RESPONSE TO NOTE TO AGENDA

EXPERTS' MEETING,22nd FEBRUARY 2012

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ITEM 1.1.a) COMMENT ON YOUR CONSIDERATION OF THE LITERATURE ABOUT THE RATE OF FALL (OF THE SERUM SODIUM CONCENTRATION)

Articles dealing with hyponatremia in patients have generally stressed the difference between acute hyponatremia (having lasted < 48 hrs) and chronic hyponatremia (>48 hrs) (e.g.: DH Ellison,T Berl , New Engl J Med , 356:2064-2072,2007 ; see their statements on p. 2065 ; a copy of this article can be found attached**). As the authors say , a given degree of serum sodium (<125 mmol/L) in the acute condition (acute hyponatremia) may have serious sequelae such as confusion , hallucinations , seizures , coma , decerebrate posture , respiratory arrest leading to death . The same level of serum sodium in chronic hyponatremia may be asymptomatic** .

There is consensus in the literature that the difference between acute and chronic hyponatremia is explained by different degrees of osmotically induced cell swelling . (Hyponatremia is synonymous with hypoosmolality .) When hyponatremia –i.e. hypoosmolality- first establishes itself "in blood" it will be confronted with cells of all tissues being normal or normoosmolar . Hence water will move from blood into cells (law of osmosis) to reestablish osmotic equilibrium between both fluid compartments . (Cell membranes are water permeable.) This will initially cause cells to swell and the degree of swelling will reflect the initial degree of hyponatremia (acute hyponatremia) . After some time (beginning approximately 1-2 hrs after the onset of hyponatremia and lasting 24 to 48 hrs) there will be the onset of adaptive volume regulation of cells . By this process swollen cells will pump osmotically active particles of their cellular milieu out into the extracellular space (chloride,potassium, organic osmoles) . In this way they usually return their previously increased cell volume back to normal (chronic hyponatremia). Such phenomena are of particular relevance to the brain , supposedly because of the rigid skull limiting the swelling . The described chain of events explains the difference between acute and chronic hyponatremia in terms of the different degrees of brain swelling as well as the difference in terms of its consequences and symptoms . It follows that the bigger the rate of fall of a serum sodium concentration (the more acute a hyponatremia)the more marked the consequences will be .

Research of these phenomena was performed 20 – 40 years ago . Dr.Allen Arieff has been the leader in this field . A relevant article from his laboratory (AI Arieff et al., Medicine 55:121-129,1976 ; a copy of this article can be found

attached to this comment) shows the following :

-in patients acute severe hyponatremia lead to stupor and coma . In other patients that had chronic severe hyponatremia symtoms were milder whereas still other patients with chronic hyponatremia were alert or only mildly confused .

-in experimental animals (rabbits) acute hyponatremia (119 mmol/L) induced over 2 hrs caused all of them to develop grand mal seizures and to die . Post-mortem examination showed brain edema in all . Their measured brain water content was significantly increased by approximately 15% . The chloride- as well as the osmotic-content of the brains was normal . – When a similar degree of hyponatremia (122 mmol/L) was induced over 3.5 days (chronic hyponatremia) the animals were without symptoms . On post-mortem examination the brains appeared normal , there was no brain edema . The brain water content was not significantly increased (+ 5 %) . The brain chloride content had diminished by 15 % .

Another similar article by Arieff where he summarizes findings from several authors (arriving at similar conclusions) is published in Kidney International , 10:104-116 , 1976 . (A copy is attached to this comment).

A further article in kind is for example that by PR Dodge et al., Studies in Experimental Water Intoxication , Arch Neurol 5:513-529, 1960 . These authors enforced a positive water balance of 5% of body weight over 143 – 192 min (both resembling Adam's situation) in 15 anesthetized rabbits . Osmolality fell from 295 mOsm/kg to approximately 275 . Six/fifteen rabbits died . Their brains were found to be" grossly swollen and were in such close approximation to the skull that removal at autopsy was difficult ." Brain water was found to be increased by approximately 10% . No chronic studies were done .

The brain adaptation to chronic hyponatremia has been studied in more detail by several authors . A representative publication is that by JG Verbalis et al , Kidney International 34 : 351-360 , 1988 (a copy is attached to this comment) . In his experiments Dr.Verbalis demonstrated complete normalization of brain volume after 14 to 28 days of sustained hypoosmolality , the major part of which could be accounted for by loss of brain electrolytes . In yet another publication he supported his previous findings even further (JG Verbalis et al.,1995 Elsevier,in:Neurohypophysis:Recent progress of Vasopressin and Oxytocin Research , T.Saito.K.Kurokawa,S.Yoshida editors ;pp. 615-626) .

ITEM 1.1.a)COMMENT ON YOUR CONSIDERATION OF PAPERS ON USE OF N/5 SALINE

Several publications have addressed this issue between 1991 and 2010 . In my comment I first would like to point out that N/5 saline (0.18% saline) and 4% dextrose/0.18% saline are similar though not identical under osmotic aspects , because the dextrose is osmotically ineffective once it has entered the body . (Playfor SD,Expert Opin Druf Saf , 2004 , 3: 67-73 ; an abstract of this article is attached to my comment .) There is consensus in the literature on dextrose being osmotically ineffective in the body.

In the papers I found (GH Kruegener et al. 1991 ; Moritz ML et al.2004 ; Playfor SD , 2004 ; Drysdale SB , 2010 ; abstracts of all articles are attached to this comment) it is indicated that 4.3% dextrose 0.18% saline("dextrose saline") has been in widespread use in children in the past . The publications go on to say that because the dextrose is metabolized by cells after infusion water remains and there is significant danger of dilutional hyponatremia . In these papers dextrose saline is called a common cause of water overload and dilutional hyponatremia . It is stated that there have been over 50 (reported) cases of death or permanent neurologic injury in children from hospital acquired hyponatremia resulting from the administration of such hypotonic infusions . It is proposed that " the practice of administering hypotonic maintainance intravenous fluids in children is unsafe and should be abandoned".

ITEM 1.1.b)COMMENT ON YOUR CONSIDERATION OF THE ARTICLES OF PAUT AND SICOT

-The publication by Paut et al. (Ann Fr Anesth Reanim 2000 , 19 : 467-473) is a description of 7 children with postoperative hyponatremia (120 mmol/L) due to infusions of hypotonic fluids –mainly dextrose 5%- and severe symptoms (seizures , status epilepticus , loss of consciousness ,vomiting , respiratory arrest.) One child which had diffuse cerebral edema died . The clinical presentation (due to symptoms) was noted to occur 11 hrs post surgery . The surgical procedures had all been done electively , there were no emergency procedures . Treatment was successful in 6/7 children . It returned the serum sodium to 135 mmol/L , which was associated with "good neurologic outcome" . – In the introduction it is said that postoperative hyponatremia in children is frequent , is often due to infusions of hypotonic fluid , may lead to severe neurologic consequences including demise . – In the conclusions it says : The use of hypotonic solute in the perioperative period can lead to hyponatremic encephalopathy , a severe neurologic complication of acute hyponatremia . It must be prevented by the use of appropriate solutions ,i.e. isotonic fluids.

-The publication by Sicot and Laxenaire (Ann Fr Anesth Reanim 2007 , 26:893-896) reports a 4 year old child that had undergone elective tonsillectomy. Postoperatively she was given infusions of 5% glucose in water (due to a misunderstandment). Over about 12 hrs she became increasingly symptomatic (vomiting , pain , convulsions , coma) , reaching a serum sodium of 115 mmol/L . She was found to be brain dead by EEG . She had severe cerebral edema with herniation of the cerebellum into the foramen magnum at autopsy .

-COMMENT : Both publications are somewhat relevant to Adam's case though not identical . They show similar degrees of hyponatremia (120 mmol/L in the paper by Paut et al.) , severe neurologic sequelae (2 deaths from cerebral edema) , and causation by infusions of hypotonic fluids . However in both publications the rate of fall of the serum sodium must have been considerably less than in Adam's case , because the patients took more than 10 hours to reach the reported degree of hyponatremia (in Adam 2.5 hrs) . On the basis of what is known about cell volume regulation in acute hyponatremia the much brisker onset of hyponatremia in Adam should have caused a more marked effect in terms of cerebral edema in him than in the reported patients . The difference between "intraoperative" and "postoperative" hyponatremia as such in my opinion is not very important for the subsequent brain swelling , except that the symptoms are recognizable in the postoperative situation . Likewise the difference between 5% glucose (as in

these publications) and 4%dextrose/0.18% NaCl (as in Adam) is not very important in my opinion . Both solutions are similarly (though not exactly) hypoosmotic and it is hypoosmolality which causes brain edema in hyponatremia .

ITEM 1.2.: IDENTIFY ANY PARTICULAR PAPERS OF Dr.VERBALIS THAT YOU CONSIDER TO BE OF PARTICULAR RELEVANCE

1) JG Verbalis , MD Drutarosky : Adaptation to chronic hypoosmolality in rats . Kidney International 34 : 351-360 , 1988 (A copy of this article is attached to section 1.1.a –rate of fall- of this report .)

2) JG Verbalis , S Adler , GE Hoffman , AJ Martinez : Brain adaptation to hyponatremia : physiological mechanisms and clinical implications . 1995 Elsevier . Neurohypophysis : Recent progress of vasopressin and Oxytocin research . T.Saito , K.Kurokawa , S.Yoshida , editors ; pp. 615-626

ITEM 2,3.:INFORMATION ON ADAM's ELECTROLYTE TESTS . NEW MEASUREMENT SHOWING 133 mmol/L , POSSIBLY TAKEN AT 23:00 ON NOV. 26 , 1995 , DOES THIS HAVE AN IMPACT ON THE RATE OF FALL OF THE SERUM SODIUM ? YOU INDICATED THAT YOU WISHED TO REVIEW YOUR CALCULATIONS IN LIGHT OF DATA TO BE CLARIFIED

-There may be a misunderstanding here . As I recall it I asked for the sodium concentration in the peritoneal dialysate (and not in Adam) , because Dr.Coulthard said in his report that it was normal , implying that it might have been 136 or 138 or even 140 mmol/L . In contrast in my report I had used a sodium concentration in peritoneal dialysate of 132 mmol/L , which I had looked up in Germany . If Dr.Coulthard's figures would have applied then I would have had to revise my calculation . However I received a note from the Inquiry (IHRD) about 2 weeks ago confirming that the sodium concentration in the peritoneal dialysate used by Adam was 132 mmol/L . Hence there is no need to change the calculation .

-As concerns the new measurement : In my report I argued that Adam's serum sodium at 7 a.m. should have been 132 mmol/L or close to that value because a patient's natremia approximates that of the dialysate in the course of peritoneal dialysis treatment and because Adam seems to have had no further input between the end of dialysis at 5 a.m. and the begin of anesthesia at 7 a.m. . The possibility of Adam having had a serum sodium of 133 at 11 p.m. the night before (i.e. very close to the 132 in the dialysate) therefore has no impact on my considerations/calculations of the rate of fall of the serum sodium between 7 a.m. and 9:32 a.m. .

ITEM 4,a) :PLEASE COMMENT ON YOUR VIEW OF THE RATE OF FALL IN SERUM SODIUM IN ADAM's PREVIOUS EPISODES OF HYPONATREMIA , AND WHETHER HE WAS SYMPTOMATIC/ASYMPTOMATIC AT THOSE TIMES

-I identified 9 episodes of hyponatremia <129 mmol/L in Adam . There was one episode which I could not analyze (Dec 14 , 1993 . Serum sodium of 119 mmol/L . Ref. 055-054-159 .) For this episode the rate of fall could not be determined because the preceding measurement of serum sodium appears to have been obtained 25 days earlier . In addition the notes available to me did not comment on any symptomatology , they only stated "Foley catheter replaced" .

-1) Episode of Oct 15 , 1991 , Ref. 049-029-078 , **serum sodium of 128 mmol/L .**
Rate of fall : would be misleading to determine because the preceding measurement of the serum sodium appears to have been obtained on Sep 3 , 1991 .
Symptoms : "Irritable and off foods for 2/1 . Vomited x 2 ."

-2) Episode of Nov 25 , 1991 , 11 a.m. , Ref. 050-022-065 , **serum sodium 111** mmol/L .
Rate of fall : The previous measurement (129 mmol/L) is from Nov. 24 , time not reported . Hence the rate of fall would **be 0.75 mmol/L/hr** if the preceding measurement had been taken at 11 a.m. on Nov. 24 .
Symptoms: The only information available seems to be a transferal letter to the Royal Hosp.for Sick Children in Belfast which did not comment on any symptomatology .

-3) Episode of Dec 25 , 1991 , Ref. 050-024-165 , **serum sodium 127 mmol/L .**
Rate of fall : **0.04 mmol/L/hr** (assuming that the preceding measurement of Dec.24 was taken at a comparable time of day).
Symptoms : **"Still looks miserable . Drowsy , but also dislikes being disturbed ."**

-4) Episode of Feb 12 , 1992 , Ref. 050-024-215 **, serum sodium 128 mmol/L .**
Rate of fall : 0.16 mmol/L/hr (assuming that the 72 hr interval since the preceding measurement is valid).
Symptoms : I was unable to locate any clinical notes on this visit between the corresponding Refs. 050-024-pdf and 050-037-pdf .

-5) Episode of April 21 , 1993 , Ref. 055-053-120 , **serum sodium 125 mmol/L** at 9:42 a.m.
Rate of fall : o.75 mmol/L/hr (since the preceding measurement of April 20 at 16:26).
Symptoms : The record appears to show only a cystoscopy note , it does not comment on any symptomatology .

-6) Episode of Feb. 15 , 1994 , Ref. 056-038-097 , **serum sodium 127 mmol/L .**
Rate of fall : misleading to determine because the preceding measurement was obtained 19 days before the present one .
Symptoms : "Looks the picture of health ."

-7) Episode of June 8 , 1995 , No reference avail. , **serum sodium 124 mmol/L**
Rate of fall : misleading to determine because the preceding measurement was obtained 28 days earlier .
Symptoms : " More easily tired . Vomiting is worse ."

-8) Episode of Nov.27 , 1995 , Ref. 058-003-003 **, serum sodium 123 mmol/L** at 9:32 a.m.
Rate of fall : 3.6 mmol/L/hr (if the serum sodium was 132 mmol/L at 7 a.m. , which was the sodium concentration in the dialysate at 5 a.m. . A measurement possibly obtained at 23:00 on Nov.26 reportedly showed 133 mmol/L) .
Symptoms : Not applicable ; pat. was under general anesthesia at 9:32 a.m.

COMMENT :

RATE OF FALL

In preceding episodes of hyponatremia (occurring between Nov.25 , 1991 and April 21 , 1993) the recorded rate of fall was between 0.04 mmol/L/hr and 0.75 mmol/L/hr .

In contrast on Nov. 27 , 1995 the rate of fall was 3.6 mmol/L/hr between 7 a.m. and 9:32 a.m. and possibly larger . In other words it was approximately 5 times larger than during previous episodes of hyponatremia .

SYMPTOMS

In 3/8 episodes of hyponatremia symtoms were reported that may be attributable to hyponatremia . In most of the other episodes it appears that symptomatology as such was not reported altogether .

ITEM 2 , 4.,b, i) PLEASE COMMENT ON YOUR VIEWS OF ADAM's CLINICAL HISTORY IN RELATION TO WHETHER ADAM HAD BEEN ANEMIC IN THE PAST

-Adam's records show at least 119 measurements of his hemoglobin concentration in blood in the anemic range while 11 measurements show normal hemoglobin concentrations . During this interval (12/1991 to 10/1995) anemia was relatively severe (hemoglobin concentrations <8.7 g/L ; normal range : 12-18) on at least 21 occasions .

Together : Adam was frequently anemic .

ITEM 2 , 4.,b,ii) WHETHER ADAM HAD BEEN DEHYDRATED IN THE PAST FROM POLYURIA

-In the clinical case notes in Adam the following is found:

On Dec 27 , 1991 , ref. 050-023-072 : "Good urine output ...500 ml ...maybe a little dry ."

On Jan 4 , 1992 , ref. 050-023-075 : "Is behind fluids 300 ml" .

On May 7 , 1992 , ref. 053-026-074 : "Dehydration" . (It is unclear whether the dehydration was related to polyuria or some other change , e.g. diarrhea or vomiting).

On Nov. 28 , 1992 , ref. 054-057-147 : "Looks slightly dehydrated" . (It remains unclarified what this may have been related to , polyuria , vomiting , diarrhea , sweating , etc.)

In addition Adam was noted to be hypernatremic on Jan 11,1992 , on Feb 8 , 1992 and on March 23 , 1992 , however notes do not indicate why . Hypernatremia may be a clinical sign of dehydration from any cause .

Together : Adam may have been dehydrated on 4 occasions in the past , probably due to polyuria . This is not a high frequency .

ITEM 2 , 4., b),iii WHETHER ADAM HAD AN IRON DEFICIENCY

-I saw 130 measurements of Adam's complete blood count . The MCHC was recorded too low only twice in these measurements . (This parameter may indicate iron deficiency). The MCV –another such parameter- was normal throughout .

The serum iron was measured and reported only four times between 12/91 and 7/95 ; in each of these measurements the value was below the range of normal . This usually signifies iron deficiency .The total iron binding capacity (TIBC) was normal during 3 of the measurements , in one it was below the normal range . (In iron deficiency anemia the TIBC is often elevated).

The serum ferritin was determined twice between 12/91 and 7/95 ; both times it was elevated . (Ferritin elevation is a sign of iron overload . In kidney disease it may be elevated for other reasons such as chronic inflammation or inadequate nutrition.)

Adam received iron supplements since Feb 10 , 1993 . Physicians ordinarily prescribe iron supplements to treat iron deficiency .

Together : Adam appears to have been iron deficient repeatedly , possibly much of the time .

ITEM 2 , 4., b), iv : THE LENGTH OF TIME ADAM HAD RECEIVED ERYTHROPOIETIN

-Erythropoietin (EPO) was started on Nov. 25 , 1993 .

-A note of Dec. 14 , 1993 says that Adam objected to injections of EPO . It is very likely that EPO was stopped at that time for the reason of pain .

-EPO was restarted on Sep 8 of 1994 .

-The dose of EPO was reduced on June 8 , 1995 .

-The dose of EPO was increased again on Oct 12 of 1995 .

Together Adam received EPO for a total of approximately 14 months .

ITEM 2 , 4., c) COMMENT ON YOUR VIEW OF CYCLOSPORIN WHICH IS RECORDED AS HAVING STARTED IN PICU AT 12:00 (of Nov.27,1995)

-Ref. 058-005-012 reads : "27/11/95 : Cyclosporin 3 mg/kg/12 hrs infusion iv" . (There is no time of start and no confirmation that it was actually given on the note).

-Ref. 058-035-137 says :" 27/11/95 ; 1 p.m. : cyclosporine 3 mg/kg/12 hrs ".

-In ref. 058-038-150 it looks as if the cyclosporine infusion may have been started at 12:00 noon .

2-4 mg/kg/day is the usual dose in adults and in children. I suspect that by "3 mg/kg/12 hrs" it is meant to give this regimen once a day . Cyclosporin was a standart immunosuppressant for transplantation in 1995 . Customarily one would obtain trough blood levels of cyclosporine A and then adjust the dose –if necessary- according to the results of these measurements .

At the time of these notes the physicians probably intended to treat the transplant according to usual routine procedure at least for the time being – not knowing that it was infarcted as shown later and not being certain of the state of Adam's brain and its pathology . In my opinion this was an appropriate procedure under the circumstances .

ITEM 2 , 5.: ADVISE ON THE EXTENT TO WHICH YOU CONSIDER THAT IN ADAM's CASE THERE WERE ANY OTHER RISK FACTORS FOR CHRONIC OR ACUTE VENOUS THROMBOSIS WHICH COULD HAVE INVOLVED THE CEREBRAL VENOUS SINUSES , AND EXPLAIN WHAT THEY WERE AND YOUR REASONS FOR CONSIDERING THAT THEY COULD HAVE BEEN PRESENT

-This is a question outside my expertise . It ought to be addressed to a neurologist or an angiologist .
(I looked up an article by J Stam , New Engl J Med 352 : 1791-1798 , 2005 . This article considers the following established risk factors for the condition of sinus venosus thrombosis :

1) thrombophilia (factor V Leyden ; deficiencies of : protein C , protein S , antithrombin III)

2) nephrotic syndrome

3) chronic inflammatory disease

4) pregnancy and puerperium

5) polycythemia vera and paroxysmal nocturnal hemoglobinuria

6) hormonal contraception

7) meningitis and infections of ear/nose/throat

8) direct injury to the venous sinuses

9) medical procedures in the head and neck area .

Conditions 2 , 4 – 8 were not present in Adam .

Condition 1 supposedly was never tested for in Adam , however it seems less likely that sinus venosus thrombosis would happen before peripheral venous thrombosis as a first manifestation of thrombophilia .

Condition 3 may have applied to some degree because of Adam's repeated urinary tract infections with fever and perhaps also because of him having had an implanted catheter for dialysis as well as having a gastrostoma .

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Condition 9 may have applied because Adam appears to have been catheterized in his neck veins before , including possibly having received a ligation to his left internal jugular vein .)

ITEM 2 , 6 : Dr.COULTHARD STATED THAT " ADAM's POLYURIA RELATIVE TO HIS BODY SIZE FELL AS HE GOT OLDER AND WENT INTO RENAL FAILURE ." PAGES 45-49 . HAVING HAD AN OPPORTUNITY TO REVIEW THE TRANSSCRIPT PLEASE COMMENT ON THOSE STATEMENTS AND INDICATE WHETHER OR NOT YOU AGREE OR DISAGREE WITH THEM

-I HAVE NOT RECEIVED THE TRANSSCRIPT IN QUESTION .

-The measurements of urinary output in 1991 and 1992 seem to indicate a tendency for the urinary output per unit of body size to fall . I saw no further measurements of urinary output recorded in 1993 , 1994 , 1995 . Therefore there is no data in Adam to substantiate the statement that polyuria fell during 1993 – 1995 . However in a general sense there is usually a decline of the urinary flow rate when a kidney develops chronic renal failure .

ITEM 2 , 7 : SEIZURES IN PREVIOUS OPERATIONS : PLEASE COMMENT ON HOW IT COULD BE DETERMINED WHETHER ADAM WAS EXPERIENCING SEIZURES DURING ANY OF HIS OPERATIONS WHILST ANESTHETIZED

You are asking a foot-doctor (myself) a difficult question about the electrical activity of the brain . I am not knowledgable in this special area . You ought to ask a neurologist or a neurophysiologist .

(According to my guesswork a patient with seizures during operations may also have signs of a tendency to develop seizures when awake and such signs might show in an EEG . Perhaps such a patient would even have physical signs of seizure activity occasionally when awake . – Prof.Kirkham has said that during an operation seizure activity may be indicated by the patient developing sudden tachycardia and sudden increase of blood pressure that are not explained by any other changes . Whether an EEG during operation would make sense I do not know .)

ITEM 2 , 8. : COMMENT ON THE POINT AT WHICH YOU CONSIDER THAT ADAM's CONDITION WOULD HAVE CEASED TO HAVE BEEN REVERSIBLE AND EXPLAIN THE REASONS WHY

My study of the literature and of Adam's details lead me to conclude that the most likely major event leading to Adam's brain swelling with entrapment of the cerebellum and brain stem was his acute hyponatremia , i.e. water intoxication .

A small additional contributing event could have been Adam's rapidly progressive anemia . (I had mentioned this in my initial report of Jan. 2 , 2011 . However in my opinion the argument was weak at the time because of the documented absence of morphological signs of ischemia . This has now changed somewhat . I learned from Dr.Waney Squier's comments on Feb.22 and March 9 that it is conceivable that the brain could have been affected by ischemia causing functional changes where however the duration was too short to lead to the typical histological alterations of ischemia . Adam's hematocrit was approximately 31% before his operation on Nov.27 , 1995 (normal range 35 – 40 %) and dropped to 18% at 9:32 a.m. . This is a reduction by 42 % . At a normal oxygen consumption rate this would drop the interstitial fluid partial pressure of oxygen from 40 to 25 mm Hg . Only 3 mm Hg are normally required for full support of the metabolic processes of cells . This seems to be a large reserve . However in a swollen brain the distance of diffusion that oxygen would have to travel from blood to cells is usually increased and this would inhibit oxygen delivery . I failed to find data on whether an increased interstitial pressure could diminish the blood flow rate –if the arterioles were dilated already- which might be an additional cause for an inhibited oxygen delivery . Finally the increased CVP of 17 mmHg should have diminished the perfusion pressure –the driving force for the blood flow rate- bringing it close to the range of what is considered a critical perfusion pressure for the brain .- Together : I do not want to exclude that Adam's relatively severe anemia caused a minor contribution to his brain swelling.)

