REPORT ON LUCY CRAWFORD,
Prepared for the Inquiry into Hyponatraemia Realated Deaths in Northern Ireland

By: Dr Simon R. Haynes,
Consultant in Paediatric Cardiothoracic Anaesthesia and Intensive Care,
Freeman Hospital, Newcastle upon Tyne NE7 7DN,
UK

This report has been prepared after a discussion which took place with Professor Ian Young, also a witness to the inquiry; this was a discussion held by telephone in conjunction with senior counsel to the inquiry, which took place on Friday June 28th 2013. Professor Young and myself had previously been asked to offer, independently of each other, calculations as to what the lowest serum concentration may have been in Lucy Crawford at approximately 02:50hrs on 13th April 2000. We both approached this separately and independently, and had arrived at disparate conclusions. The purpose of the telephone meeting was to identify any flaws in previous calculations on both parts, and to produce a consensus opinion.

This report supersedes that written by me on 21st June 2013 which I wish to retract.

Signed:

9th August 2013

1: My qualifications:

MBChB University of Edinburgh 1983

FRCA 1990

2: My expertise:

I have been employed as a consultant in paediatric cardiothoracic anaesthesia and intensive care at the Freeman Hospital from August 1994 – present. My clinical duties are centred around the provision of anaesthesia and intensive care to children or adults with congenital heart disease undergoing cardiothoracic surgery or invasive cardiological investigation. My specialist interest is the management (including mechanical cardiac support) of life-threatening cardiac failure and cardiopulmonary transplantation in children. I was Clinical Director of Cardiothoracic Surgery and Anaesthesia at the Freeman Hospital from May 1999-2005; this is an administrative role which includes overseeing the clinical governance activity of a directorate of 30 consultants and is carried out in addition to full-time clinical duties. An important component of my routine work is the management of fluid and electrolyte abnormalities present in children in the paediatric intensive care setting.

2: Brief:

I have been given a very specific brief by the Inquiry. Lucy was admitted to the Erne Hospital with gastroenteritis, the cause subsequently being identified as rotavirus infection. She received intravenous fluids commencing at 22.30h on 12th April 2000, and had a seizure at approximately 02.50h on 13th April, developed fixed dilated pupils, was ventilated and was transferred to the Royal Belfast Hospital for Sick Children where she was subsequently diagnosed as brain stem dead.

I have been provided with information regarding results of blood tests taken, and information regarding the possible nature and volume of fluids given to her whilst at the Erne Hospital. On the basis of these pieces of information I have been asked to estimate what the concentration

of sodium present in her serum is likely to have been immediately before her seizure (ie at approx 02.50h on 13th April 2000).

3: Information available:

- Lucy weighed 9.14kg (presumably her weight on admission to hospital)
- Serum sodium at approximately 20.00h 12th April 2000 (lab report at 20.50h therefore blood sample likely to have been taken at 20.00h) was 137 mmol/l ie within normal range.
- Serum sodium in sample taken at 03.30h on 13th April 2000 was 127 mmol/l (ie lower than normal)
- Intravenous fluid was administered between 22.30h and 02.30h. According to the brief given to me by the enquiry this was NaCl 0.18%/glucose 4% at 100 ml/h, so approximately 400 mls may have been given during this period.
- Somewhere between 250 and 500 mls of 0.9% saline was given between 0300h and 0400h

4: Complexities surrounding this issue:

a. There are limited amount of clinical data available with regards to Lucy, These are listed in paragraph 3 above.

b. There are well recognised, published formulae used in clinical applications to *predict* the effects of known volumes of administering electrolyte solutions to patients, these formulae are all prospective and are not designed or tested when looking retrospectively at a clinical situation

c. A further complexity is that formulae used to prospectively evaluate changes in electrolyte concentration all assume "closed systems" i.e. that there are no other losses or exchanges of fluid taking place simultaneously which are unaccounted for in the formula used. In Lucy's case there was a quantitatively unknown

ongoing loss of water and electrolyte into her gastrointestinal tract, as well as some urinary losses.

d. There is some uncertainty as to the rate at which 0.9% saline was administered to Lucy. The published formulae mentioned above all use total body water as the volume of distribution of saline solution administered. When fluid of any kind is administered to a patient it is administered initially into the blood stream, and it is then subsequently redistributed throughout the complete volume of distribution- that being total body water rather than either blood volume or extracellular fluid. The rate at which this occurs is unknown, and the rate at which fluid is administered will also undoubtedly have a bearing on this.

e. A further unknown is the effect of anti-diuretic hormone secretion produced in response to viral gastroenteritis, and the effect this will have had on reabsorption of water in Lucy's kidneys

5. <u>Previous approach:</u>

In my previous report dated 21.06.2013 I had attempted to adapt a formula commonly known as the Adrogue Formula, this is formula 4 in table 2 , ref 1.

$$[Na]_{fin} - [Na]_{ini} = \frac{[Na]_{fin} - [Na]_{ini}}{TBW_{ini} + 1}$$

Where:

$[Na]_{fin}$ = final (post-infusion) serum sodium concentration
$[Na]_{ini}$ = initial (preinfusion) serum sodium concentration
TBW_{ini} = initial (preinfusion) Total Body Water

This formula was devised to predict the effect of *giving* known volumes of electrolyte containing solutions. To produce such a formula will have taken many months of clinical observation and data recording to verify it. I attempted to modify the formula to predict what might have been the case *before any 0.9% sodium chloride solution had*

been administered to Lucy. **Subsequent evaluation of this has modification demonstrated an arithmetic/algebraic flaw which is why I wish my report dated 21.06.2013 to be discounted**.

Professor Young had used the Adrogue Formula to identify the change in serum sodium which would have occurred in Lucy following administration of 1litre of 0.9% saline solution. In his report (WS-342-1, p 6, 7), Professor Young assumed that if a smaller volume of 0.9% saline had been administered the effect would have been linear. I felt that this assumption was not correct; the initial smaller volume of a more concentrated electrolyte solution will have a greater effect on the overall serum concentration than subsequent volumes administered, which raised the possibility of inaccuracy if the formula was thus applied.

6. Where we are now:

Professor Young and myself had a lengthy discussion on the telephone on 28.06.2013; the discussion has been transcribed for the purposes of the inquiry. We both agreed that it was appropriate to use a published modification of the Adrogue Formula (formula 7, table 2, ref 1) to attempt to retrospectively calculate serum sodium in Lucy at its nadir. We agreed that the application of this formula would give us as close an estimate as possible (within the limitations of the complexities described earlier in this report), of the lowest serum sodium present in Lucy. We noted that any calculation reached will not consider the complexities which are listed in paragraph 4 above

The formula is as follows:

$$[Na]fin = \frac{(TBWini \times [Na]ini) + (Vinf \times [Na]inf)}{TBWini + Vinf}$$

Where:
$[Na]_{fin}$ = final (post-infusion) serum sodium concentration
$[Na]_{ini}$ = initial (preinfusion) serum sodium concentration
TBW_{ini} = initial (preinfusion) Total Body Water
$[Na]_{inf}$ = Sodium concentration in the infusate
V_{inf} = volume of saline infused

We both agreed that the above formula uses the total body water as the volume of distribution of any electrolyte solution given. We then discussed a series of calculations made using this formula allowing for different assumptions about Lucy's total body water which would include calculating both for her presenting in "well, normally hydrated" condition and for presenting as 10% dehydrated. It transpired that the difference between normal hydration and 10% dehydration had very little influence on the figure reached.

These calculations are worked through below (calculations i– iv) using the following values:

Weight = 9.14kg
TBW ini = 0.6 x 9.14 = 5.48 litres(if one assumes no dehydration)
TBW ini = 0.6 x 8.24 = 4.94 litres (if one assumes 10% dehydration)
Vinf = either 0.5 or 0.25 l
Na inf = 154mmol/l
Na fin = 127 mmol/l
Na ini is the unknown for which the equation has to solved.

Thus:

$$[Na]fin = \frac{(TBWini \times [Na]ini) + (Vinf \times [Na]inf)}{TBWini + Vinf}$$

Rearranged:
⇒ ([Na]fin x TBWini) + ([Na]fin x Vinf) = (TBWini x [Na]ini) + (Vinf x [Na]inf)

This is now solved for Na ini for various combinations of the above variables:

i: Under circumstances where initially 10 % dehydration present where TBW ini = 4.94 l, Vinf = 0.5 l,

(127 x 4.94) + (127 x 0.5) = (4.94 x Na ini) + (0.5 x 154)

⇒ 690.9 = (4.94 x Na ini) + 77

⇒ 690.9 – 77 = 4.94 x Na ini

⇒ Na ini = 124.3 mmol/l

ii: Assuming no dehydration present where TBW ini = 5.48 l, Vinf = 0.5 l.

