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Dear Etta,

It was good to talk to you on Friday and thank you for your understanding. I feel frustrated and want to get the report out and am happy to defend it! However I understand the position.

I enclose some stuff on hyponatraemia. Malcolm Holliday (who is 80 yrs old now) knows more about it than anyone I know. The article is a draft which he has submitted for publication and he responded to the Lancet article on their website. Let me know if I can help. I hope the weekend brought cheerful thoughts!

V. best

Cyril

006-044

October 26, 2003

A CRITIQUE OF SHORT TERM FLUID THERAPY IN HOSPITALIZED CHILDREN: AVOIDING HYPONATREMIA AS A TREATMENT RISK

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A CRITIQUE OF SHORT TERM FLUID THERAPY IN HOSPITALIZED CHILDREN: AVOIDING HYPONATREMIA AS A TREATMENT RISK

ABSTRACT

Objective: To review the settings in which hospital induced hyponatremia occurred in children given short term fluid therapy because of admission for acute illness, diarrheal dehydration, or surgery. To determine the frequency of mild hypovolemia in this group and the frequency of excess maintenance fluid therapy as factors contributing to the cause of this hyponatremia. To review protocols for rehydrating/restoring ECF with isotonic saline or with oral rehydration and those for estimating maintenance therapy including the method for indexing maintenance therapy to metabolic rate.

Methodology: We reviewed articles over the last twenty years in which hyponatremia was reported in children given short term fluid therapy. We used elevated ADH levels with normal or low plasma sodium as evidence of hypovolemia, reinforced by history of restricted intake, diarrhea, or dislocation of ECF. We noted where excess maintenance therapy was given. We cited the effectiveness of giving extra ECF to restore circulation and control of salt and water balance in burn shock. We redefined fluid therapy protocols.

Results: A preponderance of children with hospital induced hyponatremia met our criteria for hypovolemia; rehydration/restoration of circulation prevented or reversed it. Maintenance therapy often was given in excess of need and protocol.

Conclusions: Rapidly correcting hypovolemia with isotonic saline and providing maintenance therapy in accordance with protocol reduces the risk for hospital induced hyponatremia and its complications.

A CRITIQUE OF SHORT TERM FLUID THERAPY IN HOSPITALIZED CHILDREN: AVOIDING HYPONATREMIA AS A TREATMENT RISK

Introduction: Hyponatremia is a frequent complication of short term fluid therapy given to children admitted to hospital for acute illnesses[1,2] or surgery[3]. It sometimes causes water intoxication, convulsions, brain injury or death[4]. A review of the literature describing hyponatremia in this setting has led us to conclude that it is commonly caused by unrecognized hypovolemia which elevates plasma levels of antidiuretic hormone [ADH] irrespective of plasma sodium. When hypotonic maintenance solutions are given intravenously the elevated plasma ADH inhibits excretion of the free water leading to hyponatremia. Less commonly it is caused by giving miscalculated maintenance fluids that exceed renal capacity for excreting free water even with ADH suppressed.

The purpose of this article is to review the nature of maintenance therapy as originally described; to cite the clinical findings supporting the case that hypovolemia or giving excess free water are primary causes of hyponatremia. Further we describe protocols for correcting hypovolemia and the method for calculating maintenance fluid. Advantages of using oral rehydration therapy in treating diarrheal dehydration are noted.