Another small additional contribution to the brain swelling in Adam may have resulted from the head down position plus the fact that the CVP was elevated (17 mmHg) to begin with . Both will increase the venous pressure at the end of cerebral capillaries , resulting in a raised capillary pressure and hence more filtration of fluid from the lumen of capillaries into the interstitium . (If the arterial pressure increased as well then the capillary pressure will rise even further as will fluid filtration into the interstitium .)

As far as the possibilities of cerebral venous sinus thrombosis and PRES are concerned I consider them interesting hypotheses but I do not find the evidence for these diagnoses plausible . I am not certain whether diagnoses can be based primarily on risk factors . Hence I will not include PRES and cerebral venous sinus thrombosis with respect to the timepoint that I propose .

CONCLUSION

Because in water intoxication the rate of fall of the serum osmolality is a critical aspect and since Adam's rate of fall was 3.6 mmol/L/hr between 7 a.m. and 9:32 a.m. of Nov.27 , whereas it slowed down thereafter and was only 1.1 mmol/L/hr between 9:32 a.m. and 1 p.m. it is more likely that the timepoint in question was between 7 a.m. and 9:32 a.m. rather than later .

At approximately 9:32 a.m. Adam's serum sodium had dropped from 132 mmol/L to 123 , which is a fall by approximately 7% . This should have translated into a corresponding degree of brain swelling (brain volume increase) . Arieff et al. (BMJ , 1992 , report on the 16 children with hyponatremia) state that "the human brain can expand by only about 5-7% of its normal volume before herniation occurs " . Hence the similarity of these percentages indicates that Adam could have reached the critical volume at approximately 9:32 a.m. or perhaps within 20 min before that time . In fact there were 2 cases in Arieff's series who died from brain edema at a serum sodium concentration of 123 mmol/L .

Adam reached the trough level of his hematocrit at approximately 9:32 a.m. , when it was 18% . Shortly thereafter the first bag of red blood cells was transfused into him .

Taken together I believe that the events leading to Adam's brain edema culminated around 9:32 a.m. . I think it is likely that the herniation of the cerebellum and the brain stem occurred around that time . As far as I know these latter changes are not reversible .

Dresden, March 18, 2012

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CLINICAL PRACTICE

The Syndrome of Inappropriate Antidiuresis

David H. Ellison, M.D., and Tomas Berl, M.D.

A 62-year-old woman noted an unpleasant, sweet taste in her mouth. She otherwise felt well and was taking no medications. Because dysgeusia is a rare manifestation of hyponatremia, her serum sodium level was tested and was 122 mmol per liter. The serum osmolality was 250 mOsm per kilogram of water, the urinary osmolality 635 mOsm per kilogram of water, the urinary sodium 85 mmol per liter, and the urinary potassium 40 mmol per liter. Her thyroid function and adrenal function were normal. A computed tomographic (CT) scan of the thorax showed a mass in the lower lobe of the left lung, which proved to be a small-cell carcinoma. How should her hyponatremia be treated?

THE CLINICAL PROBLEM

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N Engl J Med 2007;356:2064-72.

Hyponatremia, defined as an excess of water in relation to the sodium in the extracellular fluid, is the most common electrolyte disorder in hospitalized patients.[1] Mild hyponatremia (serum sodium, <135 mmol per liter) occurs in 15 to 22% of these patients and in approximately 7% of ambulatory patients[2]; moderate hyponatremia (serum sodium, <130 mmol per liter) occurs in 1 to 7% of hospitalized patients.[3,4] Hyponatremia is important to recognize both because of potential morbidity and because it can be a marker of underlying disease.

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is the most frequent cause of hyponatremia, although hyponatremia associated with volume depletion of the extracellular fluid also occurs commonly.[5] SIADH was first described in patients with bronchogenic carcinoma in whom a physiologic stimulus for the release of the antidiuretic hormone was lacking.[6] Thus, the level of secretion of the antidiuretic hormone was deemed "inappropriate." After the syndrome was described, the antidiuretic hormone in humans was found to be arginine vasopressin.

Initial reports suggested that secretion of arginine vasopressin in SIADH was independent of plasma osmolality. Although this is the case in about one third of patients with SIADH[7] (Fig. 1), in other patients with this condition, secretion of arginine vasopressin is fully suppressed, resulting in dilute urine, but at a serum sodium level lower than normal (a "reset osmostat"). Less commonly, plasma levels of arginine vasopressin are low or undetectable in patients with SIADH, even in the presence of hyponatremia. In some patients, mutations of the aquaretic (i.e., water-channel–regulating) vasopressin receptor are present, resulting in concentrated urine in the absence of arginine vasopressin.[8] Because not all patients with the syndrome have elevated circulating levels of arginine vasopressin, the term syndrome of inappropriate antidiuresis (SIAD) was proposed as an accurate description of this condition.[8] Although inappropriate antidiuresis is an essential feature of this syndrome, excessive water intake, driven by nonosmotic stimuli, is also required for hyponatremia to develop.

Certain populations are at increased risk for hyponatremia associated with SIAD.

The risk rises with increasing age and is especially high among residents of nursing homes.[4] Although the causes of SIAD are myriad, they can be categorized as related to malignant diseases, pulmonary diseases, and disorders of the central nervous system, among others (Table 1). In addition, a variety of drugs can stimulate the release of arginine vasopressin or potentiate its action (Table 1); traditionally, some medical authorities include such drugs among the causes of SIADH,[9,10] whereas others do not include them in this category.[11]

Severe hyponatremia (serum sodium <125 mmol per liter), especially when the condition develops rapidly (within 48 hours), has serious sequelae, including confusion, hallucinations, seizures, coma, decerebrate posture, and respiratory arrest, leading to death. Milder symptoms of hyponatremia include headache, difficulty concentrating, impaired memory, muscle cramps, and weakness; dysgeusia has also been reported. Patients with chronic hyponatremia may be asymptomatic, although some data suggest that neurologic deficits, such as those causing falls, may be more common in patients with chronic hyponatremia than in persons with normal serum sodium levels.[12] The threshold serum sodium levels at which neurologic complications occur appear to be higher among women than among men.[13]

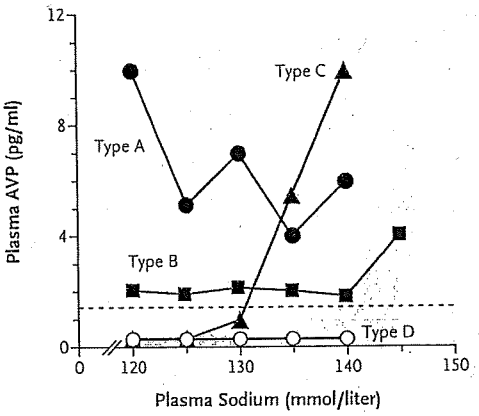

Figure 1. Types of the Syndrome of Inappropriate Antidiuresis (SIAD).

Patterns of plasma levels of arginine vasopressin (AVP; also known as the antidiuretic hormone), as compared with plasma sodium levels in patients with SIAD, are shown. Type A is characterized by unregulated secretion of AVP, type B by elevated basal secretion of AVP despite normal regulation by osmolality, type C by a "reset osmostat," and type D by undetectable AVP. The shaded area represents normal values of plasma AVP. Adapted from Robertson,[7] with the permission of the publisher.

STRATEGIES AND EVIDENCE

DIAGNOSIS

Formal criteria for the diagnosis of SIAD are summarized in Table 2.[14] Serum osmolality must be measured to rule out pseudohyponatremia, a laboratory artifact occurring when levels of serum lipids or proteins are elevated and serum sodium levels are measured by means of common, indirect techniques.[15] Hypertonic (or translocational) hyponatremia occurs when osmotically active solutes (glucose or mannitol) draw water from cells. For each increase of 100 mg per deciliter (5.6 mmol per liter) in plasma glucose levels, serum sodium declines by 1.6 to 2.4 mmol per liter.[16] (The traditional correction factor of 1.6 mmol per liter may underestimate the actual change.) A normal or elevated measured osmolality value, however, does not rule out hypotonic hyponatremia, because urea is an ineffective osmole. Thus, the effective osmolality (sometimes called tonicity) is equal to the measured osmolality minus (blood urea nitrogen ÷2.8), with blood urea nitrogen measured in milligrams per deciliter.[17] For a diagnosis of hypotonic hyponatremia, the effective osmolality must be less than 275 mOsm per kilogram of water (Table 2).

To make the diagnosis of SIAD, the urinary osmolality must exceed 100 mOsm per kilogram of water when the effective plasma osmolality is low (Table 2). The presence of clinical euvolemia is considered to be essential, because depletion of the effective arterial blood volume stimulates the secretion of arginine vasopressin appropriately. When expansion of the volume of extracellular fluid is associated with depletion of the effective arterial blood volume (as in cirrhosis), edema is usually evident. Detecting extracellular-fluid volume depletion as a cause of hyponatremia, however, is more difficult than detecting volume expansion, because the sensitivity of clinical assessment is limited[18]; laboratory tests are often used to provide additional guidance. Hypouricemia, low blood urea nitrogen, and a urinary sodium level greater than 40 mmol per liter in patients

Table 1. Causes of the Syndrome of Inappropriate Antidiuresis (SIAD).*

Malignant Diseases	Pulmonary Disorders	Disorders of the Central Nervous System
Carcinoma	Infections	Infection
Lung	Bacterial pneumonia	Encephalitis
Small-cell	Viral pneumonia	Meningitis
Mesothelioma	Pulmonary abscess	Brain abscess
Oropharynx	Tuberculosis	Rocky Mountain spotted fever
Gastrointestinal tract	Aspergillosis	AIDS
Stomach	Asthma	Bleeding and masses
Duodenum	Cystic fibrosis	Subdural hematoma
Pancreas	Respiratory failure associated with positive-pressure breathing	Subarachnoid hemorrhage
Genitourinary tract		Cerebrovascular accident
Ureter		Brain tumors
Bladder		Head trauma
Prostate		Hydrocephalus
Endometrium		Cavernous sinus thrombosis
Endocrine thymoma		Other
Lymphomas		Multiple sclerosis
Sarcomas		Guillain–Barré syndrome
Ewing's sarcoma		Shy–Drager syndrome
		Delirium tremens
		Acute intermittent porphyria

Drugs	Other Causes
Drugs that stimulate release of AVP or enhance its action	Hereditary (gain-of-function mutations in the vasopressin V_2 receptor)
Chlorpropramide	Idiopathic
SSRIs	Transient
Tricyclic antidepressants	Endurance exercise
Clofibrate (Atromid-S, Wyeth–Ayerst)	General anesthesia
Carbamazepine (Epitol, Lemmon; Tegretol, Ciba–Geigy)	Nausea
Vincristine (Oncovin, Lilly; Vincasar, Pharmacia and Upjohn)	Pain
Nicotine	Stress
Narcotics	
Antipsychotic drugs	
Ifosfamide (Ifex, Bristol-Myers Squibb)	
Cyclophosphamide (Cytoxan, Bristol-Myers Squibb; Neosar, Pharmacia and Upjohn)	
Nonsteroidal antiinflammatory drugs	
MDMA ("ecstasy")	
AVP analogues	
Desmopressin (DDAVP, Rhone–Poulenc Rorer; Stimate, Centeon)	
Oxytocin (Pitocin, Parke–Davis; Syntocinon, Novartis)	
Vasopressin	

* AIDS denotes the acquired immunodeficiency syndrome, AVP arginine vasopressin, SSRI selective serotonin-reuptake inhibitor, and MDMA 3,4-methylenedioxymethamphetamine.

with hyponatremia suggest SIAD, but are not diagnostic[5]; for example, a serum uric acid level of less than 4 mg per deciliter (238 μmol per liter) (in the presence of hyponatremia) has a positive predictive value for SIAD of 73 to 100%.[19-21] A urinary sodium level of less than 30 mmol per liter has a positive predictive value of 71 to 100% for an infusion of 0.9% saline to increase the serum sodium level.[18,22]

When diagnostic uncertainty remains, volume contraction of the extracellular fluid can be ruled out by infusing 2 liters of 0.9% saline over a period of 24 to 48 hours. Even though 0.9% saline is not the preferred treatment for SIAD, it is usually safe when the baseline urinary osmolality is less than 500 mOsm per kilogram of water[17,22,23]; correction of the hyponatremia suggests underlying volume depletion of extracellular fluid. Measurement of the serum level of arginine vasopressin is not recommended routinely, because urinary osmolality above 100 mOsm per kilogram of water is usually sufficient to indicate excess of circulating arginine vasopressin.

MANAGEMENT

The only definitive treatment of SIAD is elimination of its underlying cause. Most cases caused by malignant disease resolve with effective antineoplastic therapy, and most of those due to medication resolve promptly when the offending agent is discontinued. When the hyponatremia is chronic and asymptomatic, a diagnosis can be pursued before treatment is initiated.

Acute Symptomatic Hyponatremia

The most important factors dictating the management of SIAD are the severity of the hyponatremia, its duration, and the presence or absence of symptoms (Fig. 2).[11,24,25] For symptomatic patients with severe hyponatremia known to have developed within 48 hours, clinical experience suggests that rapid treatment is warranted.[26] The goal is to raise the serum sodium level by 1 to 2 mmol per liter per hour by infusing 3% saline; these recommended rates are guided by data from case series, in the absence of data from randomized trials, but they are widely accepted.[1] Many authorities recommend concomitant furosemide,[1] although some recommend avoiding it[10] or reserving it for patients with extracellular-fluid volume expansion.[9,27] Many experts believe that the magnitude of correction during the first 24 hours of treatment should be no

more than 8 to 10 mmol per liter, and during the first 48 hours no more than 18 to 25 mmol per liter, even when the hyponatremia is acute.[1,2,27] One approach is to aim for the cessation of neurologic symptoms, such as seizures, and then reduce the correction rate.[25] An increase in serum sodium levels of less than 10 mmol per liter is usually sufficient to reduce the symptoms and prevent complications.[28] (Specific treatment regimens are discussed below.)

Hyponatremia of Long or Unclear Duration

Most cases of hyponatremia that occur out of the hospital are chronic and minimally symptomatic, except in marathon runners, users of 3,4-methylenedioxymethamphetamine (MDMA, also known as "ecstasy"), and people who drink water to excess; in these groups, severe symptoms usually indicate acute hyponatremia and require rapid correction.

The treatment of hyponatremia with an unclear duration and nonspecific symptoms or signs (e.g., headache or lethargy) is particularly challenging. Some reports suggest a high risk if patients are not treated aggressively[29]; others suggest that rapid correction increases morbidity or mortality.[30] Unlike patients with acute hyponatremia, those with hyponatremia of longer duration have a documented risk of osmotic demyelination if the serum sodium level is corrected by more than 12 mmol per liter over a period of 24 hours. This disorder, which includes both central pontine and extrapontine myelinolysis, begins with lethargy and affective changes (generally after initial improvement of neurologic symptoms with treatment), followed by mutism or dysarthria, spastic quadriparesis, and pseudobulbar palsy.[31] Case series and experimental data indicate that this complication may result from rapid correction of hyponatremia that has been present for more than 48 hours.[31]

To balance the risks of chronic hyponatremia against the risks of rapid correction, many authorities recommend a modest rate of correction (an increase in serum sodium of 0.5 to 1.0 mmol per liter per hour), using lower rates of saline infusion for patients with symptomatic hyponatremia of unknown duration. Many limit correction to 8 mmol per liter over a period of 24 hours and 18 mmol per liter over a period of 48 hours; close monitoring of the rate of correction (every 2 to 3 hours)[25] is recommended to avoid overcorrection. Some authorities recommend brain imaging (e.g., CT or magnetic resonance imaging) to determine whether cerebral edema is present and to gauge the urgency of the need for correction, although evidence that imaging improves outcomes is lacking.[32]

Asymptomatic patients with chronic hyponatremia have a low risk of serious neurologic sequelae but a well-described risk of osmotic demyelination with rapid correction.[31] Therefore, treatment is aimed at correcting the hyponatremia very gradually. Fluid restriction, estimated on the basis of levels of urinary and plasma electrolytes (Fig. 2), is a cornerstone of therapy.[6,33] The maximum tolerated fluid intake is proportional to the oral osmotic load, so adequate intake of dietary protein and salt should be encouraged. Oral intake of urea (30 g per day) is effective but is poorly tolerated. Demeclocycline (Declomycin, Wyeth–Ayerst) (300 to 600 mg twice daily) reduces urinary osmolality and increases serum sodium levels, but its effects

Table 2. Diagnosis of SIAD.*

Essential features
Decreased effective osmolality (<275 mOsm/kg of water)
Urinary osmolality >100 mOsm/kg of water during hypotonicity
Clinical euvolemia
No clinical signs of volume depletion of extracellular fluid
No orthostasis, tachycardia, decreased skin turgor, or dry mucous membranes
No clinical signs of excessive volume of extracellular fluid
No edema or ascites
Urinary sodium >40 mmol/liter with normal dietary salt intake
Normal thyroid and adrenal function
No recent use of diuretic agents
Supplemental features
Plasma uric acid <4 mg/dl
Blood urea nitrogen <10 mg/dl
Fractional sodium excretion >1%; fractional urea excretion >55%
Failure to correct hyponatremia after 0.9% saline infusion
Correction of hyponatremia through fluid restriction
Abnormal result on test of water load (<80% excretion of 20 ml of water per kilogram of body weight over a period of 4 hours), or inadequate urinary dilution (<100 mOsm/kg of water)
Elevated plasma AVP levels, despite the presence of hypotonicity and clinical euvolemia

* AVP denotes arginine vasopressin. Data are adapted from Schwartz et al.[6] and Janicic and Verbalis.[9] The test for water load and measurement of AVP are rarely recommended. To convert the value for blood urea nitrogen to millimoles per liter, multiply by 0.357.

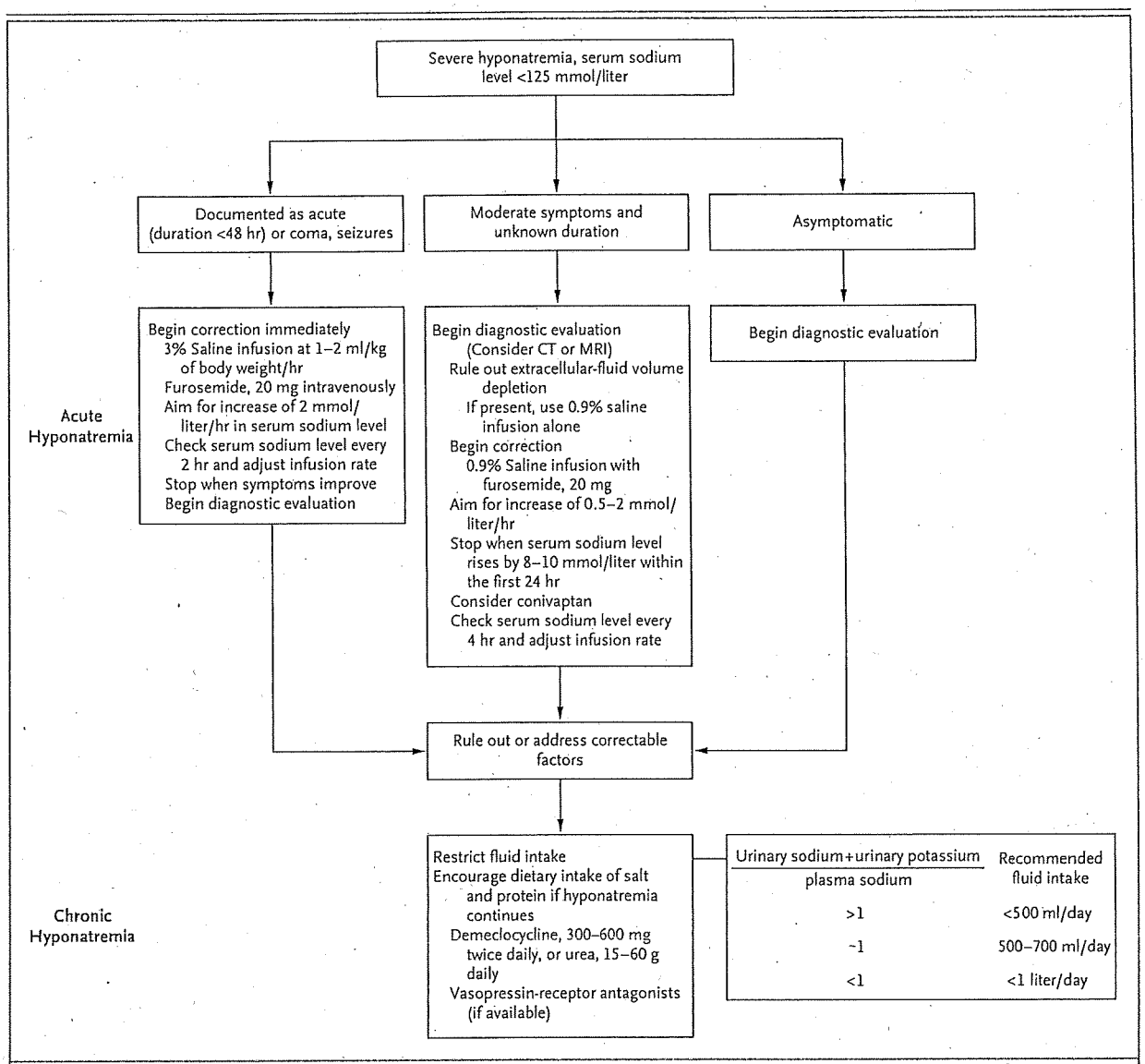

Figure 2. Algorithm for the Treatment of Hyponatremia Associated with SIAD.

can be variable and it can cause nephrotoxicity. Lithium (Eskalith, GlaxoSmithKline; Lithobid, Solvay Pharmaceuticals) is no longer recommended.

Vasopressin-Receptor Antagonist Therapy

A more recent option for treating SIAD is conivaptan (Vaprisol, Astellas Pharma), a vasopressin-receptor antagonist approved by the Food and Drug Administration in 2005 for intravenous treatment of euvolemic hyponatremia[34] and approved in 2007 for intravenous treatment of hypervolemic hyponatremia[35] (Table 3). In a double-blind, randomized trial, in patients assigned to conivaptan for 4 days, as compared with those assigned to placebo, the serum sodium levels increased by 6 mmol per liter. Although hypotension has not been reported in association with conivaptan, it is a risk, because conivaptan is a nonselective vasopressin-receptor antagonist; blocking the vasopressin V_1 receptor induces vasodilation. Currently, conivaptan use is limited to the treatment of hospitalized patients; it might be considered particularly for those who have moderate-to-severe hyponatremia and symptoms but not seizures, delirium, or coma, which would warrant the use of hypertonic saline. Infusion-site reactions are common (occurring in

Table 3. Vasopressin-Receptor Antagonists.*

Drug	Dose of Drug	Vasopressin Receptor	Route of Administration	Urinary Volume	Urinary Osmolality	Sodium Excretion over 24 hr
Conivaptan (Vaprisol, Astellas Pharma)†	20–40 mg daily	V_{1A} and V_2	Intravenous	Increased	Decreased	No change
Tolvaptan (Otsuka)	15–60 mg daily	V_2	Oral	Increased	Decreased	No change
Lixivaptan (CardioKine)	100–200 mg	V_2	Oral	Increased	Decreased	No change with low dose; increased with high dose
Satavaptan (Sanofi-Aventis)	12.5–50 mg	V_2	Oral	Increased	Decreased	No change

* Data are adapted from Lee et al.[35]
† Conivaptan was approved for clinical use in 2005 by the Food and Drug Administration.

as many as 50% of patients, according to the package insert for the drug), and its metabolism by the 3A4 isoform of cytochrome P450 (CYP3A4) can result in drug interactions.

Although not yet clinically available, oral vasopressin-receptor antagonists that are selective for the vasopressin V_2 receptor have been developed (Table 3). In two randomized, controlled trials of tolvaptan, serum sodium levels rose from a mean baseline level of 129 mmol per liter within 24 hours after the administration of the first dose of active drug and remained significantly higher (by 4 mmol per liter) than the levels in the placebo group ($P<0.001$) 30 days after the start of treatment.[4] The tolvaptan group also had a clinically and statistically significant improvement in the mental component of the Medical Outcomes Study 12-item Short-Form General Health Survey[36] ($P=0.02$). In an open-label study, in patients with SIAD, another long-acting oral vasopressin-receptor antagonist, satavaptan (Sanofi-Aventis), maintained serum sodium levels within the normal range (135 to 147 mmol per liter) at 1 year, without major side effects.[37] The appropriate clinical role of the vasopressin-receptor antagonists remains to be defined.

One theoretical concern is that vasopressin-receptor antagonists might increase serum sodium levels too rapidly, putting patients at risk for osmotic demyelination. To date, this complication has not been reported, but trials of these agents have involved very close monitoring and minimal or no water restriction. These agents frequently cause dry mouth and thirst,[36] which stimulate water intake, slowing the rise in serum sodium levels. Use of these agents in practice would require similarly close monitoring of serum sodium levels.