(127 x 5.48) + (127 x 0.5) = (5.48 x Na ini) + (0.5l x 154)

⇒ 759 . 5 = (5.48 x Na ini) + 77

⇒ Na ini = 124.5 mmol/l

iii: 10% dehydrated where TBW ini = 4.94l, Vinf = 0.25l

(127 x 4.94) + (127 x 0.25) = (4.94 x Na ini) + (0.25 x 154)

⇒ 620.7 = (4.94 x Na ini)

⇒ Na ini = 125.6 mmol/l

iv: No dehydration where TBW ini = 5.48 l, V inf = 0.25 l

(127 x 5.48) + (127 x 0.25) = (5.48 x Na ini) + (0.25 x 154)

⇒ 689.2 = 5.48 x Na ini

⇒ Na ini = 125.8 mmol/l

To provide an estimate of the possible transient nadir in Lucy's serum Na+ (which I believe may have occurred had the 250 – 500 mls of 0.9%% saline been infused instantly into the circulation and not had time to redistribute throughout TBW), the equation is now solved replacing the values for TBW with estimates for initial Extra Cellular Fluid volume (ECF ini) = TBW/3 = 4.94/3 = 1.65 litres or 5.48/3 = 1.83 litres.

Calculations v – viii use ECF in place of TBW

v; 10% dehydrated where ECF ini = 1.65 l, Vinf = 0.5l

(127 x 1.65) + (127 x 0.5) = (1.65 x Na ini) + (0.5 x 154)

⇒ 196.1 = 1.65 x Na ini

⇒ **Na ini = 118.9 mmol/l**

vi: No dehydration, where ECF ini = 1.83 l, Vinf = 0.5l

⇒ (127 x 1.83) + (127 x 0.5) = (1.83 x Na ini) + (0.5 x 154)

⇒ 218.91 = 1.83 x Na ini

⇒ **Na ini = 119.6 mmol/l**

vii: 10% dehydration where ECF ini = 1.65, Vinf = 0.25 l

⇒ (127 x 1.65) + (127 x 0.25) = (1.65 x Na ini) + (0.25 x 154)

⇒186.29 = 1.65 x Na ini

⇒ **Na ini = 123.9 mmols/l**

viii: Not dehydrated where ECF ini = 1.83 l, Vinf = 0.25l

⇒ (127 x 1.83) + (127 x 0.25) = (1.83 x Na ini) + (0.25 x 154)

⇒ 225.66 = 1.83 Na ini

⇒ **Na ini = 123.3 mmols/l**

7. What can be concluded?

Professor Young and myself were in agreement that using the conventional value for distribution of electrolyte solution i.e. total body water, that depending upon Lucy's initial state of dehydration and the volume of sodium chloride solution given that the lowest calculable value for serum sodium lies in the range 124-126 mmol/L. (calculations i – iv above)

When making these calculations the assumption that the system is "closed" has to be i.e. that there were no other sodium or water losses – which almost certainly was not the case given Lucy's gastroenteritis, and I have also raised the possibility of the unknown velocity with which electrolytes move to redistribute from the bloodstream into the total body water compartment. The implication of the latter point is that I believe it possible at some point the lowest serum sodium present in Lucy may have been less than that described, therefore I have included calculations v – viii above to demonstrate the effect of this .

Thus the *highest* possible concentration present in Lucy the time of her seizure would have been 126 mmol/l, and it may well have been lower, how much lower I cannot say with confidence.

8. Significance of the rate of fall of serum sodium:

Professor Young and myself were in agreement that a decrease of 11mmol/Lfrom 137 to 126 mmol/l in serum sodium concentration over 6 hours or so is significant and it is my opinion from clinical practice that this would be potentially dangerous, running the risk of producing cerebral oedema.

A small section of Arieff's paper,(table III page 306 ref 2) has in my opinion been over emphasised, and that the rate of fall of serum sodium is in fact important in terms of

the genesis of cerebral oedema. This statement has been extracted from a 2x2 chi squared table and makes no proper attempt to correlate the velocity of a decrease in serum sodium with the clinical outcome.

9. **Idiosyncrasies:**

It must be remembered that a child's brain grows more rapidly than the skull, and that the young child is more susceptible than an adult to untoward effects from cerebral oedema. Years of clinical practice in Paediatric Intensive Care medicine have demonstrated to me that different children with the same severity of the same illness may respond differently in terms of water retention as a consequence of inappropriate antidiuretic hormone excretion. There is certainly a widespread of normal response in the population in terms of this, and if Lucy was unfortunate enough to lie at the more extreme end of the normal range of responses she would have been more severely affected by this. Antidiuretic hormone is secreted in response to illness, causing reabsorption of water from the collecting ducts in the kidneys.

10. **Current research:**

I am not directly involved in any current research regarding idiosyncrasies of either renal response to antidiuretic hormone or variables in the magnitude of antidiuretic hormone secretion in response to injury.

8. **Cause of death:**

I am surprised that hyponatraemia was not mentioned on the death certificate, and it is my opinion this is an important omission

References:

1: Tzamaloukas AH, Malhotra D, Rosen BH, Raj DS, Murata GH, Shapiro JI. **Principles of management of severe hyponatremia:** Journal of the American Heart Assoc. 2013 Jan 23;2(1):e005199. doi: 10.1161/JAHA.112.005199.

2: Arieff AI. Management of Hyponatraemia; BMJ 1993 307: p305 – 308.

Expert witness declaration

I, Simon Haynes declare that:
1: I understand that my duty in providing written reports and giving evidence is to help the Court, and that this duty overrides any obligation to the party by whom I am engaged or the person who has paid or is liable to pay me. I confirm that I have complied and will continue to comply with my duty
2: I confirm that I have not entered into any arrangement where the amount or payment of my fees is in any way dependent on the outcome of the case
3: I know of no conflict of interest of any kind, other than any which I have disclosed in my report.
4: I do not consider that any interest which I have disclosed affects my suitability as an expert witness on any issues on which I have given evidence
5: I will advise the party by whom I am instructed if, between the date of my report and the trial, there is any change in circumstances which affect my answers to 3 and 4 above
6: I have shown all the sources of information I have used
7:I have exercised reasonable care and skill in order to be accurate and complete in preparing this report
8: I have endeavoured to include in my report those matters of which I have knowledge or of which I been made aware, that might adversely affect the validity of my opinion. I have clearly stated my qualifications to my opinion
9: I have not, without forming an independent view, included or excluded anything which has been suggested to me by others, including my instructing lawyers.
10: I will notofy those instructing me immediately and confirm in writing if, for any reason, my existing report requires any correction or qualification.
11: I understand that:
11.1: my report will form the evidence to be given under oath or affirmation
11.2: questions may be put to me in writing for the purposes of clarifying the report and that my answers shall be treated as part of my report and covered by the statement of truth
11.3; The court may at any stage direct a discussion to take place between experts for the purpose of identifying and discussing the expert issues in the proceedings, where possible reaching an agreed opinion on those issues and identifying what action, if any, may be taken to resolve any of the outstanding issues between the parties.
11.4: the court may direct that following a discussion between the experts that a statement should be prepared showing those issue which are agreed , and those issues which are not agreed, together with a summary of the reasons for disagreeing
11.5: I may be required to attend court to be cross-examined on my report by a cross-examiner assisted by an expert
11.6: I am likely to be the subject of public adverse criticism by the judge if the court concludes that I have not taken reasonable care in trying to meet the standards set out above
12: I have read part 35 of the Civil Procedure Rules and the accompanying practice direction including the “Protocol for Instruction of Experts to give evidence in Civil Claims” and I have complied with the requirements
13: I am aware of the practice direction on pre-action conduct. I have acted in accordance with the Code of Practice for Experts.

Statement of Truth:

I confirm that I have made clear which facts and matters referred to in this report are within my own knowledge and which are not. Those that are within my own knowledge I confirm to be true. The opinions I have expressed represent my true and complete professional opinions on the matters to which they refer.

Signed:
Dr Simon R. Haynes

Dated:
9th August 2013

Dr Simon Haynes MBChB, FRCA

Fortnightly Review

Management of hyponatraemia

Allen I Arieff

Division of Geriatrics, Department of Medicine, Veterans Affairs Medical Center, and University of California School of Medicine, San Francisco, California 94121, USA
Allen I Arieff, *professor of medicine*

Correspondence to:
Department of Medicine (111 G), Veterans Affairs Medical Center, San Francisco, California 94121, USA.

