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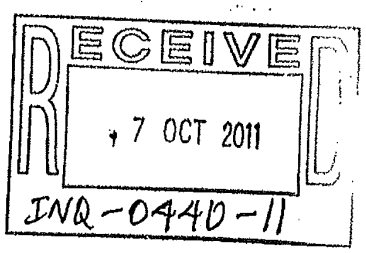

Mrs Bernie Conlon
Secretary to the Inquiry
Arthur House
41 Arthur Street
Belfast
BT1 4GB

Dear Madam,

RE: INQUIRY INTO HYPONATRAEMIA RELATED DEATHS

I refer to your letter of 29th September 2011 and now enclose the following documents, which are referred to in Dr Taylor's statement, for your attention:-

1) Cansick J, et al. A fatal case of cerebral oedema with hyponatraemia and massive polyuria after renal transplantation. Pediatr Nephrol (2009) 24:1231-4)
2) O'Flynn PE and Milford CA. Fasting in children for day case surgery. Annals of the Royal College of Surgeons of England (1989); 71:218-9
3) Thomas DKM. Hypoglycaemia in children before operation: Its incidence and prevention. BR J Anaesth 1974;46:66-8
4) Maze A, Samuels SI. Hypoglycaemia-induced seizures in an infant during anaesthesia. Anesthesiology 1980;52:77-8
5) Jenson BH, Wernberg M, Ansersen M. Pre-operative starvation and blood glucose concentrations in children undergoing in-patient and out-patient anaesthela. Br Anaesth 1982;54:1071-4
6) The Association of Anaesthetists of GB & Ireland, Monitoring Standards
7) Hatch and Sumner, Paediatric Anaesthesia 1999. P380 "superior vena cava pressures.... In the range of 10-15 mmHg"
8) Mathur A, et al. Hypotonic vs isotonic saline solutions for intrevenous fluid management of acute infections. Cochrane Satabase Syst Rev. 2004;(2):CD004169)
9) Neville KA, et al. Isotonic is better than hypotonic saline for intravenous rehydration of children with gastroenteritis: a prospective randomised study. Arch Dis Child. 2006 Mar;91(3):226-32. Epub 2005 Dec 13)
10) Choong K, et al. Hyptonic versus isotonic saline in hospitalised children:a systematic review. Arch Dis Child. 2006 Oct;91(10):828-35. Epub 2006 Jun 5

11) Yung M and Keeley S. Randomised controlled trial of intravenous maintenance fluids. J Paediatr Child Health. 2009 Jan-Feb;45(1-2):9-14 Epub 2007 Nov 2
12) Textbook of Pediatric Intensive Care, Rogers M 1987 p 656
13) Textbook of Pediatric Intensive Care, Rogers M 1987 p 627

Yours faithfully

JRBolton

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Attachments appended to WS-008-3 Originals with Statement.

Dr. R. Taylor WS008/4 Revised answer to Q54a,b,c,d.

54 Answer to Question 37(a) at p.18:

"I cannot remember who [I worked with to determine the cause of Adam's death]. It would have been with the nephrologists and anaesthetists in PICU."

(a) State whether you were present during Adam's autopsy and if so: (i) for how long you were present; (ii) the circumstances in which you came to be there; (iii) exactly what was discussed between yourself and Dr. Alison Armour, the pathologist.

I do not remember being present at his autopsy.

(b) State whether it was you who filled in Adam's autopsy request form (copy attached, Ref: INQ-0343-11). If not, state who filled in this document.

Yes I filled in the Autopsy request form.

(c) If you did fill in the autopsy request form, explain what you meant by *"osmotic disequilibrium syndrome"*. State if you still consider this to have been a possible cause of Adam's death. If so, explain your reasons why. If not, explain why.

The words "osmotic dysequilibrium syndrome" were Dr Webb's (058-035-140).

(d) Explain what you meant by Adam being *"a somewhat bizarre case of a child undergoing renal transplantation"* and explain the basis on which you formed that view.

I considered it an odd case in that I could not explain the findings on the basis of the Clinical Presentation I recorded on the Autopsy Request Form.

Robert Taylor 3/10/11

Pediatr Nephrol (2009) 24:1231–1234
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BRIEF REPORT

A fatal case of cerebral oedema with hyponatraemia and massive polyuria after renal transplantation

Janette Cansick · Lesley Rees · Geoff Koffman · William Van't Hoff · Detlef Bockenhauer

Received: 9 October 2008 / Revised: 25 November 2008 / Accepted: 25 November 2008 / Published online: 20 January 2009

Abstract We report the case of a child who died from severe cerebral oedema in the context of hyponatraemia and extreme polyuria immediately after renal transplantation. The patient was treated according to a standard post-transplantation protocol, receiving 0.45% saline solution for urine output replacement. The case highlights the dangers of massive fluid therapy in the context of polyuria and, therefore, the need for intensive monitoring.

Keywords Hyponatraemia · Seizure · Cerebral oedema · Kidney transplant · Hypotonic fluid · Polyuria · Salt wasting

Introduction

We report the case of an 11-year-old boy, who had extreme polyuria shortly after live-related renal transplantation. He developed seizures associated with a serum sodium concentration of 126 mmol/l and his condition rapidly progressed to tonsillar herniation and death. We detail the sequence of events, discuss potential causes of this tragic occurrence and describe how we changed our post-transplantation care protocol to enable earlier detection of such abnormalities.

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Case report

An 11-year-old boy weighing 30.3 kg was admitted for a pre-emptive live-related transplant. He had suffered meningococcal septicaemia at the age of 34 months, complicated at that time by severe neurological dysfunction, with coma, seizures and peripheral vascular involvement with skin and bone loss. He had been undergoing short-term dialysis for nearly 4 weeks, but his renal function [glomerular filtration rate (GFR) by the chromium-51–ethylene diamine tetra-acetic acid (Cr^{51}-EDTA) method was 37 ml/min per 1.73 m^2 body surface area at 3 years] had recovered sufficiently to be managed conservatively. He was left with a minor seizure disorder treated with sodium valproate at the time of transplantation. Electroencephalography (EEG) showed discharges over the right temporoparietal area, and a cerebral magnetic resonance imaging (MRI) scan when he was aged 4.5 years showed mild cerebellar atrophy, with normal ventricular size. He attended mainstream school and had learning support.

His renal function deteriorated from the age of 10 years, with his serum creatinine rising from 1.6 mg/dl to 3.8 mg/dl (145–330 μmol/l), so work-up was commenced for renal transplantation. He was polyuric, with a daily urine output of 3–4 l.

He underwent a live-related renal transplantation, with 0,1,1 mismatch, from his mother. He was given 0.25 mg/kg tacrolimus and prednisolone 600 mg/m^2 before theatre and had a urethral catheter placed after being anaesthetised. The operation was uneventful; the patient had normal vessel

anatomy. There was good blood flow and immediate urine output. The cold-ischaemia time was 30 min, and anastomosis time was 25 min. Intraoperatively, his systolic blood pressure (SBP) was 100-130 mmHg and central venous pressure (CVP) was 10-15 cmH_2O. He was given a total of 2,200 ml of fluid during the procedure [1,000 ml Hartmann's solution (near isotonic sodium lactate) and 1,200 ml 4.5% albumin] and 60 mg furosemide. A dopamine infusion (3 μg/kg per minute) and a patient-controlled morphine infusion were commenced. He received routine immunosuppression with tacrolimus, azathioprine and prednisolone.

Immediately postoperatively, he was warm and well perfused, with a core–toe temperature gap of 2.4°C. He had a normal heart rate (HR; 90-105 beats/min) but was hypertensive (SBP 130-140 mmHg). His CVP was 8-11 cmH_2O. He regained consciousness fully and was extubated, with saturations of 98–100% in room air, respiratory rate 25/min. He had mixed metabolic and respiratory acidosis; pH 7.25, with a carbon dioxide partial pressure (pCO_2) of 42 mmHg (5.6 kPa) (venous gas). His initial postoperative serum sodium level was 141 mmol/l (see Table 1). A bedside fluid balance sheet was established, which included the volume of urine in the catheter bag (1,180 ml) but not the fluids given in theatre (2,200 ml) or the undocumented losses (urine lost during anastomosis of the ureter to the bladder, and blood losses). These losses were retrospectively estimated by the surgeon to be 300–500 ml.

The patient developed massive polyuria almost immediately after anastomosis, passing urine up to 58 ml/kg per hour. He was treated according to the unit's protocol, with replacement of insensible losses of 400 ml/m^2 per day and of the previous hour's urine volume with the same volume of 0.45% saline solution, alternating with 0.45% saline solution/2.5% dextrose. Two hours postoperatively he developed signs of poor peripheral perfusion, with a core–toe temperature gap of 6°C; HR was 90–105 beats/min, and SBP was 130–150 mmHg. It was concluded that he had a fluid deficit, and he was given an extra 1,449 ml 0.9% saline solution over 2 h. At 4 h he had a generalised tonic–clonic seizure, which was terminated immediately following administration of 0.1 mg/kg lorazepam. Blood glucose measured with a stix was 8.6 mmol/l, and central venous gas showed uncompensated metabolic acidosis, with a pH of 7.1. He was hyponatraemic (126 mmol/l), initially thought to be an artefact but confirmed on a repeat sample (121 mmol/l). At 5 h he had a further generalised tonic–clonic seizure, which again responded to lorazepam, but at that time his pupils were fixed and dilated. He was

Table 1 Results of blood and urine tests and fluid balance

Parameter	Time after anastomosis							Normal range	Unit
	Preoperative	Postoperative	1 h	2 h	3 h	4 h Seizure	5 h Seizure		
Sodium	140	141				126	121	133–146	mmol/l
Total CO_2	22	18				15	17	20–30	mmol/l
Urea	97 (34.5)	76 (27.2)				38 (13.7)	33 (11.7)	7–17 (2.5–6.0)	mg/dl (mmol per litre)
Creatinine	6.0 (528)	4.3 (379)				2.0 (178)	1.6 (143)	0.4–0.9 (35–80)	mg/dl (μmol/l)
Total calcium	11.3 (2.81)	9.7 (2.42)				6.8 (1.7)	6.5 (1.61)	8.8–10.7 (2.19–2.66)	mg/dl (mmol/l)
Magnesium	1.9 (0.8)	2.0 (0.83)				0.9 (0.36)	0.7 (0.28)	1.7–2.3 (0.7–0.95)	mg/dl (mmol/l)
Albumin	42	51				41	37	37–56	g/l
Glucose		202 (11.2)				175 (9.7)		63–99 (3.5–5.5)	mg/dl (mmol/l)
Osmolality								270–285	mosmol/kg
Haemoglobin	11.6	9.3				8.6		11.5–15.5	g/dl
Urine									
Sodium	112								mmol/l
Osmolality									mosmol/kg
Fluids									
In		2,200[a]	1,303	1,485	2,383	2,591	1,898		ml
Out[b]		1,240[c]	1,170	1,760	1,740	1,620	1,150		ml
Cumulative Balance		+960	+1,093	+818	+1,461	+2,432	+3,180		ml

[a] Total amount of fluid given intra-operatively
[b] Except for 200 ml from the wound drain, all output was urine
[c] Immediate postoperative output did not include intra-operative losses, which were not documented (see text)

intubated and ventilated; a computed tomography scan revealed severe cerebral oedema, with uncal and tonsillar herniation; he was diagnosed as being brainstem dead the following morning. Using hypertonic (3%) saline solution, we achieved normonatraemia after 8 h to allow organ donation.

Discussion

Our case highlights the dangers of massive fluid therapy and biochemical disturbances in the face of extreme polyuria. There are obvious questions regarding the aetiology of the patient's seizures, hyponatraemia and polyuria. Moreover, considering that the patient was treated according to a standard protocol, used for over 15 years in more than 200 paediatric renal transplantations, we describe how the protocol was changed in order to prevent a similar tragedy from occurring.

What caused the patient's seizures and subsequent tonsillar herniation?

Seizures are a recognised complication after renal transplantation, with a frequency of up to 24%, with potential causes including fluid overload, and corticosteroid and calcineurin-inhibitor therapy [1–3]. Our patient was known to have had seizures previously, indicating that he had a lowered seizure threshold which was reduced further by the hypocalcaemia and hypomagnesaemia after transplantation (Table 1). The first seizure in our patient occurred when the serum sodium level was 126 mmol/l, a level not usually associated with seizure activity. However, hypo-osmolality was likely to have been the key aetiological factor, as the drop in serum sodium level was compounded by the rapid fall in urea after transplantation. His calculated serum osmolality dropped by approximately 80 mosmol/kg between transplantation and first seizure.

Why was the patient polyuric?

The massive diuresis after anastomosis (58 ml/kg per hour) was extremely unusual. There is one report of an adult with diuresis of 25–50 ml/kg per hour after having received a live-unrelated renal transplant, who was also given fluid replacement with 0.45% saline solution and who developed hyponatraemia [lowest serum sodium (Na) concentration 113 mmol/l] and multiple generalised tonic–clonic seizures [4].

Our patient had 3–4 l/day (4–5 ml/kg per hour) native urine output, and the massive fluid losses after transplantation would have included a proportion from the native kidneys. However, excretion of ~1,800 ml/h requires a GFR of at least 30 ml/min, whilst the estimated GFR in our patient was 6 ml/min, uncorrected for surface area. Therefore, the majority of urine must have derived from the graft. Glucose given in the replacement fluid caused mild hyperglycaemia, with levels of 10–11 mmol/l, leading to osmotic diuresis. However, this leads to free water losses and hypernatraemia and is, thus, probably less relevant here.

Why did the patient become hyponatraemic?

The patient's venous sodium level had dropped from 141 mmol/l post-operatively to 121 mmol/l 5 h later. Hyponatraemia is due to either a deficiency in salt or an excess of water.

A separate quantitative analysis of water and salt balance, also called tonicity balance, can help identify the pathophysiology of hyponatraemia [5]. From the beginning of surgery till his death, the patient was given 11.8 l and lost 8.6 l (see Table 1), a net positive balance for water of 3.2 l. An expansion of his total body water (estimated at 20 l or 65% of body weight) by this amount is consistent with the observed dilution of his serum sodium from 141 mmol/l to 121 mmol/l ($141 \times 20/23.2 = 121.6$). Based on this first part of the tonicity balance, excess fluid accounted for the hyponatraemia. This fits also with the observed decrease of albumin and haemoglobin in the blood (see Table 1). However, in order to retain the extra 3.2 l as free water, he must have been in equal sodium balance, i.e. the amount of sodium lost in the urine must have been equal to the sodium received. Whilst the urinary sodium was not measured, the amount received can be calculated from the fluids administered, and it totalled 1,140 mmol. An excretion of 1,140 mmol sodium in 8.6 l of urine equates to 133 mmol/l and represents 20% of sodium filtered during that time (assuming a GFR of 100 ml/min), indicating sodium wasting. This compares to reports of fractional sodium excretion (FE_{Na}) as high as 46% in deceased-donor renal allografts on the day of transplantation [6].

Why did the patient have sodium wasting?

Sodium wasting is likely to have been due to hypoxic–ischaemic injury to the graft. The high FE_{Na} reported in deceased-donor allografts was associated with ischaemic changes on biopsy [6]. In another study, hyponatraemia was seen in 88 of 125 adult recipients, also associated with an increased FE_{Na} [7]. The dramatic postoperative decrease of serum calcium and magnesium concentrations (Table 1), which clearly exceeded the 16% dilution explained by the fluid balance, also suggests tubular dysfunction.

Sodium wasting can also be an appropriate physiological response of the kidney to volume overload, but it should not lead to hyponatraemia, as water can be excreted

alongside. However, other factors could have led to water retention, such as stress and morphine, recognised non-osmotic stimuli for antidiuretic hormone [8], or furosemide, which impairs urinary dilution.

How should a polyuric patient be treated?

For a patient with gross polyuria (> 10 ml/kg per hour) we suggest giving a fixed intake of 10 ml/kg per hour, with frequent (two-hourly) clinical and biochemical assessments that include blood pressure, peripheral perfusion, CVP, and serum and urine sodium and osmolality, to guide further replacement. We use 0.45% saline solution, based on our subsequent experience with typical post-transplantation urinary sodium concentrations of approximately 80 mmol/l. Any extra fluid for perceived volume depletion must be given in isotonic form. We use a glucose-containing solution at a steady rate for replacement of insensible losses, but fluids given for urine output replacement and boluses are glucose-free.

Conclusion

Our patient developed seizures and tonsillar herniation due to hypo-osmolality associated with the administration of large volumes of hypotonic intravenous fluids in the context of extreme polyuria. Other factors, such as his previous brain injury, might have contributed to the fatal outcome. Regardless, the case highlights the importance of close clinical and biochemical monitoring after transplantation, especially in the context of polyuria. Although, in this case, the rapidity of events suggests that these measures might not have prevented death, we hope that lessons from this case will help to modify practice and prevent future tragedies.

References

1. Awan AQ, Lewis MA, Postlethwaite RJ, Webb NJ (1999) Seizures following renal transplantation in childhood. Pediatr Nephrol 13:275–277
2. McEnery PT, Nathan J, Bates SR, Daniels SR (1989) Convulsions in children undergoing renal transplantation. J Pediatr 115:532–536
3. Qvist E, Pihko H, Fagerudd P, Valanne L, Lamminranta S, Karikoski J, Sainio K, Ronnholm K, Jalanko H, Holmberg C (2002) Neurodevelopmental outcome in high-risk patients after renal transplantation in early childhood. Pediatr Transplant 6:53–62
4. Montas SM, Moyer A, Al-Holou WN, Pelletier SJ, Punch JD, Sung RS, Englesbe MJ (2006) More is not always better: a case postrenal transplant large volume diuresis, hyponatremia, and postoperative seizure. Transpl Int 19:85–86
5. Carlotti AP, Bohn D, Mallie JP, Halperin ML (2001) Tonicity balance, and not electrolyte-free water calculations, more accurately guides therapy for acute changes in natremia. Intensive Care Med 27:921–924
6. Kwon O, Corrigan G, Myers BD, Sibley R, Scandling JD, Dafoe D, Alfrey E, Nelson WJ (1999) Sodium reabsorption and distribution of Na^+/K^+-ATPase during postischemic injury to the renal allograft. Kidney Int 55:963–975
7. Higgins R, Ramaiyan K, Dasgupta T, Kanji H, Fletcher S, Lam F, Kashi H (2004) Hyponatraemia and hyperkalaemia are more frequent in renal transplant recipients treated with tacrolimus than with cyclosporin. Further evidence for differences between cyclosporin and tacrolimus nephrotoxicities. Nephrol Dial Transplant 19:444–450
8. Robertson G (2008) Thirst and vasopressin. In: Alpern R, Hebert S (eds) The kidney. Raven Press, New York, pp 1123–1142

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Fasting in children for day case surgery

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Key words: PREOPERATIVE; HYPOGLYCAEMIA; CHILDREN; DAY CASE

Summary

Thirty-four children admitted for day case surgery were studied to determine the period of preoperative fasting and blood sugar concentrations at the time of induction of anaesthesia.

Of these, 88% fasted for 12 h or more, 20% fasted for 16 h or more. Three were found to be hypoglycaemic.

The introduction of routine 'mid-day' operating lists for paediatric day case surgery is suggested as a method of reducing the period of fasting and risk of hypoglycaemia.

Introduction

Day case surgery is increasing. Children requiring short procedures such as insertion of grommets are particularly suitable for this as they recover rapidly and there are few postoperative complications.

Since the early 1970s several studies have been undertaken to determine the optimal period of preoperative fasting. Anaesthetists generally feel that adequate preoperative fasting is essential for gastric emptying and to minimise the risk of regurgitation of stomach contents at the time of induction of anaesthesia *(1)*. A period of 4–6 h is accepted as adequate. However, a number of authors have noted that a minority of young children become hypoglycaemic by the time of induction of anaesthesia *(2)*. Hypoglycaemia reduces cerebral tolerance to hypoxaemia and hypotension. Young children may not tolerate fasting as well as adults as they have a relatively higher obligative glucose requirement *(3)*. Thomas *(4)* found 28% of children less than 4 years of age and 15.5 kg were severely hypoglycaemic at the time of induction of anaesthesia. This finding has not generally been confirmed.

The aim of this study is to determine the actual period of preoperative fasting in children admitted to our day care unit and to assess their blood sugar levels at the time of induction of anaesthesia.

Routinely, all patients to be admitted to the day care unit are advised to fast from 12 midnight on the eve of admission, until after the operation.

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Patients and methods

A total of 34 consecutive children admitted to the day care unit aged between 11 months and 99 months for insertion of grommets were studied. The age and weight of each child was recorded preoperatively, together with the *actual* period of fasting. This was assessed by enquiring from a parent the time that food or drink was last taken and recording the time of induction of anaesthesia. After induction, blood was taken from the antecubital vein for laboratory analysis of glucose concentration by the glucose oxidase method. Patients had no known illness (except surgical indication) and were suitable for day case surgery in accordance with the guidelines of the Royal College of Surgeons (1985).

Each had grommets inserted, a procedure which takes approximately 10 min.

Results

The age, weight, period of fasting and blood sugar level at the time of induction of anaesthesia, together with the mean, standard deviation and range for each is recorded in Table I.

Two aspects of these results were further analysed and are reported below.

PERIOD OF PREOPERATIVE FASTING

The period of preoperative fasting was in all cases much longer than that required for gastric emptying. The mean preoperative fasting time was 14 h (SD=1.9 h); 88% of children fasted ≥12 h, 20% fasted ≥16 h.

BLOOD SUGAR CONCENTRATIONS (AT INDUCTION)

In three of 34 cases (8.8%) the blood sugar level was found to be less than 3.0 mmol/l (2.3, 2.7 and 2.9 mmol/l).

TABLE I *Summary of results*

Parameter	*Mean*	*SD*	*Range*
Age (months)	59	24	(11–99)
Weight (kg)	18.4	4.25	(10.8–25.2)
Blood sugar (mmol/l)	4.16	0.63	(2.3–5.4)
Fasting (h)	14	1.88	(9.5–17)

No child showed any clinical evidence of hypoglycaemia. All other patients had levels in the normal laboratory range (3.3–5.6 mmol/l).

The relationship between age and blood sugar, weight and blood sugar, and fasting time and blood sugar was assessed. No simple indicator could be found to predict which cases would have a low blood sugar at the time of induction.

Discussion

FASTING PERIOD

The most remarkable result of this study was the prolonged period of preoperative fasting to which these children were subjected. This arose partly because 'standard' advice was given to parents (namely 'Nothing to eat or drink from midnight') and failing to take into account the age and daily routines of these children.

Since many young children eat their last meal of the day in the early evening (say 7 pm) and then go to bed, they will already have starved for 5 h before midnight. Our day case operating sessions start at 8.30 am, therefore the first child on the list will have fasted for 13.5 h. Children late on the list will have fasted for longer periods.

The period of fasting in this study was recorded until the time of induction of anaesthesia. There is, therefore, a further period of fasting during the operation and until recovery from the anaesthetic permits an oral intake. During the operative period a rise in the blood sugar concentration is typical, probably a stress related adrenergic response. However, a fall in blood sugar concentration has been documented in some children. The period of time between induction of anaesthesia and first oral fluids is not usually prolonged—typically 1–3 h in our experience. Payne and Ireland *(5)* measured a mean of 3 h and a range of 1–7 h in their study.

HYPOGLYCAEMIA

When comparing the various studies on this subject one must look at the definition of hypoglycaemia used. Various levels have been accepted by different authors.

Allison *(3)* suggested a grading system—less than 3.3 mmol/l=mild; less than 2.8 mmol/l=moderate and less than 2.2 mmol/l=severe. This system is helpful as some children may be symptomatic at levels above 2.2 mmol/l *(6)*.

In this study we found one case of mild and two cases of moderate hypoglycaemia. In common with other authors except Thomas *(4)* and Welborn *et al. (7)* we could find no simple predicting factor in terms of age, weight or period of starvation. In both the Thomas and Welborn *et al.* studies the children were planned for afternoon surgery. Welborn *et al.* found two children who became hypoglycaemic after a period of 17 and 19 h fasting respectively. All other studies have been based on morning operating sessions and a diurnal variation in glucose utilisation may account for the difference found.

Hypoglycaemia during anaesthesia is not without risk, and case reports of hypoglycaemia-induced seizures have been recorded *(8)*.

MANAGEMENT

Various methods have been suggested to satisfy the requirement of preoperative fasting and to avoid the risk of hypoglycaemia. Many authors have suggested feeding either milk or glucose solutions in proportion to the child's weight 4 h preoperatively. On a day case basis this would involve waking a child at 4.30 am to feed. This is naturally disruptive and a substantial number of children, 29% in one study *(9)*, refused the feed in the middle of the night. In those children who accept a feed at this time 4–6 h preoperatively there is a significantly raised blood sugar concentration only in those *over* 4 years of age *(9)*. Some authors have suggested the use of glucose solutions intravenously during the anaesthetic. There is a significant rise in blood sugar concentrations in these cases.

Management of these children in the preoperative period remains contentious with widely differing advice being given in the various centres referred to in this account.

Overnight fasting leads to excessively long periods of abstinence which, if not hazardous, are undesirable. Feeding in the middle of the night is disruptive and may be refused.

One possible solution would be the introduction of 'mid-day' lists for day case surgery starting at 11 am and ending at 1 pm. This would allow a light breakfast to be taken at 7 am with little inconvenience. No child would fast preoperatively for more than 6 h, reducing the risk of hypoglycaemia and leaving ample time for postoperative recovery.

References

1 Graham IFM. Pre-operative starvation and plasma glucose concentrations in children undergoing out-patient anaesthesia. Br J Anaesth 1979;51:161–4.

2 Bevan JC, Burn MC. Acid–base and glucose levels of pediatric cases at induction of anaesthesia: the effects of preoperative starvation and feeding. Proceedings of Anaesthetic Research Society 1973:115.

3 Allison GW, Cater JI, Gray IG, Staziker AC. Pre-operative starvation in children. Anaesthesia 1982;37:274–7.

4 Thomas DKM. Hypoglycaemia in children before operation: Its incidence and prevention. Br J Anaesth 1974;46:66–8.

5 Payne K, Ireland P. Plasma glucose levels in the perioperative period in children. Anaesthesia 1984;39:868–72.

6 Pagliara AS, Haymond IE, Kipnis DM. Hypoglycaemia in children and infants. J Pediatr 1973;82:365–9.

7 Welborn LG, McGill WA, Hannallah RA, Nisselsen CL, Ruttiman UE, Hicks JM. Perioperative blood glucose concentrations in pediatric out-patients. Anesthesiology 1986;65:543–7.

