Strictly Private and Confidential
Mr Ian Howell
Investigation Officer
Fitness to Practise Directorate
General Medical Council
5th Floor, St James's Buildings
79 Oxford Street
Manchester
M1 6FQ

Our ref: RMcM/RMcA/M389
Your ref: IH/2004/3139/06

1st July 2010

BY FAX (020 7189 5103) (ENCLOSURES TO FOLLOW)
AND BY POST

Dear Sir,

RE: Our client - Dr James F Kelly

We acknowledge safe receipt of a copy of your correspondence to Dr Kelly, dated 20th May 2010 plus enclosures. We are grateful to you for providing an extension of time for the provision of this correspondence.

As you will be aware, we act on behalf of Dr James F Kelly, Consultant Geriatrician, on the instructions of the Medical Protection Society. We would ask you to quote our above reference on all future correspondence with ourselves in relation to this matter.

We note that you have sought Dr Kelly's responses to your correspondence in accordance with Rule 7 of the General Medical Council's ('the Council's') (Fitness to Practise Rules) 2004. As the Council will be aware, the Public Inquiry into the Hyponatraemia Related Deaths is due to take place in the Autumn. Dr Kelly may well be called to give evidence at that Inquiry and, therefore, he reserves the right to add to, remove or amend comments made in this correspondence should further information come to light at that Hearing. Despite the fact that a Public Inquiry is to be held, Dr Kelly has decided to provide full comments to the Council at this stage (rather than seek an extension of time until after the Public Inquiry had taken place), given that the Council have confirmed that the Case Examiners will be considering this issue and reaching a decision on whether to refer the matter for Hearing upon receipt of the various correspondence from those clinicians to whom the Council have written.

Curriculum Vitae

By way of background, Dr Kelly qualified from Queen's University Belfast in 1981, with the qualifications MB, BCH, BAO. Dr Kelly gained membership of the Royal College of Physicians in 1984 and was awarded a Medical Doctorate, by thesis, from Queen's University, Belfast in 1988. Dr Kelly was made a Fellow of the Royal College of Physicians (Edinburgh and London) in 1997.

Post qualification, Dr Kelly worked as a House Officer at the Mater Infirmorium Hospital between August 1981 and August 1982. Dr Kelly was subsequently employed as a Senior House Officer at the Royal Victoria Hospital between August 1982 and August 1985.

Dr Kelly worked as a Registrar in Geriatric Medicine at Belfast City Hospital between August 1985 and August 1986. Dr Kelly subsequently undertook a one year Research Fellowship at Belfast City Hospital. Dr Kelly was employed as a Senior Registrar in Geriatric Medicine at Belfast City Hospital between August 1987 and August 1988. Dr Kelly subsequently worked as a Senior Registrar in Respiratory Medicine at Belfast City Hospital from August 1988 and 30th November 1988.

Dr Kelly took up his current post as a Consultant Geriatrician at Erne Hospital, Enniskillen, on 1st December 1988. From January 1996 to September 1999 Dr Kelly was the Clinical Coordinator for the Medical Directorate.

Dr Kelly was appointed Medical Director of the legacy Sperrin Lakeland Health & Social Services Trust (now part of the Western Health &Social Care Trust) from 1st December 1999 until 30th November 2003.

Aside from Dr Kelly's full-time responsibilities as a Consultant Geriatrician, Dr Kelly's post as Medical Director included the following responsibilities (as set out in the attached Job Description dated February 1999):

1. Advising the Chief Executive, the Board of the Trust, Clinical Directors and Programme Directors on all medical policies and strategy matters;
2. Corporate responsibility for clinical governance, under-graduate education and post-graduate training and continuing education of medical staff;
3. Chairing forums involving the Clinical Directors and General Practitioners, as appropriate, as a means of securing medical policy and advice for the Trust commensurate with its aims and objectives and relevant to the National/Regional trends;
4. Responsibility for medico-legal matters and working closely with the Director of Corporate Affairs in ensuring that the policy of risk management was in operation;
5. Sitting on Advisory Appointment Panels for consultant appointments and, on behalf of the Chief Executive, review consultant job plans in conjunction with the appropriate Programme Director and/or Clinical Directors;
6. Responsibility for disciplinary procedures associated with professional matters for medical staff, taking action, such as, initiating professional review mechanisms, in conjunction with the Chief Executive and Programme Director;
7. Receiving notification when more serious matters were referred to the Board of the Trust and the General Medical Council; and
8. Promoting high standards of professional practice and undertaking complaints procedure investigations as appropriate.

The facts

The facts of this matter are clearly set out in Dr Kelly's statement (copy enclosed) that he provided to the Police Service of Northern Ireland when he attended voluntarily for interview on 6th April 2005.

Allegations

"Despite being registered under the Medical Act 1983 (as amended):-

1. *Between 1994 and 2007, you were the Medical Director of the Sperrin and Lakeland Health and Social Care Trust"*

1. Denied. Dr Kelly was appointed Medical Director for Sperrin Lakeland Health and Social Services Trust for the period 1st December 1999 to 30th November 2002. However, at the request of the then Chief Executive (Mr Hugh Mills), Dr Kelly agreed to serve a further one year (between 1st December 2002 and 30th November 2003) in this post. It is worthy of note that Dr Kelly received no induction training in advance of taking up his role as Medical Director and when the new Medical Director was appointed in 2004, she had almost full time Medical Director duties in comparison with Dr Kelly who was expected to continue to carry a full clinical caseload.

2a *"At 7.30pm on 12th April 2000, LC was admitted to the Erne Hospital, Enniskillen"*

2a. Whilst he was not involved in LC's care, Dr Kelly accepts that numbered paragraph 2a would appear (from LC's notes) to be factually correct.

2b. "At 11.00pm on 12th April she began to received IV fluids to treat her dehydration"

2b. Whilst he was not involved in LC's care, Dr Kelly accepts that numbered paragraph 2b would appear (from LC's notes) to be factually correct.

2c. "At 2.55am on 13th April, LC collapsed.

2c. Whilst he was not involved in LC's care, Dr Kelly accepts that numbered paragraph 2c would appear (from LC's notes) to be factually correct.

2d. "At 6.30am on 13th April, LC was transferred to the Royal Belfast Hospital for Sick Children.

2d. Whilst he was not involved in LC's care, Dr Kelly accepts that numbered paragraph 2c would appear (from LC's notes) to be factually correct.

2e. "At 1.15pm on 13th April LC was declared dead."

2e. Whilst he was not involved in LC's care, Dr Kelly understands that at 1.15pm on 14th (not 13th, which was the date of her transfer to the Royal Belfast Hospital for Sick Children) April, following brain stem tests, LC was declared dead.

2f. "It has been established that her dehydration was treated with the wrong fluids and the wrong quantities."

2f. Dr Kelly accepts that numbered paragraph 2f is correct, in so far as the Coroner for Greater Belfast (Mr John L Leckey) came to this conclusion on 19th February 2004 following the Inquest touching upon the death of LC. It was not, however, apparent at in April 2000 that this was the cause of death. The IV fluid prescription and the

administration were identified as the cause of death in 2003. We would refer you to the following enclosed publications in an attempt to out into context the state of knowledge of the medical profession in Great Britain and Northern Ireland on this issue at that time and subsequently:

(a) Lesson of the week: 'Acute hyponatraemia in children admitted to hospital: retrospective analysis of factors contributing to its development and resolution' Halberthal, Halperin and Bohn; BMJ 2001; 322: 780-2 (distributed by Dr Kelly to All Consultant Paediatricians & Staff Grades at Erne Hospital on 21st June 2001);

(b) 'Prevention of Hyponatraemia in Children'; 25th March 2002 letter from Dr Henrietta Campbell, Chief Medical Officer (GMC Bundle; pages 54 and 55);

(c) Editorial: Prevention of hyponatraemia in children receiving fluid therapy'; Dr J G Jenkins, Dr B Taylor and Dr M McCarthy; The Ulster Medical Journal, Volume 72, No.2, pp 69-72, November 2003;

(d) 'Pediatrics; Official Journal of the American Academy of Pediatrics – Acute Hyponatraemia Related to Intravenous Fluid Administration in Hospitalized Children: An Observational Study' Hoorn, Geary, Robb, Halperin and Bohn: Pediatrics 2004; 113; 1279-1284;

(e) 'What routine intravenous maintenance fluids should be used? An introduction to the debate' N P Mann, 'Pouring salt on troubled waters – The case for isotonic parenteral maintenance solution' D Taylor, A Durward and 'Rubbing Salt in the wound – The case against isotonic parenteral maintenance solution' M Hatherill; Arch Dis Child 2004; 89; 411-4;

(f) 'Paediatrics: Doctors ignore advice on IV fluids in children'; Hospital Doctor; page 11; 27th October 2005; and

(g) NPSA: Patient Safety Alert: 'Reducing the risk of hyponatraemia when administering intravenous infusions to children'; NPSA/2007/22.

It should be noted that Dr Kelly (with one other Medical Director) was involved in bringing this issue to the attention of the Chief Medical Officer, which then resulted on her issuing her correspondence dated 25th March 2002 (as detailed at (b) above).

3a. *"On 14th April 2000, Dr Jarlath O'Donohoe, told you that LC had died and that he was concerned about what might have caused her death."*

3a. Dr Kelly accepts numbered paragraph 3a in that Dr Jarlath O'Donohoe raised LC's death with him under Clinical Incident Reporting. This conversation with Dr O'Donohoe took place on either Thursday, 13th April 2000 or Friday 14th April 2000 (Dr Kelly does not have a precise recollection as these events took place over 10 years ago). Dr O'Donohoe informed Dr Kelly that LC had been admitted with diarrhoea and vomiting and had subsequently suffered an unexplained collapse requiring resuscitation and intubation. Dr O'Donohoe further explained to Dr Kelly that he had had LC transferred to the Royal Belfast Hospital for Sick Children (RBHSC) (part of the legacy Royal Group of Hospitals and Dental Hospital HSS Trust). Dr O'Donohoe informed Dr Kelly that LC was on a ventilator and that her prognosis appeared very poor and that brain stem tests were planned. Dr O'Donohoe stated that he was not sure what had happened and explained that there may have been a misdiagnosis, that the wrong drug may have been prescribed or that LC had had an adverse drug reaction. Dr Kelly informed Dr

O'Donohoe that there would need to be a full review of the case and this would be established in the coming days.

3b. *"You asked for a copy of LC's notes to be obtained as you thought it likely they would be passed on to the Coroner."*

3b. Dr Kelly accepts numbered paragraph 3b. Dr Kelly asked Dr O'Donohoe to retain a photocopy of the relevant clinical notes as Dr Kelly considered it likely that, based on previous experience, LC's notes would be sent to the Coroner for Greater Belfast (the Coroner's district in which Lucy died) when he requested them via the Royal Group of Hospitals and Dental Hospital HSS Trust, as the reporting Trust. Dr Kelly wished to retain a copy of the relevant clinical notes in order to facilitate any internal investigation.

3c. *"You did not, at any stage, bring to the Coroner's attention that LC had not died of natural causes and so an inquest was indicated".*

3c. Dr Kelly accepts that he did not speak to the Coroner for Greater Belfast (Mr Leckey) at any time regarding LC's death. However, LC's death occurred at the Royal Belfast Hospital for Sick Children (part of the Royal Group of Hospitals and Dental Hospital HSS Trust) and, therefore, the Paediatricians at this hospital (rather than the referring Erne Hospital, where Dr Kelly was Medical Director) would be responsible for referring LC's death to the Coroner for Greater Belfast. Had LC died at the Erne Hospital, Dr Kelly would have, in accordance with practice at the time, liaised with his local Coroner. Dr Kelly understood that a Post Mortem was being performed, which he believed was a Coroner's Post Mortem rather than a Hospital Post Mortem, which was actually being performed.

From the outset when he requested a copy of LC's notes to be retained, Dr Kelly fully expected that an Inquest would be held. We understand that discussions did take place between clinicians at the Royal Belfast Hospital for Sick Children and the Coroner for Greater Belfast. Whilst he accepts that he, or members of the review team, could have telephoned the Coroner for Greater Belfast or the Royal Belfast Hospital for Sick Children to ascertain the position of events, Dr Kelly was never appraised that a Death Certificate had been issued or that the Coroner was not aware that a Post Mortem had been performed within 24 hours of death. Dr Kelly would have anticipated that the Pathologist's report prepared by Dr M D O'Hara dated 17th April 2000 (GMC Bundle; pages 33-40 (inclusive) would have been sent to the Coroner for Greater Belfast by those at the Royal Belfast Hospital for Sick Children.

It would not, in our experience, have been unexpected at that time for an Inquest to take place a number of years after a patient's death.

A Letter of Claim in respect of a civil claim for damages being brought by LC's parents was sent to the Trust in April 2001, with a Writ of Summons commencing a civil claim for damages being issued on 15th June 2001. Upon receipt of the Letter of Claim, the handling of the litigation and the Coroner's Inquest fell to be dealt with by the Trust's legal advisors. On two occasions, Dr Kelly enquired of the Trust's legal advisors as to the progress of the Inquest. Dr Kelly was informed that delays in the Inquest process were not unusual. Dr Kelly submits that had he been informed that an Inquest was not

planned, he or one of the members of the Review Team would have contacted the Coroner's Office.

With the benefit of hindsight, Dr Kelly wishes that he had contacted the Coroner for Greater Belfast to enquire as to the progress of an Inquest that he believed was always going to take place.