Maintenance therapy: Maintenance therapy as originally described[5] was to replace ongoing physiological losses of water when oral intake is suspended. The average vary as metabolic rate[a] and are net insensible water loss [~35 ml] and urinary water loss [~65 ml] per 100 kcals/da. Maintenance allowance for water therefore should be indexed to

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[a] Infant: 3-10 kg, 100 kcals/kg
Preschool: 10-20 kgs, 1000 + 100 kcals for each 2 kg > 10.
Older: 20-70 kgs, 1500 +100 kcals for each 5 kg > 20.

metabolic rate [see footnote a and Table], not body weight [BW]. Average maintenance allowance for water is 100 ml/100 kcal/da usually met by giving hypotonic [between 0.45 and 0.18 %[b]] saline. Exceptions to the average figures for net insensible losses are uncommon in the modern hospital setting except with mechanical ventilation; exceptions for urinary losses are uncommon but can be inferred from clinical findings; maintenance therapy should be adjusted accordingly. For example, when hyponatremia is present and there is no evidence for hypovolemia, the syndrome of inappropriate ADH [SIADH] may be suggested and its cause sought; in that case maintenance therapy should be reduced to half average [not "half maintenance"] or 50 ml/100 kcal/da [see Table], because renal loss is reduced to a minimum. Using isotonic saline for all maintenance therapy, as recently recommended[6], incurs needless additional risks[7].

The case for hypovolemia: Hypovolemia stimulates release of ADH even though plasma sodium is normal or low[8]. This release inhibits normal renal free water excretion so that giving hypotonic solutions intravenously in this setting leads to free water retention and hyponatremia. The hypovolemia seen in these children is of two types[9]: 1) dehydration due to the loss of extracellular fluid [ECF] as seen with diarrhea or loss of other body fluids, 2) plasma volume displacement seen post surgery or with infectious disease due to inflammation or to pooling of blood into dependent areas, as occurs with bed rest[10]. Hypovolemia responds to giving normal saline which restores circulation, venous return and renal regulation of salt and water balance, and depresses ADH.

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[b] The term normal saline, though widely used, is not permitted in labeling by FDA because it is not a chemically defined Normal solution. Isotonic saline is 0.9% saline (154 meq/L Na). Hypotonic saline solutions vary between 0.45 and 0.18% saline (77 and 30 meq/L Na) and deliver between half and 4/5 of their volume as free water.

The evidence for hypovolemia is taken from several reports. In one[11] 25 of 27 acutely ill patients with hyponatremia had elevated plasma ADH levels. In another ADH levels were elevated in children with hyponatremia due to gastroenteritis and dehydration[12]. In a prospective study, children with meningitis and elevated ADH levels who were given "maintenance plus replacement" fluids lowered ADH levels, whereas children given maintenance fluids alone did not[13]. In another prospective study, children who were given isotonic saline during surgery had lower plasma levels of ADH postoperatively than those given no fluids although plasma sodium was the same for both groups[14]. When children with diarrheal dehydration and elevated ADH levels were given 0.45% saline [77 meq/L] as therapy for dehydration, many became hyponatremic; when they received isotonic saline [154 meq/L], plasma sodium generally remained normal[15].

In each instance cited, the children were hypovolemic and vulnerable to hyponatremia when given just maintenance therapy. When ECF was expanded before giving maintenance therapy plasma ADH decreased and hyponatremia was avoided.

The case for excess water: Maintenance therapy is often given well in excess of that recommended[5]. In one report[2] physicians gave >150% recommended maintenance fluid to 16 of 23 patients. Commonly, orders are written for "one and a half" maintenance without evidence that physiologic losses are increased. More may not be better! In other instances maintenance fluids are indexed to BW at a rate of 100 ml/kg/da [not per 100 kcals] increasing the intake by as much as three times recommended [see Table]. Giving maintenance fluid in excess of recommended will rarely exceed the patient's capacity to excrete free water, so long as plasma ADH is not elevated, because that capacity is

generous. But sometimes it is a cause of hyponatremia. Occasionally egregious amounts of free water are given as hypotonic saline and death has resulted[4].

The Nature of Water intoxication: When hyponatremia develops due to free water retention, regardless of cause, solutes of both extracellular and intracellular fluid are diluted because water rapidly equilibrates across cell membranes and solutes do so only slowly. Cell and extracellular volumes increase. Given the unique anatomic and physiologic features of the brain, this causes brain swelling and increased intracranial pressure. If of sufficient magnitude, brain ischemia follows which is the physiological basis of water intoxication. With time brain solutes are lost and brain volume returns to normal. In the interim convulsions and brain injury may have occurred.