8 Maze A, Samuels SI. Hypoglycaemia-induced seizures in an infant during anaesthesia. Anesthesiology 1980;52:77–8.

9 Jensen BH, Wernberg M, Andersen M. Pre-operative starvation and blood glucose concentrations in children undergoing in-patient and out-patient anaesthesia. Br J Anaesth 1982;54:1071–4.

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Br. J. Anaesth. (1974), 46, 66

HYPOGLYCAEMIA IN CHILDREN BEFORE OPERATION: ITS INCIDENCE AND PREVENTION

D. K. M. THOMAS

SUMMARY

Two groups of children, comparable in age and weight were studied. The first, the Starvation Group (SG), underwent normal preoperative starvation. The second, the Milk Group (MG), received milk orally 4 hours prior to operation. At operation the mean blood glucose concentration was 53.3 mg/100 ml in the SG and 66.4 mg/100 ml in the MG. The difference between the two groups was statistically significant. Hypoglycaemia occurred only in those children in the SG who were less than 47 months of age and 15.5 kg body weight.

The mean normal fasting blood glucose concentration at birth is 54 mg/100 ml with a range of 28–96 mg/100 ml (Bowie, Mulligan and Schwartz, 1963). The concentration increases in childhood to a mean of 77 mg/100 ml at 2 years and 92 mg/100 ml at 15 years (Mayer, 1951).

After the third day of life hypoglycaemia is defined as a blood glucose concentration of less than 40 mg/100 ml (Cornblath and Schwartz, 1966; Habbick, McNeish and Stephenson, 1971). This level has been accepted for this study although other authors have suggested higher limits of 50 mg/100 ml (Ehrlich, 1971) and 60 mg/100 ml (Bowie, Mulligan and Schwartz, 1963). Hypoglycaemia is provoked by fasting, although it is not an inevitable consequence of withholding food. The body conserves glucose by a decrease in the concentration of circulating insulin and an increase in the concentration of growth hormone (Glick et al., 1965). The concentrations of circulating growth hormone, glucagon, cortisol and adrenaline are increased by a fall in blood glucose concentration to hypoglycaemic levels (Marks and Rose, 1965). Hypoglycaemia is not a disease but is a clinical sign (Conn and Seltzer, 1955). In a study of blood glucose concentrations in children prior to surgery it was found that 10% of the children had a blood glucose concentration in the hypoglycaemic range (Watson, 1972). Blood glucose concentrations less than 60 mg/100 ml were found in 30% of starved children at the time of induction of anaesthesia (Bevan and Burn, 1973).

This study was designed to compare blood glucose levels in two groups of children and to assess the influence of preoperative feeding on the frequency of hypoglycaemia.

METHOD

The children were all admitted to the same ward the day before operation. The operations occurred between 1400 and 1600 hours and were for correction of strabismus. After an overnight fast they received a bowl of cereal and a drink of milk at 0600 hours.

The children were in the weight range 9–36 kg and were aged between 19 and 166 months. They were divided into two groups. The first group (30) received no further food prior to operation. The second group (29) were given a drink of milk, 3 ml/kg body weight, up to a maximum of 300 ml, 4 hours before operation.

All the children were given trimeprazine 1.7 mg/kg body weight (maximum 30 mg) orally 4 hours before operation. Morphine 0.25 mg/kg and atropine 0.02 mg/kg were given by intramuscular injection 1 hour before operation. Anaesthesia was induced with thiopentone 4 mg/kg followed by pancuronium 0.13 mg/kg given intravenously. The lungs were ventilated with oxygen and nitrous oxide from a facepiece until an oral endotracheal tube could be passed. Ventilation was continued manually with oxygen 30% in nitrous oxide using a modified T-piece system. A Ryle's tube was passed into the stomach and the contents were aspirated. After removal of the tube a mouth pack was inserted. Two minutes after endotracheal intubation 2 ml of blood were taken from the long saphenous vein and stored in a fluoride bottle. The blood glucose concentrations were measured by the autoanalyser method of

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... Dawson and Marks (1968). This method ... accuracy of ±5%.

... the end of the operation the neuromuscular ... was reversed with atropine (0.02 mg/kg) and ...igmine (0.07 mg/kg) injected intravenously. ... mouth pack was removed and the children were ...ated while lying on their sides.

... was no vomiting or regurgitation in either ... during induction of anaesthesia, operation or ...very.

... volume of the aspirated stomach contents ...asured and the pH measured by a dipstick ...od.

RESULTS

... I and II show the ages and weights of the ...ren. There was no significant difference between ...o groups.

... SG the mean blood glucose concentration ...3.3 mg/100 ml (SD 16.1). The MG had a ... blood glucose concentration of 66.4 mg/100 ml ...2.6) (table III). Using the Student *t*-test the ...ence between the means of the two groups was ...ficant (P<0.0005). 15.2% of the SG children ...ome of the MG children were hypoglycaemic ...blood glucose concentration less than 40 mg/ ...ml). The difference was significant (P=0.05). ...hypoglycaemia was observed only in the ...der and smaller children in the SG, those older ...47 months and weighing more than 15.5 kg ...e excluded from further analysis (table IV). The ...ger children in the SG had a mean blood glu- ...e concentration of 46.4 mg/100 ml (SD 16.5). ...mean for the MG was 60.0 mg/100 ml ...0.2) (table V). The difference between the two ...ups is significant (P<0.0005). 28% of the SG ...dren were hypoglycaemic (table VI).

... amount of stomach contents aspirated did ...exceed 15 ml in any child. The mean pH of the ...ach contents in the SG was 2.9 and in the ... (table VII).

DISCUSSION

... author's experience the duration of preopera- ...starvation in children undergoing operations in ...afternoon is 8–10 hours. For a morning opera- ...this period of starvation extends to more than ...ours. It has been stated that starvation does not ...ally lead to hypoglycaemia (Glick et al., 1965) ...this study has shown that 28% of children ...-47 months old and 15.5 kg in weight were ...glycaemic in terms of the criteria of Cornblath ...

TABLE I. *Mean weight of the children.*

	Number	Mean weight (kg)	SD	Range (kg)
Starvation group	33	18.6	6.6	9–36
Milk group	29	20.0	6.4	11–35

TABLE II. *Mean age of the children.*

	Number	Mean age (months)	SD	Range (months)
Starvation group	33	59	30.9	23–141
Milk group	29	69	37.2	19–166

TABLE III. *Mean blood glucose levels.*

	Number	Mean blood glucose (mg/100ml)	SD	Range (mg/100ml)
Starvation group	33	53.3	16.1	10–80
Milk group	29	66.4	12.6	40–95

Difference significant (P<0.0005).

TABLE IV. *Incidence of hypoglycaemia in starvation group in relation to age and body weight.*

	Number	Hypo-glycaemic	Normal blood glucose conc.
Starvation group less than 47 months and 15.5 kg	18	5	13
Starvation group more than 47 months and 15.5 kg	15	0	15

TABLE V. *Mean blood glucose in children less than 47 months of age and 15.5 kg weight.*

	Number	Mean blood glucose (mg/100ml)	SD	Range (mg/100ml)
Starvation group	18	46.4*	16.5	10–65
Milk group	11	60.0*	9.2	40–70

*P<0.0005.

TABLE VI. *Incidence of hypoglycaemia in children less than 47 months in age and 15.5 kg in weight.*

	Number	Hypoglycaemic	%
Starvation group	18	5	28
Milk group	11	0	0

TABLE VII. *Mean volume of stomach contents and pH.*

	Number	Mean volume stomach contents (ml)	SD	pH
Starvation group	33	6.0	3.1	2.9
Milk group	29	8.0	2.8	2.7

and Schwartz (1966) and Habbick, McNeish and Stephenson (1971). The mean fasting blood glucose concentration in children is in the range 50–90 mg/100 ml (Baron, 1970) but this study showed a range from 10 to 80 mg/100 ml with a mean value very close to that for newborn infants.

Some children examined by the author before operation have shown signs that could be attributed to hypoglycaemia, including sweating, paleness of the skin and complaints of headache. Random blood glucose estimations using dextrostix had suggested that hypoglycaemia may have been present; this was a stimulus to the present study. In the present study none of the children with confirmed hypoglycaemia had clinical signs or symptoms of the condition. Nevertheless this study would suggest that starvation lasting 8 hours or more is excessive.

The MG showed no patient with hypoglycaemia and had a significantly greater mean value of blood glucose. In the present small series there was no vomiting or regurgitation. This would suggest that the administration of milk, 4 hours prior to anaesthesia, may be a safe and advantageous procedure if the same method of premedication and anaesthesia are followed. This is supported by the small volumes of stomach contents that were aspirated.

A study of the possible morbidity resulting from hypoglycaemia, due to preoperative starvation, would seem to be a useful field of study. It may be that the presence of hypoglycaemia is unde and that its prevention in a safe and simple is an advantage.

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REFERENCES

Baron, D. N. (1970). *A Short Textbook of Cl Pathology*, p. 186. London: English University Ltd.

Bevan, J. C., and Burn, M. C. (1973). Acid-ba blood glucose levels of paediatric cases at induc anaesthesia: the effects of preoperative starvati feeding. *Br. J. Anaesth.*, **45**, 115.

Bowie, M. D., Mulligan, P. B., and Schwartz, R. Intravenous glucose tolerance in the normal n infant: the effects of a double dose of gluco insulin. *Pediatrics*, **31**, 590.

Conn, J. W., and Seltzer, H. S. (1955). Spon hypoglycaemia. *Am. J. Med.*, **19**, 460.

Cornblath, M., and Schwartz, R. (1966). *Disor Carbohydrate Metabolism in Infancy*, p. 193. delphia: Saunders.

Ehrlich, R. M. (1971). Hypoglycaemia in infan childhood. *Arch. Dis. Child.*, **46**, 716.

Glick, S. M., Roth, J., Yalow, R. S., and Berson (1965). The regulation of growth hormone se *Recent Prog. Horm. Res.*, **21**, 241.

Habbick, B. F., McNeish, A. S., and Stephenson, (1971). Diagnosis of ketotic hypoglycaemia of hood. *Arch. Dis. Child.*, **46**, 295.

Marks, V., and Rose, F. C. (1965). *Hypoglycaemia* Oxford: Blackwell.

Mayer, J. B. (1951). Blood sugar levels in chi *Stschr. Kinderh.*, **69**, 232.

Morley, G., Dawson, A., and Marks, V. (1968). and autoanalyser methods for measuring blood levels using guiacum and glucose oxidase. *Pr Clin. Biochem.*, **5**, 42.

Watson, B. G. (1972). Blood glucose levels in during surgery. *Br. J. Anaesth.*, **44**, 712.

Wright, P. H., Ashmore, J., and Malaise, W. J. *Biochemical Disorders in Human Disease*, 3 (eds. Thompson, R. H. S., and Wootton, I.D.P. London: Churchill.

index. The lower limit of the therapeutic range is 5 mg/dl, and although eight of ten patients in this study had magnesium concentrations below this minimum therapeutic level, none of the levels was so low that fasciculations occurred.

The interactions of magnesium and neuromuscular blocking drugs have been previously studied. Morris and Giesecke[2,3] showed that the effects of *d*-tubocurarine and magnesium sulfate are additive and that *d*-tubocurarine is approximately a thousand times as potent as magnesium sulfate as a neuromuscular blocking agent. Aldrete *et al.*[4] gave healthy male surgical patients 1 g magnesium sulfate intravenously and found that this dose decreased the frequency and intensity of muscle fasciculations following the injection of succinylcholine, as well as preventing the rise in serum potassium that otherwise occurred.

The present study has demonstrated that succinylcholine-induced muscle fasciculations are extremely unlikely to occur in the toxemic patient who has received sufficient magnesium sulfate to increase her serum concentration of magnesium significantly above the upper limit of normal. These patients do not need pretreatment with *d*-tubocurarine before succinylcholine administration to prevent fasciculations.

References

1. Aldrete JA, Barnes DR, Aikawa JK: Does magesium produce anesthesia? Anesth Analg (Cleve) 47:428–433, 1968
2. Morris R, Giesecke AH: Potentiation of muscle relaxants by magnesium sulfate therapy in toxemia of pregnancy. South Med J 61:25–28, 1968
3. Giesecke AH, Morris R, Dalton MD, et al: Of magnesium, muscle relaxants, and cats. Anesth Analg (Cleve) 47:689–695, 1968
4. Aldrete JA, Zahler A, Aikawa JK: Prevention of succinylcholine induced hyperkalemia by magnesium sulfate. Can Anaesth Soc J 17:477–484, 1970

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Hypoglycemia-induced Seizures in an Infant during Anesthesia

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Ketamine hydrochloride is a popular drug for producing immobility during radiation therapy in young children. In certain patients methohexital sodium, 5 per cent, given by deep intramuscular injection has also proven to be a useful agent for this purpose. We present a case in which convulsions occurred following treatment with methohexital sodium.

Report of a Case

A 4-month-old, 6.5-kg male infant had been diagnosed at 8 weeks of age as having a retinoblastoma. He underwent enucleation of the left eye, and radiation therapy to his right eye was begun. His first seven treatments were uneventful. For his eighth treatment an intramuscular injection of methohexital, 65 mg, was given into the anterior aspect of the thigh. Three minutes later the infant fell asleep and was placed on the radiation table for treatment. At that time his blood pressure was 80 torr and heart rate 120/min. Ten minutes after the injection of methohexital and at the end of the treatment, the child had a bilateral tonic clonic seizure, and it was noticed that his eyes rolled backwards. Heart rate was 120/min and blood pressure was 90 torr by palpation. Mild respiratory obstruction and central cyanosis were treated by the use of an oral airway and administration of oxygen by mask. A new bottle of Dextrostix® in which the Dextrostix strips all matched the "O" color block was obtained. The bottle had been stored at approximately 28–30 C. The Dextrostix analysis showed a blood glucose level of 25 mg/dl. The child was given dextrose, 25 per cent, 20 ml. The seizures, which had lasted about 5 min, stopped shortly after the infusion. Analysis of blood drawn at this time showed a calcium concentration of 10.2 mg/dl, normal electrolyte values, and no ketonemia. The temperature was 37 C. A lumbar puncture showed three cells, protein 27 mg/dl, and glucose 48 mg/dl. A blood glucose test performed an hour later showed 109 mg/dl. Within 30 min of the seizure the child was active and behaved normally. Two hours after the seizure the child ate without incident. On further inquiry, it was determined that the mother usually fed the child at about 2 AM each night, but on the evening before therapy the child had slept from 6 PM until just prior to their arrival at the hospital. Hence, the mother had not fed the child for nearly 13 hours. The child subsequently underwent further radiation therapy without problems. Blood glucose levels were periodically checked and found to be normal. To rule out latent epilepsy, an electroencephalogram (EEG) was performed; it disclosed no abnormality. Methohexital sodium, 65 mg, given intramuscularly, did not provoke an epileptiform EEG.

Discussion

Convulsions during anesthesia are extremely dangerous and, unless promptly treated, may lead to a vegetative state.[1] Hence, rapid treatment is of primary consideration, and should be followed by an attempt to reach a diagnosis of the cause of the convulsions. This patient had a seizure following prolonged starvation and the use of methohexital sodium. Clinically, methohexital sodium is associated with involuntary

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muscle movements[2]; a literature search has failed to record any tonic–clonic seizure due to this agent. Wilder demonstrated activation of temporal lobe epileptic foci by the use of intracarotid and intravenous administration of methohexital in small doses.[3] Sleep is known to enhance epileptiform activity in psychomotor epilepsy.[4] Therefore, an EEG was performed to exclude this diagnosis.

In this patient the cause of the seizure was hypoglycemia. Over the years, anesthesiologists have commented on the occurrence of hypoglycemia with clinical signs such as lethargy, sweating, pallor, and tremulousness, which accompany the adrenergic response to a rapid decrease in blood glucose concentration.[5,6] Thomas[7] studied blood glucose levels after induction of anesthesia in two groups of children: one group was starved for as long as eight hours and another group was allowed to drink milk until four hours before anesthesia. The study, using 40 mg/dl as the level for hypoglycemia, showed that 28 per cent of children less than 47 months of age and weighing less than 15.5 kg, who had been starved, were hypoglycemic.[8,9] There was no patient with hypoglycemia in the group that had been fed until four hours prior to anesthesia. In neither group was there any sign of regurgitation or vomiting. Also found in the study was the fact that none of the children with confirmed hypoglycemia had clinical signs or symptoms of the condition. Of interest is the case report of a 5-year-old girl who underwent adenotonsillectomy and who convulsed postoperatively. At that time "no glucose was found in the blood."[10]

Once the diagnosis of a hypoglycemic seizure has been made, or even contemplated, speed is of the essence, as repeated seizures can lead to brain injury. Studies of paralyzed animals subjected to repeated seizures have demonstrated that a point is reached when the compensatory factors that increase substrate supply to a convulsing brain cannot compensate, leading to a decrease in ATP.[11] When a pediatric patient has a seizure during or after anesthesia a sample of blood for glucose determination should be obtained and an intravenous infusion of glucose started. The use of a Dextrostix is invaluable for an immediate and relatively accurate estimation. When the patient is suspected to be hypoglycemic, dextrose, 25 per cent, 2–4 ml/kg (0.5–1.0 mg/kg), is given intravenously.[12] Thereafter, one should maintain dextrose infusion at a rate of 0.5 g/kg/hr until the child can maintain an adequate blood glucose value. If, after treatment, one is still unsure of the diagnosis, a full evaluation, including measurements of blood levels of calcium, magnesium, and ketone, lumbar puncture, and EEG, should be performed.

References

1. Best CH, Taylor NB: Physiological Basis of Medical Practice. Eighth edition. Section VIII. Baltimore, Williams and Wilkins, 1966, p 1354
2. Vickers MD, Wood-Smith FG, Stewart HC (editors): Drugs in Anaesthetic Practice. Fifth edition. London, Butterworths, 1978, p 52
3. Wilder BJ: Activation of epileptic foci in psychomotor epilepsy. Epilepsia (Amsterdam) 10:418, Sept 1969
4. Fuster B, Gibb EL, Gibbs FA: Pentothal sleep as an aid to diagnosis and localization of seizure discharges of the psychomotor type. Dis Nervous System 9:199–202, 1948
5. Bevan JC, Burn MC: Acid base and blood glucose levels of paediatric cases at induction of anaesthesia. The effect of preoperative starving and feeding. Br J Anaesth 45:115, 1973
6. Watson BG: Blood glucose levels in children during surgery. Br J Anaesth 44:712–715, 1972
7. Plum F, Howse DC, Duffy TE: Metabolic effects of seizures. Brain Dysfunction in Metabolic Disorders. Edited by F Plum. New York, Raven Press, 1974, pp 141–157
8. Volpe JJ: Management of neonatal seizures. Crit Care Med 5:43–48, 1977

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V-Lead Adapter

Donald J. Sass, Capt MC USN*

Tektronix® Models 408, 412, and 414 patient monitoring oscilloscopes were designed to record from conventional limb leads of the electrocardiogram (ECG). One can record a precordial ECG with these monitors by one of several methods that include: 1) a Tektronix 408 or 412 with modification 735D, or type 414 with option 4; 2)modified limb-lead placement[1]; 3) a V-lead adapter (013-0180-01) recently introduced by Tektronix. The modified oscilloscopes have full-lead selectors and will display precordial and limb-lead ECGs. However, one loses the option to record from limb leads when the modified limb-lead and V-lead adapter methods are used.

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PREOPERATIVE STARVATION AND BLOOD GLUCOSE CONCENTRATIONS IN CHILDREN UNDERGOING INPATIENT AND OUTPATIENT ANAESTHESIA

B. H. JENSEN, M. WERNBERG AND M. ANDERSEN

SUMMARY

Blood glucose concentrations were measured in 82 children undergoing inpatient anaesthesia and in 46 children undergoing anaesthesia as outpatients. The children were aged between 6 months and 9 yr. Outpatients were fasted from bedtime, while inpatients were randomly allocated to two groups. In group A the children were fasted from bedtime, whereas in group B the children were fed 6 h before anaesthesia. There was no difference in mean blood glucose concentration between the fasted inpatients and outpatients nor between children younger than, or older than, 4 years of age. A blood glucose concentration of less than 40 mg dl^{-1} was found in only one of the fasted children (1%). The mean blood glucose concentration was greater in group B than A, but only significantly so for children older than 4 yr. It is concluded that to minimize the risks of hypoglycaemia and inhalation of vomit on induction of anaesthesia children older than 6 months should be fasted overnight and operated on in the morning.

Since the risks of vomiting, and the inhalation of gastric contents, are inherent in the administration of general anaesthesia, established practice ordains that no patient for elective surgery be anaesthetized without a period of starvation and fluid deprivation. This period varies from 6 to 12 h or even more, in different institutions.

In studies of prolonged starvation adults were able to sustain normal glycaemic values (Cahill et al., 1966). The risk of hypoglycaemia from prolonged preoperative starvation in children was investigated by Thomas (1974), who studied the blood glucose concentrations on induction of anaesthesia in two groups of children and introduced feeding regimes in which children under 4 yr received milk or fruit syrup 4–6 h before operation.

In another study in children younger than 5 yr undergoing outpatient anaesthesia, no patient had a blood glucose concentration less than 40 mg dl^{-1}, despite at least 8 h starvation (Graham, 1979).

The purpose of the present study was to investigate the blood glucose concentrations in children undergoing inpatient and outpatient anaesthesia who were fasted and in children who received fruit syrup 6 h before inpatient anaesthesia.

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PATIENTS AND METHODS

Patients

One hundred and thirty-four otherwise healthy children, aged 6 months to 9 yr, and scheduled for elective minor surgery such as tonsillectomy, adenoidectomy and myringotomy were included in the study. The parents were informed of the purpose of the investigation and all gave their consent.

The children formed two main groups: 88 children were inpatients and 46 children were outpatients operated by a specialist outside the hospital. Each of the main groups was subdivided further into two sub-groups, group I consisting of children younger than 4 yr and group II of children greater than 4 yr.

Outpatients were all fasted from bedtime. Inpatients in both groups were randomly allocated such that some of the children were fasted from bedtime (group A) whereas others received fruit syrup and water in a dose of 7.5 ml kg^{-1} 6 h before anaesthesia (group B). The fruit syrup and water contained invertose 20 g dl^{-1}. Six children less than 4 yr refused to take the fruit syrup and were discharged from the study.

The ages, body weights and durations of starvation in the various groups are given in table I.

Anaesthesia

All children were anaesthetized in the morning. Inpatients were premedicated with nicomorphine

TABLE I. *Age, body weight, duration of starvation and blood glucose concentration before operation in 82 children undergoing inpatient and 46 children undergoing outpatient anaesthesia. Group I: Children younger than 4 yr, II: Children older than 4 yr; A: Fasting from bedtime, B: Received fruit syrup 6 h before anaesthesia. Mean values ±1 SD and range (in parentheses)*

Group	n	Age (yr)	Body weight (kg)	Duration of starvation (h)	Blood glucose concentration (mg dl^{-1})
Inpatients					
I-A	24	2.2±0.9 (0.8–3.8)	13.0±2.3 (8–17)	12.9±1.6 (7–16)	74±10 (55–102)
I-B	15	1.9±0.9 (0.5–3.8)	12.5±2.2 (9–17)		76± 9 (65–90)
II-A	22	5.9±1.7 (4–9)	21.3±4.9 (14–32)	13.6±1.5 (11–17)	72±16 (32–96)
II-B	21	5.9±1.6 (4–9)	21.8±4.9 (14–34)		82±10 (73–106)
Outpatients					
I	25	2.3±0.8 (0.7–3.5)	13.5±2.0 (9–17)	13.5±1.9 (8–16)	70± 7 (55–84)
II	21	5.7±1.7 (4–9)	20.9±4.4 (14–30)	14.5±2.0 (12–19)	70± 6 (59–81)

(Vilan) 0.2 mg kg^{-1} and atropine 0.01 mg kg^{-1}. Outpatients received no premedication. Outpatients were accompanied by a parent during the induction of anaesthesia, whereas this was not the case in inpatients. All children were anaesthetized by the inhalation of halothane in an oxygen–nitrous oxide mixture.

Measurement of blood glucose concentration

Immediately after the disappearance of the eylash reflex blood samples were withdrawn from a cubital vein. Just before venepuncture a tourniquet was placed. All venepunctures were performed by well-trained personnel. Samples were collected into fluoride bottles and analysed immediately by the o-toluidine method (Feteris, 1965). The mean of two measurements was determined. Hypoglycaemia was defined as a blood glucose concentration less than 40 mg dl^{-1}.

Statistics

The differences between groups were tested by Student's *t* test. The correlation between the period of starvation and the blood glucose concentration was estimated by Spearman's rank correlation coefficient. *P* values less than 0.05 were considered significant.

RESULTS

The mean values of the blood glucose concentrations in the different groups are given in table I. The distribution of blood glucose concentrations in all the fasted children is depicted in figure 1.

Inpatients and outpatients were comparable with respect to age and body weight whether less than, or greater than, 4 yr (groups I and II). Fasted inpatients and all outpatients were comparable with respect to their durations of starvation.

There were no differences in mean blood glucose

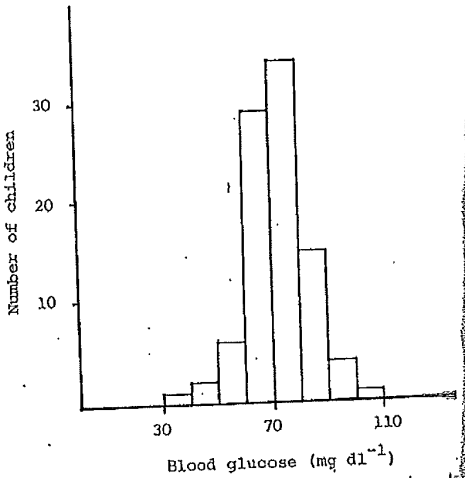

FIG. 1. Distribution of blood glucose concentrations in 92 children fasted before operation.

concentrations between the fasted inpatients (group A) and outpatients less than 4 yr ($P>0.1$, $t=1.34$) or greater than 4 yr ($P>0.5$, $t=0.58$). Likewise, there were no differences in mean blood glucose concentrations either when fasted (group A) inpatient children of groups I and II were compared ($P>0.7$, $t=0.34$) or when outpatients of groups I and II were compared ($P>0.8$, $t=0.14$).