BMJ 1993;307:305-8

Hyponatraemia occurs in many different systemic disease states and is the most frequent electrolyte abnormality seen in a general hospital population, with an incidence of about 1%.[1,2] Hyponatraemia is usually the result of dilution, although both total body water and extracellular volume may be high, low, or normal. Asymptomatic hyponatraemia is often benign, but when patients have central nervous system symptoms treatment is mandatory to prevent permanent brain damage. Almost all of the morbidity associated with hyponatraemia is due to brain damage, and recent studies show that the age and sex of the patient are major determinants of such brain damage. The incidence of symptomatic hyponatraemia is similar among men and women,[2] but most patients who develop permanent brain injury are children and menstruant women (tables I and II).[2,3] Earlier studies suggesting that severe hyponatraemia was often benign had generally evaluated only postmenopausal women and older men,[4] groups not generally susceptible to hyponatraemia induced brain injury.[2,3]

Summary points

- The morbidity associated with hyponatraemia is most closely related to the age or sex of the affected patient (highest in children and menstruant women) and is not related to either the magnitude or duration of the hyponatraemia
- When hyponatraemia is accompanied by central nervous system manifestations (hyponatraemic encephalopathy) there is substantial morbidity, whereas asymptomatic hyponatraemia is often benign
- A major cause of hyponatraemic encephalopathy and subsequent morbidity is hypotonic fluids given to postoperative patients
- Symptomatic hyponatraemia requires treatment, usually hypertonic sodium chloride infusion, limiting the magnitude of correction to about 25 mmol during the initial 24-48 hours; a loop diuretic or intubation is often indicated as adjunctive treatment
- The morbidity associated with hyponatraemic encephalopathy is primarily due to brain oedema, respiratory insufficiency, and hypoxaemia, with resultant hypoxic brain damage

Brain damage and hyponatraemia

When symptomatic hyponatraemia occurs there is usually brain oedema. If adaptation of the brain is not adequate pressure of the swollen brain on the skull can lead to a decrease in cerebral blood flow and pressure necrosis. Initial adaptation of the brain to hyponatraemia is by loss of blood and cerebrospinal fluid, followed by cellular extrusion of osmotically active cations (initially sodium, then potassium and possibly amino acids), which tends to lower the osmolality without substantial gain of water.[5] If symptomatic hyponatraemia is not corrected oedema may increase with possible tentorial herniation, often leading to respiratory arrest and cerebral hypoxia and ischaemia.[6,7]

The above sequence has been verified by computed tomography, magnetic resonance imaging, and postmortem studies in over 40 hyponatraemic patients.[2,6-8] Recent evidence suggests that contributory factors to hyponatraemic brain injury may also include (*a*) systemic hypoxaemia; (*b*) a direct vasoconstrictive effect of antidiuretic hormone on cerebral blood vessels; (*c*) female sex; (*d*) physical factors; and (*e*) pre-existing liver disease, alcoholism, or structural lesions in the central nervous system.[2,3] Neither magnitude of fall nor rate of fall in serum sodium concentration is important in the genesis of brain damage (table III).[2]

TABLE I—*Distribution of cases of permanent brain damage among men and women who suffered postoperative hyponatraemia*

	All postoperative patients (n=76 678)	All hyponatraemic controls (n=674)	All hyponatraemic encephalopathy cases (n=65)	All cases with brain damage (n=34)
No (%) of men	37 626 (49)	307 (46)	25 (68)	1 (3)
No (%) of women	39 052 (51)	367 (54)	40 (62)	33 (97)

Data from Ayus *et al.*[2]
Statistical comment: Sex distribution was not significantly different among the hyponatraemic controls or the 65 cases. But of the 34 patients who died or suffered permanent brain damage, 33 were women ($p<0.001$). Relative risk of dying or developing permanent brain damage was 28 times greater in women than men (95% confidence interval 5 to 141).

TABLE II—*Menstruant states of women with brain damage resulting from asymptomatic postoperative hyponatraemia*

	All postoperative female patients (n=39 052)	All female hyponatraemic controls (n=367)	All female cases with brain damage (n=33)
No (%) of menstruant patients	21 088 (54)	39 (11)	25 (76)
No (%) of postmenopausal patients	17 964 (46)	328 (89)	8 (24)

Data from Ayus *et al.*[2]
Statistical comment: Among female controls distribution of menstruant and postmenopausal patients was significant ($p<0.001$). Distribution of menstruant and postmenopausal patients was also significant among patients with brain damage ($p<0.001$). Relative risk of dying or developing brain damage from postoperative hyponatraemia was 26 times as great among menstruant women than among postmenopausal women (95% confidence interval 11 to 62).

Causes of hyponatraemia

POSTOPERATIVE HYPONATRAEMIA

Postoperative hyponatraemia is a frequent and potentially dangerous complication among adults in

TABLE III—*Effects of rate of fall of plasma sodium concentration and magnitude of postoperative symptomatic hyponatraemia in men and women*

	Duration of hyponatraemia (hours)		Plasma sodium concentration (mmol/l)	
	<24	≥24	86-115	116-128
No (%) of men	14 (56)	11 (44)	15 (60)	10 (40)
No (%) of women	13 (42)	27 (68)	19 (48)	21 (52)

Data from Ayus *et al.*[2]
Statistical comment: Whatever the grouping, mortality was significantly greater in women than in men ($p<0.001$). Differences in mortality between women whose plasma sodium concentration was greater than on up to 115 mmol/l or whose duration of hyponatraemia was greater than or up to 24 hours were all not significant.

the United States and United Kingdom.[1,2] In the United States the incidence of postoperative hyponatraemia is about 1%, or about 250 000 cases among the roughly 25 million inpatient operations that are performed each year.[2] Raised plasma antidiuretic hormone concentrations with impaired excretion of free water occur in almost all patients in the first two to six days after operation[1] in response to multiple non-osmotic stimuli—for example, pain, fear, blood loss, anaesthesia, anxiety, vomiting, volume depletion, and narcotics or sedative-hypnotics.[9] During certain operations—for example, transurethral prostate resection and endometrial ablation—hypotonic solutions used to irrigate the operative site may be rapidly absorbed through opened veins, with an effect similar to intravenous administration.[10,11] Thus any patient in the postoperative period should be considered at risk of hyponatraemia and be given appropriate prophylaxis. Of critical importance is the choice of intravenous fluids.

INTRAVENOUS FLUIDS

The most common cause of in hospital hyponatraemia in the United States and United Kingdom is intravenous hypotonic fluids. Apparently based on anecdotal data and recommendations made before 1950, some physicians still infuse hypotonic solutions postoperatively, often glucose in water (280 mmol/l).[7] The rationale for using hypotonic fluids in the postoperative period is unclear, as few objective data support the practice. Before 1950 there were suggestions that postoperative infusion of isotonic sodium chloride might lead to complications,[12] including worsening of glomerulonephritis,[13] with vague references to postoperative "salt intolerance".[14] However, data published after the early 1950s all suggest that the practice is probably without scientific justification. Since the 1930s a profusion of studies have shown the propensity of intravenous hypotonic solutions to cause death or permanent brain damage in the postoperative period.[9,15] Since the 1960s most textbooks of surgery, gynaecology, medicine, and nursing have emphasised the dangers of postoperative hypotonic fluids.[9,16] Permanent brain damage from hyponatraemia is very often a direct consequence of improper fluid administration.[2,3,5-7,17]

AIDS

AIDS is a major cause of hyponatraemia.[18] The hyponatraemia in AIDS may be secondary to inappropriate secretion of antidiuretic hormone, often associated with pulmonary or intracranial lesions; to volume deficiency (due to vomiting or diarrhoea) and replacement by hypotonic fluids[18,19]; or to mineralocorticoid deficiency, often with intact glucocorticoid secretion.[18,20] In the presence of mineralocorticoid deficiency the result of the corticotrophin stimulation test may be normal, possibly because AIDS often affects the zona glomerulosa of the adrenal gland.[20] In such patients fludrocortisone acetate is indicated if renal salt wasting can be shown in the presence of hyponatraemia.

ROLE OF HORMONES

The plasma antidiuretic hormone concentration is often "inappropriately" raised in hyponatraemia.[6] Associated clinical conditions include volume depletion, secretion of antidiuretic hormone by certain malignant tumours, and certain brain and pulmonary lesions.[9] Symptomatic hyponatraemia may occur during labour and delivery or during treatment for gastrointestinal haemorrhage in patients receiving hypotonic fluid and either vasopressin or oxytocin. These agents should be given in isotonic sodium chloride. Desmopressin given with excess free water has been associated with symptomatic hyponatraemia.[8] Both adrenal insufficiency and hypothyroidism may contribute to hyponatraemia. Finally, oestrogen may impair and testosterone augment brain adaptation to hyponatraemia.[8]

PHARMACOLOGICAL AGENTS

Many pharmacological agents may interfere with the ability of kidney to excrete free water. They include sedatives, hypnotics, analgesics, oral hypoglycaemics, tranquillisers, narcotics, antineoplastic drugs, antipsychotic agents, and diuretics. In most instances there is retention of ingested free water. In the case of thiazide associated hyponatraemia there is often an idiosyncratic reaction to thiazides, with a combination of massive loss of sodium and potassium in the urine and associated polydipsia.[21] Often hyponatraemia which occurs as a side effect of a drug will respond to discontinuation of the offending agent. If such patients have symptoms hypertonic sodium chloride should be instituted in order to prevent respiratory insufficiency and permanent brain damage.[21,22]

PSYCHOGENIC POLYDIPSIA

Another common setting in which symptomatic hyponatraemia may occur is psychogenic polydipsia.[23] Maximal free water clearance in adults is around 700 ml/h (17 l/day) or more. Thus to develop hyponatraemia in the absence of raised plasma concentrations of antidiuretic hormone a 60 kg adult would need to drink over 20 l/day. Most patients who have psychogenic polydipsia and hyponatraemia associated with oral water intoxication have actually ingested less water than the maximal daily renal excretion. Instead, they have a smaller fluid intake but abnormal urinary dilution with excessive antidiuretic hormone secretion.[24] Beer potomania somewhat resembles psychogenic polydipsia, but the hyponatraemia is associated with massive ingestion of beer and carries a high mortality.[25]

Treatment

ASYMPTOMATIC HYPONATRAEMIA

Asymptomatic hyponatraemia generally does not require aggressive treatment with hypertonic sodium chloride, as pharmacological measures combined with water restriction are often sufficient, particularly if the plasma sodium concentration exceeds 120 mmol/l. In patients who are obviously volume depleted isotonic (154 mM) sodium chloride is usually the fluid of choice. When adrenal insufficiency or hypothyroidism has been identified appropriate hormone replacement is warranted. If the patient is receiving drugs which might contribute to hyponatraemia they should be discontinued if possible. Water restriction is theoretically important in patients without symptoms, but from practical considerations, particularly compliance, it is generally not useful. Fluid restriction of less than 1 l/day will result in a negative water balance but only a

slow increase in the serum sodium concentration, rarely exceeding 1·5 mmol/l/24 h.