Expanding ECF to suppress ADH: Further evidence that isotonic saline infusion suppresses plasma ADH and prevents hyponatremia is noted in management of severe hypovolemia as seen in burn or septic shock. For example, a 40% skin surface area burn, releases vasoactive agents that effect a huge transfer of plasma and albumin into both the burn site and normal interstitium. Circulation and renal perfusion are severely compromised; the stimulus to ADH secretion is intense. Current treatment is to give 80 ml/kg [2 ml/% skin surface burn] of isotonic saline or Ringers solution in the first four hours[16]. That dose or more is repeated in the next 12-16 hours until blood pressure and pulse are stable, urine output and organ perfusion normal and the patient, as defined by Moyers[17] "is alert, able to converse and drink fluids". Hyponatremia seldom develops[18]. Managing the hypovolemia of burn shock by generous expansion of ECF with isotonic saline restores circulation and suppresses ADH with no change in plasma sodium[19]. Renal regulation of salt and water balance are restored to normal. As inflammation

subsides, the "extra" ECF is recovered into plasma and excreted as urine. Septic shock is an example of extreme vasodilatation and dislocation hypovolemia that dramatically raises ADH levels[20]. A critical component of treatment is massive isotonic saline infusion given quickly to restore circulation and renal regulation of salt and water balance[21]. Once vasomotor tone is restored, ADH decreases, and the "extra" ECF is excreted.

The shock that comes with experimental "quiet standing" illustrates the capacity of gravity to cause blood pooling and dislocation even in normal subjects that is sufficient to result in shock. Normal young men, when standing with muscles fully relaxed, develop tachycardia, hypotension, and syncope within 15 minutes. These develop from blood gravitating to the capacitance vessels in the lower limbs and plasma sequestering in the dependent interstitium; venous return to the heart is compromised. Plasma ADH dramatically rises. All is reversed when the subjects lie down[22]. Bed rest or "quiet lying" as occurs in acute illness or following surgery has a comparable effect often abetted by inflammation; ECF expansion with isotonic saline maintains/restores circulation.

Steps in planning short term fluid therapy: The first priority in planning short term fluid therapy is to determine if hypovolemia, as described, is likely. If so, rehydration/restoration therapy is indicated. If it is marginal to moderate, giving 20-40 ml/kg of isotonic saline or Ringers solution quickly, should suffice. With more severe dehydration or shock, 40-80 ml/kg or even more may be needed. Note that this therapy is indexed to BW, not metabolic rate, because blood and ECF volumes vary as a function of BW. Some pre-op patients may have hypovolemia from being without fluids and from "quiet lying"; surgical trauma will sequester ECF. These patients will benefit from 20-40

ml/kg of isotonic saline. For patients needing only a 'keep-open" line going into surgery, isotonic saline offers the safest solution for ready use in case of unanticipated events.

The special case of oral rehydration therapy in diarrheal dehydration: In the case of diarrheal dehydration, the protocol, prior to introduction of oral rehydration therapy [ORT], was to infuse isotonic saline [20-40 ml/kg] to partially restore ECF volume and then plan intravenous deficit and maintenance therapy. Acute ECF expansion is still the recommendation if oral fluids aren't tolerated. But oral rehydration solution [60- 90 meq/L Na], given aggressively [60-100 ml/kg in 4-6 hrs], restores ECF volume, replaces continued diarrheal losses and normalizes plasma sodium[23]. It is the treatment recommended by the American Academy of Pediatrics[24]. As noted above[14] giving 0.45% saline [77 meq/L Na] intravenously increases the risk for hyponatremia. This apparent paradox may be explained by the different endocrine response to an intravenous versus an oral salt load of 30 ml/kg of isotonic saline given in one hour to normal subjects on a very low salt diet[25]. The intravenous load increased plasma atrial natriuretic peptide [ANP] more than the oral; plasma volume and initial salt excretion also more[c]. These findings may explain why giving 0.45% saline [77 meq/L Na] intravenously induces hyponatremia whereas giving oral rehydration solution [60- 90 meq/L Na] does not.