In group I inpatients (less than 4 yr) there was no difference in mean blood glucose concentrations between groups A and B ($P>0.3$, $t=0.87$). However, the mean blood glucose concentration was significantly greater in group B than A in inpatients older than 4 yr (group II) ($0.02<P<0.03$, $t=2.42$).

Hypoglycaemia occurred in one patient in group II-A, but not in any of the other groups. Thus, the frequency of hypoglycaemia in fasted inpatients was 2%, and in all fasted children 1%. The blood glucose concentrations in all fasted children were distributed according to a Gaussian curve (fig. 1), the distribution of the points, after probit transformation, being linear.

There was no correlation between the duration of the period of starvation and the blood glucose concentration in any of the fasted groups. For all fasted children the correlation coefficient was $r=-0.12$, $P>0.10$.

There was no vomiting or regurgitation in either group during the induction of anaesthesia.

DISCUSSION

After the 3rd day of life hypoglycaemia is most commonly defined as a blood glucose concentration of less than 40 mg dl^{-1} (Cornblath and Schwartz, 1976; Habbick, McNeish and Stephenson, 1971).

The results of the present study are different from those obtained by Thomas (1974). In 18 children younger than 47 months he found a mean blood glucose concentration of 46.4 ± 16.5 mg dl^{-1} and 28% of the children were hypoglycaemic. The children were premedicated with trimeprazine, anaesthetized with thiopentone and the blood samples were withdrawn from the long saphenous vein, all of which differ from the present study. The effect of these differences on blood glucose concentrations is unknown, so caution must be exercised when comparing the results. The most obvious difference is that in the present study all the children were anaesthetized in the morning, while all the children in the study of Thomas (1974) were anaesthetized in the afternoon. It may be that starvation is better tolerated during the night than during the morning because of diurnal variations in metabolism. This agrees with the study of Graham (1979), who in the same hospital and using the same technique of anaesthesia as Thomas (1974) found a mean blood glucose concentration of 74 ± 3 mg dl^{-1} and no cases of hypoglycaemia following overnight fasting in 31 children less than 5 yr undergoing outpatient anaesthesia in the morning. However, contrary to the hypothesis proposed by Graham (1979), we could find no differences in mean glucose concentration between the fasted inpatients and the outpatients.

The only instance of hypoglycaemia occurred in a fasted 15-kg male child (50 months), who showed no clinical signs of hypoglycaemia before anaesthesia. The size of the child could be related to the study by Thomas (1974) since he described hypoglycaemia only in children of less than 15.5 kg body weight. According to the normal distribution of the blood glucose values in children fasting overnight, there may be a risk of hypoglycaemia during surgery. Much of this risk, however, may be avoided by adequate use of i.v dextrose during operation. In agreement with other studies (Watson, 1972; Serafimovski and Ibler, 1978; Graham, 1979) there was no correlation between the duration of the period of starvation and the blood glucose concentration.

In agreement with studies by Bevan and Burn (1973) and Thomas (1974) higher values of mean glucose concentrations were found in the groups who had been fed 6 h before anaesthesia. Thomas (1974) suggested that preoperative feeding is indicated particularly in children younger than 4 yr and weighing less than 15.5 kg, but in the present study this group showed no significant difference in mean blood glucose concentrations between the fasted and the fed children. In addition, six (29%) of the children in this group refused to receive fruit syrup in the middle of the night. Thus, preoperative feeding regimes for children older than 6 months of age, who are undergoing general anaesthesia in the morning, are of minor importance and cannot be recommended when one considers the risk of pulmonary aspiration of gastric contents. Further investigations are needed to determine the value of preoperative feeding of children less than 6 months of age.

In conclusion, to minimize the risk of hypoglycaemia and inhalation of vomit on the induction of anaesthesia, children older than 6 months should be fasted overnight and operated on in the morning.

ACKNOWLEDGEMENTS

We are indebted to Miss P. Michelsen and Mrs B. Skotte for skilled technical assistance, to Dr J. Kröyer Hansen and the staff in the department of otolaryngology for selection of the patients and Mrs N. Lund for secretarial assistance.

REFERENCES

Bevan, J. C., and Burn, M. C. (1973). Acid–base changes and anaesthesia. The influence of pre-operative starvation and feeding in paediatric surgical patients. *Anaesthesia*, 28, 415.

Cahill, G. F., Herrera, M. G., Morgan, A. P., Soeldner, J. S., Steinke, J., Levy, P. L., Reichard, G. A., and Kipnis, D. M. (1966). Hormone–fuel interrelationships during fasting. *J. Clin. Invest.*, 45, 1751.

Cornblath, M., and Schwartz, R. (1976). *Disorders of Carbohydrate Metabolism in Infancy*, 2nd edn, p. 345. Philadelphia: Saunders.

Feteris, W. A. (1965). A serum glucose method without protein precipitation. *Am. J. Med. Technol.*, 31, 17.

Graham, I. F. M. (1979). Preoperative starvation and plasma glucose concentrations in children undergoing outpatient anaesthesia. *Br. J. Anaesth.*, 51, 161.

Habbick, B. F., McNeish, A. S., and Stephenson, J. P. B. (1971). Diagnosis of ketotic hypoglycaemia of childhood. *Arch. Dis. Child.*, 46, 295.

Serafimovski, N., and Ibler, M. (1978). Blood glucose levels in patients after preoperative fasting. *Ugeskr. Laeg.*, 140, 1691.

Thomas, D. K. M. (1974). Hypoglycaemia in children before operation: its incidence and prevention. *Br. J. Anaesth.*, 46, 66.

Watson, B. G. (1972). Blood glucose levels in children during surgery. *Br. J. Anaesth.*, 44, 712.

JEUNE PRE-OPERATOIRE ET GLYCEMIE CHEZ DES ENFANTS SOUMIS A DES ANESTHESIES, QU'ILS S'AGISSE DE PATIENTS HÔPITALISÉS OU AMBULATORES

RESUME

Nous avons mesuré la glycémie de 82 enfants hôpitalisés et de 46 enfants ambulatoires soumis à une anesthésie. L'âge des enfants était situé entre 6 mois et 9 ans. Les patients ambulatoires jeûnaient toute la nuit, et les enfants hôpitalisés étaient répartis de façon aléatoire en 2 groupes. Dans le groupe A, les enfants jeûnaient toute la nuit, tandis que dans le groupe B les enfants étaient nourris 6 h avant l'anesthésie. Il n'y a pas eu de différences entre la glycémie moyenne des enfants ambulatoires et hôpitalisés qui avaient jeûné, ni entre la glycémie moyenne des enfants âgés de moins de 4 ans ou de plus de 4 ans. On n'a retrouvé une glycémie inférieure à 0,40 mg dl^{-1} que chez un des enfants qui avaient jeûné (1%). La glycémie moyenne était plus élevée dans le groupe B que dans le groupe A mais ceci n'était significatif que pour les enfants de plus de 4 ans. Nous en concluons que pour minimiser le risque d hypoglycémie et d'inhalation de vomitus á l'induction de l'anesthésie, il faut faire jeûner toute la nuit les enfants de plus de 6 mois et les opérer le matin.

PRÄOPERATIVES HUNGERN UND BLUTGLUKOSEKONZENTRATIONEN VON KINDERN BEI AMBULANTER UND NICHTAMBULANTER NARKOSE

ZUSAMMENFASSUNG

Die Blutglukosekonzentrationen wurden bei 82 hospitalisierten Kindern und bei 46 Kindern, die eine ambulante Narkose erhielten, bestimmt. Die Kinder waren im Alter zwischen 6 Monaten und 9 Jahren. Die ambulanten Patienten mußten vom Zeitpunkt des Zubettgehens fasten, während die hospitalisierten nach Randomisierung in zwei Gruppen eingeteilt wurden. In Gruppe A mußten die Kinder vom Zubettgehen an fasten, während die kinder von Gruppe B 6 Stunden vor der Narkose Essen erhielten. Es gab keinen Unterschied zwischen den mittleren Blutglukosekonzentrationen der ambulanten und nichtambulanten Kinder die gefastet hatten, und auch nicht zwischen den Altersgruppen kleiner und größer als 4 Jahre. Eine Blutglukosekonzentration unter 40 mg dl^{-1} wurde bei nur einem der Kinder die gefastet hatten, gefunden (1%). Die mittlere Blutglukosekonzentration war in Gruppe B höher als in Gruppe A, aber signifikant nur für Kinder über 4 Jahre. Daraus kann man schließen, daß, um die Risiken der Hypoglykämie und der Aspiration von Erbrochenem bei der Narkoseeinleitung möglichst gering zu halten, Kinder über 6 Monate über Nacht fasten und am Morgen operiert werden sollten.

INANICIÓN PREOPERATORIA Y CONCENTRACIONES DE GLUCOSA EN LA SANGRE DE NIÑOS SOMETIDOS A ANESTESIA INTERNADOS EN HOSPITALES Y NO-HOSPITALIZADOS

SUMARIO

Se midío las concentraciones de glucosa en la sangre de 82 niños sometidos a anestesia e internados en el hospital así como en la de 46 niños sometidos a anestesia y no-hospitalizados. La edad de los niños variaba entre 6 meses y 9 años. Los niños no-hospitalizados estuvieron de ayunas desde la víspera al momento de acostarse, mientras que los niños hospitalizados estuvieron repartidos al azar en dos grupos. En el grupo A, los niños estuvieron de ayunas desde la víspera al momento de acostarse y los del grupo B recibieron comida 6 horas antes de la anestesia. No hubo diferencia en la concentración media de glucosa en la sangre de los niños hospitalizados y no-hospitalizados de ayunas ni tampoco entre los niños menores o mayores de 4 años. Se verificó una concentración de glucosa en la sangre de menos de 40 mg dl^{-1} en uno solo de los niños de ayunas (1%). La concentración media de glucosa en la sangre fue mayor en el grupo B que en el grupo A, pero de manera significante solamente en niños mayores de 4 años. Se llega a la conclusión que, para minimizar los riesgos de hipoglicemia o inhalación del vómito durante la inducción de la anestesia en los niños mayores de 6 meses, es necesario mantenerlos de ayunas desde la noche anterior y operarlos en la mañana.

Anaesthetic Record Set

Suggestions as to a reasonable content

PRE-OPERATIVE INFORMATION

PATIENT IDENTITY
- Name / ID No. / gender
- Date of birth

ASSESSMENT & RISK FACTORS
- Date of assessment
- Assessor, where assessed
- Weight (kg), [height (m) optional]
- Basic vital signs (BP, HR)
- Medication, incl. contraceptive drugs
- Allergies
- Addiction (alcohol, tobacco, drugs)
- Previous GAs, family history
- Potential airway problems
- Prostheses, teeth, crowns
- Investigations
- Cardiorespiratory fitness
- Other problems
- ASA ± comment

URGENCY
- Scheduled - listed on a routine list
- Urgent - resuscitated, not on a routine list
- Emergency - not fully resuscitated

PEROPERATIVE INFORMATION

CHECKS
- Nil by mouth
- Consent
- Premedication, type and effect

PLACE & TIME
- Place
- Date, start and end times

PERSONNEL
- All anaesthetists named
- Operating surgeon
- Qualified assistant present
- Duty consultant informed

OPERATION PLANNED/ PERFORMED

APPARATUS
- Check performed, anaesthetic room, theatre

VITAL SIGNS RECORDING/CHARTING
- Monitors used and vital signs (specify)

DRUGS & FLUIDS
- Dose, concentration, volume
- Cannulation
- Injection site(s), time & route
- Warmer used
- Blood loss, urine output

AIRWAY & BREATHING SYSTEM
- Route, system used
- Ventilation: type and mode
- Airway type, size, cuff, shape
- Special procedures, humidifier, filter
- Throat pack
- Difficulty

REGIONAL ANAESTHESIA
- Consent
- Block performed
- Entry site
- Needle used, aid to location
- Catheter: y/n

PATIENT POSITION & ATTACHMENTS
- Thrombosis prophylaxis
- Temperature control
- Limb positions

POSTOPERATIVE INSTRUCTIONS

- Drugs, fluids and doses
- Analgesic techniques
- Special airway instructions, incl oxygen
- Monitoring

UNTOWARD EVENTS
- Abnormalities
- Critical incidents
  - Pre-op, per-op, postoperative
  - Context, cause, effect

HAZARD FLAGS
- Warnings for future care.

Commentary

BACKGROUND

This document is produced jointly by the Royal College of Anaesthetists, The Association of Anaesthetists of Great Britain & Ireland and the Society for Computing & Technology in Anaesthesia. Work has been going on for some years to standardise the data kept about anaesthetic episodes. This is worth striving for several reasons: not only would there be a welcome agreement about what requires to be written down, but terms such as 'Start time' would be defined, and therefore reports derived from the data would be comparable.

A meeting was set up by the Society for Computing and Technology in Anaesthesia (SCATA) at the Association of Anaesthetists of Great Britain & Ireland in 1990, attended by representatives from the Royal College of Anaesthetists, and some terms used in the dataset were defined. [1] The next move was to define the content of the anaesthetic record. All concerned recognised that there is no ideal content - that what is appropriate for cardiac anaesthesia or a manipulation of a wrist are totally different, and the appropriate content must increase with the complexity of the anaesthetic. We therefore agreed to list the fields that could be included, and will later deal with the issues of what should be added. It was also fully recognised that datasets and content are continually changing; we expect that as thinking and requirements change, we will need to reissue this guidance at reasonable intervals. We also recognise that several of these definitions are contentious, and fully anticipate further serious discussion.

We have *not* attempted to design a form, but rather to show what information might be presented.

COMMENTS ON PARTICULAR FIELDS

Many items will be present 'by association' - in other words, already present in the patient's notes, and making it pointless to rewrite them. This does not diminish the need for key items of anaesthetic relevance to be copied on occasion - to emphasise that the anaesthetist was aware of them, but defining precisely which these are is not sensible.

URGENCY

This is a long debated issue, probably the most contentious in the whole set. The problem is that CEPOD uses a four division classification, *Elective*, *Scheduled*, *Urgent* and *Emergency*, and the difference between Elective and Scheduled is a purely surgical one not discernible by the anaesthetist. The CEPOD definitions were used in the dataset published in 1994.

Elective - Operation at time to suit both patient and surgeon.
Scheduled - An early operation but not immediately life-saving. Operation usually within 1-3 weeks.
Urgent - Delayed operation as soon as possible after resuscitation. Operation usually within 24 hours.
Emergency - Immediate operation, resuscitation simultaneous with surgical treatment. Operation usually within one hour.

Because of the difficulties with this classification, the 'Classes' of listed and unlisted were introduced.

Listed - An operation published on a scheduled list
Unlisted - Not published on a scheduled list

We are now recommending that these two classifications are amalgamated to make a more anaesthetically realistic classification that reflects daily life.

Scheduled - listed on a routine list
Urgent - not on a routine list, but fully resuscitated
Emergency - not fully resuscitated

PATIENT POSITION & ATTACHMENTS

The way in which a patient was lying during anaesthesia should be recorded, including the position of the limbs and any special precautions taken against injury.

UNTOWARD EVENTS

There is a whole series of terms developing in this field - critical incidents, complications, abnormalities, negative outcomes, recovery room impact events, and more. Thinking in this field is changing sufficiently rapidly so being dogmatic about which terms to use is not sensible.

In general terms, the need is to record events so that anaesthesia may be safer in the future; to record, therefore, not only things that went wrong (complications), but also that nearly went wrong (critical incidents). We should also record 'abnormalities' such as a difficult intubation, which are not preventable, both for the patient's future safety, and for educational reasons. The severity of the incident should also be recorded.

HAZARD FLAGS

Any important abnormalities (drug sensitivities, errors of metabolism etc.) affecting the patient clearly should be flagged both on the record and in the notes.

Reference

1. Lack, J.A., Stuart-Taylor, M.E., and Tecklenburg, A. An anaesthetic minimum dataset and report format. The Society for Computing and Technology in Anaesthesia (SCATA), The European Society for Computing and Technology in Anaesthesia (ESCTAIC). *British Journal of Anaesthesia* 1994; 73(2): 256-260.

Further copies may be obtained from
Professional Standards Directorate
Royal College of Anaesthetists
Tel: 0171-813 1900

APRIL 1996

A revised anaesthetic record set

Professor A P Adams, Chairman, Record Working Party

In 1990 following a meeting organised by the Society for Computing and Technology in Anaesthesia (SCATA) attended by a representative of the College and the Association, a set of terms of use for anaesthetic records was defined[1]. Further meetings held with representatives from the college, AAGBI and SCATA defined the content for an anaesthetic record. Whilst no record is ideal - what is needed for cardiac surgery may well differ greatly from that needed for a simple manipulation under anaesthesia - there is a need for a starting set. The list is a start. The Working Party recognises that changes will be needed with time and intends to reissue the guide at reasonable intervals. It did not attempt to design a form but aimed to show what information might be presented. The set has been discussed and approved by the Council of the College.

Some of the items in the lists will already be present in the patient's notes and it may appear pointless to rewrite them. But several items of key information should appear on the anaesthetic chart. Four points are worthy of special note:

Urgency

There is a problem in that CEPOD uses a four-division classification - Elective, Scheduled, Urgent and Emergency. The distinction between the first two classes is purely surgical. A second classification uses: Listed and Unlisted. The Working Party proposes a more anaesthetically related classification:

- *Scheduled* - a patient listed on routine list.
- *Urgent* - a patient not on a routine list but fully resuscitated.
- *Emergency* - a patient not fully resuscitated.

Patient position and attachments

The record should note the position of the patient and the limbs together with any special precautions taken against injury.

Untoward events

There are many terms such as critical incidents, complications and negative outcomes which describe events during the perioperative period. Thinking in this field is still developing. The aim should be to make anaesthesia safer in the future by recording events where things went wrong (complications) and where they nearly did (critical incidents). Abnormalities such as difficult intubations need to be recorded.

Hazard flags

Any important abnormality such as a drug sensitivity or an error of metabolism which affects the patient should be flagged both on the anaesthetic record and in the notes.

Reference

1 Lack JA, Stuart-Taylor M, Tecklenburg A. SCATA and ESCTAIC. An anaesthetic minimum data set and report format. British Journal of Anaesthesia 1994;73:256–260.

ANAESTHETIC RECORD SET

Suggestions as to a reasonable content

The record set can be divided into groups:

PRE-OPERATIVE INFORMATION

Patient Identity
- Name/Identity Number/Gender

Assessment and Risk Factors
- Date of Assessment
- Assessor and where assessed
- Weight (kg), [height (m) optional]
- Basic vital signs (BP and Heart Rate)
- Medication including contraceptive drugs
- Allergies
- Addiction (tobacco, alcohol, drugs)
- Previous general anaesthetics
- Family history
- Potential airway problems
- Prostheses, teeth, crowns
- Investigations
- Cardiorespiratory fitness
- Other problems
- ASA status ± comment

Urgency
- *Scheduled* – listed on a routine list
- *Urgent* – resuscitated, not on routine list
- *Emergency* – not fully resuscitated

PER-OPERATIVE INFORMATION

Checks
- Nil by mouth
- Consent to operation
- Premedication, type and effect

Place and Time
- Place
- Date of operation
- Time started and finished

Personnel
- All anaesthetists named
- Qualified assistant present
- Operating surgeon
- Duty consultant informed

Operation planned/performed

Apparatus
- Checks performed, anaesthetic room and theatre

Vital Signs Recording/Charting
- Monitoring used and vital signs (specify)

Drugs and Fluids
- Doses, concentrations and volume
- Cannulation
- Injection site(s), time and route
- Warmer used
- Blood loss, urine output

Airway and Breathing System
- Route, system used
- Ventilation: type and mode
- Airway type, size, cuff and shape
- Special procedures, humidifier, filter
- Throat pack
- Difficulty

Regional anaesthesia
- Consent
- Block performed
- Entry site
- Needle used, aid to location
- Catheter: yes/no

Patient Position and Attachments
- Thrombosis prophylaxis
- Temperature control
- Limb positions

POSTOPERATIVE INSTRUCTIONS
- Drugs, fluids and doses
- Analgesic techniques
- Special airway instructions
- Oxygen therapy
- Monitoring

UNTOWARD EVENTS
- Abnormalities
- Critical Incidents
- Pre-, per- or post-operative
- Context, cause and effect

HAZARD FLAGS
- Warnings for future care

Hatch & Sumner 1999

index.[38,39] The inability to increase effective pulmonary blood flow and stroke volume during strenuous exercise underscores the importance of the pulmonary vascular bed in determining ventricular filling and the dependence on heart rate to increase cardiac output.

Cardiac catheterization should be considered if a patient has deteriorating symptoms or function. In particular, prior to major surgery or if significant fluid shifts are anticipated, performing a haemodynamic study under fluoroscopy immediately before surgery is often beneficial. Besides being able to assess baseline haemodynamics, a balloon-tipped catheter can be left positioned in the pulmonary artery for intraoperative and postoperative measurement of pulmonary artery pressure and mixed venous oxygen saturation. Pulmonary capillary wedge pressure can be measured to monitor the transpulmonary gradient. However, the pulmonary catheter is often difficult to wedge without direct vision because there is no pulsatile arterial pulmonary flow and the balloon may not readily float out to a lung segment. Positioning the catheter using pressure tracings alone may be difficult and direct vision using fluoroscopy is preferable. An important consideration, however, is the risk of thrombosis and obstruction to venous return after central venous line placement.

Considerations for anaesthetic management following a successful Fontan procedure are shown in Table 14.4. Ideally, the Fontan baffle, superior vena cava and branch pulmonary artery pressures should be similar in the range of 10–15 mmHg, with pulmonary venous and atrial pressure between 5 and 10 mmHg.

There are few reports in anaesthesia literature about the potential problems posed by this group of patients when presenting for non-cardiac surgery. Significant haemodynamic abnormalities may persist or develop over time, and 'correction' does not necessarily imply 'cure'. Knowledge of long-term outcome data and potential complications are important when planning anaesthesia management. The disparity between subjective or reported symptoms and objective evaluation of function often seen in these patients, highlights the value of exercise testing preoperatively as a potential means by which the response to stress during surgery and anaesthesia can be assessed.

Table 14.4 Management considerations for patients following a single-ventricle repair

Aim		Management
Right atrium	RAp 10–15 mmHg	→ or ↑ preload
	Unobstructed venous return	Low intrathoracic pressure
Pulmonary circulation	PVR < 2 Wood units m^{-2}	Avoid increases in PVR, e.g. from acidosis, hypoinflation and hyperinflation of the lung, hypothermia and excess sympathetic stimulation
	Mean PAp < 15 mmHg	Early resumption of spontaneous respiration
	Unobstructed pulmonary vessels	
Left atrium	LAp 5–10 mmHg	Maintain sinus rhythm
	Sinus rhythm	
	Competent A-V valve	→ or ↑ rate to increase CO
	Ventricle:	
	normal diastolic function	→ or ↓ afterload
	normal systolic function	
	no outflow obstruction	→ or ↑ contractility
		Inodilators useful because of vasodilation, inotropic and lusiotropic properties

RAp, right atrial pressure; PVR, pulmonary vascular resistance; PAp, pulmonary artery pressure; LAp, left atrial pressure; A-V, atrioventricular; CO, cardiac output.

REFERENCE

1 Graham, T.P., Jr. ' heart disease. *Circ*
2 Murphy, J.G., Ger outcome in pati tetralogy of Fallot 1993; 329: 593–9
3 Nollert, G., Fischle survival in patient year follow-up of surgical repair. *J Cardiology* 1997;
4 Bove, E.L., Byru influence of pul function following *of Thoracic and C* 6.
5 Carvalho, J.S., . Sl Exercise capacity Fallot: deleterious gitation. *British He*
6 Gatzoulis, M.A., T oelectrical interact 1995; 92: 231–7.
7 Cullen, S., Shore, tion of right ver complete repair o 91: 1782–9.
8 Deanfield, J.E., Mc Detection of late bances after correc *Journal* 1980; 44:
9 Chandar, J.S., Wo arrhythmia in post *Journal of Cardiol*
10 Deanfield, J.E., M Ventricular arrhyt tetralogy of Fallot. haemodynamic st 77–81.
11 Marie, P.Y., Mar ventricular overloa tachycardia in ope *American Journal*
12 Kirklin, J.W., Blac Clinical outcomes transposition. *Circ*
13 Wernovsky, G., M influencing early a operation for trans *of Thoracic and Ca* 302.
14 Tanel, R.E., Wer Coronary artery catheterization fol for transposition of *Cardiology* 1995;
15 Weindling, S.N., Myocardial perfus

Hypotonic vs isotonic saline solutions for intravenous fluid management of acute infections (Review)

Duke T, Mathur A, Kukuruzovic RH, McGuigan M

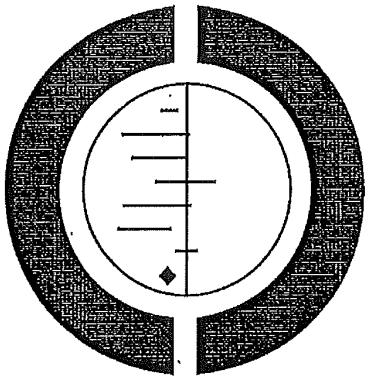

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TABLE OF CONTENTS

[Intervention Review]

Hypotonic vs isotonic saline solutions for intravenous fluid management of acute infections

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ABSTRACT

Background

Hypotonic saline (such as 0.18–0.3% NaCl with dextrose) is commonly used as maintenance fluid in the management of acute infections. In recent years there have been numerous reports of hypotonic saline solutions being associated with adverse outcomes. To reduce the rates of adverse outcomes, use of isotonic saline as maintenance fluid has been proposed.

Objectives

To assess adverse events and benefits associated with infusion of hypotonic saline compared with isotonic saline solutions in the management of acute infections.

Search strategy

We searched MEDLINE, EMBASE, the Cochrane Controlled Trials Register, Current Controlled Trials and the Specialised Register of the Injuries Group.

Selection criteria

Randomised trials comparing hypotonic saline to isotonic saline in the management of acute infections.

Data collection and analysis

Three reviewers independently evaluated all potentially relevant articles, examined each study for possible inclusion and assessed the methodology quality using the Cochrane guidelines.

Main results

No trials met our inclusion criteria.

Authors' conclusions

Although there is ample evidence elsewhere that administration of large volumes of hypotonic fluids has led to severe hyponatraemia and adverse neurological outcomes in many patients with a variety of medical and surgical conditions, we found no randomised controlled trials investigating whether use of isotonic saline as maintenance fluid in those who require intravenous fluid would a be safer alternative. Careful research with adequate design and sample sizes is needed to evaluate the benefits and safety of using isotonic saline as maintenance fluid in a variety of acute clinical conditions.

