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 mL/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.[5,6]

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Centre for International Child Health, Department of Paediatrics, University of Melbourne, Royal Children's Hospital, Parkville, Victoria, Australia (T Duke MD); **and Department of Paediatrics, College of Medicine, Blantyre, Malawi** (E M Molyneux FRCPCH)

Correspondence to: Dr Trevor Duke, Centre for International Child Health, Department of Paediatrics, University of Melbourne, Royal Children's Hospital, Flemington Road, Parkville, 3052, Victoria, Australia
(e-mail: Trevor.duke@rch.org.au)

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.[7] 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[8,9,10]
	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
	Increased right atrial pressure
Natriuretic peptide activity (ANP/BNP)	
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**

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.[1]

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,[9] during the later phases of illness there is a theoretical risk of hypernatraemia if isotonic saline is used. Diuresis and low urine osmolality 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;[10] 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.

these circumstances results in the excretion of hypertonic urine, the retention of free water, and the development of hyponatraemia.[4]

Despite clear and repeated warnings over the past few years,[5–7] the routine administration of 4% dextrose/0.18% saline remains standard practice in many paediatric units. This practice is based on formulas developed for calculating maintenance fluid and electrolytes in healthy children over 40 years ago and there seems little understanding of the potential risks associated with their use during acute illness.

A global change of clinical practice is required to prevent these needless deaths. This is a challenge that the RCPCH should face up to, together with the Medicines Control Agency and the National Patient Safety Agency. A useful first step would be to label bags of 4% dextrose/0.18% saline with the warning that severe hyponatraemia may be associated with its use.

S Playfor

Consultant Paediatric Intensivist, Royal Manchester Children's Hospital, Hospital Road, Pendlebury, Manchester M27 4HA, UK; Stephen.Playfor@CMMC.nhs.uk

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Thyroid screening in Down's syndrome: current patterns in the UK

Children and adults with Down's syndrome are at increased risk of developing thyroid dysfunction, and screening for thyroid dysfunction is recommended as part of their health surveillance.[1] Clinical history and examination are known to be unreliable indicators of thyroid dysfunction in Down's syndrome. Venous blood for thyroid stimulating hormone (TSH) assay remains the gold standard. Capillary blood spot on filter paper TSH has been proposed as a simpler and more convenient alternative screening method for hypothyroidism in these children.[2]

To establish current screening practices, we undertook a postal questionnaire of community paediatricians registered with the British Association for Community Child Health (BACCH). Community paediatricians are the group mostly likely to see children with Down's syndrome for health surveillance. Paediatricians were asked whether they routinely screened children with Down's syndrome for thyroid dysfunction. They were asked at what age of child they began screening, how often they screened, and which method they used.

The questionnaire response rate was 64% (209/325). All the paediatricians who returned completed questionnaires routinely looked after children with Down's syndrome. As expected, almost all of respondents, 93% (194/209), were screening routinely. Most paediatricians began screening before 5 years of age, and screened every two years (table 1). Venous blood TSH was the most frequently used method of screening (83%, 174/209). Only a small number have begun using capillary blood spot on filter paper TSH (7%, 15/209). A few paediatricians were relying on clinical suspicion alone. Those paediatricians not routinely screening for thyroid dysfunction, were either measuring TSH opportunistically or were undertaking biochemical screening only when symptoms or signs raised suspicion.

The Down's Syndrome Medical Interest Group (DSMIG) has recommended biochemical screening for thyroid dysfunction at least every two years after the first year of life.[1] Most paediatricians' practice is consistent with this recommendation. Capillary blood sampling has practical advantages over venous sampling, with regard to patient acceptability, particularly in adolescents with Down's syndrome and with regard to cost. There is growing evidence that capillary blood spot TSH is a reliable screening tool for thyroid dysfunction in children with Down's syndrome.[2,3] Capillary blood spot TSH may, in the future, come to replace venous TSH sampling in children with Down's syndrome.