AREAS OF UNCERTAINTY

OPTIMAL STRATEGIES FOR CORRECTING SERUM SODIUM LEVELS

There are no data from randomized trials to guide optimal strategies for correction of serum sodium levels in patients with either acute or chronic hyponatremia, and the relative risks of osmotic demyelination and of hyponatremic encephalopathy continue to be debated.[24] Acute symptomatic hyponatremia is routinely treated with hypertonic saline; many authorities recommend concomitant use of furosemide. Although some suggest that complete correction may be safe,[33] others note that osmotic demyelination might occur even in this setting[25] and recommend that correction with 3% saline during the first 24 hours be limited to 8 to 12 mmol per liter.[9] In patients with seizure and coma, it is reasonable to use 3% saline at a rate of 1 to 2 mmol per liter per hour, even if the hyponatremia has been present for longer than 24 hours, keeping the maximal correction to 8 to 12 mmol per liter per day.[1,9,10,25,27,33] When milder symptoms are present, correction is generally slower (rate, 0.5 mmol per liter per hour)[9]; some authorities avoid the use of 3% saline in this setting.

The best method for determining an initial rate for hypertonic saline infusion is also controversial[38]; Table 4 presents some suggested strategies. The traditional approach is to estimate a sodium deficit and is not physiologically based, because SIAD is characterized by a water excess, rather than a sodium deficit. Another approach is to calculate the effect of 1 liter of an infusate on the serum sodium level, then estimate the volume needed for infusion; this formula predicts actual changes in the serum sodium level reasonably well,[38] but it involves two calculations, which can

Table 4. Formulas for Calculating Initial Saline Infusion Rates.*

Source	Step 1	Step 2	Example of Rate (ml/hr)
Traditional[1]	$\text{Na required} = \text{TBW} \times ([\text{Na}]_2 - [\text{Na}]_1)$	$\text{Volume (liter)} = \frac{\text{Na required (mmol)}}{513\ \text{mmol/liter}}$	82
Adrogué and Madias[1]	$\Delta[\text{Na}]_s\ \text{(with 1 liter)} = \frac{[\text{Na}]_{inf} - [\text{Na}]_1}{\text{TBW} + 1}$	$\text{Volume (liter)} = \frac{\text{Desired } \Delta[\text{Na}]_s}{\Delta[\text{Na}]_s\text{(with 1 liter)}}$	107
Barsoum and Levine[39]	$\Delta[\text{Na}]_s = \frac{(V_{inf})[\text{Na}]_{inf} - (V_u)[\text{E}]_{urine} - (\Delta V)[\text{Na}]_1}{\text{TBW} + \Delta V}$	$\text{Volume (liter)} = \frac{\text{Desired } \Delta[\text{Na}]_s}{\Delta[\text{Na}]_s\ \text{(with 1 liter)}}$	107
Nguyen and Kurtz[40]		$\text{Volume (liter)} = \frac{\text{TBW} \times \left(1 - \frac{[\text{Na}]_1 + 23.8}{[\text{Na}]_2 + 23.8}\right) + V_{input} - \frac{[\text{E}]_{input} \times V_{input}}{[\text{E}]_{urine}}}{\frac{[\text{E}]_{inf}}{[\text{E}]_{urine}} - 1}$	90
Janicic and Verbalis[9]		Rate (ml/hr) is the goal rate of $[\text{Na}]_s$ rise (mmol/liter/hr) per kg of body weight	70

* The examples assume a body weight of 70 kg, current serum sodium ($[\text{Na}]_s$) level of 110 mmol per liter, desired $[\text{Na}]_s$ level of 120 mmol per liter, total body water (TBW) of 42 liters, time of 10 hours, urinary volume of 1 liter, urinary sodium level of 80 mmol per liter, urinary potassium level of 40 mmol per liter, and treatment fluid (infusion) of 513 mmol per liter, where $[\text{Na}]_1$ is the current $[\text{Na}]_s$ and $[\text{Na}]_2$ represents the $[\text{Na}]_s$ level desired after treatment, $\Delta[\text{Na}]_s = [\text{Na}]_2 - [\text{Na}]_1$; [E] is [Na]+[K]. If the actual rate of correction is different from that predicted, it may be useful to calculate the electrolyte-free water clearance, to help guide treatment. The electrolyte-free water clearance is calculated as

$$C^e_{H_2O} = V\left(1 - \frac{U_{Na} + U_K}{P_{Na}}\right),$$

where $C^e_{H_2O}$ denotes electrolyte-free water clearance, U_{Na} urinary sodium, U_K urinary potassium, and P_{Na} plasma sodium. If the clearance value is greater than 0, then ongoing losses of free water are contributing to the rise in $[\text{Na}]_s$. In all cases, the formulas are used only to estimate the initial infusion rate; the rate must be adjusted on the basis of the measured rate of the rise in serum sodium. Inf denotes infused fluid.

be confusing. Other formulas incorporate amounts of salt and water infused and excreted[39,40]; these add precision, but at the price of complexity. A simpler strategy that results in similar infusion rates is to infuse 3% saline (513 mmol per liter) at a rate of 1 to 2 ml per kilogram of body weight per hour[9] to increase the serum sodium level by 1 to 2 mmol per liter per hour; twice this infusion rate (2 to 4 ml per kilogram per hour) may be used for a limited period in patients with coma or seizures; half the rate (0.5 ml per kilogram per hour) should be used if symptoms are mild.[9] Many authorities recommend using furosemide (20 to 40 mg intravenously) with saline because it promotes free-water excretion and prevents extracellular-fluid volume expansion. Loop diuretics also increase the rate of increase in the serum sodium level. The rate of change in serum sodium levels must be monitored every 2 to 3 hours, and the infusion adjusted as needed.

OSMOTIC DEMYELINATION

When symptoms of osmotic demyelination develop during the treatment of hyponatremia, case reports suggest that it may be possible to reverse the neurologic deficits by again lowering the serum sodium level. In two patients who had neurologic symptoms after rapid correction of serum sodium levels,[41,42] symptoms diminished when serum sodium levels were modestly reduced by administering the vasopressin analogue desmopressin (DDAVP, Rhone–Poulenc Rorer; Stimate, Centeon) and 5% dextrose.

CEREBRAL SALT WASTING

SIAD may be difficult to distinguish from cerebral salt wasting, a syndrome of hyponatremia and extracellular-fluid volume depletion in patients with insults to the central nervous system.[43,44] The primary feature that differentiates cerebral salt wasting from SIAD is extracellular-fluid volume depletion, but clinical assessment of volume status is imprecise.[18,45] In a study that used central venous pressure (<5 cm of water) to differentiate these conditions in patients with subarachnoid hemorrhage and hyponatremia, 63% of cases were attributed to SIADH, and only 6.5% to salt wasting.[46] Although cerebral salt wasting may be less common than is often suggested,[45,46] many physicians favor the use of saline infusion rather than fluid restric-

tion for patients who have hyponatremia with subarachnoid hemorrhage, because of the risks associated with volume depletion in these patients.

PREVENTION OF POSTOPERATIVE HYPONATREMIA

Surgical procedures typically increase circulating levels of arginine vasopressin; nevertheless, hypotonic intravenous fluids are frequently administered perioperatively.[47] Most authorities recommend 0.9% sodium chloride in adults during the perioperative period, as long as hypernatremia is not present.[48,49]

GUIDELINES FROM PROFESSIONAL SOCIETIES

There are no professional guidelines for evaluating and treating SIAD.

SUMMARY AND RECOMMENDATIONS

The patient described in the vignette apparently has chronic hyponatremia attributable to SIAD; she has no neurologic symptoms. Treating the underlying cause (in this case, small-cell lung cancer) is the definitive means of correcting the hyponatremia. In the absence of symptoms, gradual correction of the hyponatremia is appropriate and should involve adequate solute intake (including salt and protein) and fluid restriction, starting at 500 ml per day of water (on the basis of the formula shown in Fig. 2). If the patient were disoriented, we would recommend increasing her serum sodium level by 0.5 to 1 mmol per liter per hour for a total of 8 mmol per liter during the first day. This increase can be accomplished by promoting free-water excretion with the use of furosemide and replacing sodium and potassium losses with 0.9% saline. Alternatively, conivaptan might be used to increase the serum sodium level, although clinical experience with vasopressin-receptor antagonists remains very limited.

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NEUROLOGICAL MANIFESTATIONS AND MORBIDITY OF HYPONATREMIA: CORRELATION WITH BRAIN WATER AND ELECTROLYTES

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INTRODUCTION

Hyponatremia is a common clinical entity which may occur during the course of many medical illnesses. The etiologies of hyponatremia are diverse, and include many iatrogenic causes, such as administration of excessive amounts of free water, thiazide diuretics, barbiturates, hypoglycemic drugs, and many other pharmacological agents, as well as beer drinking and potassium depletion (10, 11, 15, 16, 18, 25, 33). Non-iatrogenic causes of hyponatremia usually relate to the inability to excrete free water which is either administered or generated from endogenous sources (22). Such causes include inappropriate secretion of antidiuretic hormone (IADH), hepatic cirrhosis, adrenocortical insufficiency, congestive heart failure and cachexia (4, 5, 16, 22, 24).

The usual symptoms of hyponatremia are often vague and nonspecific, and may include anorexia, nausea, emesis and muscular weakness. Symptoms may also consist of lethargy and confusion (32) which can be mistaken for a frank psychotic reaction (8). Because these symptoms are so nonspecific, the diagnosis of central nervous system lesion may be entertained, which, on occasion, has led to performance of elaborate diagnostic procedures for suspected intracranial lesions (8) and delay in the diagnosis of hyponatremia. Hyponatremia often presents as a psychiatric problem, which may also delay diagnosis and treatment (8, 14). Hyponatremia thus prolonged may cause irreversible brain damage (23).

In experimental animals with hyponatremia, the brain appears to undergo internal adaptation, so that adjustment to hyponatremia often occurs with only minimal alteration of brain volume (19, 21, 27). However, the relationship between such internal adaptation and neurological manifestations of hyponatremia has not been systematically evaluated. Furthermore, the extent of brain damage in hyponatremic patients does not appear to bear any constant relationship to either the degree or duration of hyponatremia (23).

The object of the present study is to attempt to evaluate the pathophysiology of symptoms associated with hyponatremia as related to the effects of hyponatremia on brain water and electrolytes. The effects on survival and symptomatology of both duration and degree of hyponatremia are also evaluated.

PATIENTS AND METHODS

Patient Studies

Studies were carried out on all patients with hyponatremia referred for renal consultation* over a 30-month interval. A total of 66 patients whose serum Na^+ was 128 mEq/L or less† were evaluated for: a) neurological status; b) state of consciousness; c) presence of seizure activity; d) presence of underlying medical problems. Laboratory studies in all patients consisted of measuring the concentrations of Na^+, K^+, Cl^-, bicarbonate, urea nitrogen, albumin, creatinine, Mg^{++}, Ca^{++}, phosphate and glucose in plasma, concentration of Na^+ in urine, and osmolality in plasma and urine. Any patient who had an obvious reason for depression of sensorium, such as a central nervous system lesion or another metabolic abnormality (hyper- or hypocalcemia, hyper- or hypoglycemia, hypophosphatemia, or uremia), was excluded from the study.

The state of consciousness was classified as described by Plum and Posner (26). Correlation of

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† Normal range for plasma Na^+ (mean ± 2 SD) was 135–145 mmol/L.

depression of sensorium with plasma Na^+ was done as previously described (1). Laboratory studies were done by routine methods in the clinical laboratory at Cedars-Sinai Medical Center. Determination of the state of consciousness was made by at least one of the authors.

The patients were divided into three groups on the basis of either symptomatology or acuteness of their hyponatremia. Patients in group 1 had hyponatremia of less than 12 hours duration, as determined by clinical history in association with a normal plasma Na^+ concentration less than 12 hours previously. Patients in groups 2 and 3 had hyponatremia of at least 3 days duration. Group 2 patients had minimal to absent depression of sensorium (alert or lethargic) while those in group 3 were either obtunded, stuporous or frankly comatose (26).

After all patients had been evaluated, it was then attempted to produce hyponatremia and duplicate the clinical situations in experimental animals, in order to evaluate the effects on brain water and electrolytes.

Studies in Experimental Animals

Studies were made in six groups of New Zealand white rabbits, 1.9–2.8 kg, as follows: 1) normal rabbits; 2) unanesthetized rabbits with acute hyponatremia of 2–3 hrs duration; 3) anesthetized rabbits with acute hyponatremia of 2–3 hrs duration; 4) rabbits with hyponatremia induced over 3–4 days; 5) rabbits with hyponatremia induced over a period of 2–3 weeks.

Evaluation of gait, muscular strength, and response to loud noise or noxious stimuli was done while rabbits were awake. Plasma Na^+ in all such animals (groups 2–5) was measured on venous blood drawn from an ear vein. All rabbits in whom brain and CSF were evaluated (groups 1, 3, 4, 5) were studied while under general anesthesia (intravenous sodium pentobarbital, 20 mg/kg) as previously described (3). Hyponatremia was induced in groups 2 and 3 by subcutaneous injection of 3 units aqueous vasopressin, followed by nasogastric administration of distilled water, 75 ml/kg, over a period of 10 min, followed by another 75 ml/kg water 30 min later. Rabbits in groups 4 and 5 were put on a low sodium diet and were permitted to drink 10% glucose in water ad lib. Additionally, they received daily both 3 units aqueous vasopressin subcutaneously and 35 ml/kg of 10% glucose in distilled water (via nasogastric tube) for either 3–4 days (group 4) or 1–3 weeks (group 5).

In group 2 animals, only plasma Na^+ and osmolality were measured, and the animals were observed for occurrence of seizure activity and/or death. In groups 1, 3, 4, and 5, measurements were made in plasma and CSF of osmolality and concentrations of Na^+, K^+, Cl^-, urea and glucose. In the cerebral hemispheres, osmolality and the content of H_2O, Na^+, K^+ and Cl^- were determined.

The methods for these measurements have previously been described from this laboratory (2, 3, 6, 7). Briefly, brain water content was determined by oven drying tissue for 48 hours at 105°C. The tissue was then extracted with 0.75 *N* HNO_3 and Na^+, K^+ and Cl^- were determined on the supernatants (6). Brain osmolality was determined by extraction in boiling distilled water of brain tissue which had been immediately frozen in liquid nitrogen (2).

RESULTS

Studies in Patients

In 65 patients (one patient with pseudohyponatremia is not included), depression of sensorium was correlated with plasma Na^+ and the results are shown in Figure 1. Although there is a highly significant correlation overall ($r = 0.64$, $p < .001$), there is substantial overlap between groups, suggesting that factors other than low serum Na^+, per se, contribute to depression of sensorium. However, it can be seen that all patients with plasma Na^+ less than 125 mEq/L had some degree of symptomatology. Seizures (grand mal) were observed in nine patients. The mean plasma Na^+ concentration (± SE) in patients with seizures (112 ± 2 mEq/L) was significantly less ($p < .01$) than that in patients without seizures (119 ± 1 mEq/L). All patients with seizures had plasma Na^+ less than 121 mEq/L.

Acute Hyponatremia

Among patients with acute (< 12 hours) hyponatremia, 10 of the 14 had received either large amounts of intravenous 278 m*M* glucose in water (average of 8 liters in 24 hrs to 8 patients) or distilled water by bladder irrigation during prostate surgery (2 patients). All 14 of these patients were either stuporous or comatose. The mean plasma Na^+ and osmolality in these 14 patients were 112 ± 2 mEq/L and 240 ± 10 mOsm/kg, respectively. Seven patients were post-surgical, four had congestive heart failure treated with diuretics, and three had acute renal failure. Seizures were observed in four patients and five were frankly comatose (Table 1). One postsurgical patient had neurosurgical consultation for focal seizures. A lumbar puncture, carotid angiogram and ventriculogram were all nondiagnostic. The patient was transferred to the medical service, and the level of

TABLE 1

Etiology and mortality in 66 patients with serum Na^+ of 128 mEq/L or less

	Acute Hyponatremia (n = 14)	Chronic Hyponatremia	
		Symptomatic (n = 25)	Asymptomatic (n = 27)
Fluid overload	71%	4%	0
Congestive heart failure*	31%	28%	30%
Chronic renal failure	0	12%	19%
Acute renal failure	23%	0	19%
IADH	29%	36%	15%
Post-surgical†	43%	8%	15%
Hypertension*	0	20%	19%
Mortality	50%	12%	0

n = number of patients.

IADH = inappropriate secretion of antidiuretic hormone syndrome.

* Usually associated with diuretic therapy.

† Usually associated with excessive infusion of 5% (278 m*M*) glucose in water.

plasma Na^+ was found to be 112 mEq/L. After treatment with hypertonic (862 m*M*) NaCl solution, the patient regained consciousness but was left with permanent intellectual impairment.

After hyponatremia had been diagnosed in these 14 patients, 7 were treated with hypertonic (862 m*M*) NaCl. These seven patients were given 886 ± 65 (mean ± SE) mmol of NaCl within 36 hrs, usually receiving one-half of the total amount within the initial 6–12 hrs of treatment, and the remainder within the next 24 hrs. Four of the patients were treated only with fluid restriction, while three other patients (all with acute renal failure) were not treated.

Among the four patients treated with fluid restriction, three died, all of them primarily from sequelae of hyponatremia. Of the seven patients treated with hypertonic NaCl, two died despite therapy. Among the three hyponatremic patients with acute renal failure, two died of complications unrelated to the hyponatremia (infection). All of the seven patients who died never completely regained consciousness, while the other seven patients were eventually discharged from the hospital in good condition. There was no evidence of pulmonary edema, cerebral damage or any other complication related to the administration of hypertonic NaCl in any patient so treated.

Chronic Symptomatic Hyponatremia

Twenty-four patients with chronic symptomatic hyponatremia had plasma Na^+ and osmolality of 115 ± 1 mEq/L and 232 ± 3 mOsm/kg respectively. Among these patients, 2 exhibited grand mal seizures, 11 were lethargic and 3 frankly comatose. Twelve patients had been treated with diuretics, either for hypertension or congestive heart failure, and 9 had inappropriate secretion of antidiuretic hormone (IADH) (Table 1).

Treatment consisted of discontinuation of diuretics and either fluid restriction and/or intravenous solutions of hypertonic NaCl (five patients). The five patients treated with hypertonic (862 m*M*) NaCl received an average (± SE) of 622 ± 77 mmol with half administered in the first 8–12 hrs, and the remainder within the next 24 hrs. There were no complications resulting from the administration of hypertonic NaCl, i.e., no acute circulatory congestion or brain damage. Three patients died, none of whom had been treated with hypertonic NaCl, while the other patients were eventually discharged. None of the three deaths appeared to be due primarily to hyponatremia.

Asymptomatic Chronic Hyponatremia

Twenty-seven patients had hyponatremia but were either alert or only slightly confused; none had seizures. The etiology of their hyponatremia is shown in Table 1. The mean plasma Na^+ (122 ± 1 mEq/L) and osmolality (247 ± 4 mOsm/kg) in these patients were both significantly greater ($p < .001$) than corresponding values in symptomatic hyponatremic patients. These patients were treated either with fluid restriction (10 patients) or intravenous solutions of 154 m*M* NaCl (4 patients). All 27 patients recovered, although one eventually died of shock complicated by lactic acidosis. One asymptomatic patient (serum Na^+ 119 mEq/L) had pseudohyponatremia. The patient had diabetes mellitus, with plasma cholesterol of 879 mg/dl, triglycerides of 3400 mg/dl, glucose 130 mg/dl, and plasma osmolality of 297 mOsm/kg. Upon correction for plasma lipids, the serum Na^+ was greater than 130 mEq/L, and this patient has not been included in Figure 1.

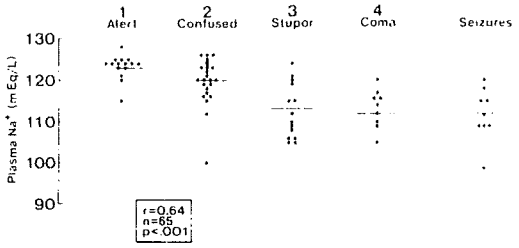

FIG. 1. The relationship between plasma Na^+ concentration and depression of sensorium in 65 patients with plasma Na^+ of 128 mEq/L or less. It can be seen that although there is a highly significant overall correlation, substantial overlap among groups of patients is present. All patients who had seizures had plasma Na^+ of less than 121 mEq/L.

Studies in Experimental Animals

Acute Hyponatremia

Seven animals had their plasma Na^+ lowered to 119 mEq/L in 2 hours with nasogastric distilled water and subcutaneous vasopressin. All of these animals had grand mal seizures (± SE) within 210 min (110 ± 31 min), the seizures continuing in six animals until their demise. All but one animal died at a mean time of 225 minutes after administration of the water. One animal survived but had intermittent seizure activity for 11 hours.

In another group of eight anesthetized animals, plasma Na^+ was lowered as above to 119 ± 1 mEq/L. All eight animals had gross brain edema. There was an osmotic gradient from brain (276 ± 7 mOsm/kg H_2O) to plasma (246 ± 4 mOsm/kg). This gradient favored movement of water from plasma to brain tissue resulting in brain edema (Fig. 2). The mean water content in brain of these hyponatremic animals (Fig. 3) was 444 ± 15 g/100 g dry wt, a value significantly higher than the normal value of 380 ± 5 g/100 g dry wt ($p < .001$). The brain content of Na^+, K^+, and Cl^-, as well as the osmole content (1202 ± 50 mOsm/100 g dry wt) were normal (Table 2). Thus, acutely hyponatremic animals had grand mal seizures and manifested gross and biochemical evidence of brain edema (Fig. 3).

Chronic Asymptomatic Hyponatremia

In six animals, plasma Na^+ was reduced to 122 ± 2 mEq/L in 3.5 ± 0.2 days. These six animals appeared to be asymptomatic. However, there was a significant increase ($p < .003$) in brain water content (406 ± 4 g/100 g dry wt) when compared to the value in six normal rabbits (380 ± 5 g/100 g dry wt) (Fig. 3). Brain osmolality (285 ± 8 mOsm/kg H_2O) was significantly greater ($p < .02$) than that of plasma (258 ± 4 mOsm/kg) so that there was a net osmotic gradient favoring movement of water into the brain. Despite the relative chronicity of

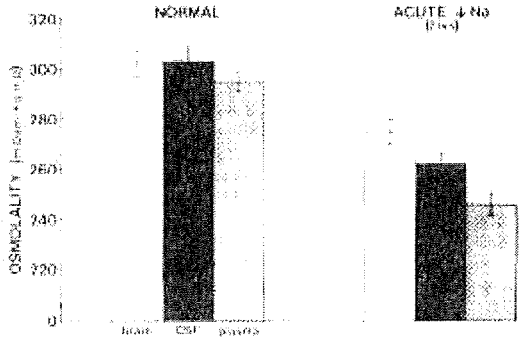

FIG. 2. Osmolalities of brain, CSF and plasma in normal rabbits and in rabbits with acute hyponatremia ($_{\downarrow}Na$). In normal animals, osmolalities of the three compartments are not different. In acutely $\downarrow Na$ rabbits, there is a significant osmotic gradient between brain and plasma. The gradient results in a net movement of water into the brain, with resultant cerebral edema and an 86% mortality.

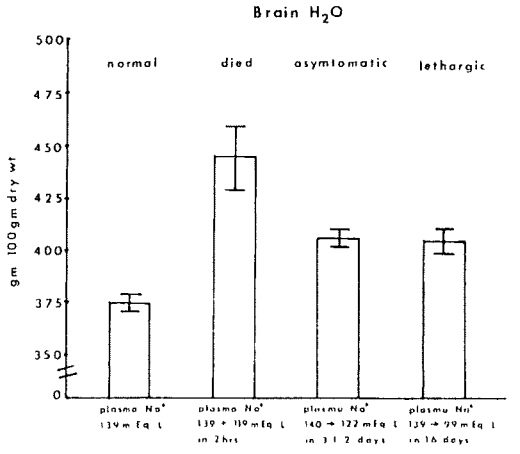

FIG. 3. Brain water content in normal animals and in three groups of hyponatremic animals. In animals where plasma Na^+ is lowered to 119 mEq/L in 2 hrs, brain water content is 17% above normal value, but when plasma Na^+ is lowered to almost the same value (122 mEq/L) in 3½ days, brain water is only increased by 7% above normal. When plasma Na^+ is decreased to 99 mEq/L in 16 days, brain water is only 7% above normal. Brackets are mean ± SE.