PLAIN LANGUAGE SUMMARY

No evidence so far to support use of isotonic saline as a maintenance fluid instead of hypotonic saline

It is common practice to give intravenous (i.v.) fluids to patients with serious acute infections but there is no agreement as to what the sodium concentration of these fluids should be. Doctors have traditionally used intravenous fluid that contains a lower sodium concentration than is found normally in human serum; this is known as hypotonic saline. However, as patients with severe infections often have low sodium levels and adverse effects sometimes occur with the use of large amounts of hypotonic saline, it has been proposed to use intravenous fluids that have a sodium concentration similar to that of a healthy person — isotonic saline. This review has been unable to find any data from randomised trials that establish which is best.

BACKGROUND

Severe pneumonia, bronchiolitis, meningitis, malaria and septicaemia are common causes of hospital admission and mortality. Standard treatment for most such infections includes antibiotics or antimalarials, oxygen if hypoxaemia is present, fluids and nutrition. It is a common practice in hospitals to give intravenous fluids to patients with these serious acute infections. Appropriate indications include: poor tolerance of enteral fluids, risk of pulmonary aspiration (such as severe respiratory distress or poor conscious state), correction of deficits of hydration, and to maintain electrolyte balance.

There is widespread agreement among clinicians that, for resuscitation of severe hypovolaemia, boluses of isotonic saline (either 0.9% sodium chloride [0.9% NaCl or often called 'normal' saline], or albumin in saline) should be used initially. The optimal composition and volume of intravenous fluid given to seriously ill patients after initial correction of hypovolaemia, to maintain hydration and electrolyte balance during the acute illness, remains uncertain. Many patients with these serious acute infections have hyponatraemia (serum Na <130 mmol/L) at the time of presentation and many have increased antidiuretic hormone levels (Dhawan 1992; Fajardo 1989; Dixon 1988; Fryatt 1989; Kaplan 1978; Little 1975; Patwari 1995; Reynolds 1972; Rivers 1981; Shann 1985; Sharples 1992; Freidrich 1994; Miller 1967; English 1996). Many routinely receive a hypotonic intravenous solution (for example 0.18-0.3%NaCl, or occasionally even 5% dextrose with no sodium) at usual maintenance volumes (Winters 1973). When given in maintenance volumes, 0.18% NaCl (one-fifth normal saline) provides the daily sodium requirements for a well person (2–3mmol/kg/day). However, as many acutely ill patients have reduced renal water excretion, the excess free water administered may exacerbate hyponatraemia. Progressive hyponatraemia and excess free water may result in intracellular water accumulation; the most worrying effects of this are seizures, brain swelling and herniation (Halberthal 2001).

An alternative approach to fluid management aims to avoid accumulation of excess body water and development or progression of hyponatraemia. Near isotonic saline solutions (e.g. 0.9% NaCl + dextrose, or Hartmann's solution) at volumes that take account of reduced free water excretion in serious illness may achieve these aims. In serious acute infections, and in common surgical conditions, there is impaired renal free water excretion, due to increased ADH activity. ADH is also secreted in response to other non-osmotic stimuli that are common in acute illness such as nausea and vomiting. Giving isotonic saline and no electrolyte-free water will reduce the risk of exacerbating hyponatraemia (Halberthal 2001). As this approach provides greater sodium (7mmol per kilogram per day if half-traditional maintenance volumes are given as 0.9% NaCl), there may be a risk of salt and water accumulation.

The safety of this approach needs to be evaluated in a variety of conditions. Although this strategy may be optimal for a majority of serious acute infections, there may be some associated conditions where it is unwise, such as severe malnutrition, congestive heart failure or renal impairment. In these conditions, the ability to handle a salt load is impaired and the risk of cardiac failure is considerable. In many hospitals in resource-poor countries, it is not possible to measure serum electrolytes or glucose routinely, so strategies for fluid management need to be empirical and proven to be safe.

OBJECTIVES

The objective of this review is to assess whether infusion of intravenous hypotonic or isotonic saline solutions lead to different outcomes in the management of acute infections. The outcomes of interest include derangements of serum sodium, seizures, cerebral oedema, fluid overload, case fatality rates for specific conditions and neurological sequelae.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials comparing:

- hypotonic saline solutions (0.45% NaCl or less, such as 0.18% or 0.3% NaCl) with
- isotonic saline solutions (e.g. 0.9% NaCl or Hartmann's solution).

We searched for suitable trials that addressed the management of acute infections, such as meningitis, pneumonia, sepsis, malaria and bronchiolitis. Studies were included if they if they were designed to evaluate differences in the above clinical or biochemical outcomes, where at least 50% of the normal maintenance fluid volume requirements were given as intravenous fluid for 24 hours or more.

Types of participants

Patients with serious acute infections: meningitis, pneumonia, bronchiolitis, septicaemia and severe malaria. The review excluded trials in gastroenteritis, where intravenous fluid is given for replacement of existing volume deficits, and trials in premature infants, where renal salt and water handling is different to that of mature individuals.

Types of interventions

Studies where patients had received 50% or more of their daily fluid requirements as intravenous fluid, either as a hypotonic (e.g. one-fifth or one-third normal saline) or as isotonic solutions (e.g. normal saline).

Types of outcome measures

Studies measuring differences between treatment groups with regard to the following.

Acute clinical and biochemical outcomes.

These included the following.

1) Progressive hyponatraemia or hypernatraemia associated with:

- seizures
- cerebral oedema
- brain herniation
- death
- other acute neurological deterioration, while patients were receiving intravenous fluids.

2) Fluid overload, the definitions of which may include oedema of the face or body or generalised oedema, substantial weight gain or signs of pulmonary oedema.

Case fatality rates.

Long-term neurological sequelae.

Search methods for identification of studies

Electronic searches

We searched:

- Cochrane Injuries Group Specialised Register
- Cochrane Controlled Trials Register (latest issue)
- EMBASE (1980-August 2002)
- MEDLINE (1966-May 2003)
- Current Controlled Trials.

The search strategies can be found in Appendix 1.

Data collection and analysis

Results of all the searches were printed and photocopied. Three reviewers (AM, TD, RK) independently searched titles, abstracts and descriptions of all the studies identified by the electronic search. Abstracts of all potentially relevant articles were copied. Each reviewer independently examined every study, applying inclusion/ exclusion criteria. An emphasis was placed on selecting RCTs directly comparing isotonic saline with hypotonic saline, when used as a maintenance fluid in the management of acute infections. Non-randomised trials were excluded. Disagreements were resolved by discussion. While selecting the studies, we also focused on the method of randomisation, the use of allocation concealment, the use of blinding, the assessment of outcomes and exclusion of participants after randomisation.

RESULTS

Description of studies

See: Characteristics of excluded studies.

We found no randomised trials that fulfilled the inclusion criteria. Four studies (Singhi 1995; Powell 1990; Duke 2002; Neville 2003) were short-listed and examined in detail. Two studies (Singhi 1995; Duke 2002) compared two regimens of different fluid volumes, one used hypotonic saline in both the arms of the trial (Singhi 1995), and the other used 0.45% NaCl in one arm and nasogastric enteral feeds in the other (Duke 2002). One study (Singhi 1995) was terminated after enrolling 50 patients because of a trend towards a poor outcome in the patient group receiving restricted fluid volumes. However, this study was not designed to compare the effect of different fluid composition. Of the other remaining two studies, one (Powell 1990) randomised subjects to the volume of fluids, but did not specify to treating clinicians what the content of fluids should be; therefore patients received hypotonic or isotonic fluid on the basis of clinician preference. This study had a small sample size (n = 19).

On study, which is currently published in abstract only (Neville 2003), compared hypotonic saline with isotonic saline in gastroenteritis. This condition has been excluded from the list of acute infections considered for this review. Although this study does not address the conditions relevant to this review a pertinent finding was that, despite giving 0.9% NaCl with dextrose in volumes required for rehydration, hypernatraemia did not occur.

The reasons discussed above have led to the exclusion of these studies from this review.

Risk of bias in included studies

No trials included.

Effects of interventions

Not applicable.

DISCUSSION

Randomised trials directly comparing hypotonic saline with isotonic saline as maintenance fluids in the management of acute infections could not be identified in the search. The trials identified by the search strategy (Powell 1990; Singhi 1995; Duke 2002) compared volumes of fluids rather than composition. One trial that came to our attention during the review process (Neville 2003) compared hypotonic saline with isotonic saline in gastroenteritis, but this condition was excluded from the review.

There is considerable clinical observational data suggesting an association between hypotonic saline and adverse outcomes in certain conditions. In addition, there is biological plausibility that giving large volumes of hypotonic saline to patients with reduced free-water excretion will lead to hyponatraemia. However, there is currently no randomised trial evidence to determine whether isotonic saline is a better maintenance fluid than hypotonic saline.

In the absence of randomised trials of adequate size, we could not assess relative adverse events and benefits associated with infusion of hypotonic saline or isotonic saline solutions.

In the absence of randomised trials, enough data could not be generated to asses adverse events and benefits associated with infusion of hypotonic saline compared to isotonic saline solutions. This suggests a need of randomised trial evidence which will be beneficial for deciding whether isotonic saline is a better maintenance fluid than hypotonic saline in the management of acute infections or not.

AUTHORS' CONCLUSIONS

Implications for practice

The limited evidence highlighted by this review indicates that, despite strong theoretical evidence elsewhere that hypotonic intravenous fluids carry substantial risks in many seriously ill patients, the safety of using an isotonic saline as maintenance fluid has not been fully established either, at least in a direct comparison with hypotonic solutions. In maintenance fluid management there are two major issues: (1) fluid composition (in this context the amount of sodium), and (2) the fluid volume that is administered. To maintain isovolaemia most seriously ill patients, after correction of volume deficits, have reduced fluid requirements because

of high antidiuretic hormone levels. Large intravenous hypotonic fluid volumes in patients with impaired free-water excretion will carry a risk of hyponatraemia. Therefore, patients with serious infections who are requiring maintenance i.v. fluids after initial resuscitation may be least prone to major sodium imbalance if they were given isotonic saline (plus dextrose) in volumes that take account of impaired free water excretion. Currently, however, there is inadequate evidence that this strategy for fluid management will result in important differences in the incidence of adverse clinical outcomes.

Implications for research

Given the large numbers of hospitalised patients throughout the world who receive intravenous maintenance fluids, further research should be encouraged in this field. The use of isotonic saline as maintenance fluid should be evaluated in controlled trials.

It would be valuable to test the hypothesis that: isotonic saline (with 5% dextrose) at less than standard 'maintenance volumes' will result in a lower incidence of hyponatraemia, seizures and adverse neurological events than hypotonic saline solutions (0.18–0.3% saline) in acutely unwell patients with serious infections.

Ideal testing of the hypothesis would involve a large randomised controlled trial of hypotonic versus isotonic saline in the management of serious infections. However, we think it would be unethical to include some infections in such a trial. This applies particularly to encephalitis and meningitis, where there is already strong theoretical evidence and clinical experience of harm from using hypotonic intravenous fluid, especially at or near maintenance volumes, and where there is a higher risk of cerebral oedema and adverse outcomes if hyponatraemia occurs. An alternative approach in hospitals where hypotonic fluids are the routine standard of care would be to change the policy such that isotonic saline becomes the standard background intravenous fluid, and to carefully audit the change. Although not as robust as an RCT, this would allow for a detailed before and after analysis. Outcomes could include differences in the proportions of patients who suffer neurological events associated with progressive hyponatraemia. Evaluation of safety could include differences in the frequency of severe hypernatraemia, the occurrence of neurological complications associated with rapidly rising serum sodium, or fluid retention.

ACKNOWLEDGEMENTS

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We wish to thank Professor Ian Roberts (Coordinating Editor), Paul Chinnock (Managing Editor) and Katharine Ker (Review Group Coordinator) of Cochrane Injuries Group for their assistance and support during the preparation of this review.

REFERENCES

References to studies excluded from this review

Duke 2002 *{published data only}*
Duke T, Mokela D, Frank D, Michael A, Paulo T, Mgone J, Kurubi J. Management of meningitis in children with oral fluid restriction or intravenous fluid at maintenance volumes: a randomised trial. *Annals of Tropical Paediatrics* 2002;22(2):145–57.

Neville 2003 *{published data only}*
Neville K, O' Meara M, Verge C, Walker J. Normal saline (NS) is better than half normal saline (N/2) for rehydration of children with gastroenteritis (GE). Royal Australian College of Physicians Annual Scientific Meeting, Hobart, Australia, 26-28 May 2003. 2003.

Powell 1990 *{published data only}*
Powell KR, Sugarman LI, Eskenazi AE, Woodin KA, Kays MA, McCormick KL, Miller ME, Sladeck CD. Normalization of plasma arginine vasopressin concentrations when children with meningitis are given maintenance plus replacement fluid therapy. *Journal of Pediatrics* 1990;117(4):515–22.

Singhi 1995 *{published data only}*
Singhi SC, Singhi PD, Srinivas B, Narakesari HP, Ganguli NK, Saily R, Walia NS. Fluid restriction does not improve the outcome of acute meningitis. *Pediatric Infectious Diseases Journal* 1995;14(6):495–503.

Additional references

Dhawan 1992
Dhawan A, Narang A, Singhi S. Hyponatraemia and the inappropriate ADH syndrome in pneumonia. *Annals of Tropical Paediatrics* 1992;12(4):455–62.

Dixon 1988
Dixon BS, Anderson RJ. Pneumonia and the syndrome of inappropriate antidiuretic hormone secretion: don't pour water on the fire. *American Reviews of Respiratory Disease* 1988;138:512–3.

English 1996
English MC, Waruiru C, Lightowler C, Murphy SA, Kirigha G, Marsh K. Hyponatraemia and dehydration in severe malaria. *Archives of Disease in Childhood* 1996;74(3):201–5.

Fajardo 1989
Fajardo JE, Stafford EM, Bass JW, Roscelli JD, Sato AK, Claybaugh JR. Inappropriate antidiuretic hormone in children with viral meningitis. *Pediatric Neurology* 1989;5(1):37–40.

Freidrich 1994
Freidrich G, Christoph J, Peter Kern, Menfred D. Inappropriate secretion of antidiuretic hormone and hyponatremia in severe falciparum malaria. *American Journal of Tropical Medicine & Hygiene* 1994;50(5):602–7.

Fryatt 1989
Fryatt RJ, Teng JD, Harries AD, Moody AH, Hall AP, Forsling ML. Plasma and urine electrolyte concentrations and vasopressin levels in patients admitted to hospital for falciparum malaria. *Tropical & Geographical Medicine* 1989;41(1):57–60.

Halberthal 2001
Halberthal M, Halperin ML, Bohn D. Acute hyponatraemia in children admitted to hospital: retrospective analysis of factors contributing to its development and resolution. *BMJ* 2001;322 (7289):780–2.

Kaplan 1978
Kaplan SL, Feigin RD. The syndrome of inappropriate secretion of antidiuretic hormone in children with bacterial meningitis. *Journal of Pediatrics* 1978;92(5):758–61.

Little 1975
Little TM, Dowdle RH. Mycoplasma pneumonia with inappropriate secretion of antidiuretic hormone (Letter). *BMJ* 1975;1(5956):517.

Miller 1967
Miller LH, Makaranond P, Sitprija V, Snebsanguan C, Canfield CJ. Hyponatraemia in malaria. *Annals of Tropical Medicine & Parasitology* 1967;61(3):265–79.

Patwari 1995
Patwari AK, Singh BS, Manorama DE. Inappropriate secretion of antidiuretic hormone in acute bacterial meningitis. *Annals of Tropical Paediatrics* 1995;15(2):179–83.

Reynolds 1972
Reynolds DW, Dweck HS, Cassady G. Inappropriate antidiuretic hormone secretion in a neonate with meningitis. *American Journal of Diseases of Children* 1972;123(3):251–3.

Rivers 1981
Rivers RPA, Forsling ML, Olver RP. Inappropriate secretion of antidiuretic hormone in infants with respiratory infections. *Archives of Disease in Childhood* 1981;56(5):358–63.

Shann 1985
Shann F, Germer S. Hyponatremia associated with pneumonia or bacterial meningitis. *Archives of Disease in Childhood* 1985;60(10): 963–6.

Sharples 1992
Sharples PM, Seckl JR, Human D, Lightman SL, Dunger DB. Plasma and cerebrospinal fluid arginine vasopressin in patients with and without fever. *Archives of Disease in Childhood* 1992;67(8): 998–1002.

Winters 1973
Winters RW. Maintenance fluid therapy. *The Body Fluids in Paediatrics*. Boston: Little, Brown and Company, 1973:113–33.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Duke 2002	The study did not compare the content of fluids given to the patients i.e. hypotonic or isotonic. Patients in both the groups received a hypotonic solution either as nasogastric feed or intravenous infusion.
Neville 2003	Abstract only. The trial was compating fluids in the management of gastroenteritis. The fluids were given in this study as re-hydration fluids and not as maintenance volumes.
Powell 1990	The patients were randomized to the volumes of fluids and not the content i.e. hypotonic or isotonic. The methodological quality of the trial was poor in that it did not specify which group of patients received hypotonic or isotonic saline and therefore the results could be subject to bias.
Singhi 1995	Randomization was done on the basis of fluid volumes and not the content. Patients in both the groups received a hypotonic saline.

DATA AND ANALYSES

This review has no analyses.

WHAT'S NEW

Last assessed as up-to-date: 13 May 2003.

11 July 2008	Amended. Converted to new review format.

HISTORY

Protocol first published: Issue 2, 2003

Review first published: Issue 2, 2004

CONTRIBUTIONS OF AUTHORS

Asish Mathur and Trevor Duke conceived the idea, designed and coordinated the review along with screening search results, retrieval of papers, screening retrieved papers against inclusion criteria, appraising quality of papers, methodological perspective, data entry into RevMan, analysis of data, clinical perspective and writing of the Review.

Renata Kukuruzovic contributed in screening search results, retrieval of papers, screening retrieved papers against inclusion criteria, appraising quality of papers, methodological perspective and writing of the Review.

Mike South: Clinical perspective

DECLARATIONS OF INTEREST

None known.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Fluid Therapy [*methods]; Infection [*therapy]; Isotonic Solutions [therapeutic use]; Sodium Chloride [*therapeutic use]

ORIGINAL ARTICLE

Isotonic is better than hypotonic saline for intravenous rehydration of children with gastroenteritis: a prospective randomised study

K A Neville, C F Verge, A R Rosenberg, M W O'Meara, J L Walker

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See end of article for authors' affiliations

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Aims: To determine whether the risk of hyponatraemia in children with gastroenteritis receiving intravenous (IV) fluids is decreased by the use of 0.9% saline.

Methods: A prospective randomised study was carried out in a tertiary paediatric hospital. A total of 102 children with gastroenteritis were randomised to receive either 0.9% saline + 2.5% dextrose (NS) or 0.45% saline + 2.5% dextrose (N/2) at a rate determined by their treating physician according to hospital guidelines and clinical judgement. Plasma electrolytes, osmolality, and plasma glucose were measured before (T_0) and 4 hours after (T_4) starting IV fluids, and subsequently if clinically indicated. Electrolytes and osmolality were measured in urine samples. Results were analysed according to whether children were hyponatraemic (plasma sodium <135 mmol/l) or normonatraemic at T_0.

Results: At T_0, mean (SD) plasma sodium was 135 (3.3) mmol/l (range 124–142), with 37/102 (36%) hyponatraemic. At T_4, mean plasma sodium in children receiving N/2 remained unchanged in those initially hyponatraemic (n = 16), but fell 2.3 (2.2) mmol/l in the normonatraemic group. In contrast, among children receiving NS, mean plasma sodium was 2.4 (2.0) mmol/l higher in those hyponatraemic at baseline (n = 21) and unchanged in the initially normonatraemic children. In 16 children who were still receiving IV fluids at 24 hours, 3/8 receiving N/2 were hyponatraemic compared with 0/8 receiving NS. No child became hypernatraemic.

Conclusions: In gastroenteritis treated with intravenous fluids, normal saline is preferable to hypotonic saline because it protects against hyponatraemia without causing hypernatraemia.

Recent publications[1–3] have highlighted the potential for life threatening hyponatraemia associated with the use of intravenous hypotonic saline in hospitalised children, including children with gastroenteritis.[2 4] Although most guidelines recommend low osmolarity oral rehydration solutions for rehydration of children with mild to moderate dehydration secondary to non-cholera gastroenteritis,[5–7] intravenous fluids are frequently used when oral rehydration is not tolerated, particularly in developed countries.[8–10] There is no consensus however on the most appropriate electrolyte composition of intravenous (IV) fluids, with recommendations ranging from 0.45% to 0.9% saline solutions.[5–7 11] Previously, we have documented antidiuretic hormone (ADH) activity inappropriate for the plasma sodium and osmolality in children receiving intravenous fluids for mild to moderate dehydration associated with gastroenteritis.[12] While this could cause dilutional hyponatraemia irrespective of the saline content of the fluid, the use of a fluid with a higher tonicity presenting less electrolyte free water should reduce this risk.[1 13]

To explore this, we studied the changes in blood and urine biochemistry in children with a presumptive diagnosis of gastroenteritis in whom a decision to treat with IV fluids had been made by their treating physician. Apart from randomisation to either normal or half normal saline, other aspects of management, including fluid rate, were determined by the treating physician based on hospital guidelines and clinical judgement. As we found previously that the biochemical response to IV fluids differed according to the plasma sodium at presentation,[12] we analysed the results according to whether children were hyponatraemic or normonatraemic at presentation.

METHODS

The study was conducted at Sydney Children's Hospital between the months of August and October 2002, corresponding to the annual peak incidence of rotavirus infection.[14] Children aged between 6 months and 14 years with a presumptive diagnosis of gastroenteritis were eligible for enrolment in the study only after a decision to treat with intravenous (IV) fluids had been made by their treating physician, independent of the study (fig 1). The reasons recorded for this decision were the combination of dehydration and either continued vomiting or inadequate intake of oral fluids in the emergency department. Children were excluded from the study if they had a known abnormality of ADH secretion, nephrogenic diabetes insipidus, pituitary or hypothalamic disease, renal disease, acute or chronic lung disease, or were receiving drugs known to stimulate ADH secretion. The study protocol was approved by the South Eastern Area Research Ethics Committee and informed consent was obtained from a parent/guardian of all children.

At enrolment, children were prospectively randomised to receive either 0.45% saline + 2.5% dextrose (N/2) or 0.9% saline + 2.5% dextrose (NS) by sequential selection of an opaque sealed envelope containing the fluid choice. The treating physician was told which fluid had been selected. The rate of infusion was not randomised, but was determined by the treating physician according to one of two clinical protocols in use in the emergency department: the "rapid replacement protocol" (RRP; 10 ml/kg/h for 4 hours), or the "slow replacement protocol" (SRP; maintenance fluids[15] +

Abbreviations: ADH, antidiuretic hormone; IV, intravenous; RRP, rapid replacement protocol; SRP, slow replacement protocol

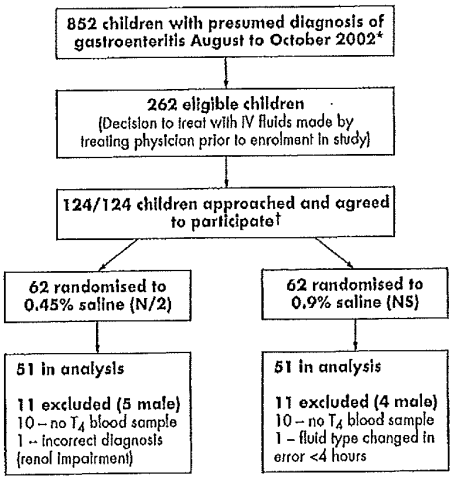

Figure 1 Flow diagram of patient selection. *Corresponding to the annual peak incidence of rotavirus infection. †A registered nurse was employed 40 hours per week (including weekends and after hours) to facilitate the correct administration of the study protocol in a busy emergency department. Enrolment was carried out only during her shifts.

estimated dehydration as a percentage of body weight replaced over 24 hours). Blood samples were collected before (T_0) and 4 hours after (T_4) the start of IV fluids, with the T_4 measurement corresponding to completion of the RRP. The study protocol permitted the treating physician to change the fluid type after the first 4 hours of infusion. However this was done in two patients only: one child was changed from NS to N/2 at 5 hours because the plasma sodium concentration had increased from 130 to 135 mmol/l; and one was changed from N/2 to NS at 10 hours because the plasma sodium concentration remained below 135 mmol/l.

Details of the illness prior to presentation were recorded. The admission weight, length (in children under 2 years), or height and body mass index (BMI; weight/height^2) were expressed as standard deviation scores (SDS)[16 17] to allow comparison across ages. The degree of dehydration at presentation was estimated using standard clinical measures.[18] Stools for culture and rotavirus antigen testing were obtained in 35/102 children, 30 of which were positive for rotavirus antigen. There were no differences in the historical, clinical, or biochemical characteristics at presentation or the fluid rate received, comparing the 51 children who received N/2 with the 51 who received NS (table 1) as would be expected from the randomisation.

The blood samples were analysed for the concentrations of sodium, potassium, bicarbonate, urea, and creatinine using ion selective electrodes, glucose using an oxygen rate method, and osmolality using freezing point depression. Urine sample collection via urine bag in incontinent children and clean catch specimens in toilet trained children was attempted for the determination of sodium and potassium concentrations, tonicity (urinary sodium plus potassium concentration), and osmolality. In addition, ketonuria was assessed by Ketodiastix (Bayer Clinitest 50, Bridgend, South Wales, UK) in the first urine specimen passed; the results were recorded as either absent, trace, small, moderate, or large. A sample of the first urine passed was collected in 76/102 children, in only 43 of whom was it passed between −1 and +2 hours of T_0, consistent with this being a dehydrated population. In 36/43 children a subsequent urine specimen (U_{2nd}) was obtained between 3 and 12 hours (median 4.8 hours) after T_0, allowing analysis of the change in electrolytes and osmolality.

The short term response of plasma and urinary electrolytes and osmolality to treatment was analysed according to whether the children were hyponatraemic (plasma sodium <135 mmol/l) or normonatraemic at T_0. A change in plasma sodium of ≥2 mmol/l was considered to be biochemically significant as this exceeds the coefficient of variation (CV) of the assay for the laboratory reference range of 135–145 mmol/l (CV 1.3–1.5%).