4a. *"You requested a full review of the case and asked that the opinion of an external Paediatrician be sought"*

4a. Following Dr Kelly's conversation with Dr O'Donohoe, Dr Kelly took the following steps:

(a) he asked Dr O'Donohoe to retain a copy of the relevant clinical notes for LC;
(b) he immediately contacted the Chief Executive (Mr Hugh Mills) to advise him of the serious adverse incident and that he needed to establish a review (to be led by senior nursing and medical personnel) to ascertain exactly what had happened. Mr Mills agreed and suggested that Mr E Fee, Chief Nurse and Acute Services Director and Mr T Anderson, Clinical Director for the Womens' and Child Health Directorate should lead the review; and
(c) when speaking with the Chief Executive, he suggested that the commissioner of services (the Western Health & Social Services Board) should be made aware of these events and the actions being taken. Mr Mills agreed and, we understand, contacted Dr W McConnell, Director of Public Health, Dr Colin Hamilton, Consultant in Public Health Medicine and the Chief Nurse, Mr Martin Bradley, at the WHSSB.

A Review Team (Mr E Fee and Mr T Anderson) was then established and, following their initial deliberations, we understand that it was agreed that an external (outside of the Sperrin Lakeland Health & Social Services Trust) Consultant Paediatrician should be asked to provide an opinion. Dr Kelly was informed of (and subsequently agreed) with their decision to seek an external opinion.

4b. *"Dr Murray Quinn, Consultant Paediatrician at the Altnagelvin Hospital Trust, was approached to write an expert report in the case."*

4b. Dr Kelly accepts numbered paragraph 4b. Mr Hugh Mills, the then Chief Executive, suggested approaching Dr Murray Quinn employed by Altnagelvin Hospital Health & Social Care Trust and Dr Kelly understands that the Chief Executive subsequently contacted Dr Quinn to request that he provide such a review. We understand that Mr Fee instructed Dr Quinn and liaised with him accordingly.

4c. *"You knew, or should have known, that as a Consultant at a neighbouring Trust, Dr Quinn did not constitute an independent expert."*

4c. This allegation is denied. No paediatricians at Sperrin Lakeland Health & Social Services Trust or any other staff linked to LC's care influenced the choice of the external Consultant Paediatrician (Dr Quinn). In a small jurisdiction such as Northern Ireland, many of the 18 Health & Social Services Trusts in existence at that time could be described as "neighbouring". To the best of Dr Kelly's knowledge and belief, Dr Quinn represented an external independent expert.

Dr Kelly did discuss the actions taken following LC's death and the ongoing Review by Dr Quinn with Dr McConnell, Director of Public Health at the Western Health Board, and no concerns were raised by him in this regard.

5a. *"On 21st June 2000 you met with Dr Quinn to discuss his preliminary findings and shared with him the final Post Mortem Report".*

5a. Dr Kelly, at the request of the Chief Executive and the Review Team, and in his capacity as Medical Director, met with Dr Murray Quinn along with Mr E Fee to discuss his findings. Dr Kelly also attended the meeting to clarify if there were any urgent concerns in terms of Dr O'Donohoe's practice that required immediate action.

Dr Kelly believes Mr Fee provided the Post Mortem Report as found at pages 80 – 88 (inclusive) of the GMC Bundle to Dr Murray Quinn at the commencement of the meeting. This Report is dated 13th June 2000 and, Dr Kelly understands, only came into the possession of the Review Team (Mr Fee) shortly before the meeting with Dr Quinn on 21st June 2000.

5b. *"Dr Quinn wrote his report using LC's medical records and Post Mortem Report".*

5b. Dr Kelly is unable to confirm nor deny numbered paragraph 5b as Dr Kelly was not involved in instructing Dr Quinn and had no discussions with Dr Quinn prior to the meeting on 21st June. It is evident from Dr Quinn's report that he held a copy of 'notes' provided to him and Dr Kelly is aware that Mr Fee provided Dr Quinn with the Post Mortem Report referred to at 5.a above.

5c. *"The Post Mortem Report specifically mentions hyponatraemia as a factor in LC's death."*

5c. Dr Kelly denies this allegation. The Post Mortem Report referred to at 5.a and 5.b above and found at pages 80-88 (inclusive) of the GMC Bundle is dated 13th June 2000. This Post Mortem Report does not specifically mention hyponatraemia as a factor in LC's death. The only mention of hyponatraemia in this Post Mortem Report is in the 'Clinical History' section details of which had been provided to the Hospital Pathologist by Dr Caroline Stewart, Specialist Registrar, Paediatrics, Royal Belfast Hospital for Sick Children (where the Post Mortem was performed following LC's death in that hospital) did not have hyponatraemia as a cause of death.

Obviously, the Post Mortem Report dated **6th November 2003** that refers to hyponatraemia being one of two pathological processes that could have caused LC's cerebral oedema was not provided to Dr Quinn on **21st June 2000**. Indeed, Dr Kelly had not seen this version of the Post Mortem Report until he received the GMC's correspondence.

5d. *"Dr Quinn's final report dated 22nd June 2000 failed to identify hyponatraemia as a probable or possible cause of LC's death despite the weight of evidence".*

5d. Dr Kelly accepts numbered paragraph 5d in that Dr Quinn's report did not identify hyponatraemia as a probable or possible cause of death.

5e. *"You knew, or should have known, that the final report was flawed and not fit for purpose".*

5e. Dr Kelly denies this allegation. Dr Kelly's medical speciality is Geriatric Medicine and is, therefore, unable to identify whether an experienced Consultant Paediatrician's report is flawed or not fit for purpose. The Review Team did not perceive the report to be flawed, and Dr Quinn's report was shared with the Lead Paediatrician and the Paediatric Ward Sister, neither of whom expressed concern to Dr Kelly about the Report. Dr Kelly, therefore, had no reason to consider the report flawed and/or not fit for purpose.

6. *"You did not refer LC's death to the Coroner upon receipt of the Post Mortem Report which mentioned hyponatraemia, as required by Section 7 of the Coroners Act (Northern Ireland) 1959, or at any time thereafter."*

The version of the Post Mortem Report dated 13th June 2000 and provided to Dr Quinn on 21st June 2000 did not mention hyponatraemia as a factor in LC's death. The only mention of hyponatraemia in this Post Mortem Report is in the 'Clinical History' section details of which had been provided to the Hospital Pathologist by Dr Caroline Stewart, Specialist Registrar, Paediatrics, Royal Belfast Hospital for Sick Children (where the Post Mortem was performed following LC's death in that hospital) did not have hyponatraemia as a cause of death.

LC's death had been referred to the Coroner for Greater Belfast by the Paediatricians at the Royal Belfast Hospital for Sick Children and Dr Kelly, the Review Team and the Trust were anticipating a Coroner's Inquest. It is clear now that the Post Mortem initially prepared by Mr O'Hara was a Hospital Post Mortem and it was not until 6th November 2003 that Mr O'Hara prepared a Post Mortem Report at the request of the Coroner. Dr Kelly's understanding was that the Coroner would have automatically received the Post Mortem Report dated 13th June 2000, however, this may not have been correct. Dr Kelly believed at all times that an Inquest would take place into LC's death.

7a. *"On 26th April 2001, Dr Moira Stewart, sent you a copy of her report commissioned by the Royal College of Paediatrics and Child Health, into four clinical cases."*

7a. Dr Kelly accepts numbered paragraph 7a. Dr Kelly suggested to the Chief Executive, and subsequently requested a report from the Royal College of Paediatrics and Child Health to comment on performance issues relevant to Dr O'Donohoe's practice. Dr. Kelly ensured that the LC case was included in this review. In our submission, Dr Kelly's actions are evidence of good governance.

7b. *"The Report raised hyponatraemia as a possible cause of LC's death."*

7b. Dr Kelly believes numbered paragraph 7b was not definite in relation to hyponatraemia as a possible cause of death, in that Dr Stewart's report raised biochemical abnormality as a <u>possible</u> cause of a seizure like episode and subsequent deterioration. The GMC will be aware that Dr Stewart's report raises several other possible causes for LC's death.

7c. *"You did not share the contents of this Report with LC's family."*

7c. Dr Kelly accepts numbered paragraph 7c, however, when Dr Stewart's report became available, LC's family had issued legal proceedings. Dr Kelly was advised by the Trust's legal advisors that Dr Stewart's report should not be shared with LC's family due to the ongoing legal action. Dr Kelly challenged this view, however, he was prevented from sharing this report with LC's family by the Trust's legal advisors until the claim for damages was concluded.

The Review Team (of which Dr Kelly did not form part) had stated in their conclusions, and in subsequent correspondence, that it was their intention to meet with LC's family and share the findings. It was not intended that Dr Kelly, as Medical Director, would be part of any such meeting.

Dr Kelly considers that he made every possible effort to advise the family and it was not his intention to withhold any information from LC's family.

7d. *"You did not share the contents of this Report with the Coroner."*

7d. Dr Kelly accepts this allegation. Dr Kelly believed (through enquiries made of the Trust's legal advisors) that an inquest would take place and that this information would be disclosed at that stage. Dr Kelly considers that Dr Stewart's report ought to (and he believes would) have been shared with the Coroner in advance of an Inquest.

8a. *"On 10th June 2001, RF died at the Royal Belfast Hospital for Sick Children."*

8a. Dr Kelly cannot accept nor deny this allegation. Dr Kelly is unaware of the exact date and location at which RF died.

8b. *"RF and LC shared the same cause of death, cerebral oedema caused by acute dilutional hyponatraemia".*

8b. Dr Kelly accepts paragraph numbered 8b, in that at the inquest touching on the death of LC in 2004, this was identified as the cause of death for both LC and RF.

8c. *"RF's death precipitated the decision to hold an inquest into the death of LC."*

8c. Dr Kelly accepts that the details presented at the inquest into the death of RF, led to the scheduling of an inquest into the death of LC.

8d. *"On 25th March 2002, revised guidelines were issued by the Chief Medical Officer regarding the prevention of hyponatraemia in children."*

8d. Paragraph numbered 8d is accepted.

8e. *"The inquest into LC's death took place in February 2004".*

8e. Numbered paragraph 8e is correct.

9a. *"Your failure to investigate LC's death adequately delayed the inquest into her death."*

9a. This allegation is denied. At Dr Kelly's request, a full and adequate investigation took place into LC's death. Following LC's death, Dr Kelly:

a. Requested and ensured that an immediate investigation was undertaken by Senior Trust Officers (medical and nursing);
b. Senior doctors at the Western Health and Social Services Board were fully informed of the establishment and format of the investigation;
c. Agreed that external opinion was sought. We would submit that the fact that DR Quinn's report does not refer specifically or identify hyponatraemia as an issue reflects the general lack of awareness of this issue at that time; and
d. Dr Kelly did not rely on the opinion of one Consultant Paediatrician and asked for the Royal College to consider LC's case as part of review of Dr O'Donohoe's performance, which they did on two occasions.

9b. *"Your failure to conduct an adequate investigation into LC's death may have contributed to the deaths of other children, including that of RF."*

9b. Dr Kelly denies this allegation. Please see 9a above.

10. *"Your actions, as described in paragraph 3c, 4c, 5e, 6, 7c, 7d and 9 above were:*
(a) unprofessional,
(b) not in the best interests of your patients,
(c) below the standards to be expected of a Medical Director,
(d) below the standards to be expected of a registered Medical Practitioner.

10.
(a) This allegation is denied;
(b) This allegation is denied;
(c) This allegation is denied; and
(d) This allegation is denied

We hope that this correspondence is of assistance to the Council, however, should you or the Council require any further information please do not hesitate to contact us.

Yours faithfully,

Carson McDowell
roger.mcmillan[redacted]
rachael.mcadorey[redacted]

Enc.

antiarrhythmic drugs are ineffective or not tolerated. Patients who have frequent atrial ectopic beats with a consistent P wave morphology indicating a single ectopic focus are most suited to focal ablation (fig 3). This procedure is new and has not yet been adopted by all regional electrophysiology centres.

For persistent and permanent atrial fibrillation, ablation of the His bundle and implantation of a pacemaker is a good option if satisfactory control of heart rate cannot be achieved with atrioventricular node blocking drugs, or if side effects occur. This procedure can also be used for paroxysmal atrial fibrillation in patients not suited to focal ablation. Although promising, linear ablation is still an experimental treatment and requires further evaluation before it can be recommended in clinical practice.

Competing interests: None declared.

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Lesson of the week

Acute hyponatraemia in children admitted to hospital: retrospective analysis of factors contributing to its development and resolution

Michael Halberthal, Mitchell L. Halperin, Desmond Bohn

Do not infuse a hypotonic solution if the plasma sodium concentration is less than 138 mmol/l

Department of Critical Care Medicine, Hospital for Sick Children, Toronto, Ontario, Canada M5G 1X8
Michael Halberthal *fellow*

continued over

Hyponatraemia (plasma sodium concentration less than 136 mmol/l) is acute if the decrease in natraemia occurs within 48 hours. The major dangers from this are brain cell swelling and herniation.[1 2] Two factors are required for hyponatraemia to develop: a source of electrolyte free water and vasopressin to prevent the excretion of that water.[3] Electrolyte free water is given routinely as maintenance fluids based on formulas developed in studies in healthy children more than 40 years ago.[4 5] There are many reasons to anticipate that vasopressin will be released in sick patients (box).[6] Patients with an acute illness may arrive in hospital with a low plasma sodium concentration because of previous water intake. Hence, to minimise the potential threat of brainstem herniation it is important to measure the plasma sodium concentration if intravenous solutions are to be given.