TABLE 2

Effects of hyponatremia (acute and chronic) on brain water content, and on electrolytes and osmolality in plasma, CSF and brain

	Plasma				CSF				Brain				
	Na^+	K^+	Cl	Osmolality mOsm/kg	Na^+	K^+	Cl	Osmolality mOsm/kg	Na^+	K^+	Cl	H_2O g/100 g dry wt	Osmolality mOsm/kg H_2O
	mEq/L				mEq/L				mEq/kg dry wt				
Control, n = 6													
mean	142	4.43	97	297	162	3.10	125	304	247	428	176	380	305
±SE	1	0.15	1	2	3	0.08	2	2	4	6	5	5	4
Hyponatremia, 2 hrs, n = 7													
mean	119	3.16	90	244	134	2.52	112	266	232	420	164	444	276
±SE	1	0.06	1	4	2	0.05	1	3	5	13	4	15	6
Hyponatremia, 1–3 days, n = 6													
mean	122	2.32	76	258	127	3.02	96	259	269	400	150	406	282
±SE	2	0.21	2	4	2	0.24	2	4	4	4	3	4	8
Hyponatremia, 7–20 days, n = 6													
mean	99	2.44	70	215	111	2.24	90	221	181	354	111	405	218
±SE	3	0.39	3	8	3	0.20	5	6	4	7	4	6	12

Data are given as mean ± standard error.
n = number of animals.

the hyponatremia brain content of Na^+ plus K^+ was normal (Table 2). Although brain Cl^- was significantly less than normal ($p < .01$), most of the decrement was extracellular. Brain osmole content (1156 ± 23 mOsm/100 g dry wt) was not different from normal (1165 ± 48 mOsm/100 g dry wt).

Chronic Symptomatic Hyponatremia

In six rabbits, plasma Na^+ was reduced to 99 ± 3 mEq/l in 16 ± 3 days. These animals were lethargic and anorexic. Their hind limbs appeared to be almost paralyzed, and two of the animals were unable to walk. Seizure activity was not noted; however, the animals had not been under continuous observation. In five of six animals, the brain appeared to be grossly swollen. Brain water content (405 ± 6 g/100 g dry wt) was significantly greater ($p < .01$) (Fig. 4) than normal. Brain osmolality (218 ± 12 mOsm/kg H_2O) was not different from that of plasma (210 ± 8 mOsm/kg). The brain content of Na^+, K^+, and Cl^- all were significantly less than normal ($p < .01$) (Fig. 4), so that the brain osmole content (852 ± 44 mOsm/100 g dry wt) was significantly less than normal ($p < .001$). Thus, over an extended period of time (7–22 days) the brain established osmotic equilibrium with plasma and CSF primarily by means of a

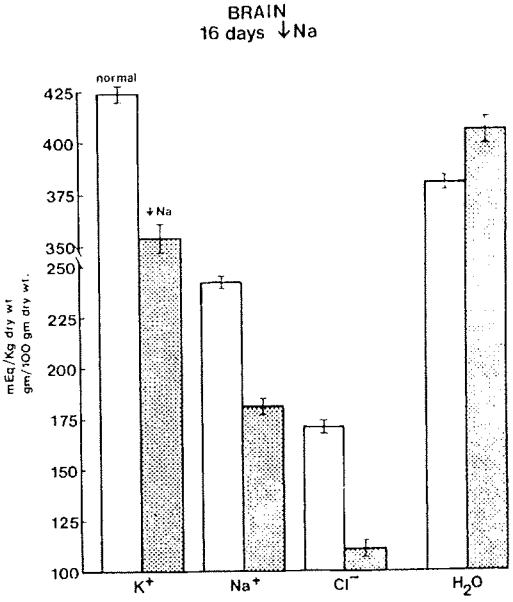

FIG. 4. Brain content of Na^+, K^+, Cl^- and water in normal animals and in rabbits with hyponatremia (↓Na) of 16 days duration (plasma Na^+ = 99 mEq/L). It can be seen that in the ↓Na animals, brain water content is 7% above normal and brain content of Na^+, K^+, and Cl^- and 17—37% below normal values. The loss of electrolytes by brain prevented a larger gain in brain water. Shaded bars represent ↓Na animals and brackets are mean ± SE.

loss of Na^+ and K^+ (Fig. 4), although brain water content was still modestly but significantly greater than normal. When compared to the asymptomatic hyponatremic animals, the most notable difference was the significant decrement in brain electrolyte content (Table 2).

DISCUSSION

These studies suggest that in patients with hyponatremia, neurologic abnormalities and morbidity are only grossly correlated with either the magnitude or duration of the hyponatremia. It seems rather that symptoms are correlated with the interplay of net increase in brain water versus loss of brain electrolyte content. Most patients with acute (< 12 hours) hyponatremia (plasma Na^+ 113 ± mEq/L) manifest substantial depression of sensorium, seizure activity and a significant mortality. However, among patients with a more protracted degree of hyponatremia, symptomatology cannot usually be correlated with either duration or magnitude of hyponatremia, although there is a tendency for those patients with lower levels of plasma Na^+ to be more symptomatic (29, 31) (Fig. 1).

In patients with chronic hyponatremia the symptomatology is usually insidious and nonspecific (32) and often occurs in the presence of serious illness (16), so that the observed symptoms may thus be attributed to the concurrent illness. Additionally, it has become evident that an ever-expanding list of drugs may produce hyponatremia. Such agents include hypoglycemic agents, antineoplastic drugs, tricyclic antidepressant compounds, clofibrate, acetaminophen, many diuretic agents and several barbiturates (10, 15, 25). Patients with chronic hyponatremia may present with apparent psychoses (8) or with a variety of neurological manifestations (32). Since such patients are frequently receiving one of the aforementioned agents as therapy for a neuropsychiatric disorder, such symptoms may well be overlooked.

The symptoms of acute hyponatremia, on the other hand, are generally abrupt and most commonly consist of seizures and coma. The most frequent cause is excessive fluid administration, often in combination with either surgery and/or the syndrome of inappropriate secretion of antidiuretic hormone (IADH). In the present study, all 14 cases of acute hyponatremia were iatrogenically induced at a time when the patient was in the hospital. The most common etiologic factor was the administration of large quantities of fluids (10 patients), while 4 patients had the syndrome of IADH, and 6 had major surgery. Among the 52 patients with chronic hyponatremia, 21 were iatrogenically induced, with most occurring in outpatients receiving diuretic therapy for hypertension or congestive heart failure. Another 20 patients with chronic hyponatremia had the syndrome of IADH, which was associated with either bacterial pneumonia (5 cases), major surgery (6 cases), drug therapy (chlorpropamide in 3 patients, vincristine in 1 patient), or malignancy (4 patients).

Among the three patients with chronic hyponatremia who died, all probably succumbed from effects of the underlying illnesses rather than the hyponatremia. One had hepatic cirrhosis with hepatorenal syndrome, one had cancer of the lung, and one, shock with lactic acidosis. However, among the seven deaths in patients with acute hyponatremia, five died primarily from the effects of hyponatremia, and at least one other patient was left with permanent intellectual impairment.

The morbidity and mortality associated with acute hyponatremia may have been due, at least in part, to delay in onset of therapy. It may not be appreciated that symptoms such as weakness, headache and lethargy may be largely due to hyponatremia with brain edema. The attending physician may arrive at a decision to initiate conservative therapy (fluid restriction) when, in fact, the patient may be suffering incipient brain damage from moderate brain edema. The attending physician may also be afraid to administer hypertonic NaCl because of the possible complications of either brain damage (due to overly rapid correction of hyponatremia) or circulatory congestion. Although these are both theoretical hazards, there are few, if any, well documented reports of cerebral damage under such circumstances. The danger of circulatory congestion can be minimized by giving hypertonic (862 m*M*) NaCl, thus decreasing the fluid volume given and perhaps combining this with furosemide administration, as has been described (17). It would appear that the threat of cerebral edema from protracted hyponatremia usually exceeds the risk of either cerebral damage or circulatory congestion (14, 21, 23). Neither the level of

serum Na^+ nor the degree of symptomatology which may be associated with significant brain edema in man is known, as there have been few, if any, evaluations of brain water and electrolytes in patients dying with hyponatremia. However, there have been several animal studies.

Animal experiments from the present studies and the work of other investigators are somewhat conflicting, but they suggest that in animals rendered hyponatremic (plasma Na^+ < 125 mEq/L), there is an initial influx of water into the brain (19, 21). The initial increase in brain water content may terminate fatally if the plasma to brain osmotic gradient is substantial.

Although the exact osmotic gradient necessary to induce lethal brain edema will doubtless vary among individual subjects, data from experimental animals suggest that a gradient of at least 30 mOsm/kg H_2O is necessary (2, 28). If the organism survives the initial osmotic insult, the brain undergoes internal adaptation. The brain content of Na^+ and K^+ remains intially unaltered, but the brain water content is less than would be predicted from the change in plasma osmolality (6, 19, 21, 27). Such a phenomenon also was observed in the present study, where animals with hyponatremia of 1 to 3 days duration had no important change in brain Na^+ content, and less of an increase in brain water than would be predicted. However, even in these animals, there were modest but significant decreases in brain content of K^+ and Cl^-. In the present study, it was found that after protracted (7 to 21 days) hyponatremia, the brain had lost significant quantities of electrolytes (Na^+, K^+, Cl^-), with a corresponding decrease in brain osmole content. Similar findings have been reported by other workers, where hyponatremia invokes a loss of cation in brain which is demonstrable within 3 hrs to 2 days in the rat, rabbit, guinea pig and cat (6, 13, 28, 30, 34).

Seizures and other neurological abnormalities have been shown to frequently accompany hyponatremia both in patients and experimental animals, and these may be related to dilution of brain intracellular K^+ and/or Na^+ concentration, alteration of membrane permeability, or brain edema per se (12, 21, 27). From the present study, it appears that these symptoms may be related to decreased brain concentration of Na^+ and/or K^+. Animals with hyponatremia of either 2–3 days or 2 weeks duration had similar brain water content. However, the symptomatic animals had significantly lower brain content of electrolytes (Fig. 4). Furthermore, the symptomatic animals also had lower plasma Na^+ concentrations, which may also have contributed to symptomatology by depressing membrane potential.

Thus, it appears that the neurological symptoms, including seizures, which are associated with hyponatremia are the resultant of the balance between gain in brain water versus loss of brain electrolytes. Such as interplay will vary substantially between individuals as well as species.

The present study suggests that even in steady state hyponatremia, brain water content is often significantly greater than normal, even in the absence of symptoms (Fig. 3). Thus, if plasma Na^+ is below 125 mEq/L, even asymptomatic individuals may have sublethal degrees of brain edema. If one can interpolate studies in animals to disease in man, it may be that many such patients with plasma Na^+ of less than 125 mEq/L should be treated with hypertonic solutions of NaCl, as well as fluid restriction. Although histologic evaluation of brain was not done in the present study, it may well be that such minimal brain edema (20) leads to significant structural damage. It has been demonstrated that hyponatremia (serum Na^+ 95–109 mEq/L) in man of 3 days duration can lead to irreversible brain damage (23), and such a complication also occurred in several patients in the present study. It is reasonable to suggest that all such patients who are symptomatic should be treated with infusion of hypertonic NaCl solutions, or NaCl plus furosemide (17).

The model used to create hyponatremia in the present study is similar to the syndrome of inappropriate secretion of ADH in man (4). There is an excess of total body water, and total body Na^+ is normal to low. Other clinical states associated with hyponatremia might conceivably have different effects upon brain water and electrolytes. In particular, hepatic cirrhosis and congestive heart failure are associated with increased total body Na^+ (5, 9). However, the majority of chronic hyponatremic patients in the present study (35 of 52 patients) had either inappropriate administration of diuretic agents or inappropriate elaboration of ADH. Thus the majority of clinical situations evaluated in this

series should be comparable to the animal models studied.

Thus, based upon the studies in hyponatremic patients and animals, neurologic symptoms associated with hyponatremia are related to the balance between gain in brain water content and loss of brain electrolytes. However, when plasma Na^+ is below about 125 mEq/L, brain water is usually elevated, even when the duration of hyponatremia is as long as 3 weeks. When such patients are symptomatic, treatment with hypertonic NaCl or NaCl-furosemide (17) is probably indicated.

SUMMARY

1. An attempt was made to evaluate the pathophysiology of symptoms of hyponatremia as related to changes in brain water and electrolytes. Studies were carried out in 66 hyponatremic patients and 5 groups of experimental animals.

2. In hyponatremic patients, symptoms (depression of sensorium, seizures) correlated well with plasma Na^+ ($r = 0.64$, $p < .001$), but there was substantial overlap. In patients with acute hyponatremia, all were symptomatic and 50% died. Among patients with hyponatremia of at least 3 days duration, symptomatic patients had plasma Na^+ (115 ± 1 mEq/L) which was significantly less ($p < .001$) than that of asymptomatic patients (plasma Na^+ 122 ± 1 mEq/L). Among symptomatic patients, mortality was 12% and 8% had seizures, while none of the asymptomatic patients died or had seizures.

3. Among 14 patients with acute (less than 12 hrs) hyponatremia, the mean plasma Na^+ was 112 ± 2 mEq/L. All such patients had some depression of sensorium and four had grand male seizures. Seven of these patients were treated with hypertonic (862 m*M*) NaCl, while four were treated only with fluid restriction. Of the seven patients treated with hypertonic NaCl, five survived, while three of four patients treated with fluid restriction died. There was no evidence of circulatory congestion or cerebral damage in the patients treated with hypertonic NaCl.

4. Among rabbits with acute (2–3 hours) hyponatremia (plasma $Na^+ = 119 \pm 1$ mEq/L), all had grand mal seizures and 86% died. All such animals had cerebral edema (brain H_2O content 17% above control value) but brain content of Na^+, K^+ and Cl^- was normal.

5. Rabbits with 3½ days of hyponatremia (plasma $Na^+ = 122 \pm 2$ mEq/L) appeared to be asymptomatic, even though brain water content was 7% above normal ($p < .01$).

6. Rabbits with 16 days of more severe hyponatremia (plasma $Na^+ = 99 \pm 3$ mEq/L) were weak, anorexic, lethargic and unable to walk. Brain water content was 7% above normal, although brain osmolality (218 ± 12 mOsm/kg H_2O) was similar to plasma (215 ± 8 mOsm/kg). Brain content of Na^+, K^+, Cl^- and osmoles was 17 to 37% less than normal values, so that the brain established osmotic equilibrium with plasma primarily by means of a loss of electrolytes.

7. These studies suggest that in patients with hyponatremia, symptoms and morbidity are only grossly correlated with either magnitude or duration of hyponatremia. Symptoms appear to correlate best with the interplay between a net increase in brain water versus a loss of brain electrolytes. However, even asymptomatic animals have subclinical brain edema when plasma Na^+ is below 125 mEq/L, and such edema may cause permanent brain damage. Thus, many patients with similar levels of plasma Na^+, particularly when they are symptomatic, should probably be treated with hypertonic NaCl infusions.

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Effects on the central nervous system of hypernatremic and hyponatremic states

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Both hyponatremic and hypernatremic patients are commonly encountered in a wide variety of clinical situations. Most prominent among the clinical manifestations of either of these electrolyte abnormalities are central nervous system symptomatology and/or disorders of sensorium. Not infrequently, such patients have other associated medical conditions, which may modify the clinical picture presented by the abnormalities of salt and water balance. Nonetheless, both hyper- or hyponatremic subjects may present with confusion, lethargy, muscle weakness or myoclonus [1], and seizures are frequently observed. Thus, it would appear that similar abnormalities of central nervous system function may be induced by dissimilar disturbances of electrolyte and osmotic equilibrium. It is the purpose of the present paper to review the clinical, anatomical and biochemical changes in the central nervous system induced by hypo- and hypernatremic states, and to attempt to correlate these changes with the observed central nervous system disorders.

Hypernatremia

Central nervous system lesions and hypernatremia: Experimental animals. Hypernatremia itself not only has profound effects upon the central nervous system, but a variety of central nervous system lesions have been reported to induce hypernatremia, usually by diminishing thirst. There are numerous reports of animal studies where hypernatremia occurred in association with hypothalamic lesions. Electrical stimulation of various regions in the hypothalamus has been reported to induce hypernatremia, generally by promoting diminished water intake [2, 3]. Similarly, destruction of the mid-hypothalamus in experimental animals is generally associated with cessation of drinking [4]. Other areas of the brain where induction of lesions has been associated with diminished water intake include the subcommissural organ [5] and pineal gland [6].

Central nervous system lesions and hypernatremia: Studies in patients. In patients, hypernatremia has been associated with various cerebral lesions, and the clinical experience has been extensively reviewed elsewhere [6–8]. In most of the reported cases, it appears that the patients were unable to obtain adequate amounts of water due to impairment of sensorium. Thus, although many different cerebral lesions have been suggested as being causative in the genesis of hypernatremia, there is good evidence only to implicate lesions of the hypothalamus or supraoptico-hypophyseal tracts [6, 9]. Evidence that other central nervous system lesions may cause hypernatremia is tenuous, primarily because of the lack of accurate fluid and electrolyte balance studies in reported cases. There are also some scattered reports of so-called "cerebral" or "essential" hypernatremia [10, 11]. In these patients, there appears to be a resetting of the cerebral "osmostat" such that forced hydration of a hypernatremic patient results only in excretion of excess water, with maintenance of plasma Na^+ at an elevated level [7, 10–13]. Most of these patients have normal renal concentrating and diluting capability, and regulation of antidiuretic hormone (ADH) secretion is normal or only partially impaired [10, 14]. Lastly, ectopic pinealomas, especially when located in the hypothalamus, frequently are associated with hypernatremia, usually due to loss of thirst [6, 15, 16].

Other medical conditions associated with hypernatremia. In addition to central nervous system lesions, there are a number of medical conditions which may cause hypernatremia, most of which are observed in the very young or the elderly. In infants, gastroente-

ritis with diarrhea is the most common cause [6, 17, 18]. In elderly individuals, hypernatremia is often associated with infirmity and inability to freely obtain water, leading to gradual desiccation [8]. Small children may also become hypernatremic after accidental administration of a high solute load, particularly the accidental substitution of NaCl for sugar in preparation of formula [19, 20] or improper dilution of concentrated formulas [21]. Other causes of hypernatremia include nasogastric hyperalimentation, nonketotic hyperosmolar coma, acute renal failure [6], renal tubular damage, dialysis, dehydration secondary to elevated ambient temperature, pituitary or renal diabetes insipidus, sea water ingestion and hyperadrenocorticoid states. These have been discussed elsewhere [6, 8, 22, 23]. More recently, hypernatremia has been reported in association with renal transplantation [24] and as a complication of dialyzer proportioning system malfunction [25, 26]. Generally, diabetes insipidus is associated with hypernatremia only under circumstances where the patient is unable to freely obtain water, such as a postoperative neurosurgical patient or one suffering from head trauma [27], or when the lesion responsible for the diabetes insipidus results in a decrease in thirst. Recent reports suggest that there may be a whole new class of hypernatremic patients who had not previously been diagnosed. Excessive administration of hypertonic solutions of $NaHCO_3$ to critically ill patients suffering cardiac arrest was associated with a hyperosmolar state (plasma osmolality = 377 ± 7 mOsm/kg) in 12 patients so treated, none of whom survived [28]. Similarly, administration of excessive amounts of $NaHCO_3$ to newborn infants has been associated with hypernatremia and intracranial hemorrhage, with a mortality of 71% [29]. Severe hypernatremia has also been observed in patients inadvertently receiving i.v. hypertonic NaCl for therapeutic abortion [30], and may also occur in patients with lactic acidosis who receive large quantities of i.v. $NaHCO_3$ [31, 32].

Symptoms of hypernatremia: Experimental animals. Most symptoms of hypernatremia relate to the central nervous system and they appear to be grossly correlated with the rate at which serum Na^+ increases. The initial symptoms of hypernatremia include lethargy and hyperirritability, which may progress to muscle rigidity and tremor, with hyperreflexia and spasticity. Seizures may also occur, and coma may supervene. In experimental animals, i.v. administration of hypertonic solutions may result in a syndrome of stupor, ataxia, convulsions and coma [33–35]. In adult rabbits receiving i.v. infusions of hypertonic solute, neurological symptoms were observed when serum osmolality was acutely elevated to over 350 mOsm/kg [34, 35], while death often occurred at plasma osmolality above 430 mOsm/kg. When serum osmolality was above 350 mOsm/kg, the animals showed restlessness with increased irritability [34–36], while at serum osmolalities between 375 to 400 mOsm/kg, ataxia and tremulousness of the extremities were present [34]. When serum osmolality exceeded 400 mOsm/kg, synchronous and asynchronous jerks and tonic spasms were observed, the animals gradually became stuporous, and a significant number did not survive [34–36].

Symptoms of hypernatremia: Patients. Most infants with chronic hypertremia have clinical evidence of dehydration, with a loss of 6 to 12% of body weight [37, 38], and they manifest a characteristic clinical picture which has been described elsewhere [38–40]. About 67% of such patients have symptoms referrable to the central nervous system. Most have marked irritability and they often emit a high-pitched cry. Depression of sensorium is characteristically present, and this varies from moderate lethargy to frank coma. Normal muscle tone is the rule, but many patients have varying degrees of increased muscle tone, which may be accompanied by hyperactive deep tendon reflexes or twitching, and many patients show frank seizure activity [38, 39]. Meningeal signs are not usually present on admission. The most frequent abnormality found on lumbar puncture is an elevated cerebral spinal fluid protein concentration, without pleocytosis [38, 39]. Although most of these patients are not diabetic, many are hyperglycemic and most have hyperkalemia and metabolic acidosis [38, 41]. Hypocalcemia is also frequently present [23].

Seizures are not commonly observed in patients with chronic hypernatremia [37, 38], but after therapy is begun, up to 40% may exhibit seizure activity [37, 38]. A similar pattern is observed in chronically hypernatremic rabbits who are rapidly treated with i.v. 140 mM glucose [42].

Both morbidity and mortality of children with chronic hypernatremia are substantial. The mortality in different series is between 10% and 71% [29, 37, 39, 43], and even when therapy has been adequate, the morbidity is high. Among 100 patients studied by Macauley and Watson [43], 8 sustained brain damage: one had tetraplegia and 7 were either retarded, hyperkinetic or clumsy. Among 32 hypernatremic patients who were successfully treated and then followed for up to 8 years, one was monoplegic, 2 had seizure disorders and 8 had abnormal electroencephalogram (EEG) findings [37].

In infants with acute hypernatremia, the most commonly observed symptoms are emesis, fever and labored respiration. Spasticity may be observed, grand

mal seizures occur in almost all patients and coma is frequent [20, 44]. Neurologic abnormalities, such as hemiparesis and Babinski sign, are not uncommon. Both mortality and morbidity are imposing. Among infants with acute salt poisoning in the Binghamton, New York episode, 6 of 14 died and the remainder had neurologic sequelae [19]. In 7 other patients with hypernatremic dehydration, all survived but 6 of 7 had severe brain damage [33].

In adults with hypernatremia, the symptoms are much less straightforward due to the presence of numerous other associated medical conditions which are often of a catastrophic nature [23, 27]. Most associated symptoms are not attributable to hypernatremia per se. The sensation of thirst is usually not verbalized because affected patients frequently have depression of sensorium. The physical signs commonly associated with dehydration, such as altered skin turgor and sunken eye sockets, may not be apparent because of the usual effects of aging [1]. Lethargy, stupor or coma may be present to varying degrees. Muscle irritability and convulsions have been reported [23] but are unusual, and it may be difficult to separate effects of hyperosmolality from the effects of therapy [43].

Hypernatremia: Electroencephalographic changes in experimental animals. In experimental animals, hyperosmolality results in a progressive slowing of background EEG frequencies, but no spikes or paroxysmal discharges are seen even in the presence of paroxysmal jerking of the body [34, 35]. These changes suggest alterations at different levels of the nervous system and probably of spinal cord or peripheral nerve trunks as well, since the paroxysmal jerks and tonic contractures do not disappear after spinal cord or sciatic nerve section [36].

Other EEG abnormalities are observed at the time symptoms of hyperosmolality become manifest. There is a generalized reduction in voltage, disappearance of fast activity and the appearance of bursts of 4 to 5/sec spindle-like activity. There is gradual progression to 1 to 3/sec high-voltage waves, with cessation of EEG activity at the time of respiratory arrest [34].

Hypernatremia: Electroencephalographic changes in patients. Electroencephalograms obtained on hypernatremic patients are usually either normal or show minor degrees of slowing of background frequencies [38]. However, some patients have generalized slow wave activity and a minority (about 7%) may demonstrate characteristic epileptic activity [37]. In the majority of instances, the previously observed EEG changes are no longer present four to six weeks after successful therapy [38].

Hypernatremia: Pathology. Evaluation of the effects of abrupt elevation of plasma osmolality by salt loading has been extensively studied in experimental animals. Because of the occurrence of a large number of cases of accidental salt poisoning in infants, information as to effects on patients is also available [19, 20].

