential diagnosis of hypernatremia

Volume status and condition	Urine sodium concentration (mEq/L)	UTV
Hypovolemic		
Renal losses (osmotic diuresis by	>20	

means of glucose, urea, mannitol [Osmitrol] use)	
Insensible losses (through sweating, fever, respiration)	<10
Gastrointestinal losses (through diarrhea)	<10

Euvolemic	
Renal losses (through diabetes inspidus--nephrogenic or central)	Variable
Hypothalamic disorder (primary hypodipsia, resetting of osmostat)	Variable

Hypervolemic	
Hypertonic saline administration	>20
Sodium bicarbonate administration	>20
Primary hyperaldosteronism	>20

The two defense mechanisms against hypernatremia are stimulation of ADH release (resulting in maximal urinary concentration) and thirst (16). Release of ADH occurs at a slightly lower serum osmolality than does stimulation of thirst, but thirst is the main defense mechanism against hypernatremia. Hypernatremia is almost never found in an alert patient who has access to water and a normal thirst mechanism. In adults, hypernatremia is more common after age 60, primarily because increased age is associated with decreased osmotic stimulation of thirst and decreased maximal urinary concentration.

Concentration of urine requires two basic conditions: (1) a hypertonic medullary interstitium, and (2) osmotic equilibrium of urine in the collecting duct that has the hypertonic interstitium (requiring ADH). Central diabetes insipidus occurs when secretion of ADH is impaired through disruption of the hypothalamic nuclei, osmoreceptors, or supraopticohypophysial tract. The most common causes of central diabetes insipidus are head trauma, hypoxic or ischemic encephalopathy, and idiopathic conditions.

Nephrogenic diabetes insipidus can occur if the countercurrent mechanism in the kidney is disrupted or the ability to respond to ADH is impaired. Lithium use, hypercalcemia, hypokalemia, osmotic diuresis, and sickle cell anemia are common causes of nephrogenic diabetes insipidus.

Clinical features

As in hyponatremia, signs and symptoms of hypernatremia are primarily related to the central nervous system. In hypernatremia, the osmotic pressure gradient favors movement of water out of brain cells and leads to a decrease in brain volume. Neurologic manifestations (eg, lethargy, weakness, irritability, hyperreflexia, seizures, coma, and even death) are the result. The mortality rate ranges from 16% to 60%, depending on the patient

population examined (17).

Patients with diabetes insipidus usually do not present with neurologic symptoms because of the powerful thirst mechanism, which protects them from hypernatremia. Instead, these patients complain of polydipsia, polyuria, and nocturia.

Diagnosis

Important information to obtain during history taking includes evidence of recent fluid losses (including insensible losses from fever, sweating, or recent respiratory infection), alteration in mental status, and thirst (if the patient is alert). Assessing the patient's volume status and measuring urine osmolality and urine sodium concentration (table 2) can be helpful in establishing the cause of hypernatremia and in guiding therapy.

As shown in the equation on page 75, serum osmolality is always greater than 290 mOsm/kg in hypernatremia, representing a hyperosmolar state. Patients should have maximally concentrated urine and urine osmolality of greater than 800 mOsm/kg if defense mechanisms are intact and the renal concentrating mechanism is normal. A normal response is seen in patients with salt overload, insensible or gastrointestinal water losses, or primary hypodipsia.

Patients with urine osmolality of less than 200 mOsm/kg usually have some form of diabetes insipidus and can be differentiated by their response to exogenous ADH (18). However, most patients have urine osmolality between 200 and 800 mOsm/kg, which can reflect volume depletion in central diabetes insipidus, partial diabetes insipidus, or osmotic diuresis.

Treatment

Treatment of hypernatremia follows the same general principles as that of hyponatremia (19,20). Rapid correction should be avoided because of the brain's adaptive response to hypernatremia and the potential risk of cerebral edema. The current recommendation is to lower the serum sodium concentration by about 0.5 mEq/L per hour and to replace no more than half the water deficit in the first 24 hours. The following formula can be used to calculate the water deficit (total body water, in kilograms, is 60% of lean body mass in men and 50% in women):

Water deficit = total body water (serum sodium concentration ÷ 140 - 1)

In patients with hypovolemic hypernatremia, normal saline solution is indicated initially to correct the intravascular volume deficit. When that is accomplished, more hypotonic fluids (eg, 50% normal saline) can be used. In patients with hypervolemic hypernatremia, removing the source of salt excess, administering diuretics, and replacing water are important to successful therapy. Patients with euvolemic hypernatremia usually require water replacement alone--either free water orally or an infusion of 5% dextrose in water.

Again, frequent monitoring of electrolytes is key to successful management.

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Summary

Disorders of sodium and water metabolism can be approached by following a few basic steps: Thorough history taking and physical examination that focuses on volume assessment and laboratory evaluation that includes serum osmolality, urine osmolality, and urine sodium concentration are usually all that are required for diagnosis. Results of these findings are helpful in guiding therapy. Monitoring serum sodium concentration often to ensure adequate treatment and to avoid potential complications is required in management of both hyponatremia and hypernatremia.

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