Several medical regimens have been used for the long term management of patients with asymptomatic hyponatraemia. With chronic "inappropriate" increase in the antidiuretic hormone concentration lithium will often induce nephrogenic diabetes insipidus, but generally produces an erratic response. Lithium toxicity may affect kidneys, central nervous system, heart, haemopoietic system, and thyroid.[15] Demeclocycline, a tetracycline antibiotic, may be used to induce nephrogenic diabetes insipidus in doses above 600 mg/day. It has been used successfully to treat patients with raised antidiuretic hormone concentrations, but acute renal failure and renal tubular toxicity have been reported in hyponatraemic patients with heart failure or cirrhosis.[15] Other possible pharmacological agents for chronic hyponatraemia include urea and inhibitors of antidiuretic hormone. Finally, correction of the functional state of intravascular volume depletion that exists in heart failure and decompensated cirrhosis are often associated with improvement of hyponatraemia. In cirrhosis with ascites this can sometimes be achieved after placing a peritoneal-jugular shunt.

SYMPTOMATIC HYPONATRAEMIA

In patients with symptomatic hyponatraemia the most frequent presenting symptoms are headache, nausea, vomiting, and weakness, the presence of at least one of these defining encephalopathy.[7] Less frequent and more severe symptoms are shown in box 1. Respiratory arrest with hypoxia is a persistent feature in symptomatic hyponatraemic patients who suffer brain damage.[2,3] Thus the therapeutic objective in such patients is reduction of brain oedema by increasing the serum sodium concentration such that the patient becomes asymptomatic with adequate ventilation. In patients with symptomatic hyponatraemia the morbidity and mortality associated with treatment by water restriction are unacceptably high.[26-28] The most appropriate therapeutic regimen for such patients is hypertonic (usually 514 mM) sodium chloride,[26] often given in conjunction with a loop acting diuretic such as frusemide (box 2).[29] In some patients, particularly those with raised antidiuretic hormone concentrations, hyponatraemia, and volume expansion or circulatory insufficiency, simultaneous administration of frusemide may be necessary to prevent circulatory overload.[29] Isotonic (154 mM) sodium chloride is indicated only if the patient is volume and sodium chloride depleted. Such patients include those with volume depletion due to vomiting, sweating, or diarrhoea, who have ingested free water.

The most appropriate setting for correction of symptomatic hyponatraemia is the intensive care unit, where neurological, respiratory, and haemodynamic function can be monitored. Patients with arterial hypoxaemia or respiratory insufficiency should be intubated and mechanically ventilated. Total body water volume should be estimated (figure); the mean in hospitalised adults is about 50%.[9]

Hypertonic (514 mM) sodium chloride should be delivered by a constant infusion pump, with correction planned over 24 to 48 hours at a rate set to increase the serum sodium concentration by about 1 mmol/l/h (box 2). The end point is a plasma sodium concentration that is increased by 20-25 mmol/l or has reached 130 mmol/l, or a patient who has become asymptomatic

Box 1—Signs and symptoms of hyponatraemia

Early hyponatraemic encephalopathy

- Headache
- Nausea
- Vomiting
- Weakness

Advanced hyponatraemic encephalopathy

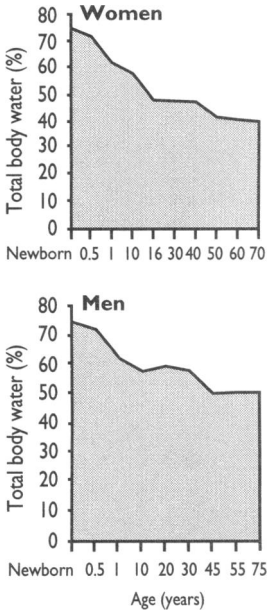
- Impaired response to verbal stimuli
- Impaired response to painful stimuli
- Bizarre (inappropriate) behaviour
- Visual hallucinations
- Auditory hallucinations
- Obtundation
- Urinary incontinence
- Faecal incontinence
- Hypoventilation

Very advanced hyponatraemic encephalopathy (manifestations secondary to increased intracranial pressure)

- Decorticate or decerebrate posturing, or both
- Unresponsiveness
- Bradycardia
- Hypertension
- Altered temperature regulation (hypothermia or hyperthermia)
- Dilated pupils
- Seizure activity (focal or grand mal or both)
- Respiratory insufficiency
- Respiratory arrest
- Coma
- Polyuria (secondary to central diabetes insipidus)

Box 2—Treatment of symptomatic hyponatraemia: basic outline

- Active treatment (infusion of hypertonic sodium chloride) is needed only if the hyponatraemia is symptomatic
- Target of treatment is a serum sodium concentration of about 130 mmol/l, but correction by no more than 25 mmol/48 h
- Determine patient's total body water volume (litres) as a percentage of body weight (kg)
- Subtract patient's serum sodium concentration (mmol/l) from 130 mmol/l. Difference is the needed correction of the serum sodium concentration (in mmol/l)
- Needed correction of the serum sodium concentration (in mmol/l) is the same as the number of hours over which the serum sodium concentration should be corrected
- Multiply the total body water volume (litres) by the needed correction of the serum sodium concentration (mmol/l). This gives the number of mmol of sodium needed to correct the patient's serum sodium concentration to 130 mmol/l
- Number of mmol of sodium needed for correction is then divided by 514 (the number of mmol of sodium in 1 litre of 514 mM sodium chloride). This number times 1000 gives the number of ml of 514 mM sodium chloride needed to correct the serum sodium value to 130 mmol/l
- Divide the number of ml of 514 mM sodium chloride to be given by the number of hours needed for correction of the serum sodium value. This gives the infusion rate of 514 mM sodium chloride in ml/h
- For patients with circulatory impairment, or hypervolaemia with raised plasma concentrations of antidiuretic hormone, give frusemide concomitantly with hypertonic sodium chloride such that there is a net free water diuresis without a net loss of sodium in the urine



Total body water volume as percentage of body weight in women and men throughout life

TABLE IV—*Change in plasma sodium concentration with rapid correction of severe symptomatic hyponatraemia in 167 paediatric and adult patients from three different countries and six different states in the United States*

	Initial plasma sodium (mmol/l)	Final plasma sodium (mmol/l)	Absolute change (after 24-48 hours) (mmol/l)	Rate of correction (mmol/l/h)
Mean (SD)	112 (8)	132 (5)	20 (5)	1·6 (0·8)

Data compiled from Arieff and Ayus,[10] Worthley and Thomas,[17] Ayus *et al*,[22] Cheng *et al*,[23] Ayus *et al*,[26] Hantman *et al*,[29] and Sarnaik *et al*.[30]

(table IV). The serum sodium concentration should not be corrected to normal values, nor should hypernatraemia be allowed to develop. The regimen may require modification in patients with severe hepatic, renal, or cardiac disease. The absolute increase in the serum sodium concentration must be limited to 25 mmol/l within the initial 48 hours of treatment,[26] but the rate of correction of hyponatraemia is not important in the outcome.[2 17 30] Initially the patient's total body water volume should be estimated (figure). Total body water volume varies with age, sex, and weight from about 72% in infants to 35% in elderly obese women.