Summary: Those prescribing short term fluid therapy for children admitted for acute disease or elective surgery often fail to identify subtle hypovolemia, or they use incorrect estimates of maintenance therapy or both. These practices follow from the common tendency to compress principles of management into readily remembered rules. The results sometimes lead to serious complications. Hypovolemia initiates ADH release

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[c] The responses of plasma levels of aldosterone and renin between the intravenous and oral sodium loads were not significantly different

which limits free water clearance. When hypotonic saline is used for maintenance therapy, without first correcting hypovolemia, water is retained causing hyponatremia, sometimes sufficient to induce water intoxication. Occasionally maintenance allowance is so miscalculated or is indexed to BW not metabolic rate and exceeds renal excretory capacity causing hyponatremia and water intoxication in the absence of ADH. These are the commonest causes of hospital induced hyponatremia and the attendant risk for water intoxication in children given short term intravenous fluid therapy. The risk is greatly reduced 1) by initially giving to children with acute illnesses or admitted for surgery who are at risk to hypovolemia, 20- 40 ml/kg of isotonic saline and 2) by correctly calculating maintenance allowance- usually 100 ml/100 kcal/da. Isotonic saline, not hypotonic maintenance fluids, should be used for rehydration/restoration therapy. Moderate diarrheal dehydration is preferably treated by oral rehydration therapy, not intravenous fluid therapy, because it has a lower risk for causing hyponatremia.

TABLE.

RELATING BW TO METABOLIC RATE [see footnote a] AND
TO AVERAGE AND HALF AVERAGE MAINTENANCE ALLOWANCES
FOR DAILY AND HOURLY PERIODS

BW	METAB RATE	MAINTENANCE ALLOWANCE			
		ML/DA		ML/HR	
KG	KCALS	AVER	1/2 AVER	AVER	1/2 AVER
3	300	300	150	12	6
5	500	500	250	20	10
7	700	700	350	24	12
10	1000	1000	500	40	20
12	1100	1100	550	45	22
16	1300	1300	650	50	25
20	1500	1500	750	60	30
30	1700	1700	850	70	35
45	2000	2000	1000	80	40
70	2500	2500	1250	100	50

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Viewpoint

Intravenous fluids for seriously ill children: time to reconsider

Trevor Duke, Elizabeth M Molyneux

Intravenous (iv) fluids are used for many sick and injured children. Such fluids generally used are 0·18% or 0·2% saline with 5% dextrose. These fluids are often given at maintenance rates—100 mL/kg for the first 10 kg of bodyweight, 50 mlL/kg for the next 10 kg, and 20 mL/kg for bodyweight exceeding 20 kg.[1] Some standard paediatric texts caution the need to modify maintenance requirements according to disease states, but this specification has been lost in some recent empirical recommendations: for example, WHO now suggests full maintenance fluids for the routine treatment of bacterial meningitis (albeit with a caution about cerebral oedema), with an emphasis on glucose but not sodium content.[2] This is partly based on concerns about dehydration, but there is no strong evidence that this advice is ideal.[3,4] Hypotonic iv fluids given at maintenance rates might be unsafe, especially in hospitals in developing countries where serum sodium concentration often cannot be measured.