In animals (kittens) rendered acutely hypernatremic (plasma Na^+ = 196 mmoles/liter), 30% died within 24 hr. Eighty-five percent of the animals had subdural hemorrhage with xanthochromic spinal fluid, and 7% had subdural hematoma [33]. Grossly, the brains were retracted 3 to 6 mm below the inner table of the skull. There was generalized capillary and venous stasis throughout the brain. Histologically, there was pyknosis of microglial nuclei and cortical neurons [45, 46].

Among children who died in the Binghamton, New York, salt poisoning episode [19, 20], pathological findings in the brain were similar to those observed in experimental animals with acute salt (NaCl) poisoning. There were multiple petechial hemorrhages throughout the cortex and subcortical white matter, and thrombotic occlusion of capillaries, veins and sinuses.

The most commonly accepted explanation for the causation of the aforementioned pathological changes is that an abrupt elevation of plasma osmolality, by establishing an osmotic gradient from blood to brain, leads to a rapid net movement of water from the central nervous system. The loss of brain water could lead to a rapid shrinkage in brain volume. The physical force of the shrinking of the brain could lead to increased stress on the falx cerebri and venous sinuses, with subdural hemorrhage. Similarly, tearing of intracerebral veins could result in intracerebral hemorrhage, as has been described [33, 46]. It is interesting to note that when plasma osmolality was elevated by a similar amount over a similar time span, but using urea rather than NaCl solution, similar gross pathological changes were induced in the central nervous system [33]. However, urea-injected animals showed less of a decrease in brain water content, and the mortality was less. Such findings suggest that the high mortality associated with acute salt (NaCl) intoxication is not due to the effects of hyperosmolality alone [33, 34].

Hypernatremia: Changes in brain water and electrolytes. Changes in water and electrolyte contents in brain have been measured in hypernatremic animals, by a number of investigators [33, 34, 47–49]. In these studies, the duration of hypernatremia has varied from a few hours [34, 48] to several days [33, 47–49].

In animals with hypernatremia of less than two hours' duration, brain water content has been found to be reduced in all cases (Table 1), with marked rises

Table 1. Effects of hypernatremia on brain water and electrolyte content

	Duration of hypernatremia	Animal species	Serum Na^+ *mmoles/liter*	Brain H_2O, % change from normal	Brain Na^+, % change from normal	Brain K^+, % change from normal	Brain Cl^-, % change from normal	Undetermined solute, % change from normal
Guisado, Lazarowitz, Arieff[a]	1 hr	rabbit	178	−5.4	+27.9	+5.6	+21.8	+5.7
Holliday, Kalayci, Harrah [48]	3 hr	rat	200	−13.9	+34.2	+2.8	+59.6	+2.4
Guisado, Arieff[a]	4 hr	rabbit	182	−7.8	+35.0	+13.2	+40.2	0
Sotos et al [34]	9 hr	rabbit	199	−15.7	+42.5	+8.0	+55.9	+23.7
Finberg, Luttrell, Redd [33]	24 hr	kitten	196	−10.6	+28.6	+0.9	+32.4	+14.6
Bradbury, Kleeman [47]	48 hr	cat	174	−4.6	+10.0	+1.9	+17.1	+27.9
Holliday, Kalayci, Harrah [48]	7 days	rat	181	−2.8	+0.6	+3.9	+88.4	+43.3
Guisado, Lazarowitz, Arieff[a]	7 days	rabbit	173	+1.9	+17.3	+8.8	+20.1	+59.8

[a] Unpublished data.

in brain Na^+ and Cl^- content, whereas brain K^+ content did not change substantially (Table 1). When hypernatremia was maintained for more than two hours, there was a 16% fall of water content in both brain and muscle [34]. After one or two days of hypernatremia [33, 47, 48], water content of brain was less than normal, but was reduced by proportionately less than was observed in skeletal muscle. In studies where hypernatremia was maintained for seven days, brain water content was normal [48]. It would seem, then, that brain is able to minimize changes in its intracellular volume in the presence of extracellular hyperosmolality which is sustained for periods of several hours to seven days.

In earlier studies of the effects of hypernatremia on the central nervous system, it was found that brain achieved osmotic equilibrium with plasma without significant changes in electrolyte (Na^+, K^+, Cl^-) content and with only minimal changes in brain water [33, 34]. Based on these findings, it was postulated that brain intracellular osmolality became elevated in hypersomolar states largely by the generation of additional undetermined solutes (idiogenic osmoles). These earlier studies, however, had some methodological problems (loss of brain electrolytes by lipid extraction) which may render some of the results invalid [23]. Even so, more recent studies have avoided such problems and the conclusions have been similar. In animals with either acute (three hours) or chronic (seven days) hypernatremia, brain content of Na^+ and Cl^- did rise significantly, but not enough to account for the observed changes in brain osmolality [48]. The suggested mechanism is that there may be generation by the brain of undetermined solute ("idiogenic osmoles") in chronic hypernatremic states.

Table 1 compares the changes in plasma osmolality with changes in brain electrolyte content reported by several investigators. It is apparent from the table that the sum of brain concentrations of Na^+, K^+ and Cl^- in both normal and hypernatremic animals does not add up to the brain osmolality (assuming measured plasma osmolality to be similar to brain osmolality in a steady state) [51, 52]. The difference between estimated brain osmolality and the brain tissue electrolyte concentration (Na^+ K^+ Cl^-), however, is similar both in normal and in acutely (one to three hours) hypernatremic animals. In animals with more protracted hypernatremia (Fig. 1) (two to seven days), the difference between estimated brain osmolality and brain electrolyte concentration is larger than control values, despite the fact that there has actually been a net gain in brain electrolyte content. It is also apparent that the loss in brain tissue water content is greater in animals with acute hypernatremia than in those animals with chronic hypernatremia, so that brain water content has returned to normal after seven days of hypernatremia (Fig. 1). Thus, brain tissue is somehow able to regulate its intracellular volume in response to hypernatremia by increasing intracellular osmolality, but this adaptation is only partially explained by a net increase in electrolyte concentration. It appears that in hypernatremia, brain tissue gains some, as yet undetermined, solute other than Na^+, K^+ and Cl^-, or there may be generation of "idiogenic" osmoles through as yet unknown mechanisms.

In both the amphibian and mouse brain, the content of certain intracellular metabolites (glutamic acid, gamma aminobutyric acid [GABA], glucose, alanine, aspartate, glutamine) changes in response to changes in extracellular osmolality [49, 52–55], thus limiting the loss or gain of water in brain. Thus, it would appear that, in chronic hypernatremia in some

animals, brain amino acid content increases, and this increase may be one of the mechanisms by which brain is able to limit volume changes in response to changes in serum osmolality. Other possible mechanisms might include the disassociation of intracellular protein-salt complexes, the action of hydrolytic enzymes in lysosomes which have been activated by hyperosmolality, or some changes in intracellular metabolism leading to accumulation in brain of other small molecular weight substances [23, 56].

Pathogenesis of hypernatremic encephalopathy. Interpretation of the effects of increased serum Na^+ concentration on neuronal activity are complicated by the concomitant effects of hyperosmolality, with resultant shifts of water across cerebral membranes. Abrupt elevation of extracellular osmolality may cause an increase in frequency of release of acetylcholine at nerve terminals [57]. However, large increases in osmolality may also block neuromuscular transmission, due both to a decrease in acetylcholine released at nerve terminals and to a block in excitation-contraction coupling [57, 58]. Sudden increases in serum Na^+, as by intracarotid infusion of hypertonic NaCl [59, 60], may induce electroencephalographic evidence of seizure activity, which may then be abolished by decreasing plasma osmolality. However, a similar effect on the electroencephalogram may also be observed following intra-arterial injection of glucose, suggesting that hyperosmolality rather than hypernatremia may be the causative stimulus [59]. Intraventricular injection of hypertonic NaCl induced both paroxysmal neuronal discharges and increases in general hyperexcitability of neurons [61], effects which were not reproduced by intraventricular injection of similar osmotic loads of mannitol or sorbitol [61]. While intracarotid injection of hypertonic glucose induced a similar pattern of increased neuronal excitability as did hypertonic saline [59], intraventricular infusion of glucose did not. Thus, it may be that changes in serum osmolality are more important than is hypernatremia in producing such neuronal changes [23, 62].

Brain energy metabolism is apparently reduced in animals with chronic hypernatremia [49], since levels of both lactate and malate in brain are low. The fall in brain malate is accompanied by an increase in brain phosphocreatine levels [49]. These changes in energy metabolism, however, have not been confirmed by others [55], although brain energy utilization has been found to be low in animals after only one hour of hypernatremia [55]. It is not clear, then, to what extent brain energy metabolism may be reduced in hypernatremia, or how such changes might contribute to the observed clinical abnormalities. It is thus apparent that further studies are needed in this area.

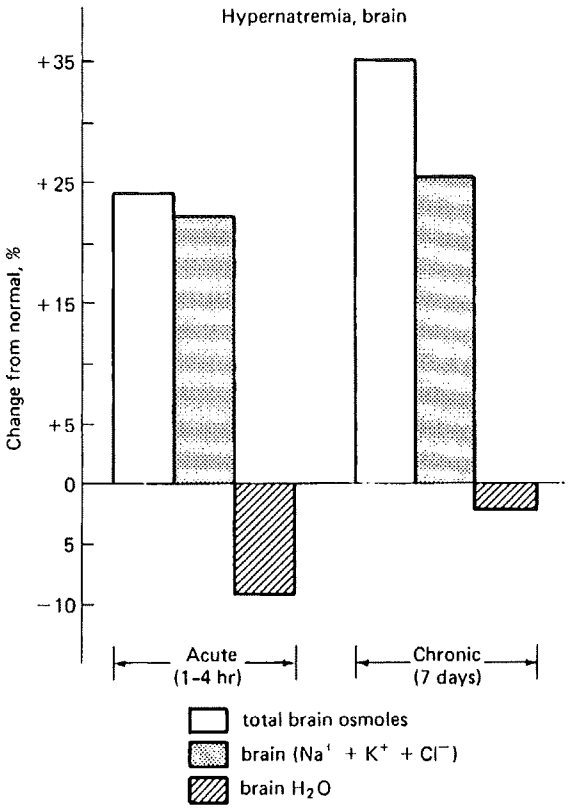

Fig. 1. *The changes in brain osmole content (mOsm/kg dry wt), brain content of $Na^+ + K^+ + Cl$ (mmoles/kg dry wt), and brain water content (g H_2O/100 g dry wt) in animals with experimental hypernatremia.* Brain osmolality has been estimated by assuming osmolality of plasma and brain to be equal in a steady state (see text for explanation). In animals with acute hypernatremia (1 to 4 hr), brain osmolality increases due both to a loss in water and gain in solute. Brain water content is 9% below control values. Brain osmole content is increased by 24% above normal values, with virtually all of the increase accounted for by increases in Na^+, K^+ and Cl^-. In chronically hypernatremic animals, brain osmolality is also elevated, but most of the increase is due to a gain in brain solute. Brain water content is similar to normal values. Brain osmole content is 35% above control levels, but most of the increase is not accounted for by changes in brain content of Na^+, K^+, Cl^-, but is due to undetermined solute (idiogenic osmoles) ([48], unpublished data: Table 1).

Hypernatremic dehydration: Therapy. Hypernatremic dehydration is associated with a significant mortality, both in infants and elderly individuals [8, 27, 29, 38]. The problem is of considerable magnitude in both age groups. In studies from several different medical centers, the reported incidence of severe hypernatremia exceeds one patient per hospital per month in elderly individuals [8, 27, 63], with a slightly higher incidence in children [29, 38]. Despite the magnitude of the problem, there is little hard data

available on the quantitative aspects of therapy of severe hypernatremia. It has been shown in patients and experimental animals that hyperosmolality per se is potentially lethal [26, 27, 29, 34, 63]. However, overly rapid treatment of hypernatremia by infusion of hypotonic solutions can cause seizures and cerebral edema, which may also be lethal [17, 26, 42, 64].

Most investigators agree that patients with hypernatremic dehydration should be treated with fluid which provides free water in excess of electrolytes. In both children and adults, fluid therapy is usually calculated so as to be administered over a period of about 48 hr [6, 17, 27]. Despite such recommendations, little data in humans or animals are available as to the ideal rate of fluid administrations. Fatal cases of cerebral edema, as well as permanent brain damage, have occurred when hypernatremia was completely corrected within 24 hr [26, 37, 38, 64, 65, 66], while seizures with cerebral edema occur in more than 50% of hypernatremic rabbits when plasma Na^+ is reduced from 185 to 142 mmoles/liter in 4 hr [42]. The aforementioned studies highlight the dangers of overly rapid correction of hypernatremia. However, they also point out the fact that there is really no data which have demonstrated how fast one can safely lower plasma Na^+ in hypernatremic states. Currently accepted therapeutic regimens for treating hypernatremia in adults or children have recently been reviewed [6, 17].

Hyponatremia

Hyponatremia is a common accompaniment of many systemic disease states and occurs as a result of dilution and/or depletion of body Na^+ stores. The etiologies of hyponatremia are diverse and include several iatrogenic causes, such as diuretic administration [67], excessive parenteral fluids [68, 69] and many pharmacologic agents [70, 71]. Self-induced hyponatremia has been reported in voluntarily water-intoxicated infants [72] and in adults consuming excessive amounts of water or beer [73–77]. Other causes of hyponatremia are related to impaired renal ability to appropriately excrete free water, and include the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), hepatic cirrhosis, congestive heart failure, Addison's disease and many others. These entities have been discussed elsewhere [78–80].

Hyponatremia: Symptoms. The symptoms of hyponatremia are dependent on the etiology, magnitude and acuteness of the condition. In general, symptoms of sustained hyponatremia which are due to a combination of Na^+ depletion and water ingestion [81] differ markedly from those which accompany acute water intoxication. In a classical experiment, individuals were maintained for 11 days on a salt-free diet which, combined with excessive perspiration and a high water intake [82], caused the serum Na^+ concentration to fall from 147 to 131 mmoles/liter. These subjects all experienced constant thirst, impaired sensation of taste, anorexia, and several experienced muscle cramps. All had a feeling of general exhaustion, with dyspnea on exertion, and dulling of sensorium. Other studies have shown that in individuals with a greater depression of serum Na^+ (120 to 130 mmoles/liter), sumptoms of nausea, emesis and abdominal cramps may occur [70, 81]. With even more severe hyponatremia (below 115 mmoles/liter), subjects may manifest weakness, lethargy, restlessness, confusion, delirium and impaired mentation [1]. In addition, muscular twitching is often present, and convulsions may occur [69, 73, 76, 83, 84]. Many other neurological abnormalities have been reported in patients with chronic hyponatremia, including focal weakness, hemiparesis, ataxia and Babinski sign [1, 73, 81].

The symptoms of acute water intoxication appear to differ substantially from those attributable to Na^+ depletion per se, although differences may actually be due to the rapidity with which plasma Na^+ is lowered. Neurological manifestations of acute water intoxication usually are not observed until plasma Na^+ has fallen below 125 mmoles/liter [76, 85, 86], and they include nausea, emesis, muscular twitching, grand mal seizures and coma. Acute (less than 24 hr) water intoxication (plasma Na^+ less than 125 mmoles/liter) has a mortality of about 50% [68, 69, 73, 74, 76, 87, 88] with a substantial morbidity (usually brain damage). However, when plasma Na^+ is slowly (several days to several weeks) lowered to 125 mmoles/liter or less by salt depletion and water ingestion, patients usually are less symptomatic [69, 81, 85, 86].

In experimental animals with acute water intoxication, coma and seizures may be seen when serum Na^+ is acutely lowered to levels of about 120 mmoles/liter over a period of two hours [69]. When serum Na^+ is reduced to 122 mEq/liter over two to three days, however, most animals are asymptomatic [69]. More profound hyponatremia (serum Na^+ = 110 mmoles/liter or lower) usually results in varying degrees of lethargy, coma and seizures [69, 89]. Thus, both in patients and experimental animals, the neurological manifestations seem to correlate grossly both with the degree of hyponatremia and with the rapidity of the fall in serum Na^+.

Hyponatremia: Pathophysiology. The pathophysiology of the symptoms associated with hypona-

tremia has not been elucidated. It has always been assumed that in patients who die of severe hyponatremia, the cause of death is brain edema, with possible brain stem herniation. However, there are very few such cases where the underlying pathology has actually been confirmed by autopsy [74, 88]. In most reported cases, either postmortem examination was not done [69] or the patients died several days after correction of the hyponatremia [68] and at that time they did not have brain edema. However, in numerous animal studies performed by many different investigators, it has been found that acute (1 to 4 hr) hyponatremia (plasma Na^+ less than 125 mmoles/liter) results in cerebral edema [35, 48, 69, 88–90]. The cerebral edema is generally accompanied by seizures, but there is no good correlation between the level of plasma Na^+ and the occurrence either of seizure activity or other manifestations of hyponatremia. In fact, the occurrence of seizures in animals with acute water intoxication may be related either to brain edema per se, or low intracellular concentration of Na^+ and/or K^+. In animals with chronic hyponatremia, at least part of the reason for the occurrence

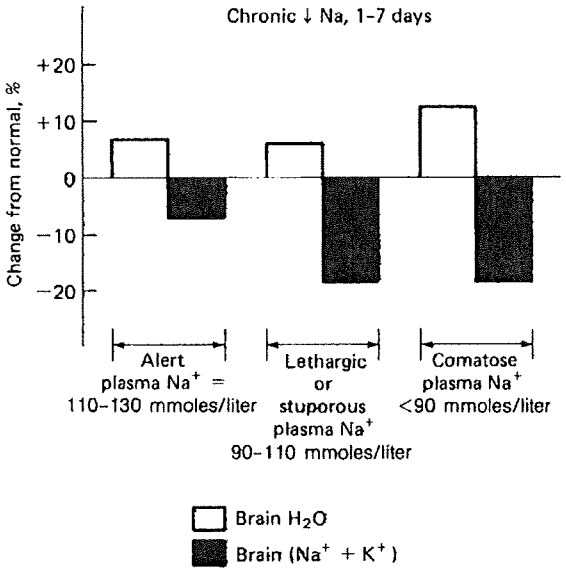

Fig. 2. *The changes in sensorium in animals with experimental chronic hyponatremia.* Clear bars indicate brain H_2O and black bars indicate brain Na^+ and K^+. Animals whose plasma Na^+ is 110 to 130 mmoles/liter are generally alert. There are small but significant changes in brain water (+7.1%) and ($Na^+ + K^+$) content (−7.8%). Animals with plasma Na^+ of 90 to 110 mmoles/liter are usually lethargic or stuporous. The increase in brain water is similar to that found in alert animals, but there are substantial decrements in brain ($Na^+ + K^+$) content (−19.2%). When plasma Na^+ is below 90 mmoles/liter, animals are generally comatose. Brain ($Na^+ + K^+$) content is similar to that of the stuporous animals, but brain water content is substantially greater ([48, 69, 89, 91], Table 2). ([Na) = hyponatremia.

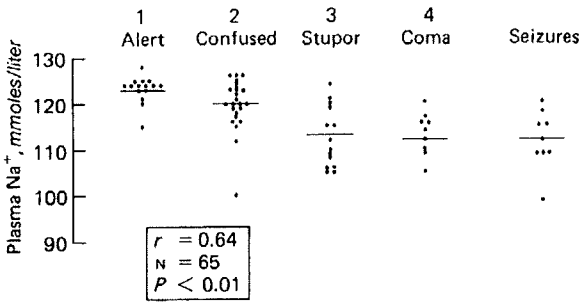

Fig. 3. *The relationship between plasma Na^+ concentration and depression of sensorium in 65 patients with plasma Na^+ of 128 mmoles/liter or less.* It can be seen that although there is a highly significant overall correlation, substantial overlap among groups of patients is present. Among patients who had seizures, the plasma Na^+ (± SE) was 112 ± 2 mmoles/liter, while in those patients who did not have seizures, plasma Na^+ was 119 ± 1 mmoles/liter ($P < 0.01$). Figure reproduced from Arieff AI et al, *Medicine* 55:121–129, 1976, with permission.

of symptoms may be the presence of minimal brain edema. Even when hyponatremia has been present for 3 to 22 days, brain water content is still 7% above normal values [69, 91]. However, chronically hyponatremic animals also have significant decrements in brain contents of Na^+, K^+ and Cl^- (Fig. 2), which may also contribute to symptomatology.

In patients, the symptoms of hyponatremia are not related to either depression of plasma Na^+ per se or to the rapidity of induction of hyponatremia. In Fig. 3 is shown the plasma Na^+ versus depression of sensorium in 65 hyponatremic patients. It can be appreciated that for almost any given level of plasma Na^+, there is marked variation in depression of sensorium. Similar findings have been reported by others [1, 8], where some patients with serum Na^+ of 108 to 132 mmoles/liter had severe neurological manifestations and others with Na^+ of 117 to 133 mmoles/liter were asymptomatic. In general, however, when plasma Na^+ is below 120 mmoles/liter most patients have some depression of sensorium and many have seizures (Fig. 3).

Hyponatremia: Electroencephalographic changes. Electroencephalographic abnormalities in hyponatremia are common but also nonspecific [68]. The most common changes are a loss of normal alpha wave activity with irregular discharges of high amplitude slow (4 to 7 Hz) wave activity [85, 92, 93]. These changes are more obvious over the posterior than the anterior portion of the head, and they tend to be more severe with lower levels of serum Na^+. The EEG changes usually return to normal after correction of the hyponatremia [76, 92, 93].

Hyponatremia: Pathology. There are few pathological studies of brain in patients who have died of

hyponatremia. In one of the first reported cases, a patient who had absorbed 9000 ml of tap water was studied one hour after death [88]. Examination of the cranial contents revealed obliteration of the subarachnoid space. The cerebral gyri were flattened, sulci were largely obliterated, there was uniform enlargement of the brain in all directions, and the ventricles were reduced in size. Microscopically, there was increased vacuolization and swelling of supportive (glial) structures, with cellular swelling apparently confined to white matter. Since this initial report, an additional pathological study of a patient who died of acute water intoxication revealed "cerebral edema" with uncal and tonsillar herniation [74]. In one other patient who died three weeks after an episode of acute water intoxication, no cerebral edema was present [68].

Several investigators have studied the effects of acute water intoxication on brain in experimental animals. In general, all have found that there is considerably less swelling in brain than in other tissues (liver, muscle) studied [48, 50, 89, 91, 94]. Edema is present in both gray and white matter of brain [89, 94], although more so in white matter [95]. The blood-brain barrier is judged to be generally intact in water intoxicated animals, as assessed by the absence of penetration into brain of parenterally administered trypan blue [94].

Microscopically, cellular swelling appears to be confined to astrocytes, with sparing of neuronal elements [96, 97]. Phase microscopy of brain in water-intoxicated rats [97] revealed mild perivascular glial swelling with severe swelling of astrocytes. Electron microscopy [97] showed no damage to cytoplasmic organelles, intact mitochondria and normal tight junctions. There was no evidence of damage to neurons or oligodendrocytes. Most swelling was confined to astrocytes, and the extracellular space was significantly enlarged.

Hyponatremia: Effects on brain water and electrolytes. Brain water and electrolyte content has been evaluated by a number of different laboratories in animals rendered hyponatremic (Table 2). Interpretation of the results reported by different authors is made more difficult by the variety of animal species used and the different degrees of hyponatremia achieved. In general, however, the increase in brain water content seems to be greater in animals with acute hyponatremia (1–4 hr, Fig. 4) or when the serum Na^+ is lowered below 100 mmoles/liter (Fig. 2). During chronic hyponatremia, however, the increase in brain water content is lower than that predicted by the extent of the hyponatremia and also lower than that seen in other tissues, such as skeletal muscle [48, 89, 97].