To gauge the prevalence of hypo- or hypernatraemia during prolonged fluid administration, plasma and urinary data in 42/102 children (22 N/2) whose IV fluids were continued for >4 hours were analysed in each child. Variable data on each child were available (between 8 and 31 hours after T_0) depending on the duration of IV infusion.

Statistical analysis

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, version 11.0 for Windows). Results were expressed as either mean (SD) or median (range) unless otherwise indicated. Means between groups were compared by independent t tests and paired variables by paired sample t tests. Medians were compared by the Mann-Whitney U test and changes over time were compared by the Wilcoxon signed rank test. Categorical data were analysed using cross tabulation and the χ^2 test or Fisher's exact test if two cells had expected counts less than 5. Statistical significance was defined as a p value less than 0.05.

RESULTS

Baseline clinical and biochemical characteristics

The mean (SD) plasma sodium concentration at T_0 in the 102 children was 135 (3.3) mmol/l (range 124–142). Thirty seven of the children (36%) were hyponatraemic at T_0, four of whom had a plasma sodium concentration less than 130 mmol/l. The median length of illness prior to presentation was longer in the hyponatraemic children (2 days, range <24 hours to 5 days) compared with the normonatraemic children (1 day, range <24 hours to 7 days; $p < 0.01$) and the mean BMI SDS was lower (−0.7 (1.2) *v* −0.1 (1.1); $p < 0.01$). Comparing the children who were hyponatraemic versus those who were normonatraemic at T_0, there were no differences in age (mean 2.8 (1.3) years *v* 2.9 (2.0) years; $p = 0.72$), sex (51% *v* 46% male; $p = 0.61$), percent dehydration (median 5% (range 3–7) *v* 5% (range 3–7); $p = 0.27$), rotavirus positivity (12/13 *v* 18/22 tested; $p = 0.74$), or the type (43% *v* 53% N/2; $p = 0.30$) or rate (78% *v* 75% RRP; $p = 0.73$) of intravenous fluids subsequently received.

The first urine was passed a median of 2.3 hours (range −1.0 to 13.5) after starting intravenous fluids. In the 76/102 in whom this was collected, the median urinary sodium concentration was higher in samples containing "moderate" or "large" ketones (57/76; 58 mmol/l, range <10–209) compared with those that were negative for ketones or had only trace or small amounts (19/76; 20 mmol/l, range <10–109; $p < 0.01$).

In the 43 children for whom a urine sample was passed and obtained within 2 hours of T_0, the median urinary osmolality was 971 mOsm/kg (range 315–1290 mOsm/kg), median urinary sodium concentration was 58 mmol/l (range <10–209 mmol/l), and median urinary potassium 71 mmol/l (range 13–232). The median urinary tonicity (urinary

Table 1 Baseline clinical and biochemical characteristics of the children randomly assigned to receive either 0.45% saline (N/2) or 0.9% saline (NS)

	N/2 n=51	NS n=51
M/F	30/21	23/28
Age, years*	3.1 (2.0)	2.7 (1.5)
% dehydrated†	5 (3–7)	5 (3–7)
Height SDS*‡	0.4 (1.1)	0.5 (1.3)
Weight SDS*‡	0.0 (1.1)	0.1 (0.9)
BMI SDS*‡	−0.4 (1.2)	−0.3 (1.2)
Duration of illness prior†	1 day (<24h–7d)	2 days (<24h–5d)
Presenting symptoms, n (%)		
Vomiting illness only	18 (35%)	11 (22%)
Diarrhoea only	1 (2%)	1 (2%)
Vomiting and diarrhoea	32 (63%)	39 (77%)
Fluid rate initiated		
RRP	40/51	38/51
SRP	11/51	13/51
Plasma biochemistry*		
Sodium, mmol/l	136 (2.8)	135 (3.6)
Potassium, mmol/l	4.0 (0.5)	4.0 (0.5)
Bicarbonate, mmol/l	17.9 (2.9)	17.8 (3.0)
Urea, mmol/l	5.1 (1.9)	5.6 (1.9)
Creatinine, μmol/l	46.6 (12.2)	45.9 (10.4)
Glucose, mmol/l§	4.3 (1.1)	4.4 (1.1)
Osmolality, mOsm/kg	281 (7)	281 (8)
Hyponatraemia (plasma Na <135 mmol/l) at T_0, n (%)	16/51 (31%)	23/51 (41%)
Urine biochemistry†¶	n=23	n=20
Sodium, mmol/l	58 (<10–204)	63 (<10–209)
Potassium, mmol/l	71 (13–171)	70 (19–232)
Tonicity (sodium + potassium), mmol/l	161 (19–285)	163 (26–300)
Osmolality, mOsm/kg	973 (315–1290)	1004 (574–1200)

SDS, standard deviation score.
Results are expressed as either *mean (SD) or †median (range). As expected from randomisation, there were no significant differences between the groups. The rate of IV fluids received conformed to either the rapid replacement protocol (RRP) or slow replacement protocol (SRP) at the discretion of the treating physician.
‡The admission weight, length (in children under 2 years), or height and body mass index (BMI; weight/height^2) were expressed as standard deviation scores (SDS) to allow comparison across ages.
§Four children aged between 0.9 and 3.7 years had blood glucose concentrations at T_0 of between 2.0 and 2.6 mmol/l. The hypoglycaemia responded to the 2.5% dextrose content of each study fluid and subsequent investigations excluded a second pathology.
¶Analysis of urine samples collected in 43 of 49 children who passed urine between −1 and +2 hours of starting IV fluid.

concentrations of sodium + potassium) was 161 mmol/l (range 19–300), approximately that of normal saline (154 mmol/l). The urinary sodium, tonicity, and osmolality were similar in the NS (20/43) and N/2 (23/43) groups (table 1) and were independent of whether children were hyponatraemic (16/43) or normonatraemic (27/43) at baseline (hyponatraemic versus normonatraemic children: median urinary sodium 52 (range <10 to 204) *v* 70 (range <10 to 209), p = 0.39; median urinary tonicity 131 mmol/l (range 19 to 285) *v* 163 mmol/l (range 22 to 300), p = 0.1; median urinary osmolality 935 (range 315 to 1290) *v* 1036 (range 356 to 1239), p = 0.35). The median urinary potassium however was lower in the hyponatraemic children (68 (range 13–91) *v* 89 (range 16–232), p = 0.03).

Effect of IV fluid infusion rate on change in plasma sodium

The infusion rate (RRP versus SRP) was not a determinant of the change in plasma sodium in either treatment arm.

In the NS group, those treated with the RRP (38/51) had a median change in sodium of +1 mmol/l (range −7 to 6) versus SRP +2 mmol/l (range −1 to 8) (p = 0.08). In children receiving N/2 the median change in plasma sodium in those who received RRP (40/51) was −1 mmol/l (range −6 to +2) versus −1 (range −5 to +3) in those treated according to the SRP (p = 0.92, Mann-Whitney U test).

Effect of IV fluid type on plasma sodium at T_4

The plasma sodium response to N/2 versus NS differed depending on whether the children were hyponatraemic or normonatraemic initially.

After 4 hours rehydration with N/2, the mean plasma sodium had not changed in the hyponatraemic children (p = 0.32) but had decreased significantly in the initially normonatraemic group (p < 0.001; table 2, fig 2). In the normonatraemic group, plasma sodium decreased by ≥2 mmol/l in 51% (18/35) compared with 13% (2/16) in the hyponatraemic group (p < 0.001; table 2). In 20% of the initially normonatraemic children (7/35), the fall was ≥5 mmol/l. The maximum decrease was 6 mmol/l in two children treated with N/2 by RRP. The maximum increase in plasma sodium over 4 hours was 3 mmol/l in a child treated with N/2 by SRP.

In contrast, after 4 hours rehydration with NS, there was a mean increase in plasma sodium of 2.4 (1.5) mmol/l in children who were initially hyponatraemic (p < 0.001) compared with no significant change in the normonatraemic group (p = 0.08; table 2, fig 2). Thirteen per cent (4/30) of the normonatraemic group and none of the hyponatraemic group experienced a decrease in plasma sodium of ≥2 mmol/l (table 2). The maximum decrease in plasma sodium concentration was 7 mmol/l (140 to 133 mmol/l) in a normonatraemic child, in whom fluids were discontinued

Table 2 Mean (SD) plasma sodium and osmolality at baseline (T_0) and after 4 hours of intravenous rehydration (T_4) in the initially hyponatraemic (plasma sodium <135 mmol/l) versus normonatraemic (plasma sodium 135–145 mmol/l) children who received either 0.45% saline + 2.5% dextrose (N/2) or 0.9% saline + 2.5% dextrose (NS)

	N/2 (n=51)			NS (n=51)		
	Hyponatraemic (n=16)	Normonatraemic (n=35)	p value	Hyponatraemic (n=21)	Normonatraemic (n=30)	p value
T_0 sodium (mmol/l)	132 (1.5)	137 (1.7)		132 (2.4)	137 (2.2)	
T_4 sodium (mmol/l)	133 (1.8)	135 (1.8)*	<0.001	134 (2.1)*	138 (2.9)	<0.001
Change in sodium (mmol/l)	+0.4 (1.7)	−2.3 (2.2)	<0.001	+2.4 (2.0)†	+0.8 (2.4)‡	0.02
Sodium decreased ≥ 2 mmol/l from 0–4 hours	13% (2/16)	51% (18/35)	<0.01	0% (0/21)	13% (4/30)	0.13
T_0 osmolality (mOsm/kg)	277 (6.3)	283 (7.2)	0.005	277 (6.9)	284 (6.9)	0.001
T_4 osmolality (mOsm/kg)	276 (4.4)	278*(5.0)	0.21	279 (4.3)	283 (6.7)	0.01

*p<0.001, T_4 versus T_0.
†p=0.003, hyponatraemic children NS versus N/2.
‡p<0.001, normonatraemic children NS versus N/2.

at completion of the RRP; it was associated with an inappropriately high urinary sodium concentration in concentrated urine at 6 hours (urinary sodium 76 mmol/l, potassium 94 mmol/l, tonicity 170 mmol/l, osmolality 885 mOsm/kg). The maximum increase in plasma sodium over 4 hours was 8 mmol/l, from 124 to 132 mmol/l in a child treated with NS by SRP. Plasma osmolality changes in all groups were consistent with changes in plasma sodium (Table 2).

Response of urinary sodium, tonicity, and osmolality to IV fluids

To assess the response of urinary electrolytes and osmolality to IV fluids, only the 36 children with a baseline (U_{base}) and subsequent (U_{2nd}) urine sample were analysed (table 3). Apart from being slightly older than the rest of the study group (median 3.8 years (range 1.1–11.9) *v* 2.0 years (range 0.8–7.5); $p < 0.001$), the 36 children's clinical and biochemical data (T_0 and T_4) were comparable with the group as a whole. Nineteen received NS and 17/36 received N/2. Eight children in each group were hyponatraemic at T_0.

Irrespective of the fluid received or the plasma sodium at T_0, urinary potassium concentration decreased (table 3), which would be consistent with a decrease in aldosterone secretion following volume expansion. In contrast, the urinary concentration of sodium in the second sample varied according to the initial plasma sodium concentration and the fluid received. The urinary concentration of sodium decreased in the hyponatraemic children treated with NS and tended to do so in those receiving N/2 (table 3), whereas it increased in the normonatraemic children receiving NS and did not change in those receiving N/2 (table 3).

In keeping with the changes in concentration of sodium and potassium, the median urinary tonicity of the second urine sample had decreased significantly in the hyponatraemic children (table 3) to less than that of half normal saline. In the normonatraemic children, the median urinary tonicity decreased, but remained above that of half normal saline in the N/2 group and remained approximately that of normal saline in the NS group.

Median urine osmolality decreased in both treatment groups irrespective of the initial plasma sodium (table 3).

Biochemical changes during more prolonged fluid administration

Forty two children (22 N/2 and 20 NS) received IV fluids for more than 4 hours. These comprised all 24/102 children who

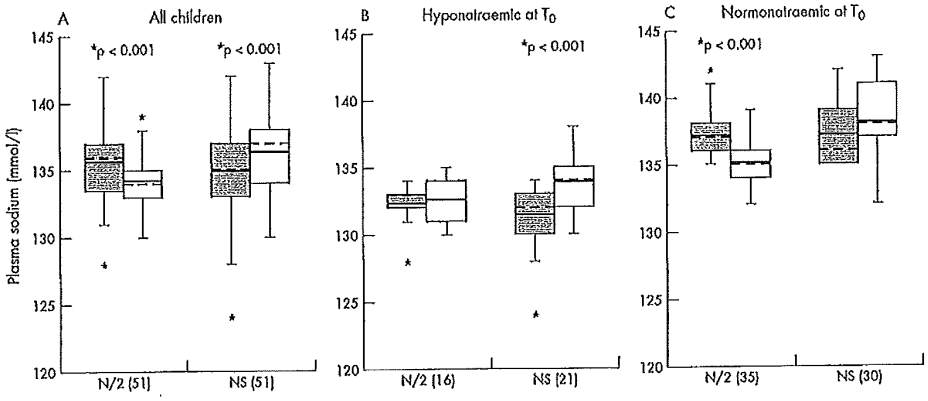

Figure 2 Box plots showing the plasma sodium concentration at baseline (T_0; shaded) and after 4 hours (T_4; white) infusion of either N/2 or NS in (A) all children and those who were either (B) hyponatraemic or (C) normonatraemic prior to starting IV fluids. Box plots show the mean (solid horizontal line), median (dashed horizontal line), interquartile range (box limits), and minimum and maximum (whiskers), except that extreme outliers (greater than 1.5 box lengths from the edge of the box) are shown as individual data points. In the N/2 group, mean plasma sodium concentration did not change in the initially hyponatraemic children and decreased in the initially normonatraemic children. In the NS group however, mean plasma sodium increased in the hyponatraemic children and did not change in the normonatraemic children. No child became hypernatraemic.
*Paired *t* test T_4 *v* T_0.

Table 3 Response of urinary sodium, potassium, tonicity (Na + K), and osmolality to either N/2 or NS, according to whether the children were hyponatraemic or normonatraemic at T_0 in the 36 children in whom a baseline urine sample (U_{base}) was collected within 2 hours of T_0 and a second sample (U_{2nd}) was collected a median of 4.8 hours (range 3–12) after T_0

	Hyponatraemic at T_0				Normonatraemic at T_0			
	N/2 (n=8)		NS (n=8)		N/2 (n=9)		NS (n=11)	
	U_{base}	U_{2nd}	U_{base}	U_{2nd}	U_{base}	U_{2nd}	U_{base}	U_{2nd}
Na (mmol/l)	72 (<10–204)	23 (<10–82)	38 (<10–109)	16 (<10–75)	80 (10–124)	59 (10–123)	79 (17–209)	125 (19–294)
p value	0.09		0.04		0.44		0.01	
K (mmol/l)	70 (12–91)	23 (4–38)	58 (19–88)	24 (6–55)	105 (57–171)	47 (10–74)	107 (42–232)	39 (9–94)
p value	0.02		0.02		0.008		0.003	
Tonicity (mmol/l)	151 (19–285)	45 (11–109)	106 (26–175)	40 (14–140)	178 (146–213)	104 (67–170)	183 (59–300)	165 (46–322)
p value	0.02		0.02		0.02		0.008	
Osmolality (mOsm/kg)	976 (322–1290)	506 (110–944)	935 (574–1072)	768 (339–1059)	1036 (856–1239)	648 (284–1139)	1076 (707–1200)	881 (317–1177)
p value	0.02		0.02		0.008		0.006	

Results are expressed as median (range).
The p values refer to the comparison by Kruskall Wallis test of U_{2nd} with U_{base}.

were treated according to the SRP (table 1) plus 18/78 (11 N/2, 7 NS) who completed the RRP but continued IV fluids according to the SRP because of continued vomiting or poor oral fluid intake. Plasma biochemistry at T_4 was similar to that of the group as a whole (data not shown). Plasma sodium concentrations were available at 24 hours in 16 children (8 N/2) who continued to receive at least half of their maintenance requirement of fluid[15] intravenously, at which time no child receiving NS had a plasma sodium <135 mmol/l (range 135–142 mmol/l) compared with 3/8 of the N/2 group (range 131–140 mmol/l). The maximum increase in plasma sodium over 24 hours was 12 mmol/l to 136 mmol/l in a child receiving NS.

To gauge the potential for clinically significant dilutional hyponatraemia among the 42 children who received prolonged IV fluids, each individual's longitudinal biochemical data were studied. Five of the 22 treated with N/2 but none treated with NS (N/2 *v* NS: p = 0.03, Fisher's exact test) had persistent significant hyponatraemia (sodium ⩽ 131 mmol/l) or falls in plasma sodium ⩾4 mmol/l to below 135 mmol/l associated with an inappropriately high urinary sodium content (range 30–140 mmol/l) and urine osmolality higher than plasma osmolality (range 462–1058 mOsm/kg), suggesting that they were at risk of dilutional hyponatraemia. The plasma and urinary abnormalities were documented to persist for a median of 19 hours (range 8–27).

As no child who received prolonged NS developed this problem, we analysed data from the 22 children who received N/2 for more than 4 hours to identify potential clinical or biochemical predictors that could allow early detection of those at risk. Comparing the five children who developed significant dilutional hyponatraemia with the remaining 17/22, no clinical or biochemical parameters emerged that would allow early identification of those at risk, except for continuation of IV fluids beyond 4 hours after completion of the RRP (completion of RRP: 5/5 affected *v* 6/17 unaffected; p = 0.04). Apart from a slightly higher median urea (6.8 mmol/l (range 5.3–9.1) *v* 5.1 mmol/l (range 1.2–8.7); p = 0.02) suggestive of more severe dehydration, there were no differences in their median age (p = 0.09), BMI SDS (p = 0.24), estimated degree of dehydration (p = 0.54), length of illness prior to presentation (p = 0.49), baseline plasma sodium (p = 0.82), bicarbonate (p = 0.09), or creatinine (p = 0.14). Three of the five children had stool cultures performed, all of whom were positive for rotavirus.

DISCUSSION

Recently, the basis for the use of intravenous hypotonic saline solutions in sick children has been questioned and it has been suggested that the use of isotonic saline solutions might decrease the frequency of iatrogenic hyponatraemia.[1 2 11] In this prospective, randomised study we have shown that when children with gastroenteritis are treated with intravenous fluids, hyponatraemia is less likely to develop or persist if an isotonic rather than hypotonic saline solution is used.

The baseline clinical and biochemical characteristics of the 102 children in our current report were similar to those in our previous study.[12] Hyponatraemia was common at presentation (36%). This has been attributed to the sodium content of diarrhoeal losses[19 20] and low salt intake;[19] but the inappropriately high urinary sodium content we again documented at presentation may also contribute. The relationship we observed between the sodium concentration in the first urine sample passed and the degree of ketonuria suggests that the excretion of ketones as sodium salts may have contributed to the relatively high urinary sodium concentrations, consistent with reported association between natriuresis and starvation.[19 21]

What is already known on this topic

- Hyponatraemia in hospitalised children, including those with gastroenteritis, is common and can be associated with cerebral oedema and death
- Hypotonic saline solutions are frequently used in children and have been suggested to contribute to the development of hyponatraemia

What this study adds

- Biochemical evidence shows that in children with gastroenteritis, hypotonic saline solutions exacerbate the tendency to develop dilutional hyponatraemia while isotonic saline solutions are protective
- Urinary biochemistry suggests that isotonic solutions are safe because hyponatraemic children retain sodium and normonatraemic children excrete it appropriately

Non-osmotic ADH activity is thought to underlie the development of hospital acquired dilutional hyponatraemia by preventing the excretion of electrolyte free water during fluid administration.[1 22] Gerigk and colleagues[23] documented raised ADH levels independent of osmolality in children with a variety of common acute childhood illnesses and we have reported that osmotically inappropriate ADH activity is common and persistent in children with gastroenteritis.[12] Consistent with this, the biochemical response to N/2 was almost identical in this and our previous study[12] in which all of the children received N/2. In both studies, the mean plasma sodium concentrations of children who were initially normonatraemic decreased, and those of children who were hyponatraemic did not improve in response to N/2. Half the normonatraemic children and 13% of the hyponatraemic children treated with N/2 experienced a decrease in plasma sodium ⩾2 mmol/l, and after 24 hours, 3 of 8 children largely dependent on IV fluids were hyponatraemic. In contrast, the use of isotonic saline over 4 hours resulted in maintenance of plasma sodium in those initially normonatraemic and an increase in those initially hyponatraemic. None developed hypernatraemia. After 24 hours, all 8/51 children still receiving normal saline were normonatraemic. Five of the 22 (23%) who received prolonged half-normal saline displayed biochemistry suggestive of dilutional hyponatraemia, compared with none of the 20 treated with normal saline. These findings suggest that in children with gastroenteritis, the use of hypotonic fluids exacerbates the tendency to develop hyponatraemia whereas the use of isotonic saline is protective.

The urinary biochemistry may provide some basis for understanding the decreased risk of hyponatraemia in children given isotonic saline and is reassuring with respect to the risk of hypernatraemia. As seen in our previous study,[12] despite mild to moderate dehydration and irrespective of the plasma sodium concentration, the median urinary sodium concentration at presentation approximated that of half-normal saline and the urinary tonicity approximated that of normal saline. Urinary tonicity is a better reflection of free water clearance than urinary osmolality[24] because an important component of osmolality is urea, which readily crosses cell membranes and therefore does not influence water movement. Administration of a fluid of lower tonicity than that of the urine being passed is predicted to result in a decrease in plasma sodium concentration because of the retention of free water implicit in the excretion of urine with a higher tonicity. After several hours of IV fluids, the urinary potassium decreased in all children in our study and the median urinary sodium concentrations of the hyponatraemic children in both treatment groups had decreased to levels consistent with maximal renal conservation of sodium (approximately 20 mmol/l;[25 26] table 3); thus the urinary tonicity of the hyponatraemic children had decreased to less than the tonicity of N/2. As a result, the plasma sodium concentrations of the hyponatraemic children receiving hypotonic saline were maintained (but not improved) over 4 hours, whereas plasma sodium increased in the hyponatraemic children who received NS, a fluid roughly isotonic with respect to their initial urinary tonicity. The normonatraemic children on the other hand, did not conserve sodium. Although urinary potassium excretion decreased in these children, the median urinary concentration of sodium was unchanged in the N/2 group and increased in the NS group. The normonatraemic children treated with N/2 therefore continued to excrete urine that was hypertonic relative to the infused fluid. This would explain the accompanying decrease in plasma sodium concentration. Those given NS continued to excrete urine isotonic with respect to the infused fluid and maintained their plasma sodium concentration unchanged.

The basis of the greater renal avidity for sodium in the hyponatraemic compared with the normonatraemic children is unclear. A similar phenomenon has been described in rats infused simultaneously with normal saline and ADH, in whom those fed a salt poor diet prior to the infusion were better able to retain sodium and maintain their plasma sodium than those whose dietary content of salt had been normal.[27] The median duration of illness was longer in the hyponatraemic children and therefore, in addition to more prolonged sodium losses in diarrhoeal stools[19] and urine,[12] their dietary intake of sodium is likely to have been lower than for those children who were normonatraemic at presentation. Relatively chronic sodium depletion therefore may have promoted the development of renal adaptive responses, resulting in more rapid reversal of the natriuresis evident at presentation. Differential suppression of aldosterone activity in the normonatraemic versus hyponatraemic children during fluid therapy might have contributed if the hyponatraemic children were more dehydrated at baseline; however there were no clinical or biochemical data to support this. Furthermore, the similar decrease in urinary potassium in the hyponatraemic and normonatraemic children and significant decrease in urinary sodium concentration in the hyponatraemic children treated with NS but not N/2 suggests that mechanisms other than aldosterone were acting.

We conclude that when intravenous fluids are deemed necessary in children with gastroenteritis, isotonic saline solutions with appropriate glucose content should be used. The question arises however as to whether this recommendation should be restricted to gastroenteritis. Non-osmotic stimulants of ADH secretion (such as nausea and vomiting, pain, and metabolic stress)[28] are common and likely to be active in a variety of clinical situations for which intravenous fluids are used. The protective effect of normal saline against the development of hyponatraemia and the ability of the normonatraemic children to increase urinary sodium excretion suggest that broadening the use of isotonic fluids with appropriate glucose content should be considered.