COMPLICATIONS OF CORRECTING HYPONATRAEMIA

Circulatory congestion is a potential complication of correcting hyponatraemia with intravenous sodium chloride solutions. Such a complication is rare and may be forestalled by giving hypertonic sodium chloride and frusemide.[29] In the past there was controversy regarding the rate of correction of symptomatic hyponatraemia. It was suggested that development of a rare neurological syndrome, central pontine myelinolysis[31] (sometimes called "osmotic demyelination"), might be the result of "rapid" correction of "chronic" hyponatraemia.[4] It had been proposed that if the increase in serum sodium concentration did not exceed some arbitrary rate, often said to be 0·6 mmol/l/h, such complications could be prevented.[4 15] Virtually all hyponatraemic patients in whom cerebral lesions developed after active correction had suffered a hypoxic episode or had their serum sodium concentration corrected to either normonatraemic or hypernatraemic levels or increased by more than 25 mmol/l during the first 48 hours.[26] The vast majority of patients with central pontine myelinolysis have not had hyponatraemia but, rather, severe associated medical conditions, such as advanced liver disease, alcoholism, extensive burns, sepsis, or malignancies.[15 31]

The diagnosis of central pontine myelinolysis requires either histological confirmation or radiological studies with computed tomography or magnetic resonance imaging.[8] With such criteria central pontine myelinolysis is almost never observed in patients who have been hyponatraemic. Rather, the observed lesions are diffuse areas of cerebral infarction with secondary cerebral demyelinating lesions.[6 8] Multiple clinical conditions occur in the absence of hyponatraemia but which are associated with brain lesions which resemble central pontine myelinolysis—for example, subcortical arteriosclerotic encephalopathy, radiotherapy, multiple ischaemic lesions, and sequelae of head trauma.[15] Furthermore, cerebral lesions similar to those sometimes called "osmotic demyelination" are found in untreated hyponatraemic patients.[6] Thus use of terms such as "central pontine myelinolysis" or "osmotic demyelination syndrome" to describe patients with hyponatraemia and brain damage seems unwarranted. The rate of correction is not a factor in the genesis of hyponatraemic brain injury. There are worldwide prospective reports of over 160 patients who have undergone "rapid" correction (mean 1·6 mmol/l/h) of symptomatic hyponatraemia without morbidity,[10 17 22 23 26 29 30] clearly documenting both the safety and the efficacy of this approach (table IV).

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Correction

Guidelines for the management of spontaneous pneumothorax

An authors' error occurred in figure 1 of this article by A C Miller and J E Harvey on behalf of the standards of care committee of the British Thoracic Society (10 July, pp 114-6). In section 4 of figure 1, on simple aspiration, the cannula is described as being of French gauge 16 or larger; this should read standard wire gauge 16.

Principles of Management of Severe Hyponatremia

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Principles of Management of Severe Hyponatremia

Antonios H. Tzamaloukas, MD; Deepak Malhotra, MD, PhD; Bradley H. Rosen, DO; Dominic S. C. Raj, MD; Glen H. Murata, MD; Joseph I. Shapiro, MD

Hyponatremia represents a serious health hazard.[1] Hospitalized patients,[2] nursing home residents,[3] women,[4,5] and children[6] exhibit high frequency and/or severity of hyponatremia. Hyponatremia developing during the course of other morbid conditions increases their severity.[7–10] Estimates of direct costs for treating hyponatremia in the United States ranged between $1.61 and $3.6 billion.[11]

Clinical manifestations of hyponatremia are universal[12,13] and range from subtle (disturbances of balance, problems in cognition detected only during specific testing) to life-threatening manifestations of increased intracranial pressure with life-threatening hypoxia[14–16] and noncardiac pulmonary edema.[17] Although the treating physicians must make an accurate diagnosis based on well-established and described clinical criteria,[1] treatment is also guided by the severity of these manifestations. The magnitude and rate of increase in serum sodium concentration ([Na]) during treatment are critical. Overcorrection of chronic hyponatremia may lead to osmotic myelinolysis,[18–21] whereas undercorrection may fail to prevent life-threatening manifestations.[1,22]

The mainstays of treatment are restricted free water intake and saline infusion, with or without furosemide. There are 2 indications for saline infusion in hyponatremia. Overt manifestations of hyponatremia are treated with hypertonic saline, whereas symptomatic hypovolemia associated with hyponatremia without overt symptoms is usually treated with isotonic saline.[23,24] In both situations, the infusion of saline results in rising [Na]. This rise can be slower or faster than desired, with potentially dire clinical consequences.[1,25]

To achieve the desired rise in [Na], several formulas, most often the Adrogue–Madias formula,[23] are used to calculate volume, rate, and strength of saline infusion. The predictive accuracy of the Adrogue–Madias formula is, in general, good.[26] However, the rise in [Na] exceeds the value predicted by this formula in some instances, particularly in patients with hypovolemic hyponatremia.[26,27]

This report presents the principles of management of hyponatremia with saline infusion. We analyzed factors that cause deviations in the change of [Na] from the predicted values. We present a clinical protocol for managing hyponatremia with saline infusion based on this analysis.

Management Principles

Figure 1 shows the application of the principles of management in a flow diagram. All principles are critical for optimizing successful patient outcomes. The principles addressing diagnosis are covered elsewhere.[1,15,16,20] We have chosen to focus on the principles addressing the quantitative aspects of management in this report.

Pathogenetic Mechanism, Chronicity

Establishing the pathogenetic mechanism of hyponatremia requires a detailed history that includes medications and drinking habits, physical examination with emphasis on neurological and respiratory signs and on volume status, and serum plus urine laboratory testing. The first step in the differential diagnosis consists of eliminating hypertonic hyponatremia and pseudohyponatremia.[1,15,23,28]

True (hypotonic) hyponatremia results from inability to excrete water loads, usual or excessive. Serum vasopressin is higher than is appropriate for the [Na] in most instances.[29] Hyponatremia with inappropriately high serum vasopressin levels can be hypovolemic (ie, body water losses relatively lower than sodium losses), euvolemic (ie, body water excess often with some sodium loss), or hypervolemic (ie, water gain in excess of sodium gain).[29]

From the Raymond G. Murphy Veterans Affairs Medical Center, University of New Mexico School of Medicine, Albuquerque, NM (A.H.T., B.H.R., G.H.M.); Department of Medicine, University of Toledo College of Medicine, Toledo, OH (D.M.); George Washington University, Washington, DC (D.S.C.R.); Marshall University, Huntington, WV (J.I.S.).

Correspondence to: Joseph I. Shapiro, MD, Joan C Edwards School of Medicine, Marshall University, 1600 Medical Center Drive, Suite 3408, Huntington, WV 25701-3655. E-mail: shapiroj@marshall.edu

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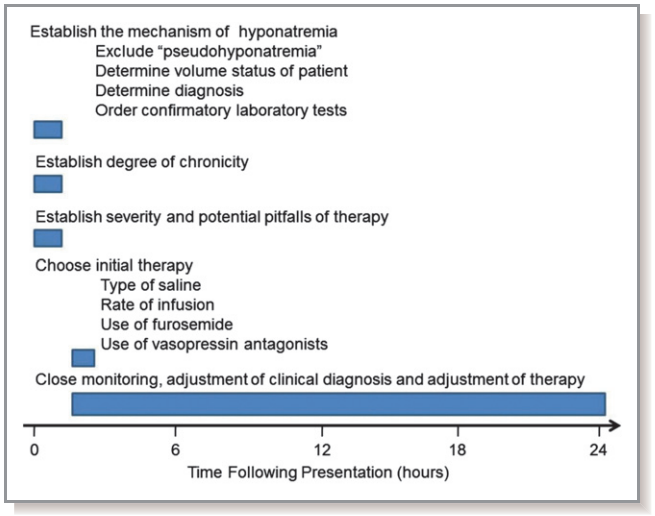

Figure 1. Clinical approach to hyponatremia shown as a flow diagram after initial presentation. Note that the authors recommend making an initial diagnosis and choice of therapy within 2 to 3 hours after presentation with careful monitoring and therapeutic adjustments made thereafter.

Hypovolemic hyponatremia presents special challenges. Previous diagnosis of a hypervolemic state, such as congestive heart failure, complicates the diagnosis. The pattern of urinary chemistries (low sodium concentration and high osmolality) is indistinguishable between hypovolemic hyponatremia from extrarenal causes and hypervolemic hyponatremia.[29] Both conditions lead to vasopressin secretion.[30] The differential diagnosis is based on careful history and clinical examination. Cautious volume replacement may help when the diagnosis of hypovolemia is doubtful. Thirst from hypovolemia may increase the water load, and alterations in renal circulation may contribute to the decreased renal ability to excrete water.

From a pathophysiological perspective, the loss of brain organic osmolytes occurs with greater chronicity of hyponatremia.[31,32] Unfortunately, this cannot be determined using existing clinical tools, but a recognition of this fact is essential in understanding potential deleterious aspects of treatment. History, prior measurements of [Na], and the neurological picture at presentation are the only available clinical criteria for determining chronicity. Acute hyponatremia exhibits pronounced brain cell swelling and more severe symptoms but lower risk of osmotic myelinolysis after rapid correction of the [Na], compared with chronic hyponatremia with a similar [Na] value. It is believed that the risk of myelinolysis is greatest where organic osmolyte recovery lags,[31] and in humans, this area is usually the pons. However, chronic hyponatremia can cause severe neurological manifestations.[33] When doubt exists, it is safer to consider hyponatremia as chronic.

Severity

Hyponatremia is considered as severe if [Na] is <115 or 110 mmol/L.[34] In addition, all cases of hyponatremia treated with hypertonic or isotonic saline infusion, including hypovolemia with hyponatremia and absence of overt neurological manifestations, should be considered as severe because of the risks from saline infusion. Saline infusion for hypovolemic hyponatremia carries arguably the highest risk of inadvertently rapid rise in[Na].