The traditional use of hypotonic maintenance fluid in paediatric medicine is based on requirements of normal physiology—eg, if an infant weighing 6 kg receives 0·18% saline fluid for 24 h, they will receive 3 mmol/kg sodium chloride, 100 mL/kg water, and 3·5 mg/kg per minute glucose. These are the amounts of (1) sodium and chloride needed for normal metabolism and growth; (2) water needed by the kidneys to excrete nitrogenous wastes in urine with similar osmolarity to plasma (so that the kidneys do not need to excessively concentrate or dilute urine); and (3) glucose needed to avoid hypoglycaemia and glycogen breakdown. This sounds ideal, but is it? Most healthy people do not drink this much water each day (average for adults is 2·5–3 L), so their kidneys usually concentrate, or if they drink more than usual dilute, their urine. Healthy people are able to excrete large amounts of free water. This is not the case for many children after surgery, or with serious infections.

Large volumes of hypotonic fluid were generally given after surgery, until reports led to recognition that postoperative patients have reduced free-water clearance, and hypotonic saline solutions at maintenance rates or greater put patients at risk of hyponatraemia and encephalopathy—the syndrome of water intoxication.[5–8]

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Children with serious infections share similar pathophysiological mechanisms and risks of adverse neurological outcomes if given hypotonic iv solutions. We outline the pathophysiology of hyponatraemia in acute infections, and argue that the safest empirical iv fluid for most children with serious infections, who cannot take enteral fluids, is 0·9% sodium chloride with dextrose, at rates of infusion that take account of reduced free-water clearance.

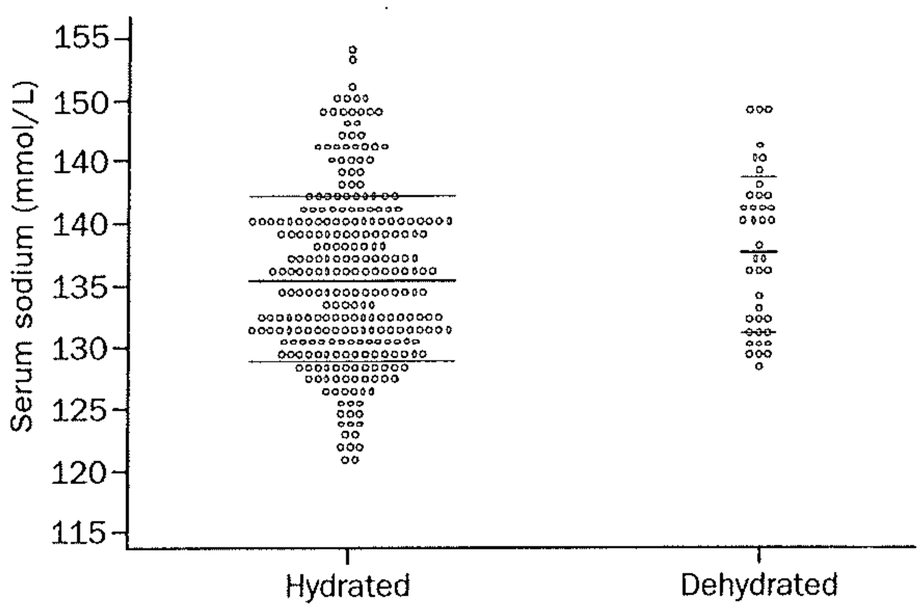
Impaired free-water excretion during severe infections

Antidiuresis during fever and sepsis has been known for over a century, especially in pneumonia and meningitis. Hippocrates' description of pneumonia included scanty and high-coloured urine. In a rhesus monkey model of pneumococcal sepsis, urine volume and free-water clearance decreased to 25% and 17% of baseline values, respectively, during the first 9 h of infection.[9] When 0·45% saline, equal to 105% of urine output in controls, was intravenously infused into septic monkeys, their bodyweight expanded by more than 10% during 9 h of experimental sepsis. Of note, serum sodium concentration or serum osmolarity did not change greatly. In a clinical investigation, 70% of infants with