Thus, it appears that the extent of the increase in water content in response to hyponatremia is somehow limited in brain tissue by mechanisms not altogether clear. Brain electrolyte content (mmoles/kg dry weight) is somewhat decreased in animals made hyponatremic over a period of 1 or 2 hr [48, 91, 94, 99] (Fig. 4). When hyponatremia is induced over longer periods of time, there is a significant fall in brain content of Na^+, K^+ and Cl^- [35, 69, 89, 98, 99] (Table 2). In general, the fall in brain content of Na^+ and K^+ in chronic hyponatremia is proportional to the fall in serum Na^+ level (Fig. 2). The principal mechanism which limits the extent of brain swelling in response to prolonged hyponatremia appears to be a secondary decrement in brain electrolyte content, chiefly Na^+ and K^+. This is substantiated by the changes in brain osmolality seen in hyponatremic animals [69]. It is apparent from Fig. 5 that brain osmolality is significantly higher than serum osmolality in animals made hyponatremic over a period of two hours. When similar degrees of hyponatremia are induced over a period of several days, brain osmolality progressively falls, eventually reaching levels similar to plasma [69]. Thus, the fall in brain osmolality limits the extent of water gain by brain, by

Table 2. Effects of hyponatremia on brain water and electrolyte content

	Duration of hyponatremia	Animal species	Brain H_2O, % change from normal	Brain Na^+, % change from normal	Brain K^+, % change from normal	Serum Na^+ *mmoles/liter*
Pappius, Oh, Dossetor [115]	1 hr	dog	+14.7	−10.6	+2.8	110
Arieff, Llach, Massry [69]	2 hr	rabbit	+16.8	−20.3	−16.3	119
Holliday, Kalayci, Harrah [48]	3 hr	rat	+7.5	0	+7.6	113
Wakim [90]	4 hr	dog	+12.0	−32.3	−39.9	76
Reymer, Fishman [89]	1 day	rat	+13.0	−22.1	−19.5	87
Reymer, Fishman [89]	2 days	rat	+14.0	−16.1	−19.5	123
Arieff, Llach, Massry [69]	3 days	rabbit	+6.8	−8.0	−6.5	122
Holliday, Kalayci, Harrah [48]	3 days	rat	+9.1	−20.0	−15.9	93
Dila, Pappius [91]	3 days	rat	+29.0	−20.6	−18.2	102
Arieff, Llach, Massry [69]	17 days	rabbit	+6.6	−26.7	−17.3	99

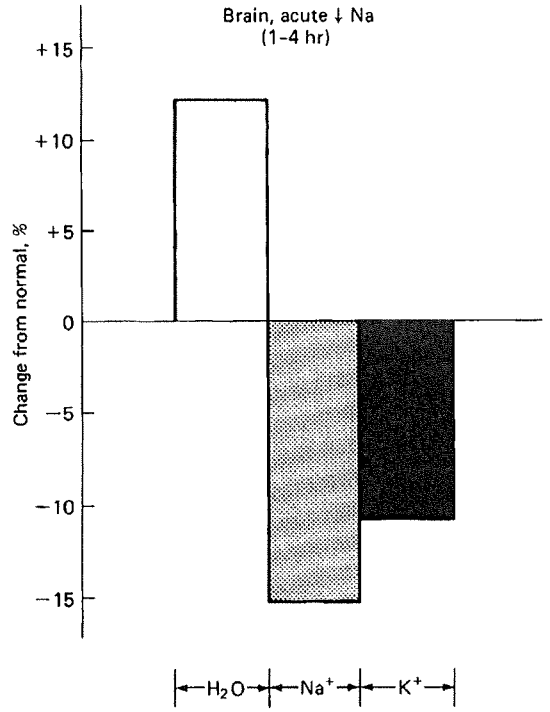

Fig. 4. *Changes in brain content of water, Na^+ and K^+ in animals with acute (1 to 4 hr) hyponatremia.* With a fall in plasma osmolality, an osmotic gradient favors the net movement of water into brain, with brain water increasing to 13% above control values. There is also a loss by brain of Na^+ and K^+ (by 11 to 16%), with a resultant fall in brain osmolality, so that the increase in brain water is lessened ([48, 69, 90, 115], Table 2).

reducing the osmotic gradient induced by the acute fall in serum Na^+.

Thus, the change in brain composition which is of the greatest order of magnitude in animals with acute hyponatremia is an increase in brain water content, whereas in chronic hyponatremia, there is a lesser gain in brain water, but a significant fall in both Na^+ and K^+ content. It has been suggested that the encephalopathy associated with hyponatremia may be related to the decrease in brain K^+ which is seen in experimental animals [91]. Rymer and Fishman [89], however, have recently presented evidence which suggests that the degree of encephalopathy in acutely hyponatremic rats does not correlate either with the serum Na^+ level or the brain content of Na^+ or K^+. When water-intoxicated rats who had become comatose were then allowed to recuperate, some returned to an alert state. The level of serum Na^+ as well as the brain content of both Na^+ and K^+ were similar in the comatose and alert animals, but brain water content was significantly lower in alert versus comatose animals. The acute effects of hyponatremia on brain function, then, would appear to be related to brain edema, which is present before the brain can undergo compensatory changes to adapt to the fall in serum Na^+. In animals with chronic hyponatremia, however, there are significant decrements in brain content of both Na^+ and K^+ (Fig. 2).

Sodium is an essential component for the excitability properties of both nerve and muscle tissue. Without Na^+ ions in the extracellular fluid, both nerve and muscle become inexcitable [100]. Synaptic transmission and the generation of the action potential are both dependent on the presence of Na^+. The membrane potential at the height of the action potential and the rate of rise of the action potential itself are dependent upon the sodium equilibrium potential [101]. Sodium is also involved in the release of neurotransmitters in the presynaptic terminal [102] and in the reuptake of transmitter by the nerve endings [103, 104].

Recently, transport systems for both the release and reuptake of neurotransmitter amino acids have been shown to exist in synaptomosomes of brain and spinal cord [105], as well as in peripheral nerve [106, 107]. A Na^+ gradient is assumed to be one of the major sources of energy for transport of metabolites against a concentration gradient [108]. In brain and spinal cord synaptosomes, the neurotransmitter

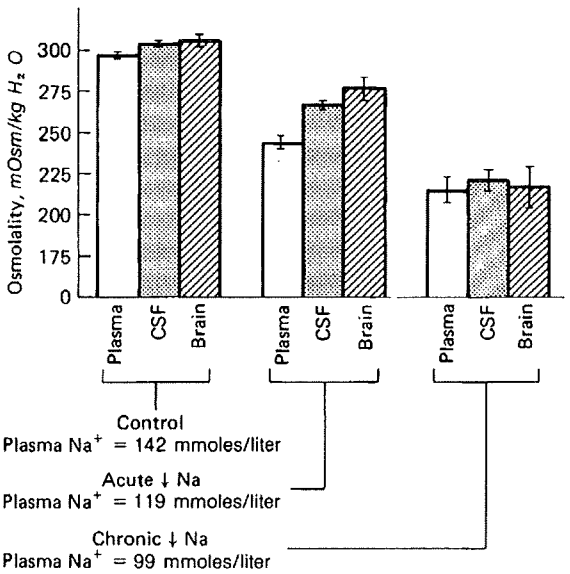

Fig. 5. *The osmolalities of plasma, cerebrospinal fluid (CSF) and brain in normal rabbits, rabbits with acute (2 hr) hyponatremia ($\downarrow Na$), and rabbits with chronic (17 days) hyponatremia.* In normal animals, osmolalities of the 3 compartments are not different. In acutely hyponatremic animals there is a significant osmotic gradient between plasma, CSF and brain, which favors net movement of water into the brain and CSF. After 17 days with chronic hyponatremia, osmolalities of the 3 compartments are not different but all are significantly less than normal [69].

amino acid transport systems are almost totally Na^+ dependent [105, 109], and amino acid uptake in brain slices either is decreased or completely inhibited by the absence of Na^+ [110].

Hyposmolality per se has been observed to result in a decrease in the level of phosphocreatine in brain tissue slices, but there is no change in brain tissue levels of either adenosine triphosphate (ATP), adenosine diphosphate (ADP) or adenosine monophosphate (AMP) [56]. It may be that, in hyposmolar states, brain energy production is inhibited, but that for a period of time, normal brain levels of ATP are maintained at the expense of reduced phosphocreatine [56].

Hyponatremia, then, may affect brain function by any of several mechanisms. Initially, the symptoms of acute hyponatremia may probably be explained by brain edema, with a secondary increase of intracranial pressure. As hyponatremia becomes prolonged over a longer period of time (more than 3 to 4 hr), brain becomes depleted of Na^+ and K^+, thereby limiting the increase in brain water content. Sodium depletion, however, may result both in an inhibition in brain energy metabolism and interference with neurotransmitter amino acid release at the synaptic level. These changes may directly affect brain function and may in part be responsible for the encephalopathy of hyponatremia.

Acute water intoxication: Therapy. Despite a substantial amount of literature pertaining to both patients and experimental animals with acute symptomatic hyponatremia, there is suprisingly little available information as to the appropriate therapeutic approach. There is general agreement that if hyponatremia is due to a specific underlying medical illness (cirrhosis, congestive heart failure, Addison's disease), therapy should be directed primarily at the underlying process. However, in the patient with acute symptomatic hyponatremia, there is apparently no unanimity of opinion as to appropriate therapy. Most standard medical textbooks [111–113] agree that acute symptomatic hyponatremia is a medical emergency and suggest the use of hypertonic (500 to 860 mM) NaCl. These same sources also advise caution in treating hyponatremia "too rapidly" because of the dangers of congestive heart failure or cerebral hemorrhage. However, there are few recommendations as to how much hypertonic NaCl to infuse over how rapid a period of time.

The lack of such recommendations reflects the fact that it is not known how fast one can safely raise plasma Na^+ in patients with acute hyponatremia, or how long it takes for acute hyponatremia to cause permanent brain damage. Studies directed at the aforementioned problems, either in patients or experimental animals, have yet to be undertaken. It is known that in patients, acute water intoxication with plasma Na^+ below 125 mmoles/liter can cause irreversible brain damage within 12 hr [68, 69, 74, 88], but the time span whereby complete recovery is possible is not known. It is known, however, that rapid infusion or ingestion of large quantities of hypertonic NaCl can cause congestive heart failure and subdural and intracerebral hemorrhage, with a prohibitive morbidity and mortality [20, 28–30]. The problem of congestive heart failure is intensified by the fact that hyponatremia per se appears to decrease cardiac output [90]. However, either the infusion of 862 mM NaCl at a rate of about 70 mmoles/hr or establishment of a negative water balance of about 600 ml/hr will usually elevate plasma Na^+ by 2 to 3 mmoles/liter/hr [69, 114]. These forms of therapy are continued until the patient undergoes definite symptomatic improvement or until plasma Na^+ has been increased above 130 mmoles/liter. Both procedures appear to be relatively safe, and until more definitive data is available, therapy of acute symptomatic water intoxication should probably be based on similar maneuvers.

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Adaptation to chronic hypoosmolality in rats

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Adaptation to chronic hypoosmolality in rats. A method for maintaining chronic severe hypoosmolality in rats is described utilizing subcutaneous infusions of the antidiuretic vasopressin analogue 1-deamino-[8-D-arginine] vasopressin (DDAVP) at rates of 1 or 5 ng/hr via osmotic minipumps in combination with self-ingestion of a concentrated, nutritionally-balanced liquid diet. Using these methods, 97.3% of all rats studied achieved stable levels of severe hyponatremia (plasma $[Na^+]$ = 111.6 ± 0.5 mEq/liter, N = 213), which was sustained for periods of time ranging from two to five weeks. Mortality was low (1.8%) and observable morbidity was not noted over a series of studies encompassing 4,628 rat days of sustained hypoosmolality. Analysis of food intake and body weight revealed no evidence of tissue catabolism at any time with the lower (1 ng/hr) DDAVP infusion rate, and only during the first week with the higher (5 ng/hr) rate. Metabolic balance studies during 13 days of sustained hypoosmolality demonstrated the dilutional nature of the hypoosmolality, and only a limited degree of renal escape from the antidiuretic effects of DDAVP (urine osmolalities 800 to 1200 mOsm/kg H_2O). Studies of brain water and electrolyte contents demonstrated complete normalization of brain volume after 14 to 28 days of sustained hypoosmolality, the major part of which (70%) could be accounted for by loss of brain electrolytes. Both natriuresis and kaliuresis occurred during the first five days of hypoosmolality, and were of sufficient magnitude to suggest some degree of adaptation of other body fluid compartments via electrolyte losses as well. These results indicate that rats have substantial capacity to tolerate prolonged severe hypoosmolality with little morbidity and mortality as long as proper attention is paid to their nutritional requirements, and provide further evidence that brain volume regulation likely represents the major adaptive mechanism that allows survival despite sustained hypoosmolality.

Hypoosmolality is the most common disorder of body fluid and electrolyte balance encountered in the clinical practice of medicine [1], with incidences ranging from 15 to 22% in both acutely [2] and chronically [3] hospitalized patients. Various studies have suggested that hypoosmolality is an important cause of morbidity and mortality as well [4, 5], although more recent studies have questioned the actual incidence of mortality with this disorder [6]. Several studies have also suggested that rapid correction of hypoosmolality may lead to neurological deficits from brain myelinolysis in man, similar to the proven production of such lesions by rapid correction of hypoosmolality in animals [7–12]. However, substantial uncertainty exists concerning many of these issues [13, 14], to the point that it is not yet clear whether, and under what circumstances, hypoosmolality and subsequent changes in plasma osmolality cause cellular and tissue dysfunction and death. And although much is known about cellular adaptation to hypoosmolar conditions in vitro [15, 16], much still remains unknown about such adaptive changes and their consequences for mammals in vivo [17]. Consequently, methods allowing maintenance of stable hypoosmolality for long periods of time in healthy noncatabolic animals would be desirable to attempt to study some of these questions.

Review of the various methods used to induce and maintain hypoosmolality in previous studies suggests that for the most part they did not produce results analogous to human disease for several identifiable reasons. First, animals spontaneously ingest water only in response to physiological needs. Consequently, even in the presence of an antidiuretic agent, animals with free access to food and water will not become hypoosmolar because they decrease their water intake to amounts just sufficient to balance insensible water losses [18]. To overcome this, investigators have had to resort to forced intravenous or intragastric administration of hypotonic fluids in dogs [19–21] and rats [22] to achieve the desired positive water balance. However, several problems have become apparent with the use of such methods: (a) they are difficult to use for long-term studies of large groups of animals because of the need to maintain intravenous catheters and external infusion pumps, or alternatively to administer several daily gavages of fluid; (b) most of these studies have had to use large and potentially unphysiologic amounts of hypotonic infusate in order to maintain hypoosmolality, far greater than the relative ingested volumes in hypoosmolar human patients; (c) virtually all animal models utilized to date have exhibited the phenomenon of renal "escape" from the hydroosmotic effect of the antidiuretic agent used, an effect which has been shown to be due to the volume expansion produced by excess fluid administration [23]; and (d) most animal models have exaggerated the degree of natriuresis produced, again in large part because of the continued volume expansion caused by excess fluid administration. An earlier model of experimental hypoosmolality in the rat developed in this laboratory overcame many of these problems by using continuous subcutaneous infusions of the antidiuretic vasopressin analogue 1-deamino-[8-D-arginine] vasopressin (DDAVP) via osmotic minipumps in rats with access to 5% dextrose solution in the absence of food [18]. In this case, rats ingested the dextrose solution as a source of calories, but did so in limited amounts such that renal escape from antidiuresis did not occur despite severe sustained hypoosmolality [18, 24]. Unfortunately, this model tended to exacerbate yet another major

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problem frequently encountered with past animal models of hypoosmolality, namely, production of a catabolic state that limited the period of time during which the hypoosmolality could be maintained. Production of tissue catabolism with large amounts of weight loss has been a common finding in many animal models of hypoosmolality because hypoosmolar animals generally decrease food consumption, presumably as a manifestation of systemic illness. This effect not only contributes to the morbidity and mortality of the experimental animals, but also obviously complicates studies of cellular and tissue adaptation to hypoosmolar conditions in vivo. The occurrence of ongoing catabolism is particularly worrisome in studies of experimental myelinolysis because central pontine myelinolysis in humans has also been frequently associated with malnutrition in patients with chronic alcoholism [7, 10, 25]. It seems noteworthy that previous studies of myelinolysis in experimental animals have uniformly failed to consider this variable [9–12], and consequently the potential role of caloric deficiency and ongoing tissue catabolism in contributing to the brain lesions produced remains conjectural.

This report describes the development and characterization of a rat model of sustained hypoosmolality that eliminates or minimizes the problems of excess fluid administration and tissue catabolism, and allows convenient maintenance of hypoosmolality for long periods of time in relatively healthy animals with stable body weights and negligible morbidity and mortality. Analysis of brain water and electrolyte contents following prolonged hypoosmolality using these methods has revealed normalization of brain water content, thus demonstrating the ability of brain tissue in vivo to volume regulate completely in response to hypoosmolality of sufficient duration.

Methods

Animals and maintenance

Male albino rats of the Sprague-Dawley strain (Zivic-Miller Laboratories, Allison Park, Pennsylvania, USA) weighing 250 to 300 g were used for all studies. They were housed individually in wire mesh cages in a temperature-controlled room (21 to 23°C) with lights on from 7 a.m. to 7 p.m. All animals were maintained on standard rat chow (Wayne Lab-Blox, Chicago, Illinois, USA) and ad libitum tap water prior to initiation of the protocol used to induce and maintain hypoosmolality.

Induction of hypoosmolality

Rats were first acclimated for three to four days to a commercial, nutritionally-balanced liquid diet formulated for rodents (AIN-76, Bio-Serv, Frenchtown, New Jersey, USA). During this time they had access to tap water ad libitum, but no other source of food. At the normal recommended dilution, this formula supplies 1.0 kcal/ml consisting of 66% carbohydrate (as maltose dextrins), 21% protein (as casein) and 12% fat (as corn oil), along with vitamins and trace elements. Based on National Research Council estimates of caloric requirements for maintenance of body weight in adult rats (114 kcal/kg$^{0.75}$ [26]), approximately 70 ml/day of this formula are required to maintain stable body weight in 250 to 300 g rats, assuming an estimated 80% efficiency of conversion of gross energy to metabolizable energy [26]. However, in order to decrease the water content of the diet (69.1% by weight at the normal dilution) and thereby reduce overhydration and renal escape from antidiuresis, the dilution was modified as follows: 258 g of powdered formula was blended with 520 ml of a solution of 14% dextrose in water and stored at 4°C. This resulted in a formula with a caloric density of 1.9 kcal/ml and a water content of only 57.3% by weight. This modified concentrated formula was supplied to the animals in 100 ml glass liquid feeding tubes (Bio-Serv Model LDF-11) as a single morning feeding of 40 ml daily. This amount therefore provided a caloric input of 75.6 kcal/day with only 22.9 ml/day of water. Following three to four days of acclimatization to this diet, osmotic minipumps (Alzet model 2002, Palo Alto, California, USA) containing DDAVP (Desmopressin Acetate, 0.01% intranasal solution, USV Laboratories, Tarrytown, New York, USA) dissolved in 0.15 M NaCl at a concentration of either 10 or 2 μg/ml were implanted subcutaneously along the back [18] under methoxyflurane inhalational anesthesia. At these concentrations, DDAVP was infused at rates of 5 ng/hr and 1 ng/hr, respectively. After recovery from the anesthesia the rats were placed back in their cages with access to the modified concentrated formula but without water bottles for the remainder of the studies. In most cases the animals were initially given 60 to 70 ml of the normal dilution (1.0 kcal/ml) formula on the first day following pump insertion in order to produce a positive water balance and hypoosmolality more rapidly. On all subsequent days they were then given 40 ml/day of the modified concentrated (1.9 kcal/ml) formula. For studies lasting longer than two weeks, the DDAVP pumps were replaced under methoxyflurane anesthesia at 13 day intervals (allowing one day for priming of the pump in 0.15 M NaCl prior to insertion).

Metabolic studies

For metabolic studies, rats were placed in individual plastic metabolic cages (Nalgene model 650-0100, Rochester, New York, USA) as described previously [18]. Three groups were studied: control (infusion of vehicle, 0.15 M NaCl, only; N = 11), DDAVP infusion at 1 ng/hr (N = 12), and DDAVP infusion at 5 ng/hr (N = 11). Several days prior to the insertion of the osmotic pumps, indwelling jugular venous catheters were inserted for drawing blood samples as also described previously [27]. The animals were weighed daily. Daily intakes of formula were measured by weighing each feeding tube after filling with formula, and then again the next morning to ascertain the total amount consumed. Water content of the formula was determined by weighing an aliquot of each batch of formula used before and after desiccation (72 hr at 150°C). For these studies, this averaged 0.573 ± 0.006 ml H_2O per gram of concentrated formula (mean of 30 determinations on 6 batches of formula). Daily urine output was measured volumetrically. Measured water balance was calculated as intake minus output, ignoring insensible losses which were assumed to be constant for animals of similar weights housed under similar conditions [18]. Plasma samples (0.5 ml) were obtained for all animals on each of the two days prior to insertion of the osmotic pumps, and on days 1, 2, 3, 5, 10 and 13 following pump insertion. Red blood cells were reinfused in an equivalent volume of 0.15 M NaCl after each sample. After 13 days the osmotic pumps were removed and the animals were followed for another two days on the same formula intake. Additional blood samples were obtained for all animals on each of the two days following pump

removal. Plasma and urine sodium and potassium concentrations were analyzed by ion-specific electrodes (Beckmann Electrolyte II analyzer, Beckman Instruments, Fullerton, California, USA) and osmolalities by freezing point depression (Advanced Instruments Osmometer). To determine the total sodium and potassium intakes, aliquots of each batch of formula used were weighed and then ashed (800°C for 6 hr), the residues suspended in 0.75 M HNO_3, and the sodium and potassium concentrations measured as above. For these studies, these averaged 0.0262 ± 0.0005 mEq Na^+ and 0.0271 ± 0.0004 mEq K^+ per gram of concentrated formula (means of 30 determinations on 6 batches of formula). Net daily sodium and potassium balances were calculated as the differences between dietary intake and urine output (as in previous studies [18], fecal electrolyte losses were assumed to be small and constant, and were not analyzed).

An additional six rats were studied after three weeks of sustained hypoosmolality to assess the effects of alteration of the volume of formula ingested on urine concentration and volume. For this study, jugular venous catheters were implanted on day 20 of sustained hypoosmolality (DDAVP infusion rate = 5 ng/hr). After a two-day recovery period, the rats were then placed in metabolic cages and followed as described above. After two additional days of formula feedings of the modified concentrated formula at 40 ml/day, the rats were given 60 ml of the normal (1.0 kcal/ml) diluted formula for two days (water content = 0.691 ± 0.003 ml H_2O per gram of normal dilution formula), and then finally 40 ml of the concentrated formula again for two more days. This study allowed an assessment of the effects of changes in water ingestion on urine volume and osmolality during maintenance of equivalent caloric intakes.

Brain water and electrolyte contents

Total brain water and electrolyte contents were measured using standard methodologies [4, 28–33], as previously described from this laboratory with minor modification [34]. Following decapitation the brains were rapidly dissected and the entire forebrain rostral to the cerebellar-cortical junction was weighed before and after desiccation (72 hr at 150°C). Total brain water content was calculated as the difference between the brain weights before and after desiccation, and expressed per 100 g of dry brain weight (DBW). Following desiccation the entire dried residue was placed in 10.0 ml of 0.75 M HNO_3 for 72 hours at room temperature and then homogenized (Brinkmann 1810 Tissue Homogenizer, Brinkman Instruments, Westbury, New York). The homogenized brain was eluted for an additional 48 hours at room temperature then centrifuged (5,000 g for 60 min). Na^+ and K^+ content of the supernatants were determined by flame photometry (Beckman Klina Flame) and Cl^- content by coulometric titration (Haake-Buchler Digital Chloridometer). All brain electrolyte contents were expressed per kg of dry brain weight. The above brain analyses were done on a group of rats following maintenance of sustained hypoosmolality for periods ranging from 14 to 28 days (N = 25; mean days of sustained hypoosmolality 21 ± 1) and compared to identical brain analyses on a group of normonatremic control rats maintained on the same daily volume of the liquid diet for an equivalent period (N = 18; mean days on liquid diet 22 ± 1).

Table 1. Plasma [Na^+] of rats at the end of 2–5 week periods of DDAVP infusion

Days of continuous DDAVP infusion	DDAVP infusion rate	
	1 ng/hr	5 ng/hr
14	115.9 ± 1.2 (N = 17, d = 0)	106.3 ± 0.8 (N = 17, d = 2)
15–21	113.1 ± 0.9 (N = 51, d = 0)	100.7 ± 0.9 (N = 16, d = 2)
22–28	116.5 ± 0.8 (N = 63, d = 0)	107.2 ± 0.5 (N = 34, d = 0)
29–35	111.7 ± 1.3 (N = 3, d = 0)	108.0 ± 2.2 (N = 12, d = 0)
All animals	115.0 ± 0.6 (N = 134, d = 0)	104.5 ± 1.4 (N = 79, d = 4)

Abbreviations are: N, number of rats successfully studied until sacrifice in each group; d, number of rat deaths occurring before sacrifice in each group; (plasma [Na^+] means include only rats that survived until sacrifice).