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REFERENCES

1 Duke T, Molyneux EM. Intravenous fluids for seriously ill children: time to reconsider. *Lancet* 2003;362:1320–3.
2 Moritz ML, Ayus JC. Prevention of hospital-acquired hyponatremia: a case for using isotonic saline. *Pediatrics* 2003;111:227–30.
3 Halberthal M, Halperin ML, Bohn D. Lesson of the week: Acute hyponatraemia in children admitted to hospital: retrospective analysis of factors contributing to its development and resolution. *BMJ* 2001;322:780–2.
4 Playfor S. Fatal iatrogenic hyponatraemia. *Arch Dis Child* 2003;88:646–7.
5 Anon. Practice parameter: The management of acute gastroenteritis in young children. American Academy of Pediatrics, Provisional Committee on Quality Improvement, Subcommittee on Acute Gastroenteritis. *Pediatrics* 1996;97:424–35.
6 Armon K, Stephenson T, MacFaul R, *et al*. An evidence and consensus based guideline for acute diarrhoea management. *Arch Dis Child* 2001;85:132–42.
7 Sandhu BK. European Society of Pediatric Gastroenterology. Practical guidelines for the management of gastroenteritis in children. *J Pediatr Gastroenterol Nutr* 2001;33(suppl 2).
8 Ozuah PO, Avner JR, Stein RE. Oral rehydration, emergency physicians, and practice parameters: a national survey. *Pediatrics* 2002;109:259–61.
9 Hoekstra JH. European Society of Paediatric Gastroenterology. Acute gastroenteritis in industrialized countries: compliance with guidelines for treatment. *J Pediatr Gastroenterol Nutr* 2001;33(suppl 5).
10 Elliott EJ, Backhouse JA, Leach JW. Pre-admission management of acute gastroenteritis. *J Paediatr Child Health* 1996;32:18–21.
11 Phin SJ, McCaskill ME, Browne GJ, *et al*. Clinical pathway using rapid rehydration for children with gastroenteritis. *J Paediatr Child Health* 2003;39:343–8.
12 Neville KA, Verge CF, O'Meara MW, *et al*. High antidiuretic hormone levels and hyponatraemia in children with gastroenteritis. *Pediatrics* 2005;116:1401–7.
13 Taylor D, Durward A. Pouring salt on troubled waters. *Arch Dis Child* 2004;89:411–14.
14 Ferson MJ. Hospitalisations for rotavirus gastroenteritis among children under five years of age in New South Wales. *Med J Aust* 1996;164:273–6.
15 Holliday MA, Segar WE. The maintenance need for water in parenteral fluid therapy. *Pediatrics* 1957;19:823–32.
16 Hamill PV, Drizd TA, Johnson CL, *et al*. Physical growth: National Center for Health Statistics percentiles. *Am J Clin Nutr* 1979;32:607–29.
17 Rolland-Cachera MF, Cole TJ, Sempe M, *et al*. Body mass index variations: centiles from birth to 87 years. *Eur J Clin Nutr* 1991;45:13–21.
18 Adelman RD, Solhaug MJ. Pathophysiology of body fluids and fluid therapy. In: Behrman RE, Kliegman RM, Jenson HB, eds. *Nelson textbook of pediatrics*. Philadelphia, PA: WB Saunders, 2000:211–15.
19 Hirschhorn N. The treatment of acute diarrhea in children. An historical and physiological perspective. *Am J Clin Nutr* 1980;33:637–63.
20 Molla AM, Rahman M, Sarker SA, *et al*. Stool electrolyte content and purging rates in diarrhea caused by rotavirus, enterotoxigenic E. coli, and V. cholerae in children. *J Pediatr* 1981;98:835–8.
21 Komel SK, Lin SH, Cheema-Dhadli S, *et al*. Prolonged total fasting: a feast for the integrative physiologist. *Kidney Int* 1998;53:531–9.
22 Steele A, Gowrishankar M, Abrahamson S, *et al*. Postoperative hyponatremia despite near-isotonic saline infusion: a phenomenon of desalination. *Ann Intern Med* 1997;126:20–5.
23 Gerigk M, Gnehm HE, Rascher W. Arginine vasopressin and renin in acutely ill children: implication for fluid therapy. *Acta Paediatr* 1996;85:550–3.
24 Berl T, Schrier RW. Disorders of water metabolism. In: Schrier RW, eds. *Renal and electrolyte disorders*. Philadelphia, PA: Lippincott, Williams & Williams, 2003:15.
25 Berl T, Schrier RW. Disorders of water metabolism. In: Schrier RW, eds. *Renal and electrolyte disorders*. Philadelphia, PA: Lippincott Williams & Williams, 2003:36–8.
26 Kumar S, Berl T. Sodium. *Lancet* 1998;352:220–8.
27 Gowrishankar M, Chen CB, Cheema-Dhadli S, *et al*. Hyponatremia in the rat in the absence of positive water balance. *J Am Soc Nephrol* 1997;8:524–9.
28 Robertson GL. Antidiuretic hormone. Normal and disordered function. *Endocrinol Metab Clin North Am* 2001;30:671–94.

ORIGINAL ARTICLE

Hypotonic versus isotonic saline in hospitalised children: a systematic review

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Background: The traditional recommendations which suggest that hypotonic intravenous (IV) maintenance fluids are the solutions of choice in paediatric patients have not been rigorously tested in clinical trials, and may not be appropriate for all children.
Aims: To systematically review the evidence from studies evaluating the safety of administering hypotonic versus isotonic IV maintenance fluids in hospitalised children.
Methods: Data sources: Medline (1966–2006), Embase (1980–2006), the Cochrane Library, abstract proceedings, personal files, and reference lists. Studies that compared hypotonic to isotonic maintenance solutions in children were selected. Case reports and studies in neonates or patients with a pre-existing history of hyponatraemia were excluded.
Results: Six studies met the selection criteria. A meta-analysis combining these studies showed that hypotonic solutions significantly increased the risk of developing acute hyponatraemia (OR 17.22; 95% CI 8.67 to 34.2), and resulted in greater patient morbidity.
Conclusions: The current practice of prescribing IV maintenance fluids in children is based on limited clinical experimental evidence from poorly and differently designed studies, where bias could possibly raise doubt about the results. They do not provide evidence for optimal fluid and electrolyte homoeostasis in hospitalised children. This systematic review indicates potential harm with hypotonic solutions in children, which can be anticipated and avoided with isotonic solutions. No single fluid rate or composition is ideal for all children. However, isotonic or near-isotonic solutions may be more physiological, and therefore a safer choice in the acute phase of illness and perioperative period.

Intravenous (IV) maintenance fluids are designed to provide free water and electrolyte requirements in a fasting patient. The prescription for IV maintenance fluids was originally described in 1957 by Holliday and Segar, who equated free water requirements from energy expenditure in healthy children.[1] They rationalised adding 3.0 and 2.0 mEq/100 kcal/24 h of sodium and potassium respectively, as it approximates the electrolyte requirements and urinary excretion in healthy infants.[2 3] This is the basis for the current recommendation that hypotonic IV maintenance solutions are ideal for children.[4 5] The Holliday–Segar system remains the most universally used to date, because of the simplicity of their formula. While these recommendations may be appropriate for the healthy child, they do not necessarily apply in acute illness, where energy expenditure and electrolyte requirements deviate significantly from this formula.[6]

The numbers of deaths and significant neurological sequelae from hospital acquired hyponatraemia in children receiving hypotonic maintenance solutions have increased in the past 10 years.[7–11] Several narrative reviews have suggested potential harm with these solutions and recommend that routine use in children be reconsidered.[12 13] Despite these concerns, standard texts and guidelines continue to recommend hypotonic maintenance solutions for all paediatric patients.[4 5] The objective of this systematic review was to evaluate the safety of hypotonic versus isotonic IV maintenance solutions in hospitalised children. Our secondary objective was to identify subgroups who are at greater risk of morbidity, in whom hypotonic solutions should be avoided.

METHODS

Search strategy

We searched Medline (1966–2006), Embase (1980–2006), and the Cochrane Library, using the terms: "fluid therapy", "hypotonic solution", "isotonic solution", and synonyms or related terms (Appendix 1; see http://www.archdischild.com/supplemental). We searched online (FirstSearch, Conference Proceedings) or published conference proceedings, and Current Controlled Trials (www.controlled-trials.com). Abstracts from the following 2002–05 scientific forums were hand searched: World Congress on Pediatric Intensive Care, Society for Pediatric Research, Critical Care Congress, and American Academy of Pediatrics. We reviewed the reference lists of all identified studies and reviews, and also personal files, and contacted experts and first authors to identify other published or unpublished studies.

Study selection

Citations considered potentially relevant by either of two reviewers (KC or MK) were retrieved using the following inclusion criteria:

- Controlled trials, cohort, and case-control studies. Cohort studies had to compare patients receiving hypotonic IV maintenance solutions with a control group or unexposed cohort who received isotonic solutions. Case-control studies had to compare cases, to a control group who did not have the outcomes of interest.
- Children (1 month to 17 years) hospitalised for any medical or surgical condition. We included a diverse paediatric population to capture all potential patients who currently receive "standard IV maintenance therapy".
- Intervention: currently used hypotonic and isotonic IV maintenance solutions. Solutions were classified as

Abbreviations: CI, confidence interval; ECF, extracellular fluid; IV, intravenous; PNa, plasma sodium; RCT, randomised controlled trial; WMD, weighted mean difference

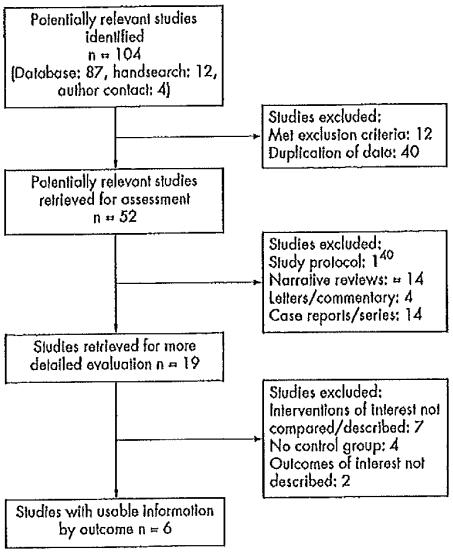

Figure 1 Flow diagram of the study selection process for this systematic review.[33]

"hypotonic" if they contained <0.9% NaCl, or "isotonic or near isotonic" (i.e. 0.9% NaCl or Ringers Lactate). We excluded case reports and studies of fluid resuscitation and oral rehydration therapy. Studies enrolling neonates, patients with pre-existing hyponatraemia and co-morbidities which result in sodium derangements (e.g. renal disease, diabetes insipidus, diuretic therapy), were also excluded.

Study outcomes

Studies were included if any of the following outcomes related to the development of acute hospital acquired plasma sodium (PNa) derangements and/or their attributed morbidity were reported: fluid balance, clinical evidence of volume overload, hypertension, seizures, cerebral oedema, death, paediatric intensive care unit admission, and length of stay. We used PNa as a surrogate outcome, as it is a convenient reflection of tonicity balance, and represents the potential for fluid shifts between intracellular and extracellular fluid (ECF) compartments. This in turn may result in clinically relevant morbidity, such as the defined outcomes of interest. A priori, we defined hyponatraemia as PNa <136 mmol/l, and severe hyponatraemia as PNa <130 mmol/l, or any level of hyponatraemia associated with symptoms. We also examined hypernatraemia since the arguments against the use of isotonic solutions in children include renal solute loading and the risk of increasing PNa. We defined hypernatraemia as PNa >145 mmol/l.

Data abstraction and study quality

In duplicate and independently, we abstracted data to describe the methodological quality and clinical characteristics of these trials. We contacted authors where necessary for additional data on outcomes of interest. We extracted the following information: study population, sample size, intervention, duration, and type of exposure and outcomes. The methodological quality of included studies was assessed using predefined criteria (Appendices 2 and 3; see http://www.archdischild.com/supplemental).

Data analysis

Cohen's Kappa statistic was used to calculate agreement between raters. For categorical outcomes, treatment effects were expressed as odds ratios (OR) and 95% confidence intervals (CI). We described treatment effects of continuous outcomes using weighted mean differences (WMD) and 95% CI. We calculated summary risk differences and 95% CI using a random effects model (RevMan Version 4.2). Where statistical pooling was not possible, we described our findings qualitatively.

RESULTS

Study selection

We identified 52 potentially relevant articles from 104 citations (fig 1); 33 did not meet inclusion criteria. Of the 19 studies retrieved for detailed evaluation, seven did not describe or compare the interventions of interest, four did not describe a control group, and two did not report any of the outcomes of interest. Six studies satisfied all criteria (table 1). Cohen's Kappa for inclusion decisions was 0.81 (almost perfect agreement).

Study characteristics

We report the characteristics of the six included studies in table 1. There were two unmasked randomised controlled trials (RCT),[14 15] and one non-randomised controlled trial.[16] Three were observational studies.[17–19] Tables 3–5 outline the study quality and methodological characteristics—the overall quality of included studies was often limited; allocation concealment, blinding of patients, clinicians, outcomes assessors, and outcomes were inconsistently or not reported across studies.

Clinical outcomes

Plasma sodium

The standard deviations (SD) were not presented for PNa in one of the studies.[14] Thus, we calculated a pooled SD to compare the PNa across studies. Hypotonic maintenance solutions significantly increased the risk of developing hyponatraemia (OR 17.22; 95% CI 8.67 to 34.2) (fig 2). Mean PNa in patients following hypotonic solutions was significantly lower (−3.39 mmol/l; 95% CI −5.35 to −1.43), than those who received isotonic solutions (fig 3). The PNa also decreased significantly greater in patients who received hypotonic solutions (−5.37 mmol/l; 95% CI −8.79 to −1.94, fig 4). None of the studies reported the development of hypernatraemia. However, three studies reported a *decrease* in PNa despite the infusion of isotonic or near-isotonic IV maintenance fluids (table 1).[15 17]

Morbidity attributed to hyponatraemia

Adverse clinical outcomes were reported in three studies.[17–19] Wilkinson reported seizures in 2/26 patients receiving hypotonic fluids (OR 6.22; 95% CI 0.29 to 135.8).[19] Hoorn reported nausea and vomiting more commonly in patients with hospital acquired hyponatraemia (68%, p = 0.008)[18] than isonatraemic controls. The presence of increased pulmonary interstitial fluid on chest *x* ray was reported by Burrows in 15/20 of patients receiving hypotonic solutions and 2/4 in the near-isotonic group.[19] The clinical significance of this finding was not commented on by the authors. Other outcomes of interest as listed in our objectives were not reported.

Table 1 Characteristics of included studies

	Brazel (1996)[14]	Degl (1997)[15]	Neville (2006)[16]	Hoorn (2004)[17]	Burrow (1983)[18]	Williamson (1992)[19]
Participants						
n	12	60	104	148	24	56
Age (years)	12–18.1	1–12	6 months–14 years	7 ± 6	2–16	2 months–14 years
Inclusion criteria	Adolescent females undergoing idiopathic scoliosis repair	ASA 1; patients undergoing elective minor surgery	Gastroenteritis with dehydration	87 patients with hospital acquired hyponatraemia; 111 isonatraemic historical controls	Previously healthy patients with idiopathic scoliosis undergoing surgical correction	Craniofacial surgery
Methodology	RCT, unmasked	Controlled trial	RCT, unmasked	Case control	Cohort study	Retrospective chart review
Intervention (all solutions included appropriate dextrose content unless otherwise stated)	Near isotonic solution (IR), n=5: v hypotonic solutions: [0.3%–0.18% NaCl], n=7	Gp 1: IR Gp 2: 1% Dextrose in 0.3% NaCl Gp 3: 3.3% Dextrose in 0.3% NaCl	Gp 1: 0.45% NaCl Gp 2: 0.9% NaCl	Standard prescription for maintenance IV fluids	Postoperative maintenance fluids: Gp 1 (IR), n=4: Isotonic (0.22–0.3% NaCl), n=20 Hypotonic (0.22–0.3% NaCl), n=26	Isotonic (IR or NS), n=30 Hypotonic (0.16–0.5% NaCl), n=26
Outcomes						
PNa mmol/l	Postop PNa in Gp 3 significantly lower (p<0.05); No significant change in Gp 1, and 2	Mean PNa after 4 hours: Gp 1: 134.3 mmol/l (2.1) Gp 2 136.3 mmol/l (3.3)	Cases: PNa dropped from 139–9 to 133 ± 2 mmol/l in 19 ± 10 hours Controls: PNa 140 ± 2 mmol/l	Greater fall in PNa in hypotonic group: 6.2 ± 2.9 mEq/l (p<0.05); 3.0 ± 0.8 mEq/l in isotonic group	Median PNa: 130.5 (121–136) in hypotonic Gp; 139 in isotonic group	
Hyponatraemia (PNa <136)	1 patient in IR group, 7 in hypotonic group (p<0.05)	PNa in hypotonic group (Gp 3): 133.3 ± 4.6 mEq/l	21/31 in Gp 1, 2/21 in Gp 2	All cases by definition	Postop PNa: 131 ± 2.8 in hypotonic group; 135 ± 1.9 mmol/l in isotonic group	20/26 patients in hypotonic group; 2/30 in isotonic group
Severe hyponatraemia (PNa <130)	4 in hypotonic group	Not described	5/22 in Gp 1 (PNa <130); 0/22 in Gp 2	Not described	5 patients in hypotonic group	11 in hypotonic group
Clinical sequelae related to hyponatraemia	Not described	Not described	None described	Main: nausea and vomiting	Increased interstitial pulmonary fluid in hypotonic group (p<0.05)	Seizures: 2/26 in hypotonic group
	Not mentioned	None	None	reported in hypernatraemic group	None	None
Hypernatraemia (PNa >145)	None	None	None	None	None	None

CVS, cardiovascular; IR, Lactated Ringers; NS, normal saline; PNa, plasma sodium; pre/post-op, pre- or postoperative; Gp, group; NaCl, sodium chloride; RCT, randomised controlled trial.

Table 2 Characteristics of excluded studies

Study	Method	Participants	Interventions	Primary outcome of study	Reason for exclusion
Neville [2005][13]	Cohort study	Children with gastroenteritis (n = 52)	Hypotonic IV fluids	PNa; osmolality; ADH; urine electrolytes and osmolality; cortisol; and thyroid hormone	No control group
Cupisti [2000][23]	Cohort study	Post-op craniofacial patients (n = 16)	Isotonic fluid	PNa	No control group
Halberthal [2001][24]	Retrospective chart review	Hospital acquired severe hyponatraemia within 48 h admission (n = 23)	Hypotonic fluid	Factors contributing to hospital acquired hyponatraemia	No control group
Gerlck [1996][21]	Case-control study	103 cases; 31 age matched controls	IV/PO fluid therapy	ADH and plasma renin activity in cases v controls	Outcomes of interest not described
Lavine [2001][24]	Cohort study	Craniofacial patients (n = 10)	Isotonic IV fluid	Serum and urine electrolytes	No control group
Judd [1990][24]	Case-control study	Tonsillectomy (n = 13)	Gp 1: perioperative NS IV fluid, GP 2: NPO, no IV fluids	Serum electrolytes, ADH, and plasma renin activity	Only one intervention of interest described
Duke [2002][25]	RCT	Children with meningitis	Hypotonic IV fluids v moderate oral fluid restriction	Survival and neurological status	Only one intervention of interest described
Cowley [1988][26]	Cohort study	8 healthy children undergoing scoliosis repair	Type of fluids not described individually	Serum and urine electrolytes; ADH and renin activity	Type of fluids not individually described
Arieff [1999][25]	Retrospective chart review	Fatal cases of post-op hyponatraemia	Not described	Volume of fluid administered	Intervention not described, primarily adult study
Waitad [1992][27]	Retrospective chart review	Patients admitted with hyponatraemia	Not described	Aetiology of hyponatraemia	Interventions of interest not described
Dunn [1997][28]	Retrospective chart review	Patients with PNa>165 or Na<130	Not described	Aetiology of hospital acquired PNa derangements	Interventions of interest not described
McCormick [1999][29]	Retrospective chart review	Elective paediatric surgical cases	Hypotonic or isotonic fluids	Not described	Outcomes of interest not described
Powell [1990][23]	RCT	Children with meningitis	Fluid restriction v maintenance plus deficit replacement	PNa; plasma AVP levels	Type of fluids not individually described

ADH, antidiuretic hormone; IV, intravenous; PO, oral.

Table 3 Quality assessment, controlled trials

Author	Subjects: Description of subjects adequate	Allocation concealment adequate	Method of randomisation described	Well matched/ objective interventions	Care taker/ pt blinding	Intervention: Definition adequate	Blinding adequate	Outcomes: Follow up adequate	Analysis: Sufficient (>90%)	ITT	Adjustment for confounders	Data provided to confirm results
Brazal	Yes	No	No	Yes	No	Yes	No	Yes	No	No	No	Yes
Dogli	Yes	No	No	Yes	No	Yes	No	Yes	No	No	No	Yes
Nerolla	Yes	Unclear	Yes	Yes	No	No	No	Yes	No	No	No	Yes

Table 4 Quality assessment; observational studies—cohort studies

Author	Selection: Representativeness of exposed cohort	Selection: Selection of non-exposed cohort	Selection: Ascertainment of exposure	Selection: Outcome of interest not present at start of study	Comparability	Outcome: Assessment	Outcome: Follow up: outcomes	Outcome: Follow up: cohorts
Burrows	*	*	*	*		*	*	*
Wilkinson	*	*	*	*		*	*	*

Table 5 Quality assessment; observational studies—case-control studies

Author	Selection: Case definition	Selection: Representativeness	Selection: Selection of controls	Selection: Definition of Controls	Comparability	Exposure: Ascertainment	Exposure: Method of ascertainment	Exposure: Non-response rate
Hoorn	*	*	*	*	*	*	*	*

Volume of IV fluid administration

Hoorn reported that patients with hospital acquired hyponatraemia did not receive significantly greater total fluid volume than isonatraemic patients, however the calculated electrolyte-free water intake was three times greater compared to the isonatraemic controls ($p < 0.001$). The total sodium intake in mmol/kg/h was not significantly different between the two groups.[18] The volume of IV fluid infused was not a determinant of the change in PNa at four hours in Neville's study of patients with gastroenteritis.[15] Fluid balance and volumes of fluid infused were not specifically presented in the other studies, but described as "same in both groups".

Subgroups

Four of the included studies were in surgical patients,[14 16 17 19] and one study enrolled patients with gastroenteritis.[15] Hoorn identified more surgical patients in the hospital acquired hyponatraemia group (16%), than in the isonatraemic controls (5%, $p = 0.04$).[18] All studies examined associations using univariate analyses; none used multivariate analyses to adjust for confounding factors.

Heterogeneity

Given the small number of studies, we chose to include and analyse results from both controlled trials and observational studies. Visual inspection of the Forrest plots indicated study heterogeneity; however formal statistical tests in this instance are underpowered to detect and adjust for clinically important heterogeneity, given the small number of outcomes, patients, and studies. We thus chose to describe the sources of clinical heterogeneity. (1) *Patients* included in this systematic review were heterogeneous, however the majority of studies were in the surgical population. (2) The degree of *exposure to the interventions* varied between studies—the timing of PNa measurements occurred after variable degrees and duration of exposure to intervention. (3) The majority of studies were limited in their *quality* (tables 3–5). Despite apparent heterogeneity in study design, participants, and quality among these studies, the treatment effect nevertheless appears to be remarkably consistent across the studies.

DISCUSSION

Intravenous fluids are used in children to either expand a contracted ECF space or as "maintenance" to replace urine

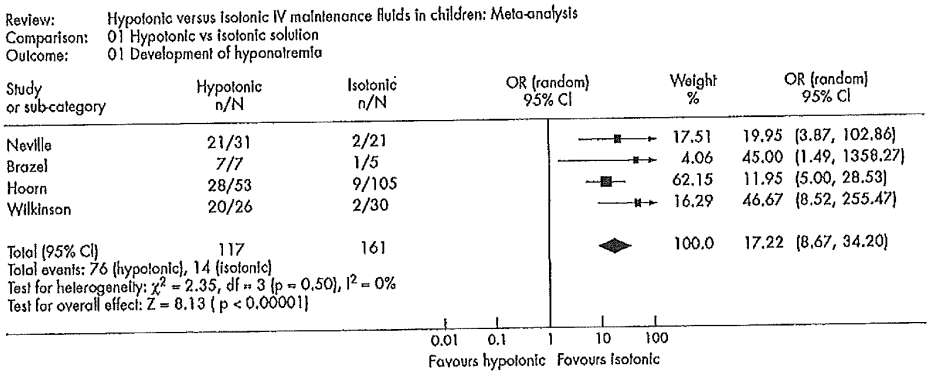

Figure 2 Forrest plot summarising the odds ratios and associated 95% confidence intervals for developing hyponatraemia in children receiving hypotonic compared to isotonic IV maintenance fluids.

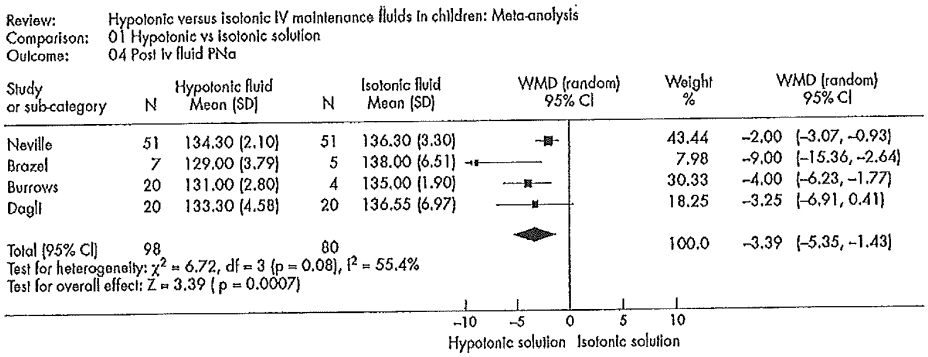

Figure 3 Comparison of PNa levels following hypotonic versus isotonic or near-isotonic IV maintenance fluids.

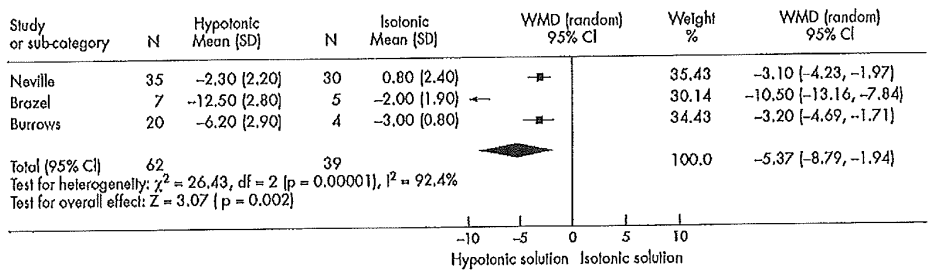

Figure 4 Mean change in PNa following hypotonic versus isotonic IV maintenance fluids.

output and insensible losses. In the former instance isotonic or near-isotonic saline is recommended on the basis that it is the physiologically appropriate solution. In the latter case hypotonic saline solutions are the accepted standard of care. This systematic review reveals that the evidence for the safety of this ubiquitous practice is limited, with only six published studies (only two of which were RCTs) reporting data on a total of 404 patients. The current level of evidence suggests that hypotonic maintenance solutions in children are not benign, but in fact potentially dangerous. The overall treatment effect is remarkable with the odds of developing hyponatraemia following hypotonic solutions being *17.2 times greater* than with isotonic fluids. Hence, there are potential risks associated with the use of hypotonic solutions in children, such as cerebral oedema precipitated by an acute fall in serum osmolality.

Hyponatraemia occurs due to a positive balance of electrolyte free water, combined with an impaired ability to excrete hypotonic urine secondary to ADH secretion. A significant correlation between free water intake and decrease in PNa has been demonstrated.[20] The primary source of electrolyte free water is the exogenous administration of hypotonic fluid. In contrast to healthy individuals, hospitalised patients have multiple non-osmotic stimuli for ADH secretion, which prevents them from producing water diuresis even in the presence of a PNa that is lower than 136 mmol/l.[12 15 21] In such patients, there will be very little if any excretion of electrolyte free water, because ADH makes the later parts of the distal nephron permeable to water.[22] The risk of hyponatraemia in these patients is under-recognised,[14 17 21] and is thus compounded by the administration of hypotonic solutions. However, the administration of isotonic maintenance solutions at least in children with meningitis, has been shown to result in a more rapid return of ADH to normal concentrations, when compared to hypotonic fluids.[23] Neville demonstrated that patients admitted with gastroenteritis have obligate urinary sodium losses irrespective of initial PNa.[15] The urinary tonicity at presentation of these patients approximates that of normal saline. Therefore infusion of a hypotonic solution which is lower in tonicity than that of urine passed is predictive of a decrease in subsequent PNa.