Mechanism	Setting
Dilution of ECFV	
High ADH activity	Despite normal or expanded ECFV and hypo-osmolarity, so-called SIADH
	Because of hypovolaemia
	Other non-osmotic ADH stimuli[13,14]
	Pain
	Nausea
	Hypoxaemia
	Drugs
	Mechanical ventilation
Increased sensitivity of renal tubules to ADH	Drugs
	Severe illness
Increased intake of free water	Excessive enteral water intake
Iatrogenic administration of free water	iv administration of hypotonic solutions
Increased urinary sodium loss	
ECFV expansion	Retention of free-water from high ADH activity
	Unrestricted oral intake
	Iatrogenic administration
Natriuretic peptide activity (ANP/BNP)	Increased right atrial pressure
Cerebral 'salt wasting'	Described in tuberculous meningitis and traumatic brain injury
Diuretic administration	..
Corticosteroids	..
ADH	ADH may have a direct effect on increasing urinary sodium excretion

ECFV=extracellular fluid volume. ANP=atrial natriuretic peptide. BNP=brain natriuretic peptide. ADH=antidiuretic hormone. SIADH=syndrome of inappropriate ADH secretion.

Table 1: **Causes of hyponatraemia in severe childhood illness**



Serum sodium in well hydrated and dehydrated children with meningitis

p=0·03. Well hydrated, n=286; dehydrated, n=40. Horizontal lines represent mean (SD).

acute bronchiolitis had impaired free-water excretion; at recovery, free-water clearance was up to 15 times more than at the time of admission.[10]

Hyponatraemia in severe infections

Hyponatraemia arises in between 20% and 45% of children with meningitis,[11,12] pneumonia,[13] encephalitis,[14] septicaemia,[15] cerebral malaria,[16,17] and somewhat less often in those with bronchiolitis.[10] The pathophysiological basis is not fully understood, but many factors could be active in the same patient (table 1). Dilution of extracellular fluid because of impaired free-water excretion and increased urinary sodium losses seem to be the main mechanisms. Other mechanisms, including shifts of water from intracellular to extracellular spaces, have been shown in some models of sepsis,[20] but not in others, and are less likely to be important in practice.[21]

Antidiuretic hormone

High concentrations of antidiuretic hormone are seen in many acute febrile illnesses,[22] and are traditionally described as inappropriate. When applied generally, this term indicates our incomplete understanding of the potency of different stimuli to antidiuretic hormone release and suppression (table 1). Hypovolaemia might be a more potent stimulus for secretion of antidiuretic hormone than hypo-osmolarity is to its suppression. In a retrospective study of 300 children with meningitis, investigators noted that serum sodium was lower in those with dehydration than in those with normal hydration.[12] Conversely, a prospective investigation showed that serum sodium concentrations were lower in children with normal hydration than in those with clinical signs of dehydration (figure).[23] Such conflicting data suggest that hyponatraemia arises either as a result of an appropriate pathophysiological response of antidiuretic hormone to restore extracellular fluid volume at the expense of hypo-osmolarity, or as a result of hormonal activity that is inappropriate to both osmolarity and fluid volume status. Antidiuretic hormone also acts centrally, via aquaporin-4 water-transporting proteins expressed in astrocyte foot processes near capillaries and in ependymal cells lining ventricles, to increase brain water.[24,25] Administration of sodium results in a more rapid return to normal of antidiuretic hormone concentrations than does use of low sodium-containing fluid.[4]

Adverse effects of hyponatraemia

In the peripheral circulation, sodium moves freely throughout the extracellular fluid; the hydrostatic pressure gradient and oncotic pressure (predominantly made up of plasma proteins) are responsible for preventing the movement of water out of the vasculature. Cerebral circulation is different. Endothelial tight junctions prevent free movement of sodium across the intact blood-brain barrier, and therefore effective osmolarity is the major determinant of water movement into the brain interstitium or into brain cells.[18] When the blood-brain barrier is intact, an abrupt fall in effective serum osmolarity of 5 mmol/L decreases osmotic pressure difference between the capillary lumen and the brain interstitium by 95 mm Hg (17·5%), favouring water accumulation in the interstitium or brain cells.[26] Many case reports have described acute neurological deterioration in children with serious infections, associated with progressive hyponatraemia and hypotonic intravenous fluid administration (table 2). Researchers who examined the aetiology of extreme hyponatraemia (<115 mmol/L) in a tertiary children's hospital, reported iatrogenic administration of excessive free water as the most common cause.[31]