The degree to which brain volume regulation in hypoosmolar animals could be accounted for by measured losses of brain electrolytes was estimated using calculations described in studies of acute hyponatremia [35]. Specifically, assuming osmotic equilibrium between plasma and brain water after sustained hypoosmolality, the change in osmotically-active brain solute (ΔQ, in mOsm/kg DBW) that would have to occur to allow any observed degree of volume regulation in the hypoosmolar brain can be estimated by the formula:

$$\Delta Q = [V_i \times C_{Osm}{}^i] - [V_f \times C_{Osm}{}^f] \quad (1)$$

where V_i and V_f are the measured volumes of total brain water (in ml/kg DBW) before and after induction of hypoosmolality, respectively, and $C_{Osm}{}^i$ and $C_{Osm}{}^f$ are the plasma osmolalities (in mOsm/liter H_2O) before and after induction of hypoosmolality (because plasma [Na^+] was measured rather than plasma osmolality for most of these studies and because ΔQ is based upon relative changes in osmolality, plasma osmolality was simply estimated as 2 × plasma [Na^+] for the purpose of this calculation).

Statistical analysis

All values are means ± SEM. All P values were determined by two-tailed Student's t-test for unpaired observations.

Results

Using the protocol described above for the induction and maintenance of hypoosmolality, a total of 223 rats were studied in this laboratory over the past two years. Of all rats studied, only six, or 2.7%, failed to achieve significant hyponatremia (arbitrarily defined as a plasma [Na^+] less than 130 mEq/liter). The final plasma [Na^+] levels for the rats that successfully achieved significant hyponatremia are shown in Table 1 divided according to the length of time that the hyponatremia was maintained for each of the two DDAVP infusion rates used (for most studies plasma [Na^+] was used as an indicator of plasma osmolality; measured basal plasma osmolalities were 226 ± 1 mOsm/kg H_2O in 62 of the animals infused at 5 ng/hr DDAVP and 242 ± 1 mOsm/kg H_2O in 87 of the animals infused at 1

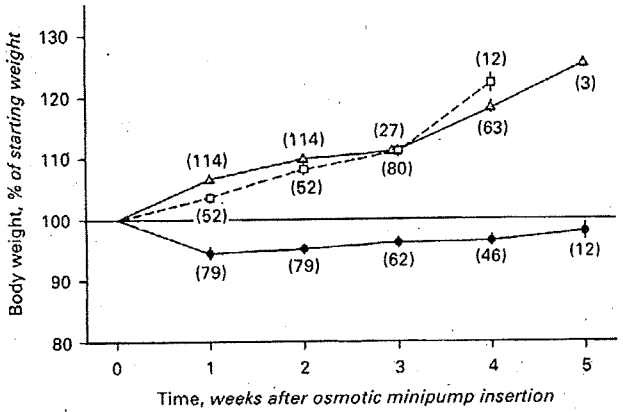

Fig. 1. *Weight changes in rats with sustained hypoosmolality compared to normonatremic controls on the same formula.* Weekly weights were obtained for 193 of the 213 hyponatremic rats described in Table 1. Shown are the weights expressed as a percentage of the starting weight (pre-DDAVP pump insertion) separately for rats infused with 1 ng/hr (△——△) and 5 ng/hr (●——●) of DDAVP. Also shown are the weekly weights of normonatremic control animals given the same daily amounts of the same formula but without DDAVP infusion (□----□). Each point shows the mean ± SE of the number of rats shown in parentheses (the numbers decrease with longer periods of hypoosmolality since studies varied in duration from 2–5 weeks).

ng/hr DDAVP, as compared to 288 ± 1 mOsm/kg H_2O in normonatremic control rats). These studies therefore represent a total of 4,628 rat days of severe hypoosmolality (mean plasma [Na^+] of all animals = 111.6 ± 0.5 mEq/liter). Only four rats died during these combined studies, representing a mortality rate of 1.8% of all rats that became hyponatremic. As shown in Table 1, half of the deaths occurred within the first two weeks of sustained hypoosmolality and all by the first three weeks. Furthermore, all deaths occurred at the higher (5 ng/hr) DDAVP infusion rate, which produced significantly lower plasma [Na^+] concentrations. No obvious morbidity was apparent in the animals that did not die, insofar as could be judged by the normal daily activities of rats (such as, feeding, ambulation, exploratory behaviour, grooming, etc.).

Figure 1 shows a summary of the weight changes for 193 of the 213 hyponatremic rats that were weighed at weekly intervals during the course of these studies. Also shown are the weights of 52 control rats fed equivalent amounts of the same diet but allowed ad libitum access to water to prevent dehydration (plasma [Na^+] = 142.1 ± 0.3 mEq/liter). All weights are expressed as a fraction of the starting weight immediately prior to DDAVP pump insertion. Rats infused with 5 ng/hr of DDAVP maintained a relatively steady weight slightly below their starting weight, while those infused with 1 ng/hr of DDAVP gained weight throughout the period of sustained hypoosmolality at a rate equivalent to that of the normonatremic control rats given identical amounts of the same formula.

Figures 2 through 4 show the results of a metabolic study of 34 rats followed for two baseline days prior to insertion of osmotic minipumps (days B_1 and B_2), 13 days following pump insertion (days 1 to 13), and two additional days after removal of the pumps (days 14 and 15). As shown in Figure 2A, the DDAVP-infused rats quickly became hyponatremic after the first day of DDAVP infusion, and thereafter maintained a stable degree of hypoosmolality until the DDAVP pumps were removed on day 14, after which plasma [Na^+] corrected to normal levels within 24 to 48 hr. Animals receiving the higher (5 ng/hr) DDAVP infusion rate maintained a plasma [Na^+] approximately 10 mEq/liter below that of the animals receiving the lower (1 ng/hr) infusion rate throughout the period of study, similar to the cumulative results for all rats studied shown in Table 1. As expected, urine osmolality remained elevated relative to the control rats throughout the period of DDAVP infusion (Fig. 2B). However, even though urine osmolalities remained near 1000 mOsm/kg H_2O for both DDAVP infusion rates, a relative decrease in urine osmolality from very high levels (1,800 to 2,000 mOsm/kg H_2O) to the range of 800 to 1200 mOsm/kg H_2O clearly occurred over the first five to seven days of DDAVP infusion. Analysis of the measured water balance (water intake minus urine output) shown in Figure 2C demonstrates the positive water balance at the start of the DDAVP infusion, which produced the dilutional hyponatremia, as well as the prompt water diuresis immediately following pump removal, which resulted in correction of the osmolality. Between these two points relative water balance generally occurred, with the differences between intake and output reflecting insensible water losses [18]. Eventually this was equivalent for both the controls and the DDAVP-infused rats, although a period of negative water balance was observed during days three through five in the animals receiving 5 ng/hr DDAVP.

Figure 3A demonstrates that an initial weight gain accompanied the water retention for both DDAVP-infused groups as expected. However, over the next several days the weights of the 5 ng/hr DDAVP infusion group then decreased and gradually returned to basal levels, after which they then remained stable throughout the subsequent days of DDAVP infusion, while those of 1 ng/hr infusion group increased at a rate comparable to the normonatremic controls (again similar to the cumulative results for all rats studied shown in Fig. 1). While this might suggest excretion of the initially retained water, the later rapid weight loss secondary to the diuresis following pump removal on day 14 indicates that a dilutional hyponatremia from excess water was still present at that time. Following the water diuresis produced by pump removal, the weights of the 5 ng/hr DDAVP-infused group decreased to approximately 12 to 15% below starting weights, while the weights of the 1 ng/hr DDAVP group decreased to levels nearly identical to their starting weights. Figure 3B shows that during the first several days of hyponatremia the DDAVP-infused rats did not eat the full 40 ml of the liquid formula. This effect was most pronounced on days three to five in the 5 ng/hr DDAVP infusion group, a period of time which coincided with the decreases in body weight (Fig. 3A) and the negative water balance (Fig. 2C) in this group. However, with gradual recovery of appetite rats in both DDAVP-infused groups eventually consumed the total amount of calories required for weight maintenance, similar to the normonatremic control animals. Interestingly, on the first day following pump removal all animals consumed the full 40 ml of the liquid formula, but on the second day the 5 ng/hr DDAVP infusion group consumed substantially less. No obvious motor or other impairments were observed to account for the decreased food intake in this group at this time.

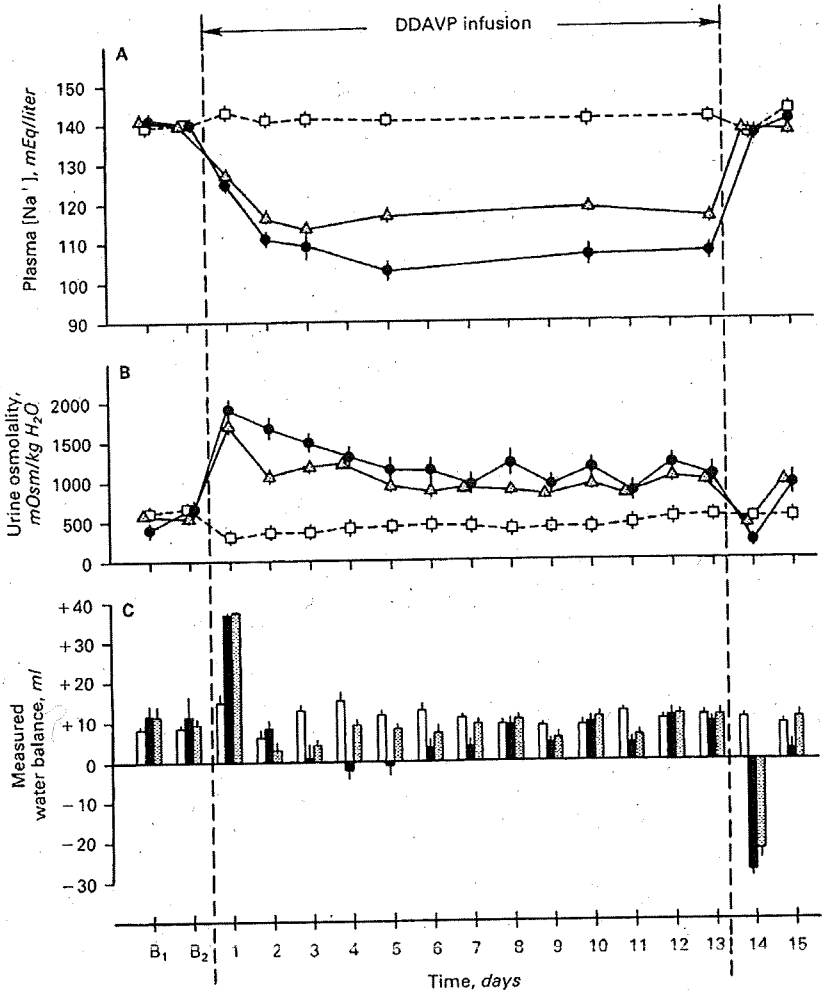

Fig. 2. *Plasma [Na^+], urine osmolality and water balance during sustained hypoosmolality.* Shown are results from rats infused with 1 ng/hr (△——△, grey bars, N = 12) or 5 ng/hr of DDAVP (●——●, solid bars, N = 11), as compared to control rats receiving subcutaneous infusions of only 0.15 M NaCl via osmotic minipump (□----□, open bars, N = 11). Rats were followed in metabolic cages for two baseline days prior to osmotic minipump insertion (B_1 and B_2), then for 13 days of either DDAVP or 0.15 M NaCl infusion (days 1–13), and finally for 2 additional days after osmotic minipump removal (days 14 and 15). All rats received identical amounts of the same formula on each day, but only the control rats also had access to tap water drinking solution. **A.** Plasma [Na^+] levels (mEq/liter) obtained via indwelling jugular venous catheters during the course of the study. **B.** 24-Hour urine osmolalities (mOsm/kg H_2O) obtained daily throughout the course of the study. **C.** 24-Hour measured water balance (ml) calculated as water content of ingested formula (plus tap water for control rats) minus urine output for each day of study. Results shown are means ± SE.

Figures 4A and B show the net Na^+ and K^+ balances, demonstrating significant natriuresis and kaliuresis, greater in the 5 ng/hr DDAVP infusion group, until after the fifth day of DDAVP infusion when relative balance was achieved for these parameters as well. The greatest natriuresis always was seen on day two, the day after water loading, in both DDAVP-infused groups. Significant kaliuresis also occurred on this day, but was far greater over days three through five in the 5 ng/hr DDAVP group, coinciding with the period of maximally decreased formula intake and weight loss in this group (Fig. 3).

Figure 5 demonstrates the changes in urine volume and osmolality with different concentrations of the liquid formula. On the modified concentrated formula at 40 ml/day, urine osmolality averaged 1056 ± 65 mOsm/kg H_2O with urine outputs of 12.7 ± 0.8 ml/day and maintenance of plasma [Na^+] at 108 ± 2 mEq/liter. Upon switching to 60 ml of the dilute formula, urine volume increased to 32.2 ± 3.1 ml/day while urine osmolality decreased to 386 ± 69 mOsm/kg H_2O, coincident with a decrease in plasma [Na^+] to 100 ± 1 mEq/liter by the second day of the dilute formula. Following reinstitution of the smaller volume of concentrated formula, all parameters reverted back toward the earlier values.

Table 2. Total brain water and electrolyte content of normonatremic rats and rats with sustained hypoosmolality

	Normonatremic N = 18	Hyponatremic N = 25	Percent change
Plasma [Na^+] *mEq/liter*	141 ± 1	107 ± 1[a]	−24.1%
Brain water *ml/100 g DBW*	372.5 ± 2.1	374.7 ± 1.2	+0.6%
Brain K^+ *mEq/kg DBW*	502.2 ± 14.6	415.2 ± 5.9[a]	−17.3%
Brain Na^+ *mEq/kg DBW*	274.5 ± 6.1	244.3 ± 1.8[a]	−11.0%
Brain Cl^- *mEq/kg DBW*	168.9 ± 5.1	113.7 ± 2.4[a]	−32.7%

[a] $P < 0.001$ relative to normonatremic controls

Analysis of total brain water and electrolyte contents after 21 ± 1 days of sustained hypoosmolality is shown in Table 2, in comparison with identical brain analyses of a group of normonatremic rats maintained on the same volume of liquid diet for an equivalent period (22 ± 1 days). The control values for total brain water and electrolyte contents are similar to

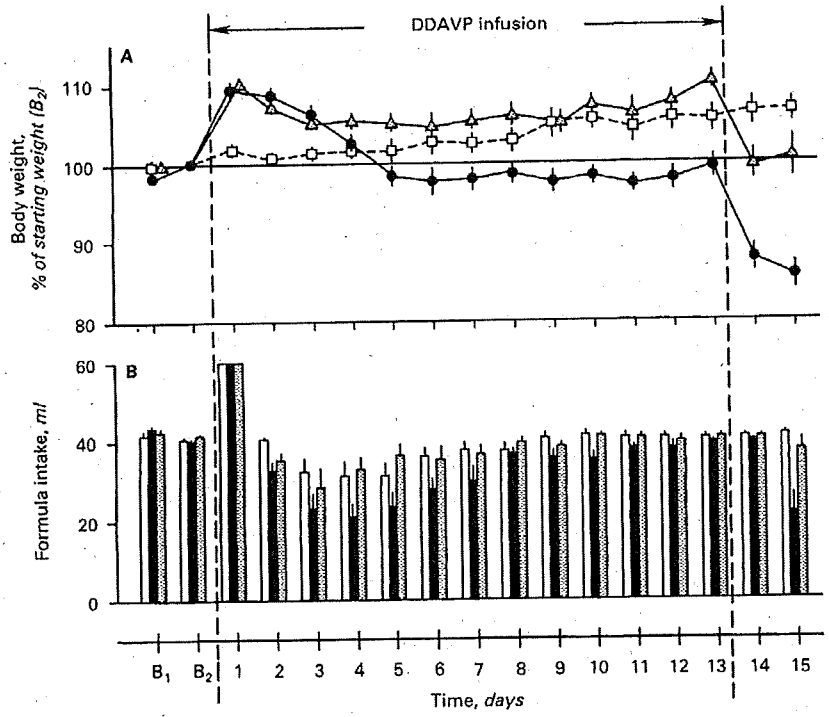

Fig. 3. *Body weight and formula intake during sustained hypoosmolality.* Shown are results from the same metabolic study described in Figure 2. **A.** Daily weights expressed as a percentage of starting weight immediately prior to osmotic minipump insertion (day B_2). **B.** Daily intakes of formul throughout the study (on day 1 all rats were allowed access to 60 ml of the regular 1.0 kcal/ml formula; on all other days they were allowed access to the more concentrated 1.9 kcal/ml formula). All symbols are as describe in Figure 2.

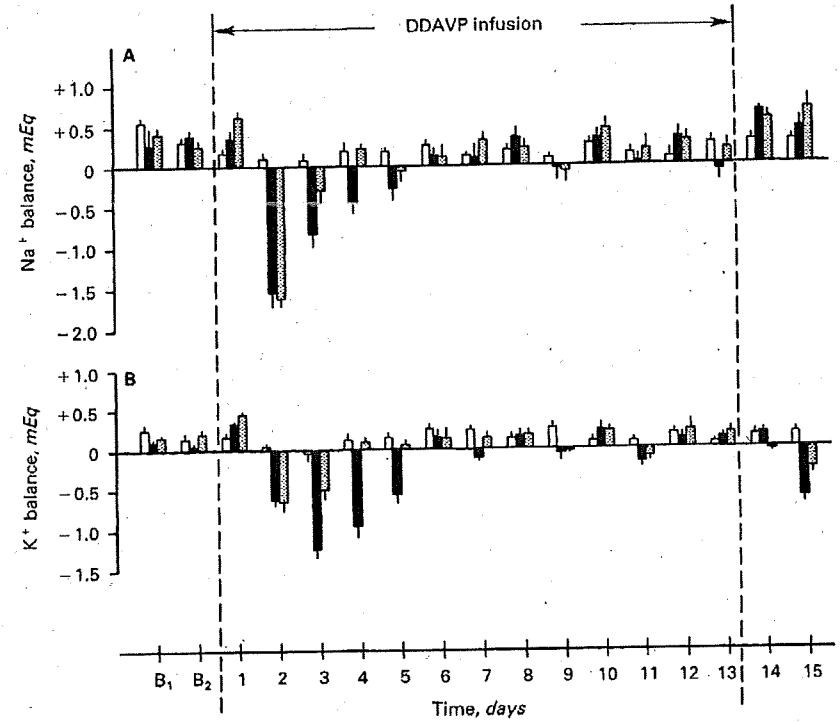

Fig. 4. *Na^+ and K^+ balances during sustained hypoosmolality.* Shown are the results of the same metabolic study described in Figure 2. For both Na^+ and K^+ the balanc was calculated as the difference between dietary intake and urinary losses, ignoring fecal losses which were assumed to be small and constant across groups. **A.** 24-Hour Na^+ balances calculated daily throughout the study. **B.** 24-Hour K^+ balances calculated daily throughout the study. All symbols are a described in Figure 2.

those reported in multiple previous studies [4, 28–35]. Despite the 24.1% decrease in plasma [Na^+], total brain water content of the hyponatremic animals was not significantly different from the control group. However, significant decreases were measured in total brain K^+ (−17.3%), Na^+ (−11.0%) and Cl (−32.7%) contents of the hyponatremic animals. Based o equation (1), ΔQ, the predicted change in osmotically activ total brain solute to allow this degree of volume regulation

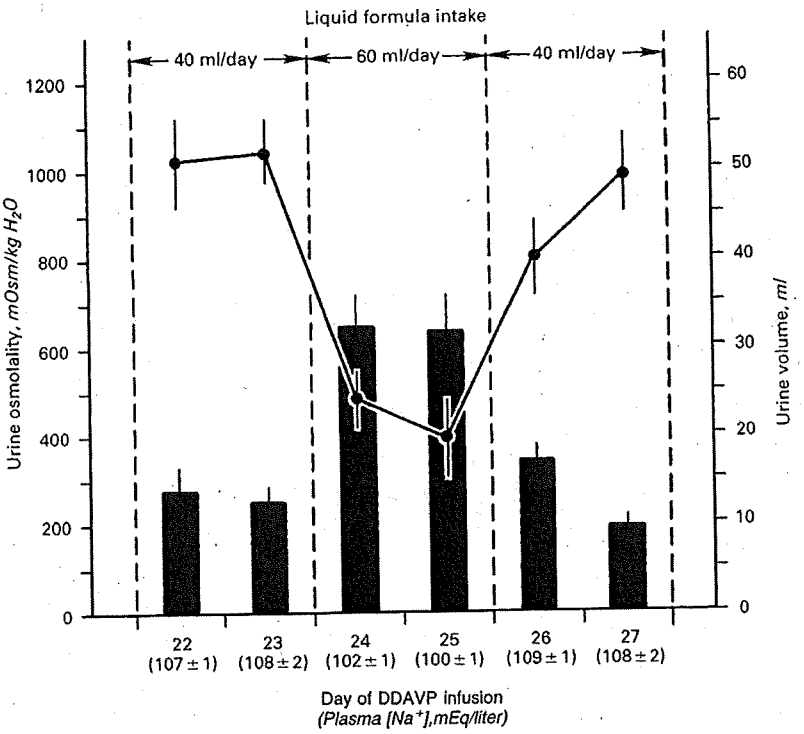

Fig. 5. *Effect of increased water intake on urine osmolality and volume during sustained hypoosmolality.* Rats with indwelling jugular venous catheters were placed in metabolic cages after 21 days of DDAVP infusion (5 ng/hr). Following 2 days with access to 40 ml/day of the concentrated 1.9 kcal/ml formula, they were given 60 ml/day of the regular 1.0 kcal/ml formula for 2 days, and then followed for 2 additional days on the concentrated formula again. Shown are the 24-hour urine osmolalities (●——●), the daily urine volumes (■) and the plasma [Na^+] levels (parentheses below days) for each of the six study days. Results are means ± SE for six rats.

would be 248.6 mOsm/kg DBW, a value substantially greater than the sum of the experimentally observed decreases in measured brain electrolytes ($\Delta Na + \Delta K + \Delta Cl = 172.4$ mEq/kg DBW, equivalent to 172.4 mOsm/kg DBW for monovalent electrolytes).

Discussion

The studies summarized in this paper demonstrate the feasibility of maintaining rats with severe degrees of hypoosmolality for long periods of time. The use of a liquid diet in combination with continuous subcutaneous administration of DDAVP by osmotic minipump offers several advantages over previous methods: (a) this model is very easy to use since the animals spontaneously ingest their water loads, an important advantage for long term studies of hypoosmolality in large numbers of animals; (b) severe degrees of hypoosmolality can be produced reliably; (c) the use of DDAVP allows evaluation of water retention without potential vascular effects from the pressor activity of vasopressin; (d) the animals remain healthy as indicated by stable or increasing body weights and very low rates of mortality despite long periods of hypoosmolality; (e) the phenomenom of renal escape from the antidiuretic effects of DDAVP can be minimized by limiting the animals' total fluid intakes; and (f) the hypoosmolality is easily reversible simply by removing the DDAVP minipumps. Consequently, this model appears particularly well-suited for studies of chronic hypoosmolality in rats, and should be easily adaptable for use in other species as well. Furthermore, in many ways it better approximates human pathophysiology than have most previous methods, insofar as chronic hypoosmolality is maintained via ingested fluids without significant renal escape from antidiuresis or ongoing tissue catabolism and weight loss.

However, certain disadvantages are nonetheless still apparent. First, some tissue catabolism does occur, especially at the 5 ng/hr DDAVP infusion rate as indicated by the initial weight loss over the first several days of hypoosmolality in this group. While this then stabilizes for the remainder of the period of DDAVP infusion, studies done during the first week using this infusion rate must take into account the liklihood of ongoing tissue catabolism during this time. Without taking this factor into account it would be more difficult to explain some of the results observed in the 5 ng/hr DDAVP-infused rats during the first five days of the metabolic balance study shown in Figures 2 to 4. The coincidence of the significantly decreased formula intake on days three to five with the weight loss, negative water balance and urinary electrolyte losses during this period, despite continued stable hyponatremia, can potentially be explained by the occurrence of tissue catabolism as a result of decreased caloric intake; in this case, despite a decreased water intake as well during this period, as reflected by the negative measured water balances, spontaneous correction of the hypoosmolality would not occur because of the added component of endogenously-generated free water as a result of the tissue catabolism [18]. Alternatively, maintenance of hyponatremia despite a decreased water intake during this period could also be due to urinary electrolyte losses as a result of ECF and ICF volume regulatory processes [18, 20], and the present data do not allow a critical assessment of the relative contributions of these two effects at this DDAVP infusion rate. On the other hand, use of the lower 1 ng/hr DDAVP infusion rate reduces or eliminates this problem. As shown in Figure 1, animals main-

tained at this infusion rate continue to gain weight at a steady rate, although most of the early weight gain probably represents retained water since removal of the DDAVP pumps after 13 days of hypoosmolality results in an abrupt decrease in weight back to the pre-infusion levels (Fig. 3A). Nonetheless, over longer periods of sustained hypoosmolality true tissue weight gain does occur in this group as shown in Figure 1. Elimination of tissue catabolism at this DDAVP infusion rate therefore allows a clearer interpretation of the observed urinary electrolyte losses (Fig. 4) as likely being secondary to volume regulatory processes rather than catabolic processes.