The concern that isotonic maintenance fluids may cause hypernatraemia is not supported in the studies we reviewed, nor is it reported in adults where the use of isotonic solutions is routine. On the contrary, the risks of hyponatraemia may also extend to patients who receive isotonic fluid.[14-16 21 24] This can be explained at least in part by the excretion of relatively hypertonic urine as demonstrated by Neville and others.[15 21 25] Steele observed that the expansion of the ECF with Ringers Lactate in the perioperative period results in the production of a hypertonic urine resulting in "desalination".[26] However,

What is already known on this topic

- The current standard of prescribing maintenance IV fluids is based on historical evidence
- The safety of this practice is yet to be tested in well conducted clinical trials

What this study adds

- This is the first systematic review which examines the evidence for standard IV maintenance solutions in children
- This review provides evidence that, at least in some paediatric patients, hypotonic solutions exacerbate the risks of hyponatraemia, while isotonic solutions may be protective

hypernatraemia can occur during the administration of isotonic saline if a hypotonic urine is produced, leading to a positive sodium balance.

The traditional guidelines for fluids in children, published 50 years ago, and more recently reiterated,[27 28] were derived from estimates of insensible water losses, and electrolyte requirements for normal growth.[1] These calculations have since been criticised, and may lead to an overestimation of hypotonic fluid requirement in sick children.[6 29] It has been demonstrated that it is not simply Na^+ intake, but moreover its ratio to electrolyte free water intake that influences PNa.[18] These findings challenge the previous recommendations made by Holliday and Segar, and argue for a maintenance solution and volume which maintains tonicity balance during acute illness, rather than one which merely provides a daily sodium or caloric requirement. We used PNa as a surrogate measure of morbidity related to fluid shifts between intra- and extracellular compartments. PNa is a convenient marker as it reflects the ratio between effective osmoles and total body water. As Na^+ is the principal extracellular cation and therefore the main determinant of ECF volume, it regulates water movement across cell membranes and explains the development of intracellular oedema that occurs in the presence of hyponatraemia. The expansion of intracellular fluid volume is of major importance in the central nervous system as the brain is confined in a rigid bony cage and has only limited ability to expand. Thus brain cell swelling is very likely to increase intracranial pressure and predispose to brain herniation. Children are at greater risk of this sequela because their brains have a larger intracellular fluid volume per total skull volume.[30] Certainly among children who develop symptomatic hyponatraemia, the incidence of permanent brain damage is substantially higher than in adults.[31]

The results of this systematic review validate the growing concerns expressed in reports which question the safety of our current practice.[11 12] The strengths of this report include a comprehensive search strategy, explicit selection criteria for relevant primary studies, reliability assessment of study screening and study quality, validity assessment of primary studies, statistical pooling of effect sizes, focus on adverse events, and reporting according to QUOROM guidelines.[32] The weaknesses are that most studies reviewed were heterogeneous in design, small, and of variable quality, did not allow for confounding factors, and focused on a limited paediatric population. Therefore we cannot state with certainty that the principles are applicable to all children prescribed IV maintenance fluids. On the other hand, we can state that, based on published case reports of deaths and neurological injury from acute hyponatraemia that the administration of hypotonic solutions to children with a PNa <138 mmol/l is potentially hazardous, given the fact that ADH is likely to be acting.

Conclusions

The current practice of prescribing IV maintenance fluids in children is not based on clinical experimental evidence using patient-important outcomes, and does not provide optimal fluid and electrolyte homeostasis in hospitalised children. There is evidence that, at least in some paediatric patients, hypotonic solutions exacerbate the risks of hyponatraemia, while isotonic solutions may be protective. Our current responsibility however, is to refrain from adopting a "new standard of care", until rigorous clinical trials comparing the safety and effectiveness of different IV fluid regimens in children have been completed.

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REFERENCES

1 Holliday MA, Segar ME. The maintenance need for water in parenteral fluid therapy. *Pediatrics* 1957;19:823–32.
2 Wallace WM. Quantitative requirements of infant and child for water and electrolytes under varying conditions. *Am J Clin Pathol* 1953;23:1133–41.
3 Darrow DC, Pratt EL. Fluid therapy, relation to tissue composition and expenditure of water and electrolytes. *JAMA* 1950;143:432–9.
4 Siegel NJ. Fluids, electrolytes and acid-base. In: *Rudolph's pediatrics*, 21st edn. New York: McGraw Hill, 2003.
5 Greenbaum LA. Pathophysiology of body fluids and fluid therapy. In: *Nelson's textbook of pediatrics*, 17th edn. Philadelphia: W.B. Saunders, 2004.
6 Shafiee MAS, Bohn D, Hoorn EJ, *et al*. How to select optimal maintenance intravenous fluid therapy. *QJM* 2003;96:601–10.
7 Arieff AI, Ayus JC, Fraser CL. Hyponatraemia and death or permanent brain damage in healthy children. *BMJ* 1992;304:1218–22.
8 Armour A. Dilutional hyponatremia: a cause of massive fatal intra-operative cerebral edema in a child undergoing renal transplantation. *J Clin Pathol* 1997;50:444–6.
9 Hughes PD, Nichols D, Mutton PM. Postoperative hyponatremic encephalopathy: water intoxication. *Aust N Z J Surg* 1998;68:165–8.
10 Peeters A, Claes J, Saldien V. Lethal complications after tonsillectomy. *Acta oto-rhino-laryngologica Belg* 2001;55:207–13.
11 Paut O, Remond C, Lagier P. Severe hyponatremic encephalopathy after pediatric surgery: report of seven cases and recommendations for management and prevention. *Ann Fr Anesth Reanim* 2000;19:467–73.
12 Duke T, Molyneux EM. Intravenous fluids for seriously ill children: time to reconsider. *Lancet* 2003;362:1320–3.
13 Taylor D, Durward A. Pouring salt on troubled waters. *Arch Dis Child* 2004;89:411–14.
14 Brazel P, McPhee IP. Inappropriate secretion of antidiuretic hormone in postoperative scoliosis patients: the role of fluid management. *Spine* 1996;21:727.
15 Neville K, Verge C, Rosenberg A, *et al*. Isotonic is better than hypotonic saline for intravenous rehydration of children with gastroenteritis: a prospective randomised study. *Arch Dis Child* 2006;91:226–32.
16 Dagli G, Orhan ME, Kurt E. The effects of different hydration fluids used in pediatric anaesthesia on blood glucose, electrolytes, and cardiovascular stability. *GATA Bulteni* 1997;39:146–52.

17 Burrows F, Shutack JG, Crone R. Inappropriate secretion of antidiuretic hormone in a post surgical pediatric population. *Intensive Care Med* 1983;11:527–31.
18 Hoorn EJ, Geary D, Robb M, *et al.* Acute hyponatremia related to intravenous fluid administration in hospitalized children: an observational study. *Pediatrics* 2004;113:1279–84.
19 Wilkinson E, Rieff J, Rekate H, *et al.* Fluid, blood, and blood product management in the craniofacial patient. *Pediatr Neurosurg* 1992;18:48–52.
20 Cowley DM, Pobari M, Sinton TJ, *et al.* Pathogenesis of postoperative hyponatremia following correction of scoliosis in children. *Aust N Z J Surg* 1988;58:485–9.
21 Gerigk M, Gnehm H, Rascher W. Arginine vasopressin and renin in acutely ill children: implication for fluid therapy. *Acta Paediatr* 1996;85:550–3.
22 Roberston GL. *Vasopressin*. Philadelphia, PA: Lippincott Williams and Wilkins, 2000.
23 Powell KR, Sugarmann LI, Eskanazi AE. Normalisation of plasma arginine vasopressin concentrations when children with meningitis are given maintenance plus replacement fluid therapy. *J Pediatr* 1990;117:515–22.
24 Levine JP, Stelnicki E, Weiner HL, *et al.* Hyponatremia in the postoperative craniofacial pediatric patient population: a connection to cerebral salt wasting syndrome and management of the disorder. *Plastic & Reconstructive Surgery* 2001;108:1501–8.
25 Cupido C, Dalla-Mulle I, Holperin MI, *et al. Postoperative desalination in paediatric patients*. Toronto: Dept of Critical Care Medicine, The Hospital for Sick Children and Dept of Nephrology, St Michael's Hospital, 2000.
26 Steele A, Gowrishankar M, Abrahamson S, *et al.* Postoperative hyponatremia despite near-isotonic saline infusion: a phenomenon of desalination. *Ann Intern Med* 1997;126:20–5.
27 Chesney CR. The maintenance need for water in parenteral fluid therapy. *Pediatrics* 1998;102(1 Pt 2):399–400.
28 Holliday MA, Segar ME. Reducing errors in fluid therapy management. *Pediatrics* 2003;111:424–5.
29 Hatherill M. Rubbing salt in the wound. *Arch Dis Child* 2004;89:414–18.
30 Halberthal M, Halperin MI, Bohn D. Lesson of the week: Acute hyponatraemia in children admitted to hospital: retrospective analysis of factors contributing to its development and resolution. *BMJ* 2001;322:780–2.
31 Chung HM, Kluge R, Schrier RW, *et al.* Postoperative hyponatremia: a prospective study. *Arch Intern Med* 1986;146:333–6.
32 Moritz ML, Ayus JC. Prevention of hospital-acquired hyponatremia: a case for using isotonic saline. *Pediatrics* 2003;111:227–30.
33 Moher D, Cook DJ, Eastwood S, *et al.* Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. *Lancet* 1999;354:1896–900.
34 Judd BA, Haycock GB, Dalton RN, *et al.* Antidiuretic hormone following surgery in children. *Acta Paediatr Scand* 1990;79:461–6.
35 Duke T, Mokela D, Frank D, *et al.* Management of meningitis in children with oral fluid restriction or intravenous fluid at maintenance volumes: a randomised trial. *Ann Trop Paediatr* 2002;22:145–57.
36 Arieff AI. Fatal postoperative pulmonary edema: pathogenesis and literature review. *Chest* 1999;115:1371–7.
37 Wattad A, Chiang ML, Hill LL. Hyponatremia in hospitalized children. *Clin Pediatr* 1992;31:153–7.
38 Dunn K, Butt W. Extreme sodium derangement in a paediatric inpatient population. *J Paediatr Child Health* 1997;33:26–30.
39 McCormick A, Gande R, Lewis I. Postoperative hyponatraemic encephalopathy following elective surgery in children. *Paediatr Anaesth* 1999;9:551–2.
40 Duke T, Mathur A, Kukuruzovic R, *et al.* Hypotonic vs Isotonic saline solutions for intravenous fluid management of acute infections (review). *The Cochrane Database of Systematic Reviews* 2006(2).

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ORIGINAL ARTICLE

Randomised controlled trial of intravenous maintenance fluids

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Aim: Traditional paediatric intravenous maintenance fluids are prescribed using hypotonic fluids and the weight-based 4:2:1 formula for administration rate. However, this may cause hyponatraemia in sick and post-operative children. We studied the effect of two types of intravenous maintenance fluid and two administration rates on plasma sodium concentration in intensive care patients.

Methods: A factorial-design, double-blind, randomised controlled trial was used. We randomised 50 children with normal electrolytes without hypoglycaemia who needed intravenous maintenance fluids for >12 h to 0.9% saline (normal saline) or 4% dextrose and 0.18% saline (dextrose saline), at either the traditional maintenance fluid rate or 2/3 of that rate. The main outcome measure was change in plasma sodium from admission to 12–24 h later.

Results: Fifty patients (37 surgical) were enrolled. Plasma sodium fell in all groups: mean fall 2.3 (standard deviation 4.0) mmol/L. Fluid type ($P = 0.0063$) but not rate ($P = 0.12$) was significantly associated with fall in plasma sodium. Dextrose saline produced a greater fall in plasma sodium than normal saline: difference 3.0, 95% confidence interval 0.8–5.1 mmol/L. Full maintenance rate produced a greater fall in plasma sodium than restricted rate, but the difference was small and non-significant: 1.6 (−0.7, 3.9) mmol/L. Fluid type, but not rate, remained significant after adjustment for surgical status. One patient, receiving normal saline at restricted rate, developed asymptomatic hypoglycaemia.

Conclusion: Sick and post-operative children given dextrose saline at traditional maintenance rates are at risk of hyponatraemia.

Key words: child; fluid therapy; infusion; intravenous.

Intravenous (IV) fluids have been used in paediatrics for over 50 years. The most commonly used maintenance fluid, used to replace normal expected fluid losses in situations such as fasting, is hypotonic saline with dextrose. Volumes are typically calculated using a weight-based infusion rate: for the first 10 kg, 4 mL/kg/h, for the next 10 kg, 2 mL/kg/h and 1 mL/kg/h for each kilogram thereafter.[1–6] However, it may be inappropriate for those children who have non-osmotic production of antidiuretic hormone (ADH). The syndrome of inappropriate ADH[7] occurs in meningitis,[8,9] encephalitis,[10] pneumonia,[11] bronchiolitis[12] and after surgery.[13–16] Any consequent hyponatraemia may be exacerbated by hypotonic IV fluids.[14,17]

Natriuresis (urinary salt loss) may cause hyponatraemia. Sodium loss and hypovolaemia occur in cerebral salt wasting (CSW),[18,19] probably caused by a hormone such as atrial natriuretic hormone.[19] Hyponatraemia in neurosurgical patients may be from CSW, not the syndrome of inappropriate ADH.[20] CSW occurs in children with neurological illness, neurosurgery and craniofacial surgery.[21–23]

Key Points

1. Children who are sick or post-operative are at risk of hyponatraemia.
2. Surgical patients may have greater falls in plasma sodium concentration than medical patients.
3. The tonicity of the fluid has a greater effect than the rate of administration.

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Symptomatic hyponatraemia is uncommon if the plasma sodium ([Na]) is >120–125 mmol/L,[24,25] but depends on the rate of fall,[26] and can occur at higher values.[17] It can cause death or serious neurological morbidity.[26–28]

Recently, the prevention of hyponatraemia in hospitalised children has been debated.

Moritz and Ayus recommended isotonic maintenance fluid: 0.9% saline (NS) in 5% dextrose, instead of hypotonic fluid such as 4% dextrose and 0.18% saline (DS) or 0.45% saline, without fluid restriction.[29] Taylor and Durward recommended isotonic solutions with fluid restriction, citing small insensible losses in inactive, hospitalised children, non-osmotic ADH secretion, and increased water of oxidation.[30] Maintenance therapy for acutely ill or post-operative children is thus 50–60 mL/kg/day as NS to prevent desalination (loss of total body sodium),[13] without hypernatraemia.[31]

Others have opposed using isotonic maintenance fluid.[32] The primary cause of hyponatraemia is not desalination but dilution. Non-osmotic ADH secretion and the isotonic salt load could cause both increased total body water and over-expansion of the intravascular space. The resultant aldosterone suppression, natriuretic peptide secretion, and/or increased glomerular filtration may cause a secondary natriuresis. Hyponatraemia has developed in surgical patients receiving isotonic fluids.[13] The

lack of evidence for different fluid regimens justifies a randomised controlled trial, comparing both volumes and fluid types.[32] No such trial has been carried out.[33]

Five randomised controlled trials of IV fluids in children are reported. Three in children with meningitis suggested that fluid restriction was unwarranted.[34–36] None studied fluid tonicity. Some consider it unethical to give traditional maintenance fluid volumes to children with neurological and similar conditions.[37] Two other trials, one after scoliosis surgery[38] and one in gastroenteritis,[39] found that [Na] fell with hypotonic but not isotonic fluid. The former was in a select group of surgical patients and the latter was a trial of therapeutic fluid replacement in gastroenteritis – a very different situation from provision of maintenance fluid.

We carried out a factorial, randomised controlled trial comparing IV NS (isotonic) to DS (hypotonic), and the traditional versus restricted rate. The main outcome was the change in [Na] 12–24 h after admission. A second study arm compared isotonic and hypotonic fluid at restricted rates in children who would normally be fluid restricted. Because we recruited too few patients for the restricted arm, only the main arm is reported here. The main end point was the change in [Na], not neurological outcome, because detecting such a difference requires a prohibitively large sample size, and may be unethical. This outcome was a surrogate in a systematic review published after our study was conducted.[40]

Materials and Methods

Setting

The Women's and Children's Hospital is the tertiary paediatric referral centre in South Australia. The paediatric intensive care unit (PICU) has 12 beds and admits 500–550 patients annually. The hospital's research ethics committee approved the study.

Subjects

Eligible subjects were children admitted to the PICU who would normally receive IV fluid as DS at traditional maintenance rates for at least 12 h, with normal [Na] (135–145 mmol/L) and no hypoglycaemia. We classified the Australian and New Zealand Paediatric Intensive Care Registry diagnostic codes[41] into three groups: ineligible, eligible for both arms, and eligible only for the restricted arm. We excluded neonates, and those with diabetes, renal failure or shock. Conditions eligible only for the restricted arm included cardiac and neurosurgical patients. A list of ineligible and restricted fluid conditions is available from the authors.

We obtained written, informed consent from the parents or the patient. They were approached as soon as possible after PICU admission, once the initial [Na] and blood glucose were known, and before starting maintenance IV fluids.

Study fluids

Study fluids were prepared by non-clinical staff, using standard solutions and covering the bags with black plastic. The bags were put into sealed, numbered boxes. All clinical staff were blinded to the fluid type, but not rate. A code was kept in the pharmacy enabling unmasking if needed. Any additives were injected through the usual port without identifying the fluid.

Randomisation was by random numbers using blocks of six. Enrolled patients were assigned consecutive study numbers from a list, and received the corresponding numbered box containing study fluid, with the administration rate specified as 'maintenance' or 'restricted' inside the box, invisible until the box was opened.

For those randomised to the 'maintenance' group, the study fluid was administered at the standard, maintenance fluid rate.[1] Additional fluid boluses were permitted, as NS, if clinically indicated. Oral fluids were allowed and recorded. The 'restricted' fluid group received two-thirds of the standard rate. The treating physicians determined all other management.

We measured the plasma and urine electrolytes and osmolality on PICU admission and 12–24 h later as is our usual practice. [Na] was measured with an indirect ion selective electrode using the Beckman Coulter Synchron CX5 (Beckman Coulter, Fullerton, CA, USA). Fluid balance was documented from admission until the study period ended, when the second blood sample was taken. Other data included post-operative status, demographic data, diuretic use and whether ventilated.

The main outcome was the difference in change in [Na] for either comparison (type of fluid, and infusion rate) at 12–24 h. Secondary outcomes included change in osmolality, need for additional fluid boluses and adverse events including neurological complications, for example, seizures or headaches, and dehydration or shock.

Sample size and statistics

From previous data, the mean fall in [Na] over the first 12–24 h was 3.1 mmol/L, with a standard deviation of 4.41 mmol/L. We estimated a total sample size of 48 (12 per group) to detect a difference of 5 mmol/L, with an alpha of 0.01 and 90% power. An increase of 5 mmol/L is the suggested aim when treating symptomatic hyponatraemia.[42]

We compared both fluid type and administration rate using two-way ANOVA. For continuous data, we used Student's *t*-test and non-parametric tests as appropriate. Categorical data were analysed using Fisher's exact test. STATA version 9.2[43] was used. No adjustment was made for multiple comparisons. We could not analyse by intention-to-treat because three subjects lacked final [Na] data. All subjects received their assigned study fluid.

Results

Between 14 March and 2 November 2005 there were 332 PICU admissions, of which 53 subjects were enrolled. The reasons for exclusion are shown in Table 1. Three subjects did not have [Na] data for analysis, and were excluded. One patient was withdrawn at the parents' request because of hyperglycaemia (19.4 mmol/L) after 7 h of study fluid (DS at full maintenance rate). Two lacked final laboratory measurements owing to an oversight (NS, restricted), and early PICU discharge (NS, full). Therefore, there were 50 subjects with analysable data.

Baseline demographics and biochemistry, fluid data and change in biochemistry are shown in Tables 2–5, respectively.

Table 1 Reasons for exclusion

Reason for exclusion	n	%
Diagnosis an exclusion criterion	42	16
Not approached	69	26
Previous enrolment	10	4
Refused consent	13	5
Neonate <29 days old	29	11
Contraindication to study fluids	9	3
No IV *in situ*	2	1
No IV fluid indicated, e.g. fed enterally	58	22
Abnormal plasma Na concentration	7	3
Abnormal plasma glucose concentration	1	0
Other e.g. short (<12 h) stay	28	10
Total	268	100

Overall, [Na] decreased by a mean of 2.3 (standard deviation (SD) 4.0) mmol/L. Because of a preponderance of bigger subjects in group 2 (Table 4) we calculated fluid intakes per square metre body surface area, using a formula based on weight.[44] Change in [Na] satisfied the assumptions of ANOVA, including normality and homogeneity of variances. Fluid type significantly affected the fall in [Na]. The change in [Na] was significantly affected by fluid type ($P = 0.0063$) but not rate ($P = 0.12$) without an interaction between fluid type and rate ($P = 0.79$). Because there were only two fluid groups and no interaction, we compared them with *t*-tests to estimate confidence intervals: DS produced a greater mean fall in [Na] of 3.0 (0.8, 5.1) mmol/L compared with NS. Full maintenance rate produced a greater mean fall of 1.6 (−0.7, 3.9) mmol/L, compared with the restricted rate. One subject (DS, restricted) received furosemide, but omitting that subject did not change the results. Three subjects received non-study fluid, ranging from 9 to 27 mL/kg, after their first [Na] measurement. Omitting them made no difference to the results.

However, when the subjects were categorised for infusion duration above and below 15 h, the median only subjects with longer infusions (14 NS, 13 DS) showed an effect of fluid type: the mean difference was 4.1 (0.75, 7.5) mmol/L, $P = 0.019$. For subjects with shorter infusions (10 NS, 13 DS), the mean difference was 1.8 (−0.97, 4.5) mmol/L, $P = 0.19$. Infusion rate had no effect, regardless of duration (data not shown).

There was no difference in the proportion of subjects receiving fluid boluses (Table 4; Fisher's exact test $P = 0.89$). However, surgical patients were more likely to receive boluses, 22/37 (55%), than medical patients, 3/13 (23%), $P = 0.051$. Surgical patients received a greater median total volume of fluid boluses: 10 (interquartile range 0–20) versus 0 (0–0) mL/kg, $P = 0.006$ (Wilcoxon rank-sum test). There were no differences in the volume of boluses received between the two fluid types and the two rates.

In exploratory analyses, we compared and adjusted for surgery and ventilation. Surgical subjects had a greater fall in mean [Na] of 2.9 (SD 3.9) mmol/L than medical patients: 0.6 (SD 3.0), difference 2.3 (−0.1, 4.6) mmol/L, $P = 0.057$. Surgery was a significant covariate in the model comparing fluid type and rate for change in [Na] ($P = 0.002$), as was fluid type ($P < 0.001$), but not rate ($P = 0.13$). Among surgical patients, there were significantly greater falls in mean [Na] for DS compared with NS: 4.4 (1.9, 6.8) mmol/L, $P = 0.0009$. There were no significant differences between treatments for the 13 medical subjects. Mechanical ventilation made no difference to fall in [Na]: 2.1 (SD 4.1) and 2.8 (SD 4.0) mmol/L for ventilated and non-ventilated patients, respectively.

Findings for osmolality were similar to those for [Na].

There were no differences among groups for urine output. There were no statistically significant differences in final, or change in, urinary [Na]. Surgical patients tended to have greater increases in urinary sodium: mean difference 50 (49, 149) mmol/L ($P = 0.32$).

Two subjects had adverse events. One developed hyperglycaemia, described earlier as a withdrawal. The other was a 10-month-old, ex-premature child recovering from craniofacial surgery with asymptomatic hypoglycaemia, receiving NS at restricted rate. The blood glucose was 1.0 mmol/L, detected on the second scheduled sample. IV dextrose normalised the blood glucose.

Discussion

In this factorial, randomised controlled trial of maintenance fluids in children in ICU, we found that the type of fluid has a greater effect on [Na] concentration than its administration rate. However, we cannot exclude a smaller but important effect of administration rate. Most patients were surgical, mildly ill and not ventilated. Surgical patients had greater falls in [Na] concentration than medical patients.

The strengths of our study were as follows. First, because of the controversy between the 'dilutional'[32,45] versus 'desalination'[12,13,20,29] hypotheses, we compared both different fluid administration rates and types of fluid. Second, we conducted a randomised controlled trial with allocation concealment and blinding. Finally, although we used a surrogate marker for adverse events, hyponatraemia, this marker is considered the most important predictor of adverse events from fluid prescription.[26–28] This study is the only randomised controlled trial of maintenance fluid replacement in a general paediatric ICU population may still inform clinicians prescribing IV maintenance fluids.

The weaknesses were as follows. First, the duration was short and variable: children were only followed for 12–24 h, and while this may represent a common situation of an overnight fast we cannot extrapolate the findings to later effects on electrolytes. Furthermore, within this short time, the duration of infusion had an effect, with only longer infusions producing a statistically significant fall in [Na]. ADH effect peaks around 24 h post operation,[38,46] but can occur as early as 5–17.5 h post operation in children.[47] Second, contamination by non-study and anaesthetic fluids might have affected the results. The percentage of fluid received as study fluid ranged between 61% and 79%, but we did not record fluids received before ICU admission. This should have been accounted for by randomisation, and we have shown that the fluid prescribed post-operatively affects [Na]. Third, because of the small sample, there was a chance imbalance in patient size between groups, with group 2

Table 2 Baseline characteristics by fluid type and rate

Group	1 NS restricted	2 NS full	3 DS restricted	4 DS full
n	13	11	15	11
Surgical, *n* (%)	11 (84)	10 (91)	8 (53)	8 (72)
Craniofacial surgery, *n* (%)	4 (31)	3 (27)	4 (27)	4 (36)
Spinal surgery, *n* (%)	4 (31)	7 (64)	2 (13)	1 (9)
Age (years), median (IQR)	5.3 (0.9, 12)	15.4 (10.8, 15.9)	4.7 (1.4, 8.9)	3.7 (1.5, 14.7)
Weight (kg), median (IQR)	17 (8, 36)	44 (26, 75)	15 (8.9, 22)	13 (10, 39)
PIM2 risk of death (%), median (IQR)	0.5 (0.2, 0.9)	0.2 (0.1, 0.5)	0.3 (0.1, 1.0)	1.9 (0.4, 3.2)
Ventilated, *n* (%)	3 (23)	1 (9)	4 (27)	7 (64)

IQR, interquartile range; DS, 0.18% saline; NS, 0.9% saline; *n*, number in group.