We describe symptomatic hyponatraemia developing over 48 hours in children. In each patient, hypotonic solutions were infused using current guidelines.[7] We related the volume of electrolyte free water given to the decrease in natraemia and assessed whether actions of vasopressin persisted to guide emergency corrective therapy.[8]

Causes of vasopressin release

- Hypernatraemia (most important stimulus, but not in these patients)
- Low "effective" circulating volume (greater than 7% decrease in extracellular fluid volume)
- Nausea, pain, anxiety
- Drugs (some act through inducing nausea)
- Afferent stimuli by way of the vagus nerve—for example, lung lesions
- Disturbances of the central nervous system (meningitis, encephalitis)
- Metabolic and endocrine disorders—for example, hypothyroidism, hypoadrenalism, porphyria

We reviewed all patient charts (306 charts) with a recorded diagnosis of hyponatraemia for the past 10 years. Patients were included if their decrease in natraemia was to less than 130 mmol/l and this occurred within 48 hours, if intravenous fluids were given, and if an underlying disease did not compromise renal handling of sodium or water. Thirty patients had acute hyponatraemia. Crucial information was missing for seven, leaving 23 patients in the study group. The median age was five years (range one month to 21 years), with males predominating (18 of 23); 13 developed hyponatraemia in the postoperative period. Fifteen patients were referred to the critical care unit after the development of symptomatic hyponatraemia while receiving intravenous fluids—11 were from the hospital wards and four were transferred from other institutions. Symptoms included seizures (18 patients) and vomiting,[7] a warning sign of an increased intracranial pressure. Treatment was withdrawn from five patients after brainstem coning. One patient sustained permanent, severe neurological damage.

Results

All the children received hypotonic fluids while their plasma sodium concentration was less than 140 mmol/l, because of the wide belief in paediatric practice that "maintenance fluids" should be hypotonic.[9] In fact the volume of maintenance fluid given was 50% greater than recommended values in 16 of the 23 patients. This infusion of hypotonic fluids increased the risk of acute hyponatraemia and brain swelling because vasopressin is typically present in this setting.[1 2 10 11] In quantitative terms, some of the electrolyte free water infused was retained in six of the patients because their urine sodium plus potassium concentration was less than 25 mmol/l (fig 1). In six patients more electrolyte free water was infused than needed to cause the observed decline in natraemia (points above line of identity in fig 2). The remainder of the patients had a decrease in natraemia that exceeded the decline if the entire volume of electrolyte free water infused was retained (points below broken line in fig 2). Therefore there was either another non-recorded input of water or the excretion of a large volume of hypertonic urine (a desalination of infused isotonic saline[12]).

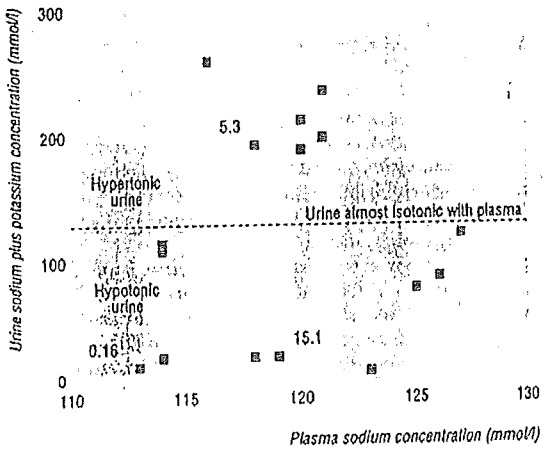

Fig 1 Concentration of sodium and potassium in urine at nadir observed for plasma sodium concentration in 17 patients (numbers represent rate of urine flow)

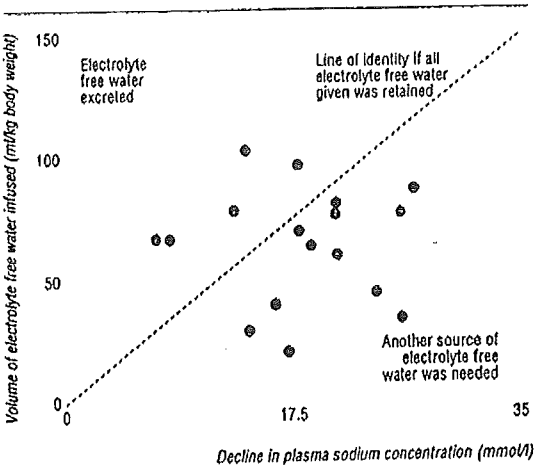

Fig 2 Comparison of decline in plasma sodium concentration with amount of electrolyte free water given in 17 patients. Difference in sodium concentration was between initial value and that at its nadir

Discussion

One objective of our study was to assess the renal actions of vasopressin. Because six patients had very hypotonic urine at their recorded nadirs of natraemia, their plasma sodium concentration might have been much lower before water diuresis began (fig 1). Had their plasma sodium concentration been measured after this large water diuresis, the erroneous conclusion might have been drawn that acute hyponatraemia had never been present. Hence its incidence may be much higher than shown by an analysis of hospital records. Therefore acute hyponatraemia could have been an occult cause of morbidity and mortality.

Another implication of cessation of the release of vasopressin concerns treatment. Treatment for acute, symptomatic hyponatraemia causes a prompt decline in the size of brain cells.[10] Hypertonic saline (3%) is the commonest treatment for shrinking brain cell volume, thereby lowering intracranial pressure. Treatment must be prompt because deterioration may be rapid and irreversible, even when symptoms are mild. Enough hypertonic saline (a total of 5 mmol of sodium chloride per litre of body water[13]) is needed acutely to lower intracranial pressure sufficiently to minimise this risk (the plasma sodium concentration should be increased by 5 mmol/l over several hours). Because an excessively rapid rate of correction of hyponatraemia might have deleterious effects,[6] hypertonic saline should not be given if there is a brisk water diuresis. For example, the plasma sodium concentration will also increase by 1.2 mmol/l/h if 6 ml of electrolyte free water are excreted per kilogram per hour (total body water is close to 600 ml/kg; 6 ml is a 1% change of 120 mmol/l). Whereas excretion of hypotonic urine indicates that electrolyte free water is being excreted (6 of 17 patients, fig 1), it is also important to consider the rate of urine flow. Little electrolyte free water was excreted in the index oliguric patient (flow 0.16 ml/kg/h). By contrast, the excretion of electrolyte free water was high enough to increase the plasma sodium

Division of Nephrology, St Michael's Hospital Toronto, Toronto, Ontario, Canada M5B 1A6
Mitchell L. Halperin *professor*
Department of Critical Care Medicine, Hospital for Sick Children, Toronto
Desmond Bohn *professor*
Correspondence to: D J Bohn dbohn@stickkids.on.ca

concentration by close to 3 mmol/l/h in the polyuric index patient who recovered (15 ml/kg/h). Vasopressin continued to act in patients excreting isotonic or hypertonic urine, so hypotonic intake must be avoided in them. With these high urine tonicities a further decrease in natraemia would be anticipated if the urine output was high (index case designated with a urine output of 5.3 ml/kg body weight, fig 1).[12] Finally, vasopressin concentrations may decline abruptly, increasing the excretion of electrolyte free water.

Serious symptoms may become evident when hyponatraemia approaches 120 mmol/l, but there are cases where symptoms become evident with a higher plasma sodium concentration, whereas others tolerate this electrolyte disorder without developing seizures.[14] Apart from underlying conditions that might make a patient more susceptible to seizures, a possible important factor could be the extracellular fluid volume of the brain. If this volume was expanded by a large infusion of isotonic saline, a higher intracranial pressure might be present at a given degree of hyponatraemia. Moreover, because there is a relatively larger proportion of brain cell volume to extracellular fluid volume in young patients, they are more vulnerable to an increase in brain cell volume.

Study limitations

Because of a reporting and referral bias, the incidence of adverse outcomes from hyponaetremia cannot be deduced from these data. Our results highlight the dangers of the routine use of hypotonic solutions when vasopressin acts. The currently used guidelines for maintenance fluids in children admitted to hospital must be changed because they do not take into account the unpredictability of vasopressin secretion. We recommend that the concentration of plasma sodium should be measured when starting an intravenous infusion. If it is less than 140 mmol/l then isotonic and not hypotonic fluids should be given. The use of hypotonic solutions should be reserved for patients who have a plasma sodium concentration greater than 140 mmol/l. If a patient receives intravenous fluid that exceeds 5% of total body water (30 ml/kg) then their plasma sodium concentration should be measured. If an intravenous infusion is started to give drugs, a small volume should be used, and the solution should be isotonic if possible.

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When I use a word ...

The last word

Sometimes short words are the most interesting. Like the definite and indefinite articles, "the" and "a(n)" (see also *BMJ* 1999;318:1758 and 2000;321:953). Not for nothing does the *Oxford English Dictionary* devote four pages to the different forms and meanings of "the."

When President Kennedy visited Berlin in June 1963 he made a famous speech in which he proclaimed that "All free men, wherever they may be, are citizens of Berlin, and, therefore, as a free man, I take pride in the words 'Ich bin ein Berliner.'" Now had he been in Hamburg and announced that he was a Hamburger, he would have immediately caused some amusement. But, at home at least, the fact that he had announced himself to be a doughnut (ein Berliner) went virtually unnoticed. And although his version was not an appalling solecism, "Ich bin Berliner" (without the definite article) would have been better.

Nowadays politicians take greater care over their definite articles. As I have previously pointed out (*BMJ* 2000;320:1480), "the" is used by modern spin doctors to give verisimilitude to non-existent entities. For instance, when Tony Blair talks about "the international community," he is trying to persuade us to believe that there is such a thing.

Politicians also sometimes talk about the psychological moment, meaning the time at which something is best done. When they do so they fail to realise that the phrase originally meant something completely different. It came from the German, das psychologische Moment, the psychological momentum. The psychological moment would have been der Moment, not das. French journalists were to blame. According to Fowler in *Modern English Usage* (1926) and Burchfield in *The New Fowler's Modern English Usage* (1996) they translated it during the German siege of Paris in 1870 as "le moment psychologique." Unfortunately, in French, as in English, moment means only moment and not also momentum.

Another journalist, Mary McCarthy, showed how much damage the definite article could wreak in a scathing comment about Lilian Hellman, for which Hellman sued for $2m (dying before judgment was passed). "Every word [Hellman] writes," said McCarthy, "is a lie, including 'and' and 'the.'"

But perhaps the (literally) last word should be left to James Joyce. He ended *Ulysses* with "the least forceful word I could possibly find ... the word 'yes,' which is barely pronounced, which denotes acquiescence, self abandon, relaxation, the end of all resistance." For *Finnegans Wake* he searched harder: "This time, I have found the word which is the most slippery, the least accented, the weakest word in English, a word which is not even a word, which is scarcely sounded between the teeth, a breath, a nothing, the article *the*."

Jeff Aronson *clinical pharmacologist, Oxford*

The Ulster Medical Journal, Volume 72, No. 2, pp. 69-72, November 2003.

Editorial

Prevention of hyponatraemia in children receiving fluid therapy

Severe hyponatraemia (serum sodium <130 mmol/1) has become increasingly recognised in recent years as a potential complication of fluid therapy in children,[1] and at least two children in Northern Ireland have died in recent years as a result. Worldwide, death or neurological morbidity related to this condition has recently been reported in more than 50 children.[2] Hyponatraemia has also been reported in as many as 5% of adults undergoing elective surgery[3] and in 25% of children following spinal fusion.[4] It has been suggested that menstruant women and prepubertal children are particularly at risk of brain damage in this situation.[5] Although risk factors include vomiting, pain, anxiety, disturbances of the central nervous system and metabolic and endocrine disorders, it has become recognised that any child receiving intravenous fluids or oral rehydration is potentially at risk. The particular risks associated with the post-operative period were highlighted by Arieff who pointed out that plasma levels of vasopressin (antidiuretic hormone, ADH) are elevated in virtually every child in the post-operative period.[5] If such children are given fluids containing less than 140 mmol/1 of sodium there will always be a tendency towards post-operative hyponatraemia.

The complex inter-relationships between multiple factors influencing decisions regarding fluid and electrolyte management in children are described in standard texts. These result in difficulty in establishing simple guidelines for fluid administration in children. A solution containing 0.18% sodium chloride in 4% glucose has commonly been used in paediatric practice and is generally held to be isotonic. However, in the catabolic child the glucose is metabolised rapidly causing the fluid to become hypotonic in vivo, with the potential for significant fluid shifts. If the child is in the post-operative period or in any other situation where there is a high level of circulating vasopressin a situation can arise where excess free water is retained within the circulation. This can be compounded by water effectively administered in the intravenous fluids. This condition has been called "dilutional hyponatraemia" because the "free" water component of the serum has increased, causing dilution of the major cation, sodium. This "free" water will pass rapidly and unhindered across cell membranes with the particular risk of development of cerebral oedema. Children may be at particular risk of brain damage due to increase in intracranial pressure in this situation.[2]

GUIDANCE AND ADVICE

A Working Group in Northern Ireland has developed guidelines (figure), which have been published by the Department of Health, Social Services and Public Safety, and can be downloaded from the internet.[6] These guidelines emphasise that every child receiving intravenous fluids requires a thorough baseline assessment, that fluid requirements should be assessed by a doctor competent in determining a child's fluid requirement, and fluid balance be rigorously monitored. They emphasise the value of accurate measurement of body weight and monitoring of serum urea and electrolytes in any child requiring prescribed fluids after 12 hours, together with the importance of assessment of fluid balance and prescription at least every 12 hours by an experienced member of clinical staff. This assessment needs to take account of all oral and intravenous intake, together with the measurement and recording of all losses (including urine, vomiting, diarrhoea, etc.) as accurately as possible.