Target Serum Sodium Concentration

The targeted rise in [Na] depends on the perceived urgency of treatment. In patients with pronounced hyponatremic symptoms, regardless of chronicity, a rapid rise of 4 to 6 mEq/L is recommended.[35] Further rises may be required if symptoms persist after the initial rise in [Na]. For chronic hyponatremia, previous recommendations set a maximal rate of rise in [Na] at 12 mEq/L in the first 24 hours and a maximal final [Na] of 125 to 130 mEq/L.[34] Because osmotic myelinolysis was observed in patients achieving the desired rate of rise in [Na],[36] the current target rise in [Na] is set at 6 to 8 mEq/L in 24 hours, 12 to 14 mEq/L in 48 hours, and 14 to 16 mEq/L in 72 hours.[35] Prevention of hypernatremia during treatment of hyponatremia is imperative.[37]

Sodium Concentration and Volume of Infused Saline

Table 1 shows the symbols for volumes and concentrations used in this report. Sodium concentration in commercial saline solutions represents 2 hypertonic (0.855 and 0.513 mol/L), 1 "isotonic" (0.154 mol/L), and 3 "hypotonic" (0.130, 0.077, and 0.034 mol/L) values.[23] Sodium concentration in the infusate is usually 0.513 mol/L for hyponatremia with pronounced symptoms[35] and 0.154 mol/L for volume replacement in patients with symptomatic hypovolemia.[29]

The sodium concentration in the infusate should not be limited by the strength of the commercial saline solutions. Mixing of saline and dextrose in water can produce any desired sodium concentration by the use of formula 1 (Table 2), which can be of help in hypovolemic hyponatremia with minimal hyponatremic symptomatology, when a large volume of infusate must be reconciled with the need to produce only a modest rise in [Na]. A suitable sodium concentration of the infusate in this instance could be the target [Na] at 24 hours. For example, the target [Na] at 24 hours would be 117 mEq/L in a patient with hypovolemic hyponatremia and initial [Na] of 111 mEq/L. By formula 1, the addition of 0.316 L of dextrose in water to 1 L of 0.154 mol/L

Table 1. Symbols and Interpretations

Symbol	Interpretation
VD_5W	Volume of 5% dextrose in water
V_{Inf}	Volume of infused saline
V_{Lost}	Volume of water lost externally through the skin, the respiratory system, the gastrointestinal system, and the lungs
TBW_I	Initial (preinfusion) total body water
$[Na]_{Inf}$	Sodium concentration in the infusate
$[Na]_{Ini}$	Initial (preinfusion) serum sodium concentration
$[Na]_{Fin}$	Final (postinfusion) serum sodium concentration
$[Na]_{Lost}$	Average sodium concentration in V_{Lost} (the sum of the amounts of sodium lost through the skin, gastrointestinal tract, and kidneys over V_{Lost})
$[K]_{Lost}$	Average potassium concentration in V_{Lost} (the fraction amount of potassium lost though the skin, gastrointestinal tract, and kidneys over V_{Lost})
Na_e	Total body exchangeable sodium
K_e	Total body exchangeable potassium
TBW	Total body water
$[Na]_{pw}$	Sodium concentration in plasma water

saline produces a sodium concentration of 117 mEq/L in the infusate.

Volume, strength, and rate of saline infused are determined by the symptoms of hyponatremia or hypovolemia and the presenting [Na]. In the past, the required amount and volume of hypertonic saline were calculated by formulas 2 and 3 (Table 2), which do not take into account the effect of infused water on the change in [Na]. The Adrogue–Madias formula[23] (formula 4 in Table 2), which calculates the predicted change in [Na] after infusion of 1 L of saline, accounts for the major factors that determine the changes in [Na] after the addition of saline to a closed system (initial [Na] and body water plus sodium concentration and volume of the infused saline). Not accounting for the water infused has caused errors in calculations of the changes in [Na] resulting from hypertonic infusions in experimental settings.[38,39] The magnitude of the error increased as the infused volume increased.

Although formula 4 represents a conceptual improvement in the prediction of changes in [Na] after saline infusion, it cannot compute directly the amount of saline required for a desired rise in [Na] or the predicted rise in [Na] after infusion of a volume of saline that is not a multiple of 1 L. To address these issues, we developed formulas 5 to 7 (Table 2) accounting for the same factors as the Adrogue–Madias formula.

Representative Patient

To illustrate quantitative differences between measured and formula-predicted [Na] values after saline infusion and the contributions to these differences by various factors affecting the accuracy of the predictive formulas, Table 3 presents details of a patient with hypovolemic hyponatremia who developed after saline infusion overcorrection of [Na] and osmotic myelinolysis. A slice of this patient's brain magnetic resonance image is shown to illustrate this myelinolysis (Figure 2).

Estimates from various formulas

For these estimates, initial [Na] was considered as equal to 111 mEq/L and initial body water as 26 L. Figure 3 shows [Na] changes after infusion of varying volumes of saline with varying sodium concentration predicted by formula 7. If potassium salts are also infused, the sum of sodium plus potassium concentration in the infusate should be substituted for sodium concentration in formulas 6 and 7.

Table 4 shows volumes of 0.154 mol/L saline required to raise [Na] to 117 mEq/L calculated by formulas 2, 4, and 6 in Table 3. Formula 4 requires 5 steps to calculate a desired volume of the infusate between 4 and 5 L. In first step, this calculated volume is 4.21 L by formula 6 but only 1.01 L by formula 2. Comparison of these predictions to the findings of Table 3 shows that formula 2 overestimated, while formulas 4 and 6 underestimated, the rise in [Na] after the first saline infusion.

Pitfalls of the Formulas for Saline Infusion

The potential pitfalls of formulas 2 to 7 include inaccuracies of estimates entered in the formulas, inaccuracies of the formulas, and problems caused by assuming a closed system.

Inaccuracies of estimates entered in the formulas

Among these estimates, sodium concentration in serum and infusate and volume of infusate can be accurately measured, but clinical estimates of body water with adjustments for volume abnormalities[1] are essentially inaccurate. Figure 4 shows that the predicted effect of widely varying estimates of body water on the changes in [Na] after infusion of various volumes of 0.154 mol/L saline is relatively small. After the first infusion of saline in the illustrative patient, predicted by formula 7, [Na] values differed by only 0.7 mEq/L, whereas initial body water estimates differed by 10 L; both substantially lower than the observed [Na] value (Table 3). Although variation in the estimates of body water has a small effect on the discrepancies between observed and predicted [Na], it is appropriate to use in the calculations realistic values for body water, especially in hyponatremia with pronounced hypovolemia when lower values of body water produce higher estimates of the postinfusion [Na].

Table 2. Formulas

Volume of 5% dextrose that needs to be added to 1 L of 0.154 mol/L saline to produce a desired sodium concentration, <154 mEq/L, of the infusate: $$VD_5W = \frac{154}{[Na]_{Inf}} - 1 \quad (1)$$
Required amount of saline, older formula $$V_{Inf} \times [Na]_{Inf} = ([Na]_{Fin} - [Na]_{Ini}) \times TBW_{Ini} \quad (2)$$
Required volume of infusate, older formula $$V_{Inf} = \frac{([Na]_{Fin} - [Na]_{Ini}) \times TBW_{Ini}}{[Na]_{Inf}} \quad (3)$$
The Adrogue–Madias formula[15] $$[Na]_{Fin} - [Na]_{Ini} = \frac{[Na]_{Fin} - [Na]_{Ini}}{TBW_{Ini} + 1} \quad (4)$$
Sodium conservation with infusion of any amount of saline into a closed system: $$TBW_{Ini} \times [Na]_{Ini} + V_{Inf} \times [Na]_{Inf} = (TBW_{Ini} + V_{Inf}) \times [Na]_{Fin} \quad (5)$$
Required saline volume (new formula derived from formula 5): $$V_{Inf} = TBW_{Ini} \times \frac{[Na]_{Fin} - [Na]_{Ini}}{[Na]_{Inf} - [Na]_{Fin}} \quad (6)$$
Final [Na] (new formula derived from formula 5)*: $$[Na]_{Fin} = \frac{TBW_{Ini} \times [Na]_{Ini} + V_{Inf} \times [Na]_{Inf}}{TBW_{Ini} + V_{Inf}} \quad (7)$$
The Edelman formula[15] $$[Na]_{pw} = -25.6 + 1.11 \times \frac{Na_e + K_e}{TBW} \quad (8)$$
Final serum sodium concentration after correction for the osmotic coefficient of infused nonisotonic saline and for external losses of water and electrolytes: $$[Na]_{Fin} = \frac{TBW_{Ini} \times [Na]_{Ini} + 1.11 \times V_{Inf} \times [Na]_{Inf} - V_{Lost} \times ([Na]_{Lost} + [K]_{Lost})}{TBW_{Ini} + V_{Inf} - V_{Lost}} \quad (9)$$

VD_5W indicates volume of 5% dextrose in water; $[Na]_{Inf}$, sodium concentration in the infusate; V_{Inf}, volume of infused saline; $[Na]_{Fin}$, final (postinfusion) serum sodium concentration; $[Na]_{Ini}$, initial (preinfusion) serum sodium concentration; TBW_{Ini}, initial (preinfusion) total body water; $[Na]_{pw}$, sodium concentration in plasma water; V_{Lost}, volume of water lost externally; $[Na]_{Lost}$, average sodium concentration in V_{Lost}; $[K]_{Lost}$, average potassium concentration in V_{Lost}.
*If the infused volume is 1 L, the Adrogue–Madias formula is derived by subtracting $[Na]_{Ini}$ from the expression of $[Na]_{Fin}$ in formula 7.