S Varadkar, G Bineham, D Lessing

Hounslow & Spelthorne Community & Mental Health NHS Trust and West Middlesex University Hospital, Isleworth, UK

Correspondence to: Dr S Varadkar, Biochemistry, Endocrinology and Metabolism Unit, Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK; sophia@varadkar.co.uk

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Changes in serum sodium levels during treatment of hyperglycaemia

Carlotti *et al*[1] state that fluid and electrolyte management might contribute to the development of cerebral oedema in hyperglycaemia. There is a simple rule of thumb, formulated by Katz, which may help calculate water and electrolyte deficits and predict the changes in sodium levels which accompany changes in glucose levels,[2] namely that a decrease of 0.29 mmol/l in serum sodium may be expected for every 1.0 mmol/l increment in serum glucose.

This may be explained as follows: hyperglycaemia causes an osmotic movement of water out of the cells, which leads to hyponatraemia by dilution. Thus, at presentation, the patient is usually severely dehydrated intracellularly. However, the serum sodium is lower than would be expected because of this dilution of the extracellular fluid. When the patient is treated with insulin, glucose enters the cells, taking water with it, leading to a relative concentration of the extracellular fluid, and thereby a rise in serum sodium. This rise may be predicted and calculated using Katz's formula.[2]

Carlotti *et al* also comment on the report of Glaser *et al* that the chance of cerebral oedema during treatment is increased in children who present with high initial serum urea levels and when there is a lack of an increase in serum sodium levels during treatment.[3] This increased risk may be explained by the fact that the urea level rises in proportion to the degree of dehydration. Urea contributes to serum osmolality and if the fall in urea is not taken into account the serum osmolality may be allowed to drop too rapidly, thereby increasing the risk of cerebral oedema. Carlotti *et al* do not take this into account in their formula for calculation of osmolality. The calculation of serum osmolality as twice the sum of sodium and potassium plus the urea and glucose levels (all in mmol/l) corresponds better with the formally measured osmolality.[4]

By treating hyperglycaemia using hypotonic solutions or glucose alone, the serum osmolality will fall rapidly and thereby increase the risk of cerebral oedema.

Serum osmolality must be monitored frequently, either by direct measurement or calculation from the sodium, potassium,

Table 1—Results of completed questionnaires (n=209)

Age screening initiated (y)	No. (%)	Screening frequency	No. (%)	Screening method	No. (%)
≤5	167 (80%)	Yearly	35 (17%)	Venous TSH	174 (83%)
5–10	28 (13.5%)	Two yearly	115 (55%)	Capillary blood spot TSH	15 (7%)
>10	1 (0.5%)	Three yearly	20 (10%)	Both venous and capillary blood spot TSH	4 (2%)
No data	13 (6%)	Opportunistically	17 (8%)	Clinical history and examination only	3 (1.5%)
		Other	10 (4.5%)	No data	13 (6.5%)
		No data	12 (5.5%)		

TSH, thyroid stimulating hormone.

TABLE 2. Electrolyte-Free Water in Parenteral Fluids

Intravenous Fluid	Sodium (mEq/L)	Osmolality (mOsm/kg/H_2O)	% Electrolyte-Free Water*
5% Dextrose in water	0	252	100
0.2% Sodium chloride in 5% dextrose in water	34	321	78
0.45% Sodium chloride in 5% dextrose in water	77	406	50
Lactated Ringer's	130	273	16
5% Dextrose Lactated Ringer's	130	525	16
0.9% Sodium chloride in 5% dextrose in water	154	560	0

* Based on a sodium plus potassium concentration in the aqueous phase of plasma of 154 mEq/L, assuming that plasma is 93% water with a serum sodium of 140 mEq/L and a potassium concentration of 4 mEq/L.

operative setting in previously healthy children who underwent minor surgery. Arieff et al[3] reported on 16 previously healthy children who died or experienced permanent neurologic damage as a result of hyponatremic encephalopathy soon after receiving hypotonic fluids after minor surgical procedures or for the treatment of common childhood infections. McJunkin et al[5] and Moritz and Ayus[6] noted that the major factor that results in neurologic deterioration in children with La Crosse encephalitis was mild hyponatremia developing after the administration of hypotonic fluid. Halberthal et al[4] reported on 23 children, without an underlying disease that impaired water handling, who developed acute symptomatic hyponatremia after the administration of hypotonic fluids. Hyponatremia in these cases seemed to be attributable to a combination of hypotonic fluid administration and ADH excess. The above authors and others[30,35] have cautioned against the routine use of hypotonic maintenance fluids in children.