While general guidance can be given regarding *maintenance* fluid requirements in children of different weights, these must be assessed in the clinical context of each individual child. Requirements for water and electrolytes should be considered separately and an appropriate solution chosen. Although the baseline maintenance requirement for 2 to 3 mmol/kg/day of sodium can be applied to children of all ages, the amount of water needed varies with weight. It will readily be apparent that this means that the concentration of sodium in the maintenance fluid has to be different for children of different ages and weights. For example, an infant of 5 kg requires 150 ml/kg/day of water, so the daily sodium requirement will be provided by a fluid

Any child receiving prescribed fluids is at risk of hyponatraemia

INTRODUCTION

- Any child on IV fluids or oral rehydration is potentially at risk of hyponatraemia.
- Hyponatraemia is potentially extremely serious, a rapid fall in sodium leading to cerebral oedema, seizures and death. Warning signs of hyponatraemia may be non-specific and include nausea, malaise and headache.
- Hyponatraemia most often reflects failure to excrete water. Stress, pain and nausea are all potent stimulators of anti-diuretic hormone (ADH), which inhibits water excretion.
- Complications of hyponatraemia most often occur due to the administration of excess or inappropriate fluid to a sick child, usually intravenously.
- Hyponatraemia may also occur in a child receiving excess or inappropriate oral rehydration fluids.

BASELINE ASSESSMENT

Before starting IV fluids, the following must be measured and recorded:

- **Weight**: accurately in kg. [In a bed-bound child use best estimate.] Plot on centile chart or refer to normal range.
- **U&E**: take serum sodium into consideration.

FLUID REQUIREMENTS

Fluid needs should be assessed by a doctor competent in determining a child's fluid requirement. Accurate calculation is essential and includes:

Maintenance Fluid

- 100mls/kg for first 10kg body wt. plus
- 50mls/kg for the next 10kg, plus
- 20mls/kg for each kg thereafter, up to max of 70kg.

[This provides the total 24 hr calculation, divide by 24 to get the mls/hr.]

Replacement Fluid

- Must always be considered and prescribed separately.
- Must reflect fluid loss in both volume and composition (lab analysis of the sodium content of fluid loss may be helpful).

CHOICE OF FLUID

- **Maintenance fluids** must in all instances be dictated by the anticipated sodium and potassium requirements. The glucose requirements, particularly of very young children, must also be met.
- **Replacement fluids** must reflect fluid lost. In most situations this implies a minimum sodium content of 130mmol/l.
- **When resuscitating** a child with clinical signs of shock, a decision is made to administer a crystalloid, normal (0.9%) saline is an appropriate choice, while awaiting the serum sodium.
- The composition of oral rehydration fluids should also be carefully considered in light of the U&E analysis.

Hyponatraemia may occur in any child receiving any IV fluids or oral rehydration. Vigilance is needed for all children receiving fluids.

MONITOR

- **Clinical state**: including hypotonic sinus: Pain, vomiting and general well-being should be documented.
- **Fluid balance**: must be assessed at least every 12 hours by an experienced member of clinical staff.

Intake: All oral fluids (including medicines) must be recorded and IV intake reduced by equivalent amount.

Output: Measure and record all losses (urine, vomiting, diarrhoea, etc.) as accurately as possible.

If a child still needs prescribed fluids after 12 hours of starting, their requirements should be reassessed by a senior member of medical staff.

- **Biochemistry**: Blood sampling for U&E is essential at least once a day – more often if there are significant fluid losses, or if clinical course is not as expected.

The rate at which sodium falls is as important as the plasma level. A sodium that falls quickly may be accompanied by rapid fluid shifts with major clinical consequences.

Consider using an indwelling heparinised cannula to facilitate repeat U&Es.

Do not take samples from the same limb as the IV infusion.

Capillary samples are adequate if venous sampling is not practical.

Urine osmolarity/sodium: Very useful in hyponatraemia. Compare to plasma osmolarity and consult a senior Paediatrician or a Chemical Pathologist in interpreting results.

SEEK ADVICE

Advice and clinical inputs should be obtained from a senior member of medical staff, for example a Consultant Paediatrician, Consultant Anaesthetist or Consultant Chemical Pathologist.

- In the event of problems that cannot be resolved locally, help should be sought from Consultant Paediatricians/ Anaesthetists at the PICU, RBHSC.

The Department of Health, Social Services And Public Safety: Guidance is also available on the Department's website: www.dhsspsni.gov.uk

containing 15 to 20 mmol/1 of sodium. The standard 0.18% saline solution contains 30 mmol/1 and so will adequately provide for this requirement. On the other hand, a child of 40 kg requires 50ml/kg/day, so a solution containing 3 times as much sodium will be needed to provide adequate maintenance sodium. A solution containing 0.18% saline will thus not provide adequate sodium to maintain the normal plasma level in the older child unless there are clinical reasons to limit sodium intake. This would require instead a solution containing 40 to 60 mmol/1. Half normal saline contains 75 mmol/1 of sodium.

Replacement fluids must reflect fluid loss, and in most situations this will imply a minimum sodium content of 130 mmol/1. This must be considered and prescribed separately, reflecting the fluid loss in both volume and composition. In some situations laboratory analysis of the electrolyte content of the fluid lost may be helpful.

It is important to remember that, while children receiving intravenous fluids are at particular risk, children receiving oral rehydrating fluids may also be at risk as these are invariably hypotonic. Vigilance is therefore required for all children receiving fluids. Medical and nursing staff need to be aware of risks in this situation, and of early signs of developing cerebral oedema such as vomiting, deteriorating level of consciousness or headache before more serious symptoms such as seizures occur, as deterioration to this extent is associated with significant morbidity and mortality.

Particular attention needs to be given to fluid management in specific situations such as diabetic ketoacidosis, renal failure and in the newborn, but attention to detail in assessment and management of intravenous and oral fluids in all children where these are required for medical or surgical reasons is essential to minimise the risks associated with hyponatraemia. It must be clearly recognized that prevention is quite different from treatment of hyponatraemia. All those working with children must be familiar with good practice to *prevent* hyponatraemia but not all will have the necessary expertise in *treating* a child with hyponatraemia which can be extremely complex. If concern is raised regarding clinical deterioration or biochemical abnormality then advice and clinical input should be obtained from a senior member of medical staff, for example a Consultant Paediatrician, Consultant Anaesthetist or Consultant Chemical Pathologist.

We recommend that complications and critical incidents related to intravenous fluids are reported to the Medicines Control Agency (MCA) in the same way as drug side-effects, by using the 'yellow card' system. Fluids are included in the British National Formulary and are under the regulatory authority of the MCA. This will permit a nationwide analysis of the problem and also direct information to clinicians. When one of the deaths locally was reported to the MCA the Agency was asked to consider issuing a 'hazard warning' about the use of a solution containing 0.18% sodium chloride in 4% glucose in children following surgery. After due consideration the MCA replied that electrolyte imbalance is a risk with the use of all intravenous solutions. The MCA Working Group on Paediatric Medicines advised that there should be no amendments to product information (personal communication).

CONCLUSION

It is important that all doctors caring for children are aware of current literature and advice in relation to the rare but serious condition known as 'Dilutional Hyponatraemia'. A complex neuro-endocrine response in susceptible children can occur where the 'free' water component of intravenous fluids can cause a sudden and unheralded decrease in the serum sodium concentration. Preventative measures to avoid this potentially fatal condition need to be instituted in all units caring for children.[7]

JG Jenkins, B Taylor, M McCarthy

J G Jenkins, MD, FRCP, FRCPCH, FRCPI, Senior Lecturer in Child Health, The Queen's University of Belfast. Consultant Paediatrician, Antrim Hospital, Antrim, BT41 2RL.

B Taylor, MB, MA, FFARCSI, Consultant Paediatric Intensivist, Royal Belfast Hospital for Sick Children, Belfast BT12 6BE.

M McCarthy, MB, BCH, BAO, MRCGP, MPH, Senior Medical Officer, Department of Health, Social Services and Public Safety, Castle Buildings, Belfast BT4 3SJ.

Correspondence to Dr Jenkins.

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Acute Hyponatremia Related to Intravenous Fluid Administration in Hospitalized Children: An Observational Study

Ewout J. Hoorn, Denis Geary, Maryanne Robb, Mitchell L. Halperin and Desmond Bohn

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Acute Hyponatremia Related to Intravenous Fluid Administration in Hospitalized Children: An Observational Study

Ewout J. Hoorn, MD*; Denis Geary, MB‡§; Maryanne Robb, MD‡§‖; Mitchell L. Halperin, MD¶; and Desmond Bohn, MB*#

ABSTRACT. *Objective.* To develop hyponatremia (plasma sodium concentration [P_{Na}] <136 mmol/L), one needs a source of water input and antidiuretic hormone secretion release to diminish its excretion. The administration of hypotonic maintenance fluids is common practice in hospitalized children. The objective of this study was to identify risk factors for the development of hospital-acquired, acute hyponatremia in a tertiary care hospital using a retrospective analysis.

Methods. All children who presented to the emergency department in a 3-month period and had at least 1 P_{Na} measured (n = 1586) were evaluated. Those who were admitted were followed for the next 48 hours to identify patients with hospital-acquired hyponatremia. An age- and gender-matched case-control (1:3) analysis was performed with patients who did not become hyponatremic.

Results. Hyponatremia (P_{Na} <136 mmol/L) was documented in 131 of 1586 patients with ≥1 P_{Na} measurements. Although 96 patients were hyponatremic on presentation, our study group consisted of 40 patients who developed hyponatremia in hospital. The case-control study showed that the patients in the hospital-acquired hyponatremia group received significantly more EFW and had a higher positive water balance. With respect to outcomes, 2 patients had major neurologic sequelae and 1 died.

Conclusion. The most important factor for hospital-acquired hyponatremia is the administration of hypotonic fluid. We suggest that hypotonic fluid not be given to children when they have a P_{Na} <138 mmol/L. *Pediatrics* 2004;113:1279–1284; *antidiuretic hormone, concentration of the urine, electrolyte-free water, intravenous fluids.*

ABBREVIATIONS. ECF, extracellular fluid; ADH, antidiuretic hormone secretion; P_{Na}, plasma sodium concentration; EFW, electrolyte-free water; TBW, total body water.

From the *Department of Critical Care Medicine, Hospital for Sick Children, Toronto, Ontario, Canada; #Department of Anesthesia, University of Toronto, Toronto, Canada; ‡Department of Paediatrics, Hospital for Sick Children, Toronto, Ontario, Canada; §Department of Pediatrics, University of Toronto, Toronto, Canada; ‖Department of Emergency Medicine, Hospital for Sick Children, Toronto, Ontario, Canada; and ¶Renal Division, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada.

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Reprint requests to (D.B.) Department of Critical Care Medicine, Hospital for Sick Children, 555 University Ave, Toronto, Ontario, Canada M5G 1X8. E-mail: dbohn@sickkids.ca

Hyponatremia is the most frequently encountered electrolyte disorder in hospitalized patients[1,2] and suggests that there is a surplus of water and/or a deficit of Na^+ in the extracellular fluid (ECF) compartment. Hence, there must be a source of water and actions of antidiuretic hormone secretion (ADH) to impair its excretion.[3] In children, the source of water is frequently the administration of hypotonic intravenous fluids. When the plasma sodium concentration (P_{Na}) falls acutely to <130 mmol/L, brain cell swelling may develop and be sufficient to lead to a devastating neurologic outcome. The most frequent clinical setting for acute hyponatremia is after elective surgery.[4–6] In this situation, the stimuli for the release of ADH are usually nonosmotic (pain, anxiety, nausea, and the use of pharmacologic agents such as narcotics and inhalational anesthetics). The problem is compounded when hypotonic fluids are given while the excretion of hypotonic urine is impaired.[7]

We recently reported on the development of acute hyponatremia in children who received hypotonic intravenous fluids.[6] We identified during a 10-year period 23 patients who had a rapid reduction in P_{Na} after surgery or in association with the administration of large amounts of hypotonic fluids. There was a 30% adverse outcome rate (death or neurologic injury). However, because that study was based on either a hospital discharge diagnosis of acute hyponatremia or patients who were referred to the critical care unit because of cerebral edema and brainstem herniation, it is unlikely to be an accurate reflection of the numbers at risk for an adverse neurologic event. We therefore conducted the present study to determine the importance of intravenous fluid therapy and the underlying diseases in its development.

METHODS

Approval was obtained from the Institutional Research Ethics Board to conduct a retrospective review of patients who were seen in or admitted through our hospital emergency department.

Study Group

Hyponatremia was defined as a P_{Na} <136 mmol/L. During the 3-month period from November 2000 to February 2001, there were 13 506 visits to the emergency department at the Hospital for Sick Children in Toronto. Those who had at least 1 P_{Na} value <136 mmol/L were identified. We then focused on patients who had a fall in P_{Na} in hospital—the hospital-acquired hyponatremia group.

The following general clinical data were included in our analysis: age, gender, weight, diagnosis, and medications. We looked for possible central nervous system symptoms of acute hyponatremia (headache, nausea, vomiting, seizures, and changes in sen-

sorium) as well as the volume of oral and intravenous fluid intake. Output values were also included when data were recorded. Data suggestive of a contracted ECF volume were included when documented in the chart (low blood pressure, rapid heart rate, and reduced capillary refill time). For each patient, the volume and type of fluid administered were compared with those recommended for maintenance fluid requirements in children based on the formula using body weight originally published by Holliday and Segar.[8] Cases in which deficits were replaced (eg, a contracted ECF volume) were incorporated into the final analysis.

Analysis of the Basis for a Fall in P_{Na}

Patients who developed hyponatremia in hospital were analyzed in greater detail because we could evaluate risk factors that contributed to its development. We calculated the amount of electrolyte-free water (EFW) input using the tonicity and volume of the administered fluid.[9] For example, the commonly used solution for maintenance fluids in our institution is 3.3% dextrose in 0.3% NaCl (51 mmol of Na^+ per liter), which is one third of the amount present in an isotonic saline. Therefore, two thirds of the volume of this solution can be thought of as EFW.[10] In our calculations, we included potassium (K^+) in defining tonicity.[11] These calculations were also performed for oral solutions.