Inaccuracies of predictive formulas

Formulas 2 to 7 do not take into account several factors potentially affecting [Na], including changes in body content of solutes other than sodium or potassium, in exchangeable potassium and sodium from body pools not readily available for rapid changes in osmolality, in plasma water content, and in the osmotic coefficients of sodium and potassium salts, plus effects of the Gibbs–Donnan equilibrium.[40] Kurtz and

Table 3. Representative Patient With Hypovolemic Hyponatremia

	Baseline	First Infusion	Second Infusion
$TBW_{Ini,}$* L	26		
$TBW_{Ini,}$† L	36		
V_{Inf}, 0.154 mol/L saline, L		1.75	0.75
Infusion duration, h		6	12
$[Na]_{Ini}$, mEq/L	111.0		
Actual $[Na]_{Fin}$, mEq/L		120.0	129.0
Predicted $[Na]_{Fin}$,*‡ mEq/L		121.4	125.8
Predicted $[Na]_{Fin}$,*§ mEq/L		113.7	114.8
Predicted $[Na]_{Fin}$,†‡ mEq/L		118.5	121.7
Predicted $[Na]_{Fin}$,†§ mEq/L		113.0	113.8
Predicted $[Na]_{Fin}$,*§¶ mEq/L		116.0	117.5

The patient was a man with left above the knee amputation; at presentation, age 55 years, height 157.5 cm, weight 60 kg. TBW_{Ini} indicates initial (preinfusion) total body water; V_{Inf}, volume of infused saline; $[Na]_{Ini}$, initial (preinfusion) serum sodium concentration; $[Na]_{Fin}$, final (postinfusion) serum sodium concentration; GI, gastrointestinal.

*TBW_{Ini} calculated from the anthropometric anthropometric Watson formula[40] corrected for the effects of above-the-knee amputation[41,42] and for the magnitude of volume depletion estimated from the change in serum albumin concentration before and after treatment.[43]

†TBW_{Ini} calculated as 60% of presenting weight.

‡From formula 2 solved for $[Na]_{Fin}$.

§From formula 7.

¶From formula 9, assuming that (1) respiratory loss of oxygen was doubled from normal because of the persistent hyperventilation (arterial P_{CO2} was in the range of 20 to 22 mm Hg in 3 measurements during the first 3 days of hospitalization), rising the estimated loss of water during the first infusion of saline through the lungs, skin and GI tract from 0.188 to 0.288 L) and (2) losses through the skin, gastrointestinal tract, and kidneys were negligible. Urine sodium concentration was 10 mEq/L and urine osmolality was 74 mOsm/kg at the end of the first infusion.

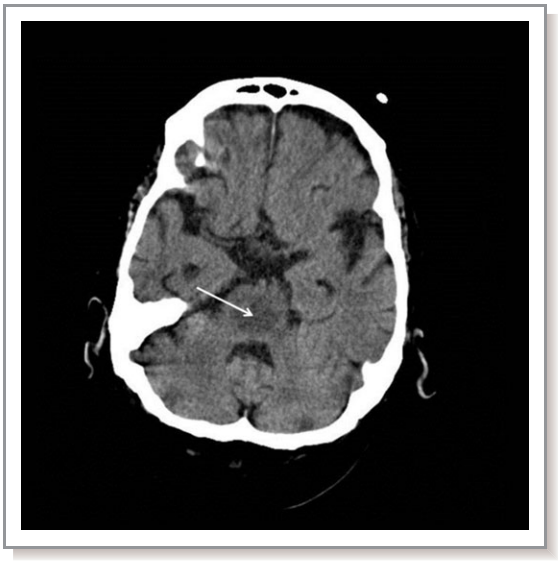

Figure 2. Magenetic resonance imaging brain slice from index patient showing myelinolysis in pons (*white arrow*).

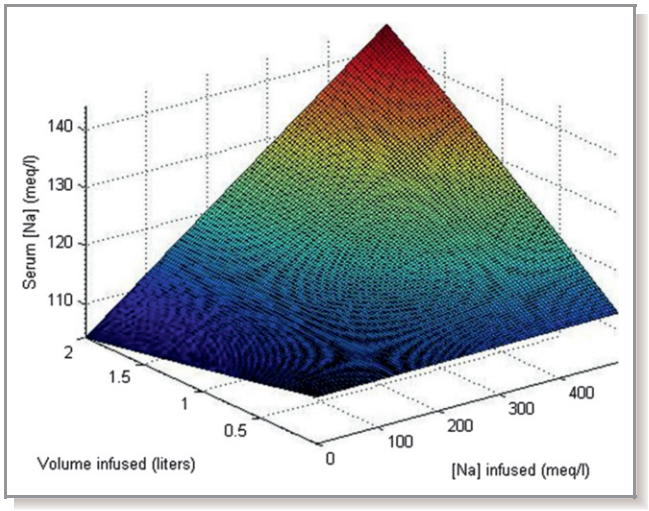

Figure 3. Serum sodium concentration changes ([Na]) after infusion of 1.75 L of saline with varying sodium concentration in a patient with initial body water of 26 L and initial [Na] of 111 mEq/L. The changes in [Na] were computed by formula 7 of this report.

Nguyen[40] suggested that the cumulative effects of all the influences on sodium concentration in plasma water are shown in the formula of Edelman[41] (formula 8 in Table 2). The effects on [Na] of these other factors can be substantial in states other than true hyponatremia, such as in hypertonic hyponatremia.[42] Areas requiring exploration are slow changes in cell volume after rapid osmotic changes[43] and changes in body sodium pools not readily available for osmotic regulation[43–45] and in intracellular solutes other than sodium or potassium induced by potassium deficits.[46]

Problems caused by assuming a closed system

Formulas 2 to 7 do not account for changes in body sodium, potassium, or water other than saline infusion. Under experimental conditions mimicking closed systems, formulas similar to formula 7 predicted accurately the changes in [Na] after the induction of hypernatremia[39,47] or hyponatremia.[46,48] However, patients with dysnatremia do not represent closed systems. They exhibit external losses of solute and water during treatment. The magnitude of these losses, which are usually hypotonic, varies depending on the pathogenetic mechanisms of the dysnatremia, the effects of treatment on these mechanisms, and other conditions present.

Losses occur through the respiratory system, the skin, the gastrointestinal track and the kidneys. Normally, average loss of water though the first 3 routes is ≈1100 mL (≈400 mL through the lungs, ≈500 mL through the skin, and ≈200 mL through the gastrointestinal system), whereas water generation from oxidation amounts to 350 mL per 24 hours. Net water loss amounts to 750 mL per 24 hours or 188 mL per 6 hours.[49] Loss of solute through the 3 routes is proportionally lower than water loss. Sodium concentration in sweat is

Table 4. Calculation, by Various Formulas From Table 2, of the Volume of 0.154 mol/L Saline Required for an Increase in Serum Sodium Concentration From 111 to 117 mEq/L in a Patient With 26 L of Initial Body Water

Formula 4 V_{Inf}, L	Formula 4 Calculation	Formula 4 Δ[Na],* mEq/L	Formula 4 $[Na]_{Fin}$, mEq/L	Formula 6 V_{Inf}, L	Formula 3 V_{Inf}, L
1	$\frac{154-111}{26+1}$	1.593	112.693		
2	$\frac{154-112.693}{27+1}$	1.479	114.072		
3	$\frac{154-114.072}{28+1}$	1.377	115.450		
4	$\frac{154-115.450}{29+1}$	1.285	116.735		
5	$\frac{154-116.735}{30+1}$	1.202	117.937	$\frac{26\cdot(117-111)}{154-117} = 4.22$	$\frac{26\cdot(117-111)}{154} = 1.01$

*Change in Na Concentration. V_{Inf} indicates volume of infused saline; $[Na]_{Fin}$, final (postinfusion) serum sodium concentration.