Children are at particularly high risk for developing symptomatic hyponatremia as they develop hyponatremic encephalopathy at higher serum sodium concentrations than adults and have a poor prognosis if timely therapy is not instituted. This seems to be attributable to the higher brain-to-skull size ratio in children, which leaves less room for brain expansion.[3,36] Children achieve adult brain size by 6 years of age, whereas full skull size is not achieved until 16 years of age. Female adolescents may also be at increased risk of developing hyponatremic encephalopathy, as women of reproductive age are >30 times more likely to develop hyponatremic encephalopathy than are men, as a result of diminished ability to adapt to hyponatremia by decreasing brain volume.[36,37]

Hyponatremic encephalopathy can be difficult to recognize in children, as the symptoms can be variable and do not correlate with either the serum sodium concentration or the rapidity of development of hyponatremia.[3] The most consistent symptoms of hyponatremia are headache, nausea, vomiting, emesis, and weakness. Advanced symptoms are signs of cerebral herniation, with seizures, respiratory arrest, noncardiogenic pulmonary edema,[38,39] dilated pupils, and decorticate posturing.[3] Failure to recognize hyponatremic encephalopathy and initiate appropriate therapy will result in a poor neurologic outcome.[3,29]

WHY ISOTONIC MAINTENANCE PARENTERAL FLUIDS SHOULD BE USED

The administration of isotonic maintenance fluids is the most important prophylactic measure that can be taken to prevent the development of hyponatremia in children who are receiving parenteral fluids. Commonly used intravenous fluids have a significant amount of free water that can contribute to hyponatremia (Table 2); therefore, they should be used with caution in maintenance fluids, to mix intravenous medications or to keep a vein open. Even isotonic saline can lead to hyponatremia if excessive fluid is administered in the presence of a fixed urine osmolality with impaired urinary dilution.[40] If an isotonic solution of 300 mOsm/kg/H_2O is administered in a state of excess vasopressin, such as SIADH or the postoperative state, for which the urine osmolality may be fixed at 500 mOsm/kg/H_2O, then a natriuresis that will result in the generation and retention of free water and the development of hyponatremia will ensue. An isotonic solution will have approximately 154 mEq/L monovalent cations, sodium plus potassium, as the average concentration of sodium plus potassium in the aqueous phase of plasma is 154 mEq/L. Although no 1 fluid rate or composition will be appropriate for all children, isotonic saline in 5% dextrose in water seems to be the safest fluid composition in most hospitalized patients. If potassium chloride is to be added to the parenteral fluids, then the sodium concentration can be lowered proportionally to maintain isotonicity. Lactated ringers with 20 mEq/L potassium chloride in 5% dextrose in water would also be an isotonic fluid. Physicians must assess children carefully to choose the most appropriate parenteral fluid rate and composition before initiating therapy. The maintenance fluid requirements of the term and preterm neonate may differ from the older child as a result of unique physiologic issues, and our recommendations do not extend to this group of patients. Children with ongoing free water losses or a free water deficit will require a more hypotonic fluid. In children with illnesses that can lead to fluid overload, such as nephrosis, cirrhosis, congestive heart failure, and glomerulonephritis, both sodium and fluid restriction is of paramount importance to avoid worsening fluid overload and the development of hyponatremia. Hospitalized children who are receiving parenteral fluid therapy should be considered at risk for developing hyponatremia and monitored closely

through daily weights, fluid balance, blood pressure, observing for signs of edema, and monitoring the serum sodium concentration. Isotonic saline seems to be the preferred fluid for administration to hospitalized patients, as they are at high risk for developing hyponatremia as a result of factors that lead to ADH excess.

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"Human progress can be compared to a storm-lashed sea; men must commit a thousand errors to arrive at the truth."

—Arj Turgot (1751)

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