The influence of EFW on the P_{Na} was analyzed using the initial measured P_{Na} and total body water (TBW) estimated as 60% of body weight, except for neonates in whom TBW was calculated as 70% of body weight. If, for example, the P_{Na} fell from 140 to 135 mmol/L as a result of a positive balance for EFW, then the TBW in a 10-kg person would have to increase from 6000 mL to 6220 mL (positive balance of 220 mL of EFW). Included in calculations for output were insensible losses, using an average of 14 mL/kg/day in the absence of fever.[12] Finally, we recorded likely reasons for high ADH levels from data in the history (disease, symptoms, drugs, and surgery) and physical examination (ECF contraction).

We also compared the patients with hospital-acquired hyponatremia with a control group of age-, gender-, and weight-matched patients who had ≥2 P_{Na} measurements in which the P_{Na} was >136 mmol/L, using a 1:3 match. Cases with a reason for a shift of water from the intracellular fluid to the ECF compartment (eg, hyperglycemia) or those who were given hypertonic mannitol were excluded from this analysis. We identified all patients who had ≥1 serum electrolyte measurements from the hospital laboratory database.

Analytical Methods and Calculations

A retrospective case-control study was performed using a *t* test and a χ^2 test. Correction for multiple variable testing included using the Bonferroni correction.[13]

RESULTS

Patients

A total of 432 patients had ≥2 P_{Na} measurements, 97 of which had a P_{Na} <136 mmol/L. The remaining 335 patients were not hyponatremic and formed the basis of our control group. Sixty-two patients were hyponatremic on presentation, whereas 35 of 97 developed hyponatremia after presentation. In 12 of 62 of these patients, the P_{Na} remained <136 mmol/L, whereas in 50 of 62, it increased to >136 mmol/L but then fell again to <136 mmol/L in 5 patients on a subsequent measurement. Thus, the total number of patients who developed hospital-acquired hyponatremia was 40 of 432. The P_{Na} in these 40 patients with hospital-acquired hyponatremia fell from a mean of 139 ± 3 mmol/L to 133 ± 2 mmol/L, a decline of 6 ± 1 mmol/L in 19 ± 10 hours.

Our next step was to relate the amount of EFW given (orally and/or intravenously) to that needed to cause their observed fall in P_{Na}; there were 2 near-equal groups (Fig 1): 1 received sufficient (or more) EFW to explain their fall in P_{Na} (all points on or above the line of identity), and the other did not receive enough EFW to explain their fall in P_{Na} (points below the line of identity). The source of this EFW load was predominantly the infusion of hypotonic fluids (66%), whereas in the remainder, the fall in P_{Na} could be attributed to the oral intake of EFW; these latter patients could have had an occult source of water intake, a reason to shift EFW out of cells (eg, a catabolic state,[14] the excretion of hypertonic urine[7,15]). The main reason for this ECF volume expansion may have been the bolus infusion of more isotonic saline than needed to reexpand the ECF volume.

We identified 16 patients with insufficient EFW to cause the observed degree of fall in their P_{Na} (Fig 1); 11 received a bolus of 0.9 NaCl (45 ± 42 mL/kg/hour; 15% expansion of ECF if all retained) on the basis of the presumption that they had ECF contraction. None of the patients on or above the line of identity received boluses of fluid.

Case-Control Study

The in-hospital group with a fall in their P_{Na} received 3-fold more EFW and had a greater positive fluid balance than the control group ($P < .001$ and $P = .02$, respectively; Table 1). Although this in-hospital group received less Na^+ per kilogram of body weight, this difference was not statistically significant. The amount of fluid infused was not only significantly higher in this in-hospital group but also well above that recommended by the standard formula for maintenance fluid administration[8] and well above what we now calculate for maintenance fluids.[16] Our analysis showed that there were no significant differences related to the underlying disease, that the symptoms of nausea and vomiting were significantly more prevalent in the in-hospital group, and that patients in the in-hospital group underwent surgery more frequently ($P < .05$). Finally, likely reasons for high levels of ADH in patients with hospital-acquired hyponatremia were found to be mainly of nonosmotic origin (symptoms, drugs, and disease; Table 1).

DISCUSSION

The principal results in this study confirm that it was not uncommon for hyponatremia to develop in the first 48 hours of admission to hospital, related in large part to intravenous fluid administration. The level of P_{Na} that we used for eligibility criterion is consistent with previously published definitions[17] and was the median level found in a large published series of children who presented to a hospital with acute medical illnesses.[18] Groups of children who previously have been reported to be at risk are those with meningitis, encephalitis, head injury, bronchiolitis, gastroenteritis, and chronic lung disease of prematurity and in association with chemotherapy.[19–27] This list was not all-inclusive because other nonosmotic stimuli were present in our population with hospital-acquired hyponatremia (Table 1). Hyponatremia is also a common event after elective surgery[2,28–30] and when acute (<48 hours) can lead to catastrophic neurologic sequelae.[5,6,31] Children

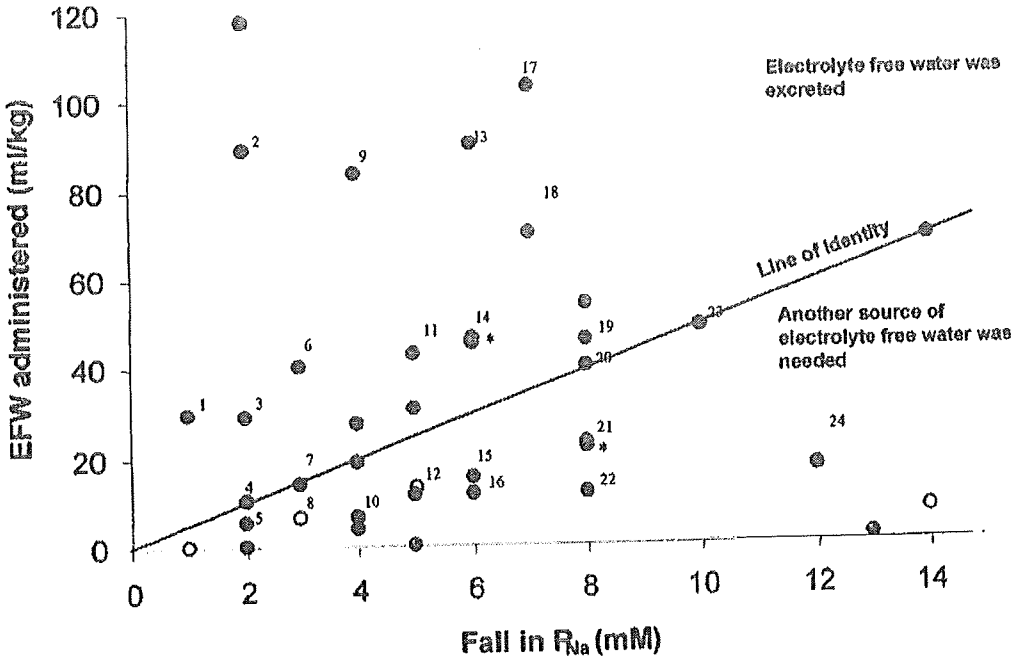

Fig 1. The relationship between EFW administration and the fall in P_{Na}. *Overlap of 2 points. Points represent individual patients with hospital-acquired hyponatremia (n = 37). The case numbers next to the dots refer to patients whose urine output is known and correspond with those in Fig 2. The solid line represents the amount of EFW that would need to be retained to cause the observed fall in P_{Na}. The patients whose points fell on or above the line of identity could have retained enough EFW to explain their fall in P_{Na}; any extra water either was excreted in the urine or sweat or was turned into an isotonic saline as a result of a positive balance for Na^+. In the patients whose points fell below the line of identity, the amount of EFW given can be only a partial explanation for their fall in P_{Na}. These patients required a concurrent excretion of hypertonic Na^+ (+ K^+) and/or an occult source of EFW to achieve their observed fall in P_{Na}.

TABLE 1. Results 1:3 Age- and Gender-Matched Case-Control Study

Category	Variable	Cases (n = 37)	Controls (n = 111)	P Value
Demographics	Age, y	7 ± 6	7 ± 6	1.0
	Gender, number (%)	15 (41) F, 22 (60) M	45 (41) F, 66 (60) M	1.0
	Weight, kg	25 ± 18	28 ± 21	.4
	Surgery, number (%)	6 (16)	6 (5)	.04
Water and sodium	P_{Na}	139 ± 3 → 133 ± 2 mM	140 ± 2 mM	—
	Decrease in P_{Na}, mmol	6 ± 3 in 19 ± 10 h	—	—
	EFW, mL/kg/h	2 ± 2	1 ± 1	<.001
	Na^+, mmol/kg/h	0 ± 1	1 ± 1	.3
	Positive water balance, ml/kg/h*	4 ± 5	2 ± 3	.02
IV-fluid regimen	Amount of fluid, ml/h	98 ± 77	47 ± 46	<.001
	% that received more than recommended maintenance†	73	23	<.001
Main disease categories	GI disorders, number (%)	11 (30)	19 (17)	1.0
	Neoplasia	8 (22)	14 (13)	1.0
	Respiratory infections	5 (14)	28 (25)	1.0
	Renal disease	1 (3)	6 (5)	1.0
Reason for elevated ADH	Disease, number (%)	5 (14)	—	—
	Symptoms	23 (62)	—	—
	Drugs	9 (24)	—	—
	Hypovolemia	0 (0)	—	—
Possible symptoms	Nausea, number (%)	10 (27)	3 (8)	.008
	Headache	2 (5)	11 (10)	.5
	Vomiting	25 (68)	46 (41)	.008
	Seizures	1 (3)	6 (5)	.7
	Sensorium changes	7 (19)	13 (12)	1.0

* Data were available for all cases and 43 controls.
† As described by the formula of Holliday and Segar.[8]

with chronic hyponatremia are not at risk for the development of cerebral edema.[32,33]

There are 2 requirements for a fall in P_{Na}: the presence of ADH and a source of water input. Although it should not be surprising to find elevated ADH levels in acutely ill patients,[18] this will not cause hyponatremia in the absence of water input. The major source for water input in our study was the infusion of a large amount of hypotonic fluid. Because close to half of the cases received a higher

amount of intravenous fluid than recommended for maintenance on the basis of the formula of Holliday and Segar,[8] the amount given was a contributing causative factor. The infusion of a large volume of saline was likely attributable to the belief that the ECF volume was contracted. For the group that did not have a recorded input of sufficient water to explain their fall in P_{Na} (Fig 1, points below line of identity), one would suspect that they had an occult water intake (eg, ice chips, water residing in the lumen of the gastrointestinal tract after admission, electrolyte-free water generation by the kidney secondary to the excretion of hypertonic urine; open dots in Fig 2). For this latter mechanism, one needs the combination of an infusion of isotonic saline and the excretion of hypertonic urine.[7] It is possible that this desalination process may have been triggered by the acute expansion of the ECF volume as a result of the administration of isotonic saline, because we could find recorded evidence that the ECF volume was contracted in only 10% of these patients. We emphasize that the clinical assessment of the degree of ECF volume contraction is a method of limited sensitivity and specificity.[34–37]

Dangers of Acute Hyponatremia

Previous studies have shown that children with acute hyponatremia have an appreciable risk for neurologic damage.[5,6,38,39] With respect to the potential dangers of acute hyponatremia in our patient population, it is possible that the observed fall in P_{Na} led to serious severe neurologic outcomes in 2 of 40 patients. One of these (Fig 1; fall in P_{Na} of 14 mmol/L) had an underlying seizure disorder and had a convulsion during the hyponatremic period. This highlights the need to be more vigilant about the fall in P_{Na} when an underlying medical condition places the patient at risk. We also emphasize a diagnostic caveat: that a seizure may raise the P_{Na} transiently by an average of 13 mmol/L, masking the original degree of hyponatremia.[40] The second patient (fall in P_{Na} of 13 mmol/L from 142 to 128 mmol/L in 1.5 hours) had a cardiac arrest. Although she was resuscitated initially, she ultimately died. Postmortem examination revealed brain cell swelling. The high incidence of nausea and vomiting (Table 1) may indicate more cases of symptomatic hyponatremia; however, because these symptoms are also known to be potent stimuli of ADH release, this deduction is not possible from this retrospective study.