	Disease state	Reduction in serum [sodium] or value at time of complication (mmol/L)	Intravenous fluid type and volume	Adverse event	Comments
Investigation					
Cooke[27]	2-year-old girl with tuberculous meningitis	From 130 to 120	Not stated	Coma, seizures	
McJunkin[14]	La Crosse encephalitis (13 of 127 children had neurological deterioration while in hospital)	All children with adverse neurological deterioration had a reduction in sodium. From 138·2 to 134·2 (reduction in mean)	Not stated	Neurological deterioration including cerebral herniation, status epilepticus, and intracranial hypertension	27 children developed hyponatraemia while in hospital, of whom 13 had neurological deterioration
Mor[28]	Infant with pneumonia	107	0·18% saline at 150 mL/kg per day for 2 days	Seizures and cerebral oedema	
Potts[29]	17-month-old with minor burns	From 133 to 113	0·2% saline at 250 mL/kg/day	Seizures	Complications ascribed to SIADH but really represent iv free water intoxication
Jackson[30]	Two children: one with viral respiratory tract infection and one with *Streptococcus pneumoniae* meningitis	121 and 128, respectively, after administration of fluid	5% dextrose at 35–40 mL per kg	Seizures, cerebral oedema, and death	

Table 2: **Adverse events after progressive hyponatraemia induced by hypotonic solutions in children with serious infection or injury**

Fluid	Volume (mL/kg/day)	Volume per day (mL)	Urine output (mL)	Insensible losses (mL)	Total output (mL)	Total net water added (ICF/ECF) (mL)	Na+ added (mmol)	24-h serum [Na]*
0·18% saline	100	600	210	180	390	210 (84/126)	7·2	130·6
0·9% saline	75	450	210	180	390	60 (0/60)	13·5	137·5

Total body water=70% of bodyweight (35% ECF, 35% ICF. ICF=intracellular fluid. ECF=extracellular fluid. Free-water excretion reduced by 50% normal (urine volume from 70–35 mL/kg/day) due to increased activity antidiuretic hormone. Starting serum [Na] 135 mmoL/L; total ECF Na=0·35×6×135=283·5 mmol.
*24-h serum [Na]=(pre-existing ECF [Na]+[Na] added)/(pre-existing ECF+ECF added).

Table 3: **Expected changes after 24 h of fluid administration to an infant weighing 6 kg**

Avoidance of hyponatraemia is essential, but not sufficient, to prevent adverse events associated with iv fluid in all children. Fluid overload occurs in children with impaired free-water clearance who receive 100% or more of maintenance fluid. In a randomised trial of fluid management in bacterial meningitis, facial oedema developed 48 h after admission in 45 of 176 (25·6%) children who received 100% of maintenance fluids using 0·45% saline. The relative risk of death or severe neurological sequelae when facial oedema was present was 2·5 (95% CI 1·4–4·8), despite the absence of differences in serum sodium or osmolarity (Duke T, unpublished). This finding suggests that fluid overload, even without progressive hyponatraemia, can contribute to adverse neurological events, which might be explained by disruptions to the blood-brain barrier in children with meningitis. Thus, generation of cerebral oedema in severe infections is multifactorial: the effective osmolar gradient, administered fluid volume, and a direct effect of antidiuretic hormone on aquaporin proteins are each important.