Table 3 Baseline biochemistry, mean (standard deviation) by fluid type and rate

Group	1 NS restricted	2 NS full	3 DS restricted	4 DS full
n	13	11	15	11
Na (mmol/L)	140 (2)	141 (2)	141 (2)	141 (3)
K (mmol/L)	4.2 (0.3)	4.1 (0.6)	4.1 (0.6)	4.8 (1.7)
Cl (mmol/L)	108 (4)	109 (3)	107 (5)	108 (5.5)
Urea (mmol/L)	4.3 (1.2)	4.2 (1.4)	5.3 (3.8)	4.9 (1.5)
Creatinine (mmol/L)	0.05 (0.02)	0.05 (0.02)	0.04 (0.01)	0.05 (0.03)
Bicarbonate (mmol/L)	22.8 (3.7)	22.7 (3.3)	20.8 (2.5)	21.9 (5.6)
Osmolality (mosm/kg)	298 (18)	299 (11)	298 (8)	299 (16)
Urine Na (mmol/L)	80 (72)	64 (45)	99 (71)	96 (60)
Urine K (mmol/L)	86 (37)	57 (36)	81 (49)	88 (37)
Urine Osmolality (mosm/kg)	571 (213)	451 (156)	639 (280)	580 (155)

Three had missing data for osmolality (one restricted rate, NS; one full rate, NS; one restricted rate, DS). Four subjects were missing data for urinary chemistry (two restricted rate, DS, one full rate, NS and one full rate, DS). DS, 0.18% saline; NS, 0.9% saline; *n*, number in group.

(NS, full maintenance rate) having larger, older children. Because of the non-linear formula for maintenance fluids, that group received less fluid per kilogram than other groups. Fourth, we did not power the study to detect fluid overload and we did not measure weight or sodium balance. Although there were no clinically apparent adverse effects, we excluded children at risk such as cardiac patients. Fifth, we did not study neurological outcomes for practical and ethical reasons. Finally, our sample was a relatively well ICU population, better reflecting post-operative and mildly ill children than the general ICU population.

Our results echo those from other non-meningitis controlled trials and a recent systematic review.[40] Brazel and McPhee randomised adolescent girls undergoing correction of scoliosis to near-isotonic or hypotonic fluid, in an unmasked study.[38] [Na] fell more in the hypotonic group. Recently, Neville *et al.* in a randomised unmasked study compared IV rapid replacement fluids in children with gastroenteritis.[39] Hypotonic fluid (0.45% saline 2.5% dextrose) reduced [Na] at 4 h but NS increased [Na]. Among normonatremic children ([Na] > 134 mmmol/L), hypotonic fluid reduced [Na] by 2.3 (SD 2.2) mmol/L, but NS increased [Na] by 0.8 (SD 2.4) mmol/L. Rate of administration made no difference, but was not randomised.

The mechanism by which fluid tonicity had a greater effect than administration rate is unclear because we did not measure regulatory hormones, extracellular fluid volume or weight. Nevertheless, our results do not support the hypothesis that high levels of non-osmotic ADH cause hyponatraemia regardless of fluid type. Potential future studies include comparing two rates of isotonic fluids with a larger sample, studies of 0.45% saline 5% dextrose and studies in different populations, for example sicker children and cardiac surgical patients. Longer follow-up, measurement of ADH and regulatory hormones, stratification to avoid chance imbalances for size and surgery, stricter protocols for non-study fluids and measurement of anaesthetic fluids should be considered.

In practice, we would not recommend using DS, 4% dextrose and 0.18% saline; NS, 0.9% saline at traditional maintenance rates in sick or post-operative children.

Table 4 Fluid volumes by group

Group	1 (NS restricted)	2 (NS full)	3 (DS restricted)	4 (DS full)
Total fluid intake (mL/kg)	45 (37, 59)	49 (36, 79)	51 (34, 68)	55 (48, 71)
Total fluid intake (mL/m²)	1108 (881, 1196)	1294 (978, 1653)	973 (841, 1535)	1354 (1177, 1507)
Total fluid intake (mL/kg/h)	2.5 (2.2, 4.1)	3.4 (1.9, 3.7)	2.6 (2.1, 4.9)	4.1 (3.7, 4.5)
Study fluid intake (mL/kg)	29 (24, 36)	29 (23, 32)	34 (30, 42)	44 (25, 61)
Study fluid intake (mL/m²)	662 (568, 848)	780 (620, 896)	758 (655, 928)	999 (666, 1230)
Study fluid intake (mL/kg/h)	2.0 (1.4, 2.6)	1.9 (1.5, 2.1)	2.2 (1.6, 2.6)	3.1 (2.4, 3.9)
% fluid as study fluid	64 (55, 79)	61 (51, 80)	78 (61, 88)	79 (66, 84)
Fluid bolus *n* (%) of subjects	7 (54)	6 (55)	6 (40)	6 (55)
Fluid boluses (mL/kg)	4.5 (0, 7.7)	10.7 (0, 19.7)	0 (0, 15.3)	10 (0, 17.7)
Duration of study fluid infusion (h)	16.7 (3.5)	15.4 (2.7)	16.4 (3.9)	14.1 (3.5)
Total fluid output (mL/kg)	23 (18, 29)	19 (12, 25)	21 (18, 46)	19 (14, 31)
Fluid balance (mL/kg)	31 (26)	36 (29)	25 (25)	39 (22)
Urine output (mL/kg/h)	1.2 (1.0, 1.4)	1.1 (0.8, 1.6)	1.4 (0.6, 2.3)	1.2 (0.8, 1.2)

Data are expressed as mean (standard deviation) or median (interquartile range) where appropriate. DS, 0.18% saline; NS, 0.9% saline.

Table 5 Change in electrolyte concentrations, mean (standard deviation), for subjects with complete data for initial and final electrolytes

Group	1 (NS restricted)	2 (NS full)	3 (DS restricted)	4 (DS full)
n	13	11	15	11
Na (mmol/L)	−0.2 (3.5)	−1.5 (4.3)	−3 (3.3)	−4.9 (4.0)
K (mmol/L)	0.01 (0.6)	0.21 (0.85)	−0.27 (0.57)	−0.63 (1.87)
Cl (mmol/L)	−0.2 (3.3)	−0.4 (3)	−3.1 (3.7)	−4.3 (2.3)
Urea (mmol/L)	0.25 (1.48)	0.11 (0.98)	−2.0 (5.03)	−0.75 (1.31)
Creatinine (mmol/L)	−0.003 (0.016)	−0.008 (0.011)	0.001 (0.014)	−0.009 (0.016)
Bicarbonate (mmol/L)	−1 (2.5)	−0.8 (1.8)	1.4 (2.3)	−1.5 (3.5)
Osmolality (mosm/kg)	−4.9 (14.8)	−5.4 (12.1)	−11.7 (9.1)	−14.9 (11.5)
Urine Na (mmol/L)	86 (69)	117 (72)	1 (89)	78 (270)
Urine K (mmol/L)	−8.2 (41)	32.4 (49)	−14 (29)	−3.6 (55)
Urine Osmolality (mosm/kg)	318 (268)	498 (233)	3 (266)	133 (264)

Two subjects had missing data for final glucose (full rate, one NS and one DS). One subject had missing data for final osmolality (restricted rate, DS). One subject had missing data for final urinary chemistry (restricted rate, DS). DS, 0.18% saline; NS, 0.9% saline.

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References

1 Holliday M, Segar W. The maintenance need for water in parenteral fluid therapy. *Pediatrics* 1957; 19: 823–32.
2 Chesney R. The maintenance need for water in parenteral fluid therapy. *Pediatrics* 1998; 102: 399–400.
3 Siegel N, Carpenter T, Gaudio K. Pathophysiology of body fluids. In: McMillan J, DeAngelis C, Feigin R, Warshaw J, eds. *Oski's Pediatrics. Principles and Practice*. Philadelphia, PA: Lippincott Williams and Wilkins, 1999; 67–85.
4 Greenbaum L. Maintenance and replacement therapy. In: Behrman R, Kliegman R, Jenson H, eds. *Nelson Textbook of Pediatrics*. Philadelphia, PA: Saunders, 2004; 242–5.
5 Portale A, Mathias R, Potter D, Rozansky D. Kidneys and electrolytes. In. Rudolph A, Kamel R, Overby K, eds. *Rudolph's Fundamentals of Pediatrics*. New York: McGraw-Hill, 2002; 593–645.
6 Campbell A. Infections. In: Campbell A, McIntosh N, eds. *Forfor and Arneil's Textbook of Paediatrics*. Edinburgh: Churchill Livingstone, 1998; 1274–543.
7 Schwarz W, Bennett W, Curelop S. A syndrome of renal sodium loss in patients and hyponatremia probably resulting from inappropriate secretion of antidiuretic hormone. *Am. J. Med.* 1957; 23: 529–42.
8 Feigin R, Kaplan S. Inappropriate secretion of antidiuretic hormone in children with bacterial meningitis. *Am. J. Clin. Nutr.* 1977; 30: 1482–4.

9 Padilla G, Ervin M, Ross M, Leake R. Vasopressin levels in infants during the course of aseptic and bacterial meningitis. *Am. J. Dis. Child.* 1991; **145**: 991–3.
10 McJunkin J, Reyes EDI, Irazuzta J *et al.* La Crosse encephalitis in children. *N. Engl. J. Med.* 2001; **344**: 801–7.
11 Creber E, Shann F, McDougall P, Gill R. Parenteral nutrition solutions [Letter]. *Med. J. Aust.* 1985; **143**: 368–9.
12 Hanna S, Tibby S, Durward A, Murdoch I. Incidence of hyponatraemia and hyponatraemic seizures in severe respiratory syncytial virus bronchiolitis. *Acta Paediatr.* 2003; **92**: 430–4.
13 Steele A, Gowrishankar M, Abrahamson S, Mazer D, Feldman R, Halperin M. Postoperative hyponatremia despite near-isotonic saline infusion: a phenomenon of desalination. *Ann. Intern. Med.* 1997; **126**: 20–5.
14 Chung H. Post-operative hyponatremia: a prospective study. *Arch. Intern. Med.* 1986; **146**: 333–6.
15 Guy A, Michaels J, Flear C. Changes in the plasma sodium concentration after minor, moderate and major surgery. *Br. J. Surg.* 1987; **74**: 1027–30.
16 Cowley D, Pabari M, Sinton T, Johnson S, Carroll G, Ryan W. Pathogenesis of postoperative hyponatraemia following correction of scoliosis in children. *Aust. N.Z. J. Surg.* 1988; **58**: 485–9.
17 Hoorn E, Geary D, Robb M, Halperin M, Bohn D. Acute hyponatremia related to intravenous fluid administration in hospitalised children: an observational study. *Pediatrics* 2004; **113**: 1279–84.
18 Harrigan M. Cerebral salt wasting: a review. *Neurosurgery* 1996; **38**: 152–60.
19 Kappy M, Ganong C. Cerebral salt wasting in children: the role of atrial natriuretic hormone. *Adv. Pediatr.* 1996; **43**: 271308.
20 Nelson P, Self S, Maroon J, Robinson A. Hyponatremia in intracranial disease: perhaps not the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). *J. Neurosurg.* 1981; **55**: 938–41.
21 Ganong C, Kappy M. Cerebral salt wasting in children. The need for recognition and treatment. *Am. J. Dis. Child.* 1993; **147**: 167–9.
22 Stidham G, DiSciafani A, Stanford R. Cerebral salt wasting in pediatric neurosurgical patients (Abstract). *Pediatr. Res.* 1987; **21**: 207.
23 Levine J, Steinicki E, Weiner H, Bradley J, McCarthy J. Hyponatremia in the postoperative craniofacial pediatric patient population: a connection to cerebral salt wasting syndrome and management of the disorder. *Plast. Reconstr. Surg.* 2001; **108**: 1501–8.
24 Ayus J, Krothapalli R, Arieff A. Treatment of symptomatic hyponatraemia and its relation to brain damage. *N. Engl. J. Med.* 1987; **317**: 1190–5.
25 Berry P, Belsha C. Hyponatremia. *Pediatr. Clin. North Am.* 1990; **37**: 351–63.
26 Halberthal M, Halperin M, Bohn D. Acute hyponatraemia in children admitted to hospital: retrospective analysis of factors contributing to its development and resolution. *BMJ* 2001; **322**: 780–2.
27 Arieff A. Hyponatremia, convulsions, and permanent brain damage after elective surgery in healthy women. *N. Engl. J. Med.* 1986; **314**: 1529–35.
28 Arieff A, Ayus J, Fraser C. Hyponatraemia and death or permanent brain damage in healthy children. *BMJ* 1992; **304**: 1218–22.
29 Moritz M, Ayus J. Prevention of hospital-acquired hyponatremia: a case for using isotonic saline. *Pediatrics* 2003; **111**: 227–30.
30 Taylor D, Durward A. Pouring salt on troubled waters. *Arch. Dis. Child.* 2004; **89**: 411–14.
31 Skellett S, Mayer A, Durward A, Tibby S, Murdoch I. Chasing the base deficit: hyperchloraemic acidosis following 0.9% saline infusion. *Arch. Dis. Child.* 2000; **83**: 514–16.
32 Hatherill M. Rubbing salt into the wound. *Arch. Dis. Child.* 2004; **89**: 414–18.
33 Duke T, Mathur A, Kukuruzovic R, McGuigan M. Hypotonic vs isotonic saline solutions for intravenous fluid management of acute infections. *Cochrane Database of Systematic Reviews* 2003, Issue 3. Art. No.: CD004169. DOI: 10.1002/14651858.CD004169.pub2. (accessed 26 June 2006).
34 Singhi S, Singhi P, Srinivas B *et al.* Fluid restriction does not improve the outcome of acute meningitis. *Pediatr. Infect. Dis. J.* 1995; **14**: 495–502.
35 Powell K, Sugarman L, Eskdenazi A *et al.* Normalization of plasma arginine vasopressin concentrations when children with meningitis are given maintenance plus replacement fluid therapy. *J. Pediatr.* 1990; **117**: 515–22.
36 Duke T, Mokela D, Frank D *et al.* Management of meningitis in children with oral fluid restriction or intravenous fluid at maintenance volumes: a randomised trial. *Ann. Trop. Paediatr.* 2002; **22**: 145–57.
37 Duke T, Molyneux E. Intravenous fluids for seriously ill children: time to reconsider. *Lancet* 2003; **362**: 1320–3.
38 Brazel PW, McPhee IB. Inappropriate secretion of antidiuretic hormone in postoperative scoliosis patients: the role of fluid management. *Spine* 1996; **21**: 724–7.
39 Neville KA, Verge CF, Rosenberg AR, O'Meara MW, Walker JL. Isotonic is better than hypotonic saline for intravenous rehydration of children with gastroenteritis: a prospective randomised study. *Arch. Dis. Childhood* 2006; **91**: 226–32.
40 Choong K, Kho ME, Menon K, Bohn D. Hypotonic versus isotonic saline in hospitalised children: a systematic review. *Arch. Dis. Child.* 2006; **91**: 828–35.
41 Slater A, Shann F, McEniery J. The ANZPIC registry diagnostic codes: a system for coding reasons for admitting children to intensive care. *Intensive Care Med.* 2003; **29**: 271–7.
42 Halberthal M, Halperin ML, Bohn D. Lesson of the week: acute hyponatraemia in children admitted to hospital: retrospective analysis of factors contributing to its development and resolution. *BMJ* 2001; **322**: 780–2.
43 StataCorp. *Stata Statistical Software: Release 9.0.* College Station, TX: Stata Corporation, 2005.
44 Current J. A linear equation for estimating the body surface area in infants and children. In: *The Internet Journal of Anesthesiology*; 1998. Available from: http://www.ispub.com/journals/IJA/Vol2N2/bsa.htm (accessed 20 February 2006).
45 Hughes P, McNicol D, Mutton P, Flynn G, Tuck R, Yorke P. Postoperative hyponatraemic encephalopathy: water intoxication. *Aust. NZ. J. Surg.* 1998; **68**: 165–8.
46 Thomas T, Morgan D. Post-surgical hyponatraemia: the role of intravenous fluids and arginine vasopressin. *Br. J. Surg.* 1979; **66**: 540–2.
47 Burrows F, Shutack J, Crone R. Inappropriate secretion of antidiuretic hormone in a postsurgical pediatric population. *Crit. Care Med.* 1983; **11**: 527–31.

Rogers 1989

TABLE 21.5.
Indications for Airway Mangement in the Child

Abnormalities of respiratory rate and rhythm
Upper airway obstruction
Loss of pharyngeal muscle activity and tone
Inability to clear secretions
Foreign body
Direct trauma
Seizures
Loss of protective airway reflexes
Pulmonary disease
Failure of oxygenation
Failure of ventilation
Pulmonary hypertension
Respiratory muscle dysfunction
Fatigue
Shock states
Secondary to nerve dysfunction
Chest wall dysfunction
Intracranial hypertension
Prophylactic

TABLE 21.6.
Summary of Drugs and Doses

Thiopental—0.5 mg per kilogram I.v., 2.5–4.5 mg per kilogram (per adequate blood pressure)
Atropine—0.01–0.03 mg per kilogram (minimum 0.15 mg)
Succinylcholine—1.0–1.5 mg per kilogram
Pancuronium—0.01 mg per kilogram (defasciculating dose); 0.1 ml per kilogram (paralysis dose, 1–2 hr)

drug usage are discussed thoroughly in Chapter 3. In general the following guidelines are used. Thiopental is administered intravenously for sedation and to blunt the observed elevation in ICP in repsonse to tube replacement. Thiopental should be used only if the systemic blood pressure is adequate. The recommended dosage is 0.5 mg per kilogram intravenously. If no systemic hypotension occurs, doses as high as 2.5 to 4.5 mg per kilogram may be used. Lidocaine may be used as an alternative to thiopental. This is primarily to blunt the ICP response to intubation and may be given via the endotracheal tube or intravenously. The recommended dosage is 1 mg per kilogram. Atropine is used to control oral tracheal secretions but more importantly to block vagal responses to succinylcholine and endotracheal tube placement. The recommended dosage is 0.01 to 0.03 mg per kilogram, with a minimum dose of 0.15 mg. Muscle relaxation is obtained by using succinylcholine. Succinylcholine is contraindicated in ocular injuries. It must be noted that succinylcholine may cause muscle fasciculations and it may affect the ICP adversely. This can be prevented by administering pancuronium initially. Pancuronium may also be used for muscle relaxation. The recommended dose of succinylcholine is 1.0 to 1.5 mg per kilogram. The recommended dose of pancuronium is 0.01 mg per kilogram for defasciculation as a pretreatment to succinylcholine use or 0.1 ml per kilogram to be used for muscle relaxation in lieu of succinylcholine. At this dosage however, paralysis may persist for 1 to 2 hr.

During the intubation it must be assumed that the patient has eaten recently, so further gastric distention must be avoided. This goal is achieved in two ways. The first is the avoidance of prolonged mask ventilation, which predisposes to further gastric distention and possible aspiration. The second is achieved by performing Sellick's maneuver, which is esophageal compression. This aids in the prevention of reflux and subsequent aspiration. Thus if the patient is breathing spontaneously, oxygenation is obtained by holding a face mask with 100% O_2 on the patient's face for 2 min. This is followed by the administration of drugs, Sellick's maneuver, and endotracheal intubation of the patient. If the patient is not breathing spontaneously, Sellick's maneuver is performed, and the drugs are administered. Simultaneously, the patient is preoxygenated with the administration of 100% O_2 by face mask, with use of about five artificial ventilations. This is immediately followed by intubation. These guidelines are useful to ensure a successful intubation with minimal trauma and complications.

After successful intubation, the position of the tube should be checked on chest X-ray. The ideal location is 2 cm above the carina. The head should be in a neutral position at the time of chest X-ray, as the position of the tube will change with changing position of the head.

Fiberoptic and/or nasotracheal intubation may need to be utilized in difficult or impossible oral intubations. These should only be considered with appropriate personnel and equipment.

Ventilation

Once the airway has been established, the patient must be ventilated. Even in relatively stable patients who are closely monitored, intermittent episodes of hypoventilation can occur. Also in small children, exhaustion of pulmonary musculature is frequently seen (84). Both of these adverse events are minimized by mechanical ventilation. In the head-injured patient, hypercarbia must be avoided. Carbon dioxide is a very potent cerebral vasodilator, and the resultant increase in cerebral blood volume may have deleterious effects on ICP and overall neurological outcome. Thus in head-injured patients requiring mechanical ventilation, hyperventilation is used with PCO_2 kept within a range of 25 to 30 torr. Immediate improvement in the EEG and overall improved outcome are seen (85, 86). The immediate physiological response to hyperventilation and relative hypocarbia include diminished cerebral blood flow with diminished cerebral blood volume, a

Rogers 1989

used in children with pulmonary edema, chronic lung disease, or liver disease. Paraldehyde has been reported to cause pulmonary hemorrhage, pulmonary edema, acidosis, hepatitis, nephrosis, and bleeding diatheses (49).

Several other anticonvulsants may be considered if patients do not respond to previous agents. *Valproic acid* is not available in parenteral form, but has been used rectally for the treatment of status epilepticus (50, 51). A major disadvantage is its relative slowness in absorption compared to drugs that are administered intravenously. *Lidocaine* (50 to 100 mg bolus in adults) may be effective in some persons when other drugs have failed (49, 52), but higher doses of this drug are epileptogenic, and its use is not advocated in children. *Clonazepam* (53) and *chlormethiazole* (49) also have been used in status epilepticus with some success, but they have not gained widespread acceptance, particularly for use in children.

In view of the potential morbidity and mortality associated with generalized tonic-clonic status epilepticus, numerous authors have recommended the use of *general anesthesia* or barbiturate coma to minimize the metabolic sequelae of prolonged seizure activity or to suppress the process permanently (54–57). Few guidelines exist regarding the depth or duration of anesthesia or the advantages of inhalation anesthesia (56) versus intravenous agents (48), and use of anesthesia for this purpose is not universally accepted (58). With general anesthesia, with or without neuromuscular blockade, the motor manifestations of status are clearly masked. However, electrical activity may persist, and EEG monitoring is helpful during such therapy (57). In addition, convulsion-like activity on the EEG may be provoked with general anesthesia utilizing halothane, enflurane, or etomidate. The anesthetic must be periodically decreased to determine whether continued therapy is required. Despite the controversy about this modality of therapy, the experimental physiologic data concerning status epilepticus support aggressive therapy and suggest that the most severe, refractory patients be considered for general anesthesia or barbiturate coma to stop the seizures.

FURTHER EVALUATION

Although the control of seizures is of utmost importance, evaluation of their etiology should be initiated within the first few minutes after the patient is seen. Laboratory tests should include determination of serum electrolytes, glucose, calcium, hepatic enzymes, urea nitrogen, and when indicated, a toxicology screen and serum magnesium. A Dextrostix test performed at bedside can be an immediate clue to ruling out hypoglycemia. If the patient is known to have epilepsy, serum anticonvulsant levels should be measured. If meningitis is suspected, a lumbar puncture should be carried out when the child is stabilized. Evidence of increased intracranial pressure or a focal neurologic examination mandates consideration of computerized axial tomography scanning or other neurologic studies as soon as possible.

SUMMARY

Status epilepticus causes significant mortality and morbidity and must be regarded as a medical emergency. The longer the seizures are permitted to continue, the more difficult they become to control, and the worse the prognosis. It is not surprising that this is true in view of the laboratory evidence reviewed earlier in this chapter. What is surprising is that some physicians continue to tolerate periods of status epilepticus that are much longer than ought to be permitted. Delayed treatment disregards an enormous amount of pathologic evidence that status epilepticus, per se, is harmful to the CNS. Immediate, rational, and potentially aggressive therapy is essential to reduce the mortaility and long-term morbidity of status epilepticus.

References

1. International League against Epilepsy: *Epilepsia* 5:305, 1964.
2. Roger J, Lob H, Tassinari CA: Status epilepticus. In Vinken PJ, Bruyn GW (eds): *Handbook of Clinical Neurology*. Amsterdam, North-Holland, 1974, p 145.
3. Delgado-Escueta AV, Wasterlain C, Treiman DM, Porter RJ: Management of status epilepticus. *N Engl J Med* 306:1337, 1982.
4. Morris HH: Current treatment of status epilepticus. *J Fam Pract* 13:987, 1981.
5. Lennox WG, Lennox MH: *Epilepsy and Related Disorders*. Voll, Boston, Luller, Bram, 1960.
6. Hunter RA: Status epilepticus: History, incidence, and problems. *Epilepsia* 1:162, 1959/1960.
7. Oxbury JM, Whitty CWM: Causes and consequences of status epilepticus in adults—A study of 86 cases. *Brain* 94:733, 1971.
8. Janz D: *Die Epilepsien*. Thieme, Stuttgart, 1969.
9. Janz D: Etiology of convulsive status epilepticus. *Adv Neurol* 34:47, 1983.
10. Aicardi J, Chevrie JJ: Convulsive status epilepticus in infants and children: A study of 239 cases. *Epilepsia* 11:187, 1970.
11. Rowan AJ, Scott DF: Major status epilepticus: A series of 42 patients. *Acta Neurol Scand* 46:573, 1970.
12. Zhang Z, Feng Y: A clinical study of 100 status epilepticus cases. *Chin Med J* 95:113, 1982.
13. Aminoff MJ, Simon RP: Status epilepticus: Causes, clinical features, and consequences in 98 patients. *Am J Med* 69:657, 1980.
14. Glaser GH: Medical complications of status epilepticus. *Adv Neurol* 34:395, 1983.
15. Woodbury DM: Experimental models of status epilepticus and mechanism of drug action. *Adv Neurol* 34:149, 1983.
16. Johnson GAR, Kennedy SME, Twitchen B: Action of the neurotoxin kainic acid on high affinity uptake of L-glutamic acid in rat brain slices. *J Neurochem* 32:121, 1979
17. Meldrum BS: Metabolic factors during prolonged seizures and their relation to nerve cell death. *Adv Neurol* 34:261, 275, 1983.
18. Meldrum BS, Horton RW: Physiology of status epilepticus in primates. *Arch Neurol* 28:1, 1973.