Rationale of the Choice of Intravenous Fluid: Hypotonic Versus Isotonic

The almost universal practice of the use of hypotonic fluids in children is based on calculations that linked energy expenditure to water and electrolyte losses, published nearly 50 years ago. Applying this formula results in the administration of large amounts of EFW, which then has to be excreted by the kidney. We believe that linking energy expenditure to water losses in hospitalized patients significantly overestimates the need for maintenance fluid. In a recent commentary,[16] we reevaluated the factors used to calculate water and electrolyte requirements in Holliday and Segar's original paper. Moreover, these calculations did not factor in the unpredictable effect of nonosmotic stimuli for ADH secretion in the acutely ill child, which can result in retention of water and hyponatremia.[18] Our conclusion was that

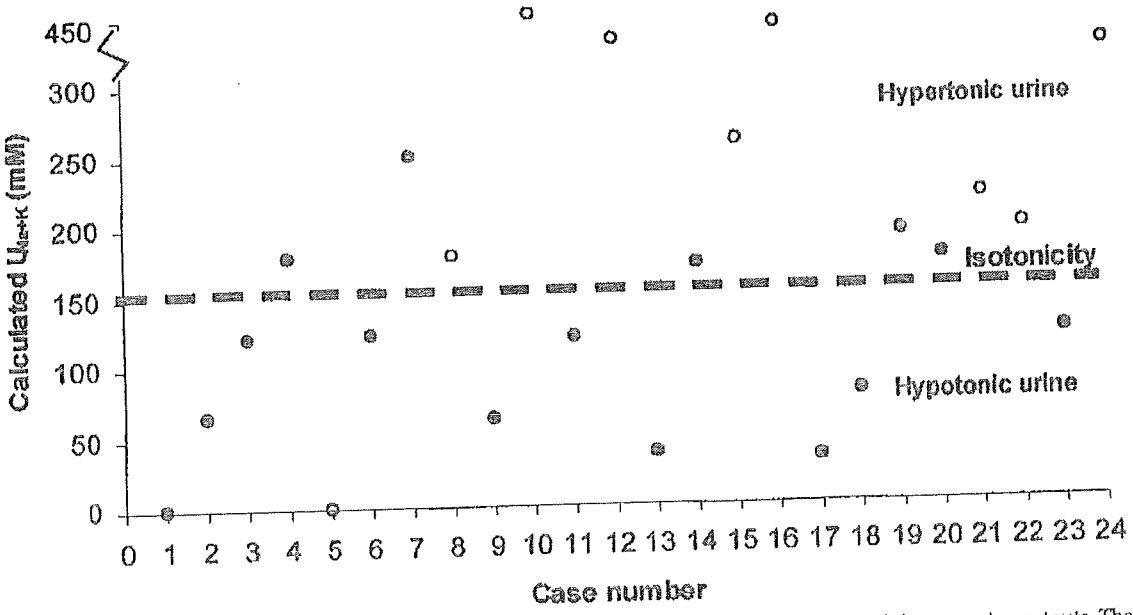

Fig 2. Calculated urine Na^+ concentration. Dots represent the urine Na^+ concentration for patients with known urine outputs. The case numbers correspond to the case numbers in Fig 1. Open dots refer to patients whose points fall under the line of identity in Fig 1. Patients whose points fell below the line representing isotonicity have urine Na^+ concentrations exceeding 150 mmol/L. In those patients, ADH levels should be high. In 2 patients, urine outputs were noted to be small, which explains their values close to 0 mmol/L. (For validation of this method, see Carlotti et al.[46])

the water requirements and the renal ability to excrete hypotonic urine were overestimated. Therefore, our general recommendation was that the P_{Na} be measured once the ECF volume is expanded >10% (30 mL/kg); and if the P_{Na} is <138 mmol/L, then do not infuse hypotonic fluids.[16]

The option of selecting isotonic rather than hypotonic for maintenance fluid in children has been advocated by some authors.[6,41–43] In a recent publication, Moritz and Ayus[43] drew attention to this idea, and our data support this position. This generally has not been accepted because of concerns about excessive administration of Na^+ and the development of hypernatremia. The comparative studies in children, although few, do not support this perceived danger. In a randomized trial of different fluid protocols in children with meningitis, Powell et al[20] compared a fluid-restricted group who received hypotonic saline with a fluid-deficit replacement plus maintenance regimen using predominantly isotonic solutions. Children in the isotonic group received an average of 6 mmol Na^+/kg/day and had normal P_{Na} levels, whereas those in the hypotonic group received an average of 2 mmol Na^+/kg/day and became hyponatremic. Likewise, in the study by Gerigk et al[18] of acutely ill children in which the median P_{Na} was 136 mmol/L at the time of admission to hospital, those who were given isotonic fluid had a more rapid fall in their ADH levels than those who received hypotonic fluids.

Children who undergo surgical procedures are particularly at risk from hyponatremia because of the association between anesthetic agents and opiates and nonosmotic ADH secretion. Moreover, the syndrome of inappropriate ADH secretion has been frequently reported in association with spinal surgery.[30,44] Burrows et al[30] compared hypotonic with isotonic intravenous fluids in children who underwent surgery for scoliosis. Both groups had a fall in their P_{Na} in the postoperative period, but the reduction was greater in those who received the hypotonic solution.

Patients who have findings of hyponatremia, with impaired excretion of EFW as a result of actions of ADH in the absence of obvious stimuli for ADH release (an ECF volume contraction of at least 8%), or either adrenal insufficiency or hypothyroidism are said to have the syndrome of inappropriate ADH secretion.[45] In this syndrome, the urine usually contains an appreciable quantity of Na^+. Therefore, we could have said that hyponatremia developed in our patients as a result of the syndrome of inappropriate ADH secretion. Notwithstanding, we have used a different way to describe the basis of hyponatremia in our population. Our description begins with the pathophysiology. Our patients had multiple nonosmotic stimuli for the release of ADH. The source of the EFW was hypotonic fluids given by the physician (hypotonic intravenous solutions), health care workers (eg, ice chips), and/or the family of the patient (oral drinks containing water). In addition, EFW could be generated by the kidneys when the urine has a higher $Na^+ + K^+$ concentration than the net of all inputs.[7] Regardless of the terminology, the most important factor is the net input of EFW in this setting because ADH is likely to be present for the nonosmotic reasons described above. Moreover, although patients have this type of ADH release, they need not develop a significant degree of hyponatremia because as their P_{Na} falls, thirst is suppressed and there is no longer a physiologic stimulus causing a large input of water. In contrast, in hospital, the physician rather than the patient determines the water intake.

Study Limitations

This study was retrospective and hence has the imperfections that characterize such studies. By evaluating every patient who arrived in our emergency department in a 3-month period, we attempted to minimize this limitation. Our actual incidence of hyponatremia is probably an overestimation because the P_{Na} was measured in only ~10% of the total population, a group that had indications for this measurement. In addition to these limitations, there was the problem of not measuring urine electrolytes and plasma ADH levels. Also, some of the patients and especially those who received insufficient EFW to explain their fall in P_{Na} could have had an occult source of water. Occult sources of water include water in the gastrointestinal tract that was not absorbed before the first measurement of the P_{Na}, the use of ice chips, or a parent's giving his or her child a drink without informing the nurse so that there is no record of that input in the hospital chart. We think that a prospective study to answer some of the obvious questions would be helpful.

CONCLUSIONS

The development of hyponatremia is unacceptably high in hospitalized children. This is attributable in large part to the administration of excessive amounts of water as hypotonic saline in situations in which ADH is secreted for nonosmotic reasons. The original guidelines for maintenance fluid may not be applicable in an era when the complexity and the severity of illness seen in hospitalized children who receive intravenous fluid therapy has radically changed (eg, leukemia, complex congenital heart disease) and irregularities of ADH secretion are more likely to be commonplace. We believe that hospital-acquired hyponatremia unnecessarily puts children at risk for the development of adverse neurologic events and is largely preventable. We suggest that the current recommendations for intravenous fluid therapy in hospitalized children be revised. Hypotonic fluids should not be used routinely in the intraoperative or postoperative period or when a patient has a P_{Na} in the low-normal or distinctly hyponatremic range (<138 mmol/L). In addition, boluses of isotonic saline should be given only when there are clear hemodynamic indications for that infusion.

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Acute Hyponatremia Related to Intravenous Fluid Administration in Hospitalized Children: An Observational Study

Ewout J. Hoorn, Denis Geary, Maryanne Robb, Mitchell L. Halperin and Desmond Bohn

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Maintenance fluid therapy

What routine intravenous maintenance fluids should be used?

N P Mann

An introduction to the debate

Intravenous maintenance fluid is widely used in general paediatric practice and more children who come into hospital receive intravenous fluid than in the past. The intravenous route is frequently used because enteral maintenance or rehydration treatment is more labour intensive and uses valuable staff time; furthermore modern pumps for delivery of fluids are safe. Nevertheless in developing countries the enteral route is still more widely used even for sick dehydrated children.

Are there are any dangers of intravenous fluids? Clearly there is a possibility of miscalculation of infusion rates and also the potential for mistakes in terms of dosing errors with additives. It has been widely recognised in recent years that there is a high incidence of hyponatraemia in children treated with intravenous maintenance fluids. Is this because of excessive water or too little salt?

Moritz and Ayus discussed the high frequency of hyponatraemia in these children in their paper in *Pediatrics* in February 2003.[1] They suggested the use of isotonic saline rather than use of hypotonic fluids for maintenance therapy. More than 20 years ago there were concerns about profound neonatal hyponatraemia causing neurological problems in infants as the result of either excessive or the wrong kind of fluid given to mothers during labour.[2]

It is therefore timely to revisit this problem. Two experts have been asked to give their views to encourage further debate (see accompanying articles[3 4]). Do write to *ADC* with your comments about how paediatric practice in this area can be improved.

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Correspondence to: Dr N P Mann; Npmann2@aol.com

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Maintenance fluid therapy

Pouring salt on troubled waters

D Taylor, A Durward

The case for isotonic parenteral maintenance solution

Intravenous fluid and electrolyte therapy for acutely ill children has been a cornerstone of medical practice for well over 50 years. The scientific methodology behind fluid regimens generated much debate in the early 1950s following the pioneering work of Darrow, Talbot, Gamble and others who recognised the important relation between caloric expenditure and requirements for water.[1–3]

Caloric expenditure was originally calculated according to body surface area, which at the bedside required either tables or nomograms.[1] In 1957 Holliday and Segar simplified this approach, relating energy expenditure to one of three weight based categories (<10 kg, 10–20 kg, >20 kg).[4] Electrolyte requirements were also calculated on a weight basis, producing an "ideal", hypotonic solution comprising 0.2% saline in 5% dextrose water (0.18% saline in 4% dextrose in the United Kingdom). This simple regime was subsequently adopted on a global scale and is recommended in current paediatric and medical textbooks.

Advances in our understanding of water and electrolyte handling in health and disease have called into question the validity of the Holliday and Segar approach. Specifically, many authors have reported how hypotonic maintenance fluid may result in iatrogenic hyponatraemia in hospitalised patients, often with devastating consequences.[5–10] In this article we re-evaluate each of the concepts on which this traditional regime is based (energy expenditure, and water and electrolytes requirements) and use this to make the case for an alternative, namely isotonic fluid.

PITFALLS OF THE WEIGHT BASED HOLLIDAY AND SEGAR APPROACH

Energy expenditure

Talbot originally estimated basal metabolic rate in children based on water loss.[11] Crawford extended this concept, by presenting *total* energy requirements (basal metabolic rate plus growth and activity) using this data in relation to body surface area (fig 1). Holliday and Segar further advanced this by indexing energy expenditure to body weight rather than surface area, assuming 1 ml of water loss was associated with the fixed consumption of 1 kilocalorie.[4] The typical fluid losses for children (table 1) thus equate with an energy requirement of 120 kcal/kg/day for a 10 kg child.[12]

There are two main flaws with this approach. First, it is now known that resting energy expenditure is closely related to *fat free mass* which includes muscle and the four major metabolic organs (heart, liver, kidneys, and brain).[13] Eighty per cent of the resting energy expenditure is accounted for by these four organs which comprise only 7% of total body mass. As a result, the use of weight alone to calculate energy expenditure may significantly overestimate caloric requirements. On average, the weight based method overestimates energy requirements in infants by 14% compared to the surface area method (fig 1).[4] Second, energy expenditure in healthy children, on whom historic models are based, is vastly different in acute disease or following surgery. Using calorimetric methods, energy expenditure in these patients is closer to the basal metabolic rate proposed by Talbot, averaging 50–60 kcal/kg/day.[14–16] This overestimate is multifactorial: ill

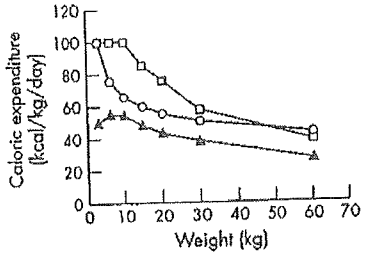

Figure 1 Daily caloric expenditure according to the weight based method of Holliday and Segar and by surface area method of Crawford, and basal metabolic rate. Comparison of two different methods for calculating caloric expenditure across weight ranges (open squares = Holliday and Segar's weight based method; open circles = Crawford's surface area method*; referenced against basal metabolic rate**).

patients are catabolic, often relatively inactive, and, in the intensive care environment may be pharmacologically sedated or muscle relaxed.[14–17] Almost half of the caloric intake suggested by Holliday and Segar is designated for growth, an unrealistic goal in acute disease.[16] Although fever and sepsis per se may increase metabolic rate this is usually limited to less than 1.5 times the basal metabolic rate, burns being an exception.

Water requirements

Historically water requirements have been based on crude estimates of both insensible (skin, respiratory tract) and sensible (urine and stool) water losses.

Insensible water loss

This was generously estimated at 930 ml/m^2/day (27 ml/kg/day).[18] Recent data suggest the true figure may be only half of this, with basal insensible losses from the skin being 250 ml/m^2/day (7 ml/kg/day) and via the respiratory tract 170 ml/m^2/day (5 ml/kg/day).[19] Additionally many other risk factors may reduce insensible water loss such as use of humidifiers in ventilated patients (80% reduction in respiratory water loss) or a thermo neutral environment.[17] Bluemle *et al* have shown insensible water losses of as little as 330 ml/m^2/day (10 ml/kg/day) in catabolic acute renal failure patients.[20]

*Crawford calculated caloric expenditure based on the calories utilised per surface area of the body. The calculated caloric expenditure at each body surface area increment can be converted to weight by cross-referencing surface area to weight using standard growth charts. The ratio of weight to surface area rapidly declines from birth to 10 kg. The Holliday and Segar method does not take this into account.

**From the data of Talbot.

Table 1 Typical water losses per 100 kilocalories (kcal) of energy expended for a healthy 10 kg child

Source of water loss	Estimated water loss (ml per 100 kcal/day)
Insensible	
Skin	30
Respiratory	15
Sensible	
Stool	10
Minimal sweating	10
Urine	50
Total	115

Data calculated according to Pickering and Winters.[12]

Urinary loss of water

According to Holliday and Segar, urinary water losses for healthy children amount to 50–60 ml/kg/day[4] based on the work of Pickering and Winters (table 1).[12] The basis of this fluid regime was the observation that 15/28 infants and 20/25 children (unspecified diagnoses) who were given intravenous dextrose produced urine with an "acceptable" urine osmolarity between 150 and 600 mosm/l H_2O.[4] They presumed patients with dilute urine received too much water and conversely those with concentrated urine too little water.