Table 3 shows the estimated effect of two types of fluid management regimens on serum sodium and volume status in an infant weighing 6 kg, with impaired free-water excretion. Renal function was assumed to be otherwise normal. After use of 0·18% saline at 100 mL/kg per day, serum sodium would be expected to fall from 135 mmol/L to 131 mmol/L within 24 h, associated with a 5% increase in total body water. With 0·9% saline at 75 mL/kg per day, serum sodium would increase by 2 mmol/L and total body water by 1·5%, with no increase in intracellular water. These are the initial changes; secondary effects might include part correction of the fall in serum sodium in those receiving 0·18% saline, because of intracellular water shifts, but increased urinary sodium losses because of expansion of the extracellular fluid.

Few clinical trials have assessed these differences. A non-randomised comparison of 0·18% and 0·9% saline in 24 postoperative patients, showed a similar biochemical effect to our predicted result. Adults receiving 0·18% saline at 3 L per 24 h had a median fall in serum sodium at 24 h and 48 h of 5·4 mmol/L and 7·1 mmol/L, respectively, but serum sodium did not change in those receiving 0·9% saline.[32] In patients in whom renal clearance of free water is reduced by more than 50%, maintenance fluid will need to be considerably less than 75% of normal maintenance volumes to avoid oedema. This approach is not fluid restriction, as it is sometimes interpreted: restriction of fluids to the point of dehydration in the hope of avoiding cerebral oedema is dangerous, and will result in worse outcomes.[23]

Potential pitfalls

Use of an isotonic, rather than hypotonic, solution does not mean that progressive hyponatraemia would not take place, but that it is much less likely. Although use of high-sodium-containing solutions in children with meningitis in the first 24 h was not associated with development of hypernatraemia,[6] during the later phases of illness there is a theoretical risk of hypernatraemia if isotonic saline is used. Diuresis and low urine osmolarity is a feature of the convalescent phase of childhood infections. However, during this phase of illness iv fluid rates are reduced, and enteral feeding reintroduced. Children with severe infections, who are not taking enteral feeds, are at risk of hypoglycaemia; isotonic saline should always have glucose added (5–10%) when given as maintenance fluid. Early correction of clinical signs of severe dehydration or shock is essential.[23]

In renal failure there is no safe substitute for measurement of urine output and serum sodium, and adjustment of water and solute intake accordingly. Severe hyponatraemia should be corrected slowly to avoid the demyelinating syndrome.[33] Although there is no evidence that correction of moderate hyponatraemia in children with isotonic saline causes a large risk of this syndrome, to increase sodium by no more than 1 mmol/L every 2 h, seems sensible when this can be measured. Isotonic saline has a pH of 5–6. When it is used in large volumes for children in shock, metabolic acidosis can persist, and in some circumstances bicarbonate or other buffer might be needed.

Possible solution

We postulate that 0·9% saline (with 5% dextrose) at less than standard maintenance volumes results in a lower frequency of hyponatraemia, seizures, and adverse neurological events than do hypotonic solutions (0·18%–0·3% saline), in acutely unwell children with brain injury of any type (meningitis, encephalitis, cerebral malaria, febrile seizures); serum sodium less than 138 mmol/L;[30] or severe infection associated with greatly impaired free-water excretion.

Ideal testing of this hypothesis would be done in a large randomised controlled trial of hypotonic versus isotonic saline in children with severe infections, stratified for types of infections. However, we think it would be unethical to include some infections, particularly encephalitis and meningitis, because there is already substantial experience of harm from hypotonic solutions and pathophysiological plausibility of the cause of such harm. Such infections also have a much higher risk than do other infections of cerebral oedema and adverse outcomes if hyponatraemia occurs.

An alternative approach, in hospitals in which hypotonic fluids at maintenance volumes are the routine standard of care, would be to change the policy such that isotonic saline at reduced infusion rates (60–70% of maintenance) becomes the standard iv fluid for seriously ill children. Although not as robust as a randomised control trial, this approach might allow for a detailed before-and-after analysis. Outcomes could include differences in the proportions of children who have neurological events associated with progressive falls in serum sodium. Assessment of harm could include differences in frequencies of severe hypernatraemia, or neurological complications associated with rapidly rising serum sodium.

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