Secondly, while renal escape from the antidiuretic effect of DDAVP is minimized, it is not absent as indicated by the relative decrease in urine osmolality during the first several days of the metabolic studies shown in Figure 2B. Nonetheless, the ability to maintain urine osmolalities chronically in the range of 800 to 1200 mOsm/kg H_2O represents an improvement over previous methods that resulted in greater degrees of renal escape from antiduresis [19, 22]. In agreement with previous studies [18], the 1 ng/hr infusion rate of DDAVP produced urine osmolalities reasonably equivalent to the higher infusion rates, although urine volumes tended to be somewhat higher with achievement of correspondingly lesser degrees of hypoosmolality in this group (Table 1, Fig. 2A). The likelihood that the degree of renal escape observed is related to the degree of volume expansion in this model is shown in Figure 5, which demonstrates induction of a greater degree of renal escape simply by increasing the volume of the ingested formula. Presumably, the mechanism causing renal escape under these conditions is related to increased renal perfusion pressure, similar to previous studies in dogs [23]. Theoretically, the urine osmolalities in this model could be maintained even higher by further reducing the volume of formula ingested, as long as the total volume of water ingested remained equal to or greater than the animals' insensible water losses [18]. However, a practical limit in this regard is that the liquid formula becomes too viscous to flow through feeding tubes in concentrations much above 1.9 kcal/ml. Although it may be possible to supplement a smaller volume of the liquid diet with a measured amount of solid food, preliminary trials using this method have not proved to be as reliable in maintaining hypoosmolality because the animals' liquid formula intake becomes much more unpredictable and variable when rats are offered even small amounts of solid food.

In addition to describing a useful method for reliably maintaining long-term hypoosmolality in rats, the present results demonstrate that rats can adapt quite successfully to hypoosmolar conditions. Previous studies in rabbits have clearly demonstrated that the rapidity of development of severe hypoosmolality is a major determinant of morbidity and mortality in experimental animals [4]. However, the deleterious effects of sustained hypoosmolality once animals have successfully survived an initial decrease in plasma osmolality have not been as well studied. Several recent studies have reported mortality rates in hypoosmolar animals ranging from 30 to 60% in rats, rabbits and dogs [10–12], but in these studies it has not been clear whether the mortality was attributable to the hypoosmolality itself or to other factors, such as the nutritional status of the animals. This question is relevant for issues of human pathophysiology, since it has been frequently suggested that severe hypoosmolality by itself carries a high risk of mortality [4]. In this large study very little mortality was observed despite achievement of degrees of hyponatremia analogous to those of previous studies, which in addition was maintained for longer periods of time than in previous studies. Furthermore, all deaths occurred in the 5 ng/hr DDAVP infusion group, in which some degree of weight loss and tissue catabolism occurred. However, this group also maintained a plasma $[Na^+]$ significantly lower than the 1 ng/hr infusion group and consequently it cannot be ascertained whether the catabolic state of the rats or the more severe degree of hyponatremia, or possibly the combination of the two, led to the small number of deaths in this group. On the other hand, some studies have also not noted high mortality rates with induction of acute hyponatremia in rats despite markedly catabolic states [18, 22], consequently additional factors such as type of anesthesia employed and the initial rate of fall of plasma $[Na^+]$ could well have been of greater importance in those studies where high mortality was noted. While rat studies obviously cannot answer questions of mortality during human disease, nonetheless the present results demonstrate clearly that animals are able to adapt to hypoosmolality with surprisingly little morbidity and mortality even over relatively long periods of sustained severe decreases in plasma osmolality.

The mechanism which allows survival of animals in the face of chronic hypoosmolality of the extracellular fluid has long been thought to be cellular volume regulation, by which cellular dysfunction secondary to osmotic swelling is minimized or prevented. In the brain this occurs predominantly via extrusion of cellular solute, in large part potassium but undoubtedly other intracellular solutes as well, as initially documented by the studies of Yannet in the 1930's [28], and later verified by multiple other investigators [4, 29–33]. Nonetheless, all of these studies still showed some residual brain edema in hypoosmolar animals, suggesting incomplete regulation of brain volume. The present studies demonstrate that with sufficiently prolonged hypoosmolality in otherwise healthy animals, complete brain adaptation in fact occurs with eventual achievement of a brain water content identical to normonatremic animals maintained on the same diet. However, unlike in the case of acute dilutional hypoosmolality, where monovalent brain electrolyte losses were found to account for all the observed brain volume regulation [35], only 69.3% of the brain volume regulation in this study could be accounted for by such measured electrolyte losses. Further analysis of this data reveals that virtually all (94.3%) of the anticipated cationic losses ($\Delta Q/2$, or 124.3 mOsm/kg DBW) could be accounted for by the measured brain K^+ and Na^+ losses, whereas only 44.4% of the anticipated anionic losses could be explained by Cl^- losses. This is consistent with the later stages of brain volume regulation during chronic sustained hypoosmolality resulting primarily from intracellular solute losses, for which K^+ would be the major decreased intracellular cationic solute, but other solutes (proteins and amino acids [16, 17]) would likely make up a significant portion of the decreased intracellular anionic solute. To what degree cellular loss as opposed to osmotic inactivation or sequestration of such non-electrolyte solute occurs in the brain remains unanswered by these studies.

Similarly still unanswered is the degree to which other body cells outside the brain are also able to volume regulate during

chronic hypoosmolality. Earlier studies have suggested that muscle tissue does not volume regulate to the same degree as brain in response to hypoosmolality [30–32], but this has not been reexamined systematically after longer periods of sustained hypoosmolality. However, the probability that more generalized solute loss is occurring in tissues other than the brain is suggested by the metabolic balance studies shown in Figure 4. In the 5 ng/hr DDAVP infusion group, the total negative K^+ balance over the first five days of sustained hypoosmolality was -0.897 ± 0.077 mEq/100 g body wt, an amount roughly equivalent to the negative Na^+ balance, -0.821 ± 0.094 mEq/100 g body wt. The maximum amount of K^+ excretion which could be accounted for by brain volume regulation based on the results shown in Table 2 is 12.9 mEq/100 g DBW, or 0.013 mEq/100 g body wt based on a mean dry brain weight of 0.100 ± 0.003 g/100 g body wt, which represents only 1.4% of the observed K^+ secretion. However, as discussed previously, significant tissue catabolism clearly occurs during the first several days of sustained hypoosmolality using this infusion rate, thereby resulting in probable overestimation of the amount of K^+ extrusion from cells as a means of adaptation to chronic hypoosmolality. A more accurate estimate of cellular volume regulation during sustained hypoosmolality can be obtained from a similar analysis of the balance data from the rats infused with DDAVP at 1 ng/hr. Although this group gained approximately 10% total body weight over the 13 days of DDAVP infusion, most of this increase probably represented retained water since following DDAVP pump removal their weights abruptly decreased to levels identical to the pre-DDAVP weights. Consequently, their K^+ and Na^+ balances likely more closely reflect adaptational changes rather than the effects of tissue catabolism or anabolism. In this group, the total negative K^+ and Na^+ balances over the first five days of sustained hypoosmolality were -0.167 ± 0.103 and -0.355 ± 0.060 mEq/100 g body wt, respectively. These amounts were both significantly less than were observed in the 5 ng/hr infusion group, suggesting that some proportion of the kaliuresis and natriuresis observed in the higher DDAVP infusion group was probably secondary to tissue catabolism rather than volume regulation via solute loss (but because the 5 ng/hr DDAVP infusion group was more hyponatremic, it must be acknowledged that a portion of the increased urinary electrolyte excretion in this group might be expected on the basis of a greater degree of solute loss as a result of volume regulation). Nonetheless, the total amount of K^+ excretion observed in the 1 ng/hr infusion group, while more variable, still was greater than that amount which would be predicted on the basis of brain volume regulation alone (in this case 7.8% of the total K^+ excretion), again suggesting some degree of cellular volume regulation by other body tissues as well. Most likely this represents more limited degrees of volume regulation in non-brain tissues, as has been suggested by in vitro studies of different cell types [15, 16].

Finally, the complete adaptation of brain water content via solute loss with prolonged hypoosmolality may also be of importance to the question of myelinolysis with subsequent correction of hypoosmolality. While most studies of experimental myelinolysis following increases in osmolality in hypoosmolar animals have appropriately emphasized the importance of the magnitude and the rate of increases in plasma osmolality in producing the lesions [9–12], two studies have suggested that chronicity of the preexisting hypoosmolality may be an important pathogenetic factor as well [12, 36]. The results of the present study suggest a mechanism whereby this might occur, since with longer duration of sustained hypoosmolality more complete brain adaptation occurs through greater losses of total brain solute. Because subsequent increases in plasma osmolality dehydrate the brains of hypoosmolar animals [34], this effect might be even more pronounced in animals with more chronic hypoosmolality and consequently less total brain solute with which to buffer the subsequent increases in plasma osmolality. However, even if this mechanism did result in increased susceptibility of the brains of chronically hypoosmolar animals to osmotic dehydration and possibly myelinolysis, an obvious limit on the degree of increased susceptibility would be reached by the time complete brain volume regulation had occurred, since there would be no ongoing stimulus to further brain solute losses beyond this point.

In summary, the very low morbidity and mortality rates observed using these methods in large groups of animals demonstrate that, at least in the rat, hypoosmolality itself does not appear to be particularly deleterious to cellular and tissue viability. We therefore anticipate that use of this model in future investigations should enable a better understanding of cellular and tissue adaptation to chronic hypoosmolality in vivo, thereby hopefully enhancing our understanding of the pathophysiological mechanisms involved in human hypoosmolar states as well.

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Hypotonic intravenous solutions in children.

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Abstract

The use of hypotonic intravenous solutions, especially 4% dextrose/0.18% saline, remains standard practice in many paediatric units in the UK. The practice of prescribing hypotonic intravenous fluids derives from the work of investigators in the 1950s, who produced arbitrarily-derived formulae for calculating the maintenance requirements for water and electrolytes in hospitalised patients. Combining these values led to the widespread acceptance of hypotonic solutions such as 4% dextrose/0.18% saline as 'standard maintenance' parenteral fluids. Unfortunately, these calculations do not account for the effects of antidiuretic hormone, the secretion of which is stimulated by many factors encountered during acute illness and especially in the perioperative period. In this setting, the administration of hypotonic intravenous fluids results in the retention of free water and the development of hyponatraemia. The routine administration of hypotonic intravenous fluids has been shown to be associated with severe morbidity and the deaths of many previously healthy children. The problem is compounded by the fact that 4% dextrose/0.18% saline is labelled as 'isotonic'. Whilst this solution is isosmolar compared to plasma, lack of osmotically-effective solutes means that it is hypotonic with reference to the cell membrane. There is no justification for the routine administration of hypotonic intravenous fluids.

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Postoperative fluid therapy – put not thy faith in dextrose saline: discussion paper

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Keywords: fluid therapy; postoperative; saline; hyponatraemia; dextrose

Introduction

Although we live in an era of controlled clinical trials few would disagree that many of our treatments become popular for no other reason than that they are fashionable. One example of this is postoperative fluid therapy and, in particular, the widespread use of dextrose saline as a replacement fluid. In the Yorkshire Region it accounted for a mean of 34% (range 9.9-64.0%) of all crystalloid solutions infused in 1989 (personal communication). The very fact that it is so often prescribed gives it a semblance of physiological respectability which itself implies usefulness and necessity. It is accepted by nursing staff without question and goes unchallenged by the majority of surgeons and anaesthetists.

The rationale used to justify the use of dextrose saline (4.3% dextrose 0.18% saline) is based on the assumptions that it adequately provides for maintenance fluid requirements, that it avoids sodium overload and that it is safe.

Maintenance requirements

As far as maintenance requirements are concerned Le Quesne recommended, on the basis of some elegant experimental studies in 1954, that postoperative surgical patients should receive 2.5 l of 5% dextrose and 0.5 l of 0.9% saline each day[1]. This standard regimen would, it was said, obviate the risk of sodium overload and provide a sound basis for postoperative fluid therapy. Now, 30 years later, 3 l of dextrose saline each day, which provides an identical fluid intake and virtually the same sodium intake is one of the most frequently recommended postoperative fluid regimens[2]. There are, however, serious objections to the adoption of such a standard, basic regimen. Firstly, and most importantly of all, it detracts from one essential prerequisite of all parenteral fluid therapy, which is, individual patient assessment. Secondly, maintenance fluid requirements are not 3 l of water and 80-90 mmol of sodium a day in each and every patient. They are, of course, extremely variable depending on the age, sex, and body size of the patient as well as ambient temperature and the effects of any coexistent illness[3]. On any account, postoperative fluid therapy should not be determined by maintenance requirements alone. A basic regimen does not take into account the almost inevitable additional needs of the surgical patient. Many patients coming to theatre are already fluid depleted and the losses incurred are primarily from the extracellular fluid compartment. During surgery, particularly prolonged abdominal surgery, further depletion of the extracellular space occurs as a result of transudation from traumatized tissues, sequestration into the intestinal tract, and evaporation from exposed viscera. Replacement of these losses with dextrose solutions alone will cause a lowering of osmolality in both intracellular and extracellular fluid compartments as, after metabolism of the dextrose, water only remains which is distributed throughout the entire total body water. The use of dextrose saline may ameliorate this to some extent but it will not completely prevent some decrease in osmolality which may become apparent as a dilutional hyponatraemia.

Postoperative hyponatraemia – prevention

Surgeons remain apprehensive about the use of saline in the early postoperative period. This reticence is related to the well-known fact that after surgery, patients have a diminished urinary excretion of sodium and are unable to excrete all of a sodium load. These physiological changes are often used as the justification for infusing dextrose or dextrose saline, in preference to normal saline, into the postoperative patient. However, although postoperative salt retention used to be regarded as an inevitable part of the stress response to surgery, it is now recognized that it is greatly accentuated by any deficit in either the plasma volume or the extracellular fluid compartment[4] and it is suggested that it may be a physiological response to a reduced extracellular volume[5].

Correction of these deficits, with either colloid or isotonic saline, minimizes this postoperative salt retention[6,7]. In other words, the antinatriuresis and antidiuresis that characterizes the metabolic response to trauma can be regarded as a beneficial homeostatic mechanism initiated to conserve salt and water when these losses could be severely detrimental. It is not surprising, then, that appropriate intravenous fluid therapy may itself modify these homeostatic mechanisms by correcting fluid losses and conversely, inappropriate therapy may actually impair homeostasis. Indeed, this was the conclusion reached by Thomas and Morgan[8], in a study which compared the effects of saline and dextrose saline on fluid balance, vasopressin and plasma sodium in the immediate postoperative period[7]. They found similar values of vasopressin in each group of patients, all of whom had undergone abdominal surgery, but inappropriately high urine osmolalities in association with hyponatraemia in the patients who received dextrose saline. This study suggested that the stress of surgery maintains vasopressin at a certain minimum level below which it could not be suppressed and that

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this minimum level determined the minimum obtainable urine osmolality. If a fluid was given, such as dextrose saline, that required for water balance a lower urine osmolality than this minimum, then water would be retained and plasma sodium would fall. In the saline group, plasma sodium remained normal, suggesting that vasopressin remained under osmotic control. They concluded that saline should be used on the first postoperative day after which dextrose saline was suitable as vasopressin was now under osmotic control. It is worth noting that in this study all the patients received 3 litres of fluid a day and no adverse effects attributable to an intake of 450 mmol of sodium each day for 7 days were observed in the saline group. Tindall and Clark[9] have also recommended giving isotonic (0.9%) saline in the first 24 h postoperatively followed by a regimen containing progressively less sodium. Their study showed that patients receiving 3 l of saline daily for one week postoperatively did not become hyponatraemic but developed sodium and water retention after 4 days. This contrasted with a group who received dextrose only in whom hyponatraemia and negative fluid balance occurred in the early postoperative period.

Fluid overload

The advocates of dextrose saline argue that it is safe and free of serious metabolic complications. Certainly, it is true that dextrose saline will prevent sodium overload, which seems to be the complication of fluid therapy most prevalent in surgeons' minds, but it will not prevent, and indeed it is a common cause of the other equally as common but less well recognized complication of fluid therapy, namely water overload. Usually the only manifestation of this is a dilutional hyponatraemia which reflects retention of water in excess of sodium. Patients, after surgery, are unable to excrete a water load as rapidly as before surgery and they become hyponatraemic if given too much dextrose solution intravenously. This fall in plasma sodium is smaller than that usually associated with symptomatic water intoxication but, as there have been few studies which have addressed themselves specifically to the potential harmful effects of even mild hyponatraemia, it would seem sensible to avoid it. The fact that the syndrome of water intoxication is infrequently diagnosed in postoperative surgical patients is not, in itself, a justification for the continued use of dextrose saline. In the maintenance of perioperative fluid balance and plasma volume colloids are much more useful if blood loss is anticipated[10].

Does an asymptomatic hyponatraemia and relative hypotonicity matter? In most cases probably not. The remarkable capacity of most patients to tolerate a wide range of fluid and electrolytes, ensures that few patients will actually suffer as a consequence of inappropriate fluid therapy, particularly as most patients only require peripheral fluids for 2 or 3 days. It must be remembered, however, that plasma sodium is low in hospital patients as a group and even lower in the severely ill. Individual postoperative fluid management is important in this subgroup. A complacent attitude to fluid therapy is to be deprecated and it would seem wise that clinicians should strive to maintain normality as it is in this way that serious metabolic problems are best avoided.

One further objection to the adoption of dextrose saline as the standard replacement fluid for postoperative surgical patients is, perhaps, more a criticism of our own teaching rather than a problem with the solution itself. This is the observation, admittedly based on personal experience rather than substantiated fact, that the majority of medical students, a great many pre-registration house staff and even a few junior anaesthetists do not know, if asked, what the precise electrolyte composition of dextrose saline actually is. If the same groups are asked the composition of isotonic saline or 5% dextrose virtually all will, without hesitation, supply the correct information. Despite this paradox, it remains common practice in many hospitals to prescribe dextrose saline almost exclusively to all patients who require crystalloid fluid replacement. Intravenous fluid therapy must, then represent one of the few areas in medical practice where a potentially dangerous substance is prescribed without precise knowledge of the dosages given. The very fact that the composition of this solution is so often unknown is in itself a sufficient justification not to recommend its routine use. After all, combinations of isotonic saline and 5% dextrose can provide identical volumes of both fluid and electrolytes and their prescription at least necessitates some consideration of the patients actual requirements.

There is nothing intrinsically wrong with dextrose saline. It is simply that it is frequently used in a random fashion without consideration of the patient's needs. The prerequisite of successful fluid therapy in the postoperative surgical patient is an initial assessment of fluid and electrolyte losses and their appropriate replacement. If this can be done with dextrose saline, well and good, but the chances are that if you insist on the use of dextrose 5% and isotonic (0.9%) saline alone, then more thought will be directed towards the patient and less to the fluid prescription chart in isolation.

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Commentary

Hospital-Acquired Hyponatremia: Why Are There Still Deaths?

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Intravenous fluids are probably the most frequently prescribed medication for hospitalized children. The current practice of administering hypotonic fluids to children is based largely on recommendations of Holliday and Segar,[1] made almost 50 years ago and on their assumption that the electrolyte composition of intravenous fluids should approximate the composition of human and cow milk. The safety of these recommendations has never been established. There have been >50 cases of death or permanent neurologic injury in children over the past decade from hospital-acquired hyponatremia resulting from the administration of hypotonic fluid.[2-5] In a recent contribution to *Pediatrics*, we introduced the concept of administering isotonic saline (0.9% sodium chloride) in maintenance fluids to prevent hospital-acquired hyponatremia.[6] In an accompanying editorial, Holliday et al[7] argued that the administration of isotonic saline is unsafe and that hyponatremia results from egregious fluid management.

In this issue of *Pediatrics*, a study by Hoorn et al[8] supports our hypothesis that the routine administration of hypotonic fluids is dangerous and can result in unnecessary deaths. In this article, Hoorn et al assess the relationship of intravenous fluid administration and the development of hospital-acquired hyponatremia. They found that 10% of children with normal serum sodium at presentation to the emergency department go on to develop hyponatremia. Of the 40 patients with hospital-acquired hyponatremia, 2 had neurologic sequelae and 1 child died from cerebral edema due to an acute fall in serum sodium from 142 to 128 mmol/L. The main contributing factor for developing hospital-acquired hyponatremia was the administration of hypotonic fluids. Since their article was submitted for publication, there have been additional reports of death and hyponatremic encephalopathy resulting from hypotonic fluid administration.[9-11]

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The data in this article, in conjunction with numerous previous reports of hospital-acquired hyponatremic encephalopathy in children, indicate that the current practice of administering hypotonic maintenance intravenous fluids in children is unsafe and should be abandoned. We disagree with the authors' recommendations that hypotonic fluids should be avoided only in postoperative patients and those with low normal serum sodiums (P_{Na} < 138 mmol/L). Their data do not support these recommendations, because the majority of patients who developed hyponatremia in their study had a serum sodium >137 mmol/L, and the 1 death occurred in a patient with a serum sodium of 142 mmol/L. The administration of intravenous fluids should be considered an invasive procedure, and all hospitalized patients should be considered at risk for developing hyponatremia. The current practice of routinely administering hypotonic fluids is unphysiologic, given the numerous stimuli for antidiuretic hormone production in hospitalized children. How many more children will die unnecessarily? One is too many. Many tragic deaths could be avoided by the administration of isotonic saline. Although no one parenteral fluid can be administered safely to all children, isotonic saline would seem to be the safest fluid for most children. The administration of hypotonic fluid is unnecessary unless there is a free-water deficit or ongoing free-water losses.[12] Until proof exists that the administration of isotonic saline could be harmful, the routine practice of administering hypotonic fluids should be abandoned.

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ORIGINAL PAPER

The impact of the National Patient Safety Agency intravenous fluid alert on iatrogenic hyponatraemia in children

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Abstract In March 2007, the National Patient Safety Agency (NPSA) issued an alert regarding intravenous fluid (IVF) prescription to hospitalised infants and children, to be implemented in UK hospitals by September 2007. Previously, the most commonly used IVF (0.18% saline/4% dextrose) has been associated with iatrogenic hyponatraemia, resulting in four deaths and one near miss since 2000. The alert recommended 0.45% (or 0.9%) saline/5% dextrose as maintenance IVF and banned 0.18% saline/4% dextrose. We audited practice and outcome in children receiving maintenance IVF in June 2007 (before guideline implementation) and June 2008 (after guideline implementation). In June 2007, 44 (30%) children were prescribed IVF, six received IVF not recommended by NPSA alert 22 and one became hyponatraemic. In June 2008, 56 (30%) children received IVF; one received IVF not recommended by NPSA alert 22 and became hyponatraemic. The median change in serum sodium levels for all children who received IVF not recommended by NPSA alert 22 [−5 (−15 to 0) mmol/l] was significantly greater than those who received IVF recommended by NPSA alert 22 [0 (−13 to +7) mmol/l, $p=0.002$]. In addition, there was a significant ($p=0.04$) reduction in the number of children who had electrolytes checked while on IVF after implementation of the guideline. Implementation of a new IVF guideline has been associated with less use of IVF not recommended by NPSA alert 22, resulting in less serum sodium level reduction. The only children who became hyponatraemic received IVF not recommended by NPSA alert 22. Despite the NPSA alert and guideline implementation, less children had electrolyte levels checked while receiving IVF.

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Keywords National Patient Safety Agency · Hyponatraemia · Hypernatraemia · Intravenous fluids

Introduction

Intravenous fluid (IVF) prescription practices until recently have been based upon the original description of maintenance fluid requirements by Holliday and Segars in 1957 [9]. Their pioneering work was performed in healthy breastfed children and was based on calorific requirements; they advised that if IVF was necessary, hypotonic fluid should be used at rates based on body weight [9]. Since then, there has been much debate how suitable hypotonic fluids are as maintenance therapy in paediatric patients [5–8, 11, 15]. Studies have demonstrated hyponatraemia after administration of hypotonic IVF [2, 4, 10, 16]. Worldwide, there have been over 50 reported deaths as a result of iatrogenic hyponatraemia, associated with the use of hypotonic IVF, often in previously healthy children undergoing routine elective surgery [12], with four deaths and, to use National Patient Safety Agency (NPSA) terminology, one near miss in the UK since 2000 [13]. To reduce the risk of iatrogenic hyponatraemia, the NPSA issued alert 22 in March 2007 [13]. The recommendations of the alert were to use 0.45% (or 0.9%) saline/5% dextrose, instead of the previously most commonly used IVF (0.18% saline/4% dextrose) as IVF for children. In addition, the alert recommended that 0.18% saline/4% dextrose should be removed completely from general paediatric wards. When treating conditions considered to be at high risk of hyponatraemia (including serum sodium level in the lower normal reference range, intravas-