Today we recognise this does not take into account the overriding influence of antidiuretic hormone (ADH) on urine flow rate.[21] When ADH is present, the renal solute load is effectively excreted in a smaller urine volume producing concentrated urine. Under these conditions urine output is often less than half the values observed in healthy children (approximately 25 ml/kg/day).[22] An increase in ADH is common during many childhood diseases, in response to stress (pain, fever, surgery) or secondary to use of opiates and non-steroidal anti-inflammatory drugs.[23–25] Under these conditions the administration of free water frequently leads to hyponatraemia because the kidneys are unable to excrete the water load.[5 6 26] Interestingly, the type of fluid administered may influence ADH levels. Judd *et al* showed that 0.9% saline but not 5% dextrose reduced ADH concentrations postoperatively.[21]

Thus the total fluid loss (sensible plus insensible) during acutely illness or following surgery may amount to approximately half that suggested by Holliday and Segar (50–60 ml/kg/day).[5 6] Also, the often overlooked production of endogenous water from tissue catabolism (water of oxidation) may be increased in acute disease.[20] In healthy children, this has been estimated to be 15 ml/100 kcal burnt.[4] Thus, all these factors need consideration when assessing overall water balance.

Electrolyte requirements

In healthy breast fed infants Holliday and Segar computed a dietary sodium intake of 1 mEq/100 calories per day.[4] Darrow recommended 3 mEq of sodium per 100 calories of energy expended per day.[4] This is based on urinary excretion rates of sodium in healthy, milk fed infants. However, daily electrolyte requirements in disease may differ considerably from this. For example, large urinary losses of sodium and potassium may occur through the phenomenon of desalination.[27 28] Furthermore, Al-Dahhan *et al* showed a beneficial effect on neurodevelopmental outcome from doubling the daily sodium intake (4 to 5 mmol/kg) in neonates.[29] This refutes the assumption that the neonatal kidney is incapable of "handling" a high sodium load. The recent discovery of the most potent natriuretic hormones, urodilatin and gut-related natriuretic peptide has also shed new light on sodium regulation.

The rationale behind the traditional approach is to balance sodium intake to match sodium loss. However, this fails to appreciate the *single* most important role of sodium in acute illness, namely maintenance of plasma tonicity.[25 29] There is a strong inverse relation between plasma sodium concentration and intracellular volume.[30] Cell membranes are permeable to water but not electrolytes. As sodium is the major extracellular cation (and hence osmole), it regulates the movement of water across cells along an osmotic concentration gradient, thus explaining cellular swelling in the presence of hyponatraemia.

It is also important to recognise the role of potassium in the regulation of tonicity balance. Potassium is a major intracellular osmole, and may directly influence extracellular sodium concentration by altering the distribution of water between fluid compartments.[25] Potassium loss, both urinary and stool, may be significant in disease; yet its direct influence on serum sodium concentration is often not considered.[25 28]

Tonicity of intravenous fluids

It is crucial that clinicians appreciate the difference between osmolarity and tonicity. The osmolarity of a solution is the number of osmoles of solute per litre of solution. The tonicity of a solution refers to the total concentration of solutes that exert an osmotic force across a membrane in vivo. For example, 5% dextrose has the same osmolarity as plasma (286 mosm/l H_2O) but is rapidly metabolised in blood to water. Thus its *in vivo tonicity*

Table 2 Approximate sodium concentration, in vitro osmolarity, in vivo tonicity, and theoretical volume of electrolyte free water (EFW) provided by commonly used intravenous solutions

Intravenous solution	Sodium* (mmol/l)	In vitro osmolarity† (mOsm/l H_2O)	In vivo tonicity‡ (mOsm/l H_2O)	Volume of EFW§ per litre infused
5% dextrose	0	286	0	1000
0.18% saline in 4% dextrose	30	300	60	824
0.45% saline	75	150	154	500
0.45% saline in 5% dextrose	75	432	150	500
0.9% saline	154	308	308	0
0.9% saline in 5% dextrose	154	586	308	0

*The apparent discrepancy between the in vitro sodium concentration (0.9% saline) of 154 mmol/l and the in vivo plasma sodium of 144 mmol/l is due to the phenomenon of pseudohyponatraemia. In human plasma, approximately 7% of the plasma volume is occupied by albumin and lipid, falsely lowering the true sodium concentration plasma by 10 mmol/l (7% of 155).
†In vitro osmolarity refers to the number of osmoles of solute per litre of solution.
‡In vivo tonicity refers to the total concentration of solutes which exert an osmotic force across a membrane in vivo (excludes the osmotic effect of dextrose because it is rapidly metabolised in blood).
§Calculated on the basis that electrolyte free water distributes to the intracellular and extracellular space in a ratio of 2:1.

is equal to that of electrolyte free water, as it contains no salt or other active osmole (zero tonicity). Every litre of 5% dextrose infused results in the expansion of the intracellular and extracellular fluid space by one litre (two thirds of this distributes to the intracellular space and one third to the extracellular space). Similarly, for every litre of 0.18% saline in 4% dextrose water infused, only 1/5th (200 ml) is isotonic to plasma (table 2). The remaining 800 ml is electrolyte free water, which will expand the intracellular fluid compartment. This is particularly relevant if excretion of water is limited by ADH.[5–7 21 26 31] This fluid shift may even occur in the absence of hyponatraemia.[32] Small increases in tissue water through the use of hypotonic fluids may be harmful in conditions such as cerebral oedema where minor increases in cerebral water may lead to disproportionately large increases in intracranial pressure.

The incidence and neurological complications of acute hyponatraemia

Hyponatraemia is a common biochemical finding in hospitalised children and is most commonly due to excess water intake rather than salt loss.[6 7 22 23] Shann and Germer showed an incidence of hyponatraemia (Na <134 mmol/l) as high as 45% in hospitalised children with pneumonia and 50% in bacterial meningitis.[8] Hanna *et al* recently reported a 30% incidence of admission hyponatraemia in infants with bronchiolitis requiring intensive care admission in the United Kingdom, 13% of which had seizures.[9] Halberthal *et al* was able to show a direct link between hyponatraemia and the use of hypotonic maintenance fluid.[7] The neurological complications of acute hyponatraemia include encephalopathy with seizures, irreversible brain damage, or brain death from cerebral herniation.[1–10] Children are also among the most susceptible to hyponatraemic brain injury.[5 6] Fatal hyponatraemia can occur within hours of hypotonic fluid administration, particularly if standard fluid maintenance rates are used (100–120 ml/kg/day).[10]

THE RATIONALE FOR ISOTONIC MAINTENANCE FLUID

The paramount consideration in the choice of intravenous fluid is the requirement to maintain serum sodium at a normal level. The use of isotonic solutions such as 0.9% saline is more appropriate in acutely sick children as they do not theoretically expand the intracellular fluid space. Isotonic solutions preserve intracellular function and integrity, by minimising changes in plasma sodium concentration and tonicity.

Use of 0.9% saline as maintenance fluid, if combined with appropriate fluid restriction, will result in a two to threefold increase in daily sodium intake compared to the traditional regime. However, the concern that this may cause severe hypernatraemia is without foundation because the sodium concentration and tonicity of 0.9% saline is similar to plasma. Andersen *et al* showed a rise in plasma sodium only after intravenous administration of hypertonic 3% saline but not 0.9% saline, despite a temporary positive sodium balance.[33] Heer *et al* showed chronic sodium loading in volunteers does not produce an increase in plasma sodium, body water, or weight as previously suggested.[34] Many of the historical assumptions concerning sodium handling are based on salt depleted subjects. Indeed massive sodium loads from large volume resuscitation of infants and children with sepsis (80–180 ml/kg/day) using 0.9% saline did not produce hypernatraemia.[35] Additionally an epidemic of hypernatraemia has not been documented in hospitalised adults where isotonic maintenance fluids are routine. When present, the aetiology of hypernatraemia in this scenario is frequently due to well recognised factors such diabetis insipidus or over-use of loop diuretics.[36]

The debate as to the optimal isotonic fluid is ongoing. For example, Hartman's solution has a more physiological concentration of chloride than 0.9% saline and hence does not cause hyperchloraemia. The benefit of Hartman's solution versus 0.9% saline is not currently known. It is important to stress that dextrose may be added to these isotonic solutions (commonly in concentration of 5–10%), when clinically indicated to avoid hypoglycaemia without changing the solution's in vivo *tonicity* (table 2). Recent evidence suggests that a 1% dextrose solution following uncomplicated paediatric surgery may be adequate.[37] A suitable solution for neonates and infants is 0.9% saline in 5% dextrose water, which is commercially available. We advocate 0.9% saline (with or without added dextrose) as a safe maintenance solution, both perioperatively and in the acute phase of most childhood illnesses requiring hospitalisation (for example, pneumonia, bronchiolitis, and meningitis). Here, the water retaining effect of antidiuretic hormone may necessitate a moderate degree of fluid restriction (50–60%) to prevent fluid overload. The concept of fluid maintenance should not be confused with replacement therapy where abnormal or excessive quantities of water and electrolytes may be lost. In this instance the biochemical composition and tonicity of the replacement solution should approximate that which is lost.

CONCLUSION

We have shown a number of pitfalls in the Holliday and Segar approach to parenteral therapy, namely that it focuses on fluid and electrolyte requirements for healthy children. In acute disease or following surgery, caloric expenditure, insensible water losses, and urine output are frequently much less than in health (often 50–60% of the reference values). Furthermore, this approach fails to recognise the importance of tonicity with its central role in the distribution of water between fluid

compartments (intracellular and extracellular space).

We therefore agree with Moritz and Ayus who advocate isotonic solutions such as 0.9% saline for routine fluid maintenance in children.[16] Hypotonic solutions, such as 0.18% or even 0.45% saline, are potentially dangerous when renal water excretion is limited by ADH. This raises a significant ethical barrier to conducting a randomised control study as most acutely ill or postoperative patients have increased ADH levels. There are few occasions in medicine where mortality could be reduced by a task as simple as changing from a hypotonic maintenance solution to an isotonic one.

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Authors' affiliations
D Taylor, A Durward, Paediatric Intensive Care Unit, Guy's Hospital, London, UK

Correspondence to: Dr A Durward, Paediatric Intensive Care Unit, 9th floor, Guy's Tower Block, Guy's Hospital, St Thomas Street, London SE1 9RT, UK; adurward@doctors.org.uk

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Maintenance fluid therapy

Rubbing salt in the wound

M Hatherill

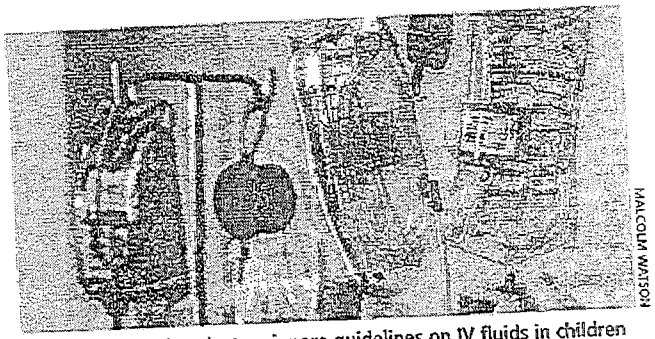
The case against isotonic parenteral maintenance solution

In a recent review, Moritz and Ayus have suggested that isotonic parenteral maintenance solution (PMS) should be used to prevent hospital acquired hyponatraemia in children.[1] Hospital acquired hyponatraemia may be exacerbated by non-osmotic production of antidiuretic hormone (ADH) associated with conditions such as bronchiolitis (33%), pneumonia (31% and 45%), bacterial meningitis (50%), and postoperative pain or nausea.[2–7] Although it has been termed a syndrome of inappropriate antidiuretic hormone secretion (SIADH), it may be more accurate to refer to non-osmotic ADH production, since haemodynamic baroreceptor stimuli, such as hypovolaemia, may be physiologically appropriate despite the adverse effect on sodium.[1 6 7]

The reported morbidity and mortality associated with hospital acquired hyponatraemia have given momentum to calls for increasing the tonicity of PMS.[1–3 6–11] Implicit in such proposals are the assumptions that hyponatraemia results from a net sodium deficit, exacerbated by hypotonic PMS, and that this sodium deficit may be avoided by using an isotonic solution.[1–3 8–11] Therefore, if we contemplate a change in practice, we must consider whether

PAEDIATRICS

Doctors ignore advice on IV fluids in children



MALCOLM WATSON

A survey found that doctors ignore guidelines on IV fluids in children

By Lisa Hitchen

lisa.hitchen@rbi.co.uk

Children continue to be mismanaged despite high-profile deaths and guidance on safe practice, says the National Patient Safety Agency (NPSA).

Prof Terence Stephenson, a paediatrics adviser for the agency, told a conference last week that the prescribing of intravenous (IV) fluids to children exemplified the problem.

Sick children can develop hyponatraemia if given excess or inappropriate fluid, often through IV. National guidance recommends baseline and daily urea and electrolytes (U&Es) are checked to ensure that children's sodium serum is monitored.

Staff at the University Hospital of Wales carried out a survey of practice by paediatric SHOs and pharmacists over a four-week period on six wards including the high dependency unit earlier this year.

In total, 59 child patients were prescribed IV infusions – 53 per cent of these were prescribed on the paediatric surgical ward where patients are at increased risk of hyponatraemia.