30 to 65 mEq/L.[49] In the stool, average sodium concentration is 40 mEq/L, and potassium, 90 mEq/L.[50] Water and solute losses increase in sweating, vomiting, or diarrhea and hyperpnea. Urinary losses vary during treatment of hyponatremia. After correction of uncomplicated hypovolemia, urine flow increases as the volume stimulus for vasopressin secretion disappears and water diuresis ensues. Overcorrection of hyponatremia may follow.[25–27]

Formula 9 in Table 2 calculates the final [Na] in patients infused with saline after correcting the osmotic coefficient of the infused saline[40,41] and taking into account losses of water, sodium, and potassium through all 4 external routes. Formula 9 and similar formulas accounting for external losses[51,52] can be used to validate the principals involved in their development by post facto observation, as was done recently in experimental acute hyponatremia.[53] Another use of these formulas is in illustrating the quantitative effects of each of the factors affecting the change in [Na] during saline infusion (see later examples). However, the magnitude of external losses cannot be predicted at the onset of treatment. Consequently, calculation of the amount of infused saline is done with closed systems formulas.

In the illustrative patient with initial body water of 26 L, formula 9 computes that infusion of 1.75 L of 0.154 mol/L saline would cause a rise in [Na] from 111 mEq/L to 116.0 mEq/L if through the lungs, skin, and gastrointestinal tract loss of water was 0.288 mL and losses of sodium and potassium were negligible during the first saline infusion (Table 3). Figure 5 shows predicted changes in [Na] from diuresis in this patient. The direction of the change in [Na] is determined by the sum of urine sodium and potassium

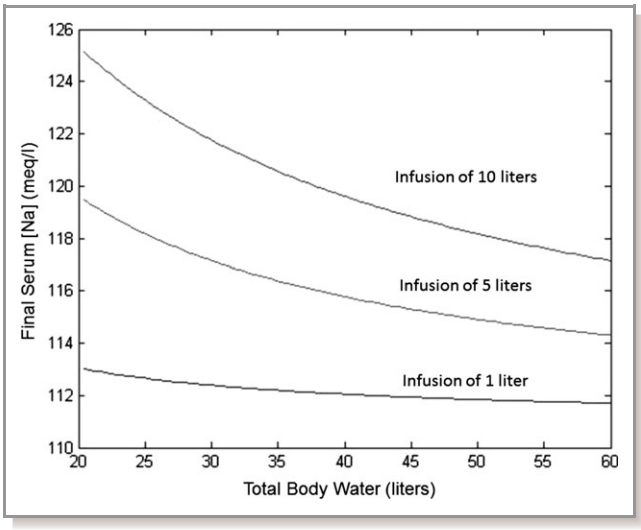

Figure 4. Effect of varying body water estimates on the change in serum sodium concentration of a patient with initial serum sodium concentration ([Na]) of 111 mEq/L infused with various volumes of 0.154 mol/L saline. Calculations from formula 7 (Table 3).

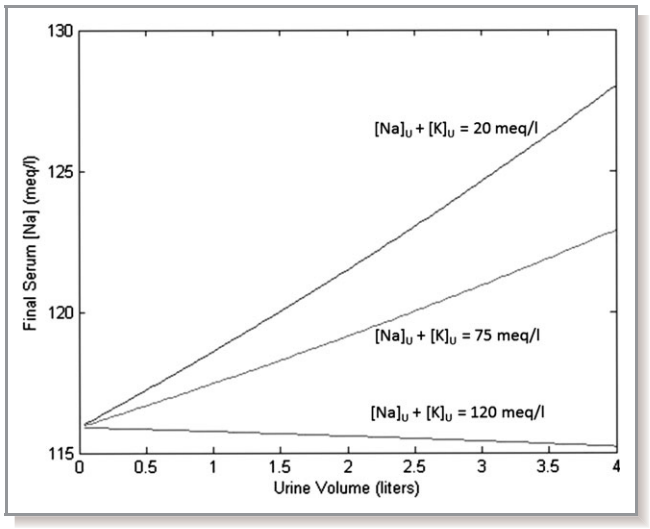

Figure 5. Effect of urine composition ($[Na]_U+[K]_U$) and flow rate on serum sodium concentration [Na] after infusion of 1.75 L of 0.154 mol/L saline in a patient with initial body water of 26 L and [Na] of 111 mEq/L calculated from formula 9 (Table 3) if all the other influences depicted in this formula except urinary losses result in an [Na] of 116.0 mEq/L (Table 5). At $[Na]_U+[K]_U$=116 mEq/L, urinary losses have no effect on [Na]. [Na] decreases if $[Na]_U+[K]_U$ >116 mEq/L and increases if $[Na]_U+[K]_U$ <116 mEq/L.

Table 5. Steps of the Management of Severe Hyponatremia

1. Evaluation of pathogenesis and chronicity History, physical examination, temporal evolution of [Na] before presentation
2. Establishment of indications for saline infusion—determination of severity Clinical manifestations of hyponatremia or [Na] <115 mEq/L Clinical manifestations of hypovolemia
3. Collection of baseline information required for saline infusion Body weight Serum electrolytes, glucose, urea nitrogen, creatinine, osmolality, albumin Other serum values (uric acid, cortisol, thyroid hormones, etc), as needed Urine sodium and potassium concentrations and osmolality
4. Calculation of the volume, strength, and rate of saline infusion using formula 6 (Table 2) (a) For symptomatic hyponatremia: hypertonic saline (b) For symptomatic hypovolemia with low presenting [Na]: isotonic saline or calculation of salinity using formula 1 (Table 2) (c) For a combination of (a) and (b): initially hypertonic saline, followed by saline with [Na] concentration computed from formula 1
5. Continuous monitoring throughout the infusion—intensive care unit preferred Clinical: neurological status, respiration, volume status every 2 to 3 hours; body weight daily, and more frequently if needed Urine flow rate: hourly Serum: sodium and potassium every 2 to 3 hours; other values (osmolality, urea nitrogen, glucose) as needed; creatinine daily; albumin at the end of the infusion Urine: sodium, potassium every 6 hours or more frequently if urinary flow rate increases during the infusion; osmolality if needed
6. Changes in the management Comparison of actual and predicted (from formula 7, Table 2) $[Na]_{Fin}$ after each measurement of [Na] Evaluation of causes of discrepancy (formula 9) Addition of furosemide to the infusion, taking care that the rate of saline infusion exceeds the rate of urine flow in patients with hypovolemic hyponatremia Infusion of hypotonic saline or vasopressin plus water

$[Na]_{Fin}$ indicates final (postinfusion) serum sodium concentration.

concentrations. Regardless of the urine volume, [Na] will be equal to the predicted value of 116 mEq/L if the sum of urine plus potassium concentration is equal to 116 mEq/L. For the same urine volume, the lower the sum of urinary sodium plus potassium, the greater the rise in [Na] will be. The volume of urine containing 10 mEq/L each of sodium and potassium needed to raise [Na] to 120 mEq/L after infusion of 1.75 L of 0.154 mol/L saline is 1.1 L.

Modest hypotonic urine production can cause large underestimates of the increase in [Na] during treatment of hyponatremia with saline. External losses, primarily though the urine during treatment of hypovolemic hyponatremia, represent the major pitfall of formulas 2 to 7.

Management Protocol

Table 5 summarizes the management of hyponatremia with saline infusion. Closed system formulas (formulas 2 to 7) provide estimates of the required saline volume and allow comparison between desired and observed changes in [Na] and, therefore, provide the frame for identifying the source of their deviations and the guide for appropriate treatment changes. The first aim of treatment is to avoid undercorrection of hyponatremia.[5] Prescription of the volume of saline infused by formula 4 or 6 is suitable for this purpose. Monitoring is critical when saline is infused, particularly in hypovolemic hyponatremia in which water diuresis, overestimation of initial body water, and initial focusing on volume rather than tonicity issues complicate the treatment. Monitoring, with reduced frequency of [Na] measurement (usually once daily), is essential during treatment of hyponatremia without saline infusion.

Many tests, especially urine chemistries and osmolality, cannot be obtained rapidly from all hospital laboratories. For this and other reasons, administration, along with saline, of loop diuretics (eg, furosemide) to make urine free water excretion more predictable may be helpful in managing hypovolemic hyponatremia. Although furosemide will initially increase urinary sodium and potassium excretion, it is reasonable to assume that the sum of urine sodium plus potassium concentration is equal to ≈75 mEq/L when a furosemide effect is present,[1,54] at least until direct laboratory measurements are available. Because patients with hypovolemic hyponatremia have reduced total body sodium and probably water, care must be taken to replace more than the predicted urinary electrolyte and water losses with infused saline.

Vasopressin V2 receptor antagonists may ultimately be extremely useful for treating complicated chronic hyponatremias.[55] However, it is unclear how to best use these new agents at present. It is fair to say that the vasopressin V2 receptor antagonists appear to be very effective in the settings of heart failure, cirrhosis, and syndrome of inappropriate antidiuretic hormone secretion and safe when administered as monotherapy.[56,57] Unfortunately, these agents are currently extremely expensive. Moreover, we would stress that these agents should be avoided during saline infusion to prevent the hazards of excessive water diuresis.

Conclusion

Accurate diagnosis of the cause, pathogenesis and chronicity, and monitoring during treatment are the critical parts of the

management of severe hyponatremias. We stress that calculation errors are possible even with the best formulas, and frequent monitoring of the patient during therapy is absolutely essential to ensure optimal chances for recovery.

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