Only 32 per cent had a baseline U&E taken and of those receiving IV fluids for more than 24 hours, 12 per cent did not have U&Es taken at any time while on IV fluids.

The NPSA has data on 26 deaths globally due to hyponatreamia from 1993 to 2003.

In Northern Ireland, a working party on hyponatraemia was set up after the death of Raychel Ferguson as a result of errors in prescribing IV fluids in 2001.

The NPSA is now looking at whether the IV fluids currently recommended for children should be changed, Prof Stephenson added.

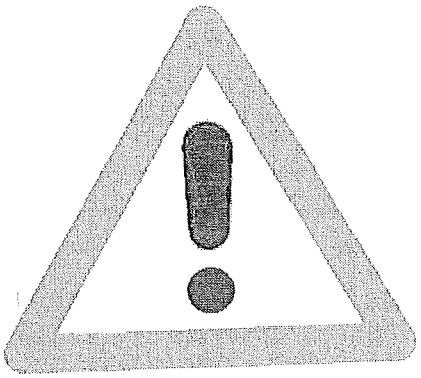
Dr David Cousins, NPSA's head of safe medical practice, said a safety alert on IV fluid use in both children and adults would be sent out to the NHS in the spring.

The conference on clinical risk management in paediatrics and child health was held in London.

Pharmacy in Practice 2005; 15: 158-60

NHS
National Patient Safety Agency

Patient safety alert 22



Alert

28 March 2007

Immediate action	☐
Action	☑
Update	☐
Information request	☐

Ref: NPSA/2007/22

Reducing the risk of hyponatraemia when administering intravenous infusions to children

The National Patient Safety Agency (NPSA) is issuing advice to healthcare organisations on how to minimise the risks associated with administering infusions to children.

The development of fluid-induced hyponatraemia in the previously well child undergoing elective surgery or with mild illness may not be well recognised by clinicians. To date, the NPSA's National Reporting and Learning System (NRLS) has received only one incident report (that resulted in no harm), but it is likely that incidents have gone unreported in the UK.

Since 2000, there have been four child deaths (and one near miss) following neurological injury from hospital-acquired hyponatraemia (see definition on page 7) reported in the UK.[1-3] International literature cites more than 50 cases of serious injury or child death from the same cause, and associated with the administration of hypotonic infusions.[4]

Action for the NHS and the independent sector

The NPSA recommends that NHS and independent sector organisations in England and Wales take the following actions by 30 September 2007 to minimise the risk of hyponatraemia in children:

1 Remove sodium chloride 0.18% with glucose 4% intravenous infusions from stock and general use in areas that treat children. Suitable alternatives must be available. Restrict availability of these intravenous infusions to critical care and specialist wards such as renal, liver and cardiac units.

2 Produce and disseminate clinical guidelines for the fluid management of paediatric patients. These should give clear recommendations for fluid selection, and clinical and laboratory monitoring.

3 Provide adequate training and supervision for all staff involved in the prescribing, administering and monitoring of intravenous infusions for children.

4 Reinforce safer practice by reviewing and improving the design of existing intravenous fluid prescriptions and fluid balance charts for children.

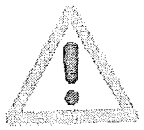
5 Promote the reporting of hospital-acquired hyponatraemia incidents via local risk management reporting systems. Implement an audit programme to ensure NPSA recommendations and local procedures are being adhered to.

For response by:
- All NHS and independent sector organisations in England and Wales

For action by:
- The chief pharmacist/pharmaceutical advisor should lead the response to this alert, supported by the chief executive, medical director, nursing director and clinical governance lead/risk manager

We recommend you also inform:
- Clinical governance leads and risk managers
- Clinical directors – paediatrics and child health
- Clinical directors – anaesthetics
- Clinical directors – surgery
- Directors of NHS laboratories
- Medical staff
- Nursing staff
- Pharmacy staff
- Patient advice and liaison service staff in England
- Procurement managers

The NPSA has informed:
- Chief executives of acute trusts, primary care organisations, ambulance trusts, mental health trusts and local health boards in England and Wales
- Chief executives/regional directors and clinical governance leads of strategic health authorities (England) and regional offices (Wales)
- Healthcare Commission
- Healthcare Inspectorate Wales
- Medicines and Healthcare products Regulatory Agency
- Business Services Centre (Wales)
- NHS Purchasing and Supply Agency
- Welsh Health Supplies
- Royal colleges and societies
- NHS Direct
- Relevant patient organisations and community health councils in Wales
- Independent Healthcare Forum
- Independent Healthcare Advisory Services
- Commission for Social Care Inspection



Action deadlines for the Safety Alert Broadcast System (SABS)

Deadline (action underway): 2 July 2007
Action plan to be agreed and actions started

Deadline (action complete): 30 September 2007
All actions to be completed

Further information about SABS can be found at:
www.info.doh.gov.uk/sar2/cmopatie.**nsf**

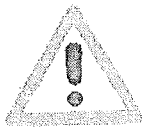
The recommendations made in this patient safety alert relate to paediatric patients from one month to 16 years old. They are not intended for paediatric and neonatal intensive care units or specialist areas such as renal, liver and cardiac units where hypotonic solutions have specialist indications.

Further information on the action points

1 **Remove sodium chloride 0.18% with glucose 4% intravenous infusions from stock and general use in areas that treat children. Suitable alternatives must be available. Restrict availability of these intravenous infusions to critical care and specialist wards such as renal, liver and cardiac units.**

There is evidence that there is a greater level of risk of hyponatraemia associated with the use of hypotonic solutions in comparison to other types of solution. Within the range of hypotonic solutions available, the use of sodium chloride 0.18% with glucose 4% presents an even greater risk. All children are potentially at risk. Since 2000, UK literature has cited four deaths and one near miss following neurological injury associated with the use of sodium chloride 0.18% with glucose 4%. In two of the institutions where these incidents took place, the solution was removed from ward stock, and no further cases of iatrogenic hyponatraemia have been reported.[1,3]

In 2003, the Royal College of Anaesthetists issued a statement advising against the use of sodium chloride 0.18% with glucose 4% due to the possibility of water overload with severe hyponatraemia, and recommended suitable alternatives.[5] This statement was supported by the Royal College of Paediatrics and Child Health (RCPCH). A subsequent survey of consultant anaesthetists showed that less than half of the respondents were aware that the statement had been issued, and this suggests that action has not been taken in some organisations.[6]



2 Produce and disseminate clinical guidelines for the fluid management of paediatric patients. These should give clear recommendations for fluid selection, and clinical and laboratory monitoring.

The NPSA has developed a template that can assist the development of local guidelines for prescribing and monitoring infusions for children outside of critical care areas. This is available at **www.npsa.nhs.uk/health/alerts**

Much of the international and UK literature on appropriate paediatric fluid management reinforces the need for rigorous clinical and laboratory monitoring, and raises concerns about the frequent absence of baseline parameters before infusions are started.[7-11]

While there is much debate about the management of paediatric fluid therapy in the literature, there are some common principles which should be applied. These are:

- when fluids are prescribed, they must be given the same consideration as other medicines with reference to indications, contraindications, dose, monitoring and, particularly, volume;[11]
- prescribed fluids must be individualised;[12]
- whichever fluid is used, the optimal way of avoiding dangerous hypo- or hypernatraemia is to calculate fluid balance and monitor the plasma sodium concentration regularly.

Carefully managed oral fluids are preferable to intravenous infusions. However, when intravenous infusions are prescribed, local guidelines should be based on the following clinical recommendations:

Resuscitation: intravascular volume depletion should be managed using bolus doses of sodium chloride 0.9% (isotonic solution).

Deficit: estimate any fluid deficit and replace as sodium chloride 0.9% with glucose 5% (isotonic solution) or sodium chloride 0.9% over a minimum of 24 hours.

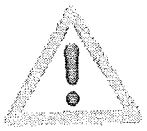
Maintenance: do not use sodium chloride 0.18% with glucose 4%.

The low sodium content of sodium chloride 0.18% with glucose 4% infusion increases the risk of the patient developing hyponatraemia, particularly in the absence of individualised prescribing and robust on-going monitoring.

The majority of children may be safely administered sodium chloride 0.45% with glucose 5% (hypotonic solution), or sodium chloride 0.45% with glucose 2.5% (hypotonic solution). There is currently little evidence to recommend a particular strength of glucose.

Some children at high risk of hyponatraemia should only receive isotonic solutions (see Table 1). These include children who are peri- and post-operative, require the replacement of ongoing losses or have:

- plasma sodium at the lower normal reference range and definitely if less than 135mmol/L;
- intravascular volume depletion;



- hypotension;
- central nervous system (CNS) infection;
- head injury;
- bronchiolitis;
- sepsis;
- excessive gastric or diarrhoeal losses;
- salt-wasting syndromes;
- chronic conditions such as diabetes, cystic fibrosis and pituitary deficits.

Some examples of isotonic solutions include sodium chloride 0.9% with glucose 5%, sodium chloride 0.9% and compound sodium lactate solution (Hartmann's solution/ Ringer-Lactate solution). The choice should be determined by the individual patient's circumstances.

Sodium chloride 0.18% with glucose 4% should be restricted to specialist areas to replace ongoing losses of hypotonic fluids. These areas include high dependency, renal, liver and intensive care units.

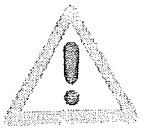
Children requiring both maintenance fluids and the replacement of ongoing losses should receive a single isotonic fluid such as sodium chloride 0.9% with glucose 5% or sodium chloride 0.9%.

While most children will tolerate standard fluid requirements, some acutely ill children with increased anti-diuretic hormone (ADH) secretion may benefit from their maintenance fluid requirement being restricted to two-thirds of the normal recommended volume. Such children include post-operative patients and those with intracranial infections or head injuries.

Children found to have significant hypernatraemia with a plasma sodium greater than 160mmol/L should receive only isotonic solutions to reduce the risk of neurological injury associated with a rapid fall in plasma sodium concentration. Where hypernatraemia exists, plasma sodium should be reduced at a maximum rate of 0.5mmol/L/hour, or more slowly if it has prevailed for more than five days.[13]

Children in the peri-operative period should receive isotonic intravenous fluids. These should contain glucose to avoid the risk of hypoglycaemia. If glucose-free solutions are used during anaesthesia and surgery then plasma glucose levels should be monitored.

Consider adding potassium chloride up to 40mmol/L to maintenance fluids once plasma potassium levels are known.



Losses

Ongoing losses should be assessed every four hours. Fluids used to replace ongoing losses should reflect the electrolyte composition of the fluid being lost. In most circumstances an isotonic solution is the safest choice, for example, sodium chloride 0.9%, or compound sodium lactate solution (Hartmann's solution/Ringer-Lactate solution) with or without the addition of potassium. In this way, for example, gastro-intestinal losses should be replaced with sodium chloride 0.9%.

Monitoring

Hyponatraemia can develop within a short timescale and a robust monitoring regime is essential. Weight should be measured, if possible, prior to commencing fluid therapy, and daily thereafter. Fluid balance including oral intake should be recorded using a fluid balance chart.

Plasma sodium, potassium, urea and/or creatinine should be measured at baseline and at least once a day. Consider measuring every four to six hours if an abnormal reading is found. This should definitely be done if the plasma sodium is below 130 mmol/L. Check plasma electrolytes immediately if clinical features suggest hyponatraemia is developing. Symptoms include increased headaches, vomiting, nausea, irritability, altered levels of consciousness, seizures and apnoea.

Ideally, use the same sample technique, either capillary or venous blood sampling, and analytical method on each occasion. This can avoid potentially misleading changes in serial sodium measurements.[14]

Urine chemistry may be useful in a small number of high-risk cases.[15]

Acute hyponatraemic encephalopathy

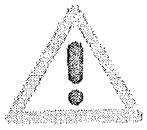
This medical emergency should be treated under senior medical supervision with hypertonic sodium chloride and should never be managed with fluid restriction alone.[1,4]

3 Provide adequate training and supervision for all staff involved in the prescribing, administering and monitoring of intravenous infusions for children.

The NPSA has developed a proposed work competence statement for the prescribing and monitoring of intravenous infusions in the format developed by Skills for Health (**www.skillsforhealth.org.uk**). It is available at **www.npsa.nhs.uk/health/alerts** The NPSA will work with Skills for Health to develop these proposed competences as national workforce competences in the future.

The NPSA has developed an e-learning module to enable practitioners to assess their current level of competence and knowledge. The module also provides training materials to improve knowledge and understanding of the safe prescribing and use of infusion fluids in children. The e-learning module is available at **www.npsa.nhs.uk/health/alerts**

Doctors in training are responsible for prescribing 80 to 90 per cent of intravenous fluids on general wards.[9,16] A research study tested pre-registration and senior house officers' knowledge of fluid prescribing practices. This study showed significant gaps in knowledge. Conclusions from the survey included the need to review the fluid and electrolyte prescribing of doctors-in-training and also supervision arrangements. It recommended that under- and post-graduate medical training puts an emphasis on practical application.[16]



The 1999 report of the National Confidential Enquiry into Perioperative Deaths recorded 20 per cent of patients sampled had either poor documentation of fluid balance or unrecognised/untreated fluid imbalance. The report recommended that prescribing fluids be accorded the same status as other medicines. It also recommended that medical and nursing staff should receive training to raise their awareness of risks with infusion therapy and spread good practice of prescribing, monitoring and completion of healthcare documentation.[17]

4 Reinforce safer practice by reviewing and improving the design of existing intravenous fluid prescriptions and fluid balance charts for children.

A suggested template for an infusion fluid prescription chart that can be adapted for local use is available at **www.npsa.nhs.uk/health/alerts**

The design of the intravenous fluid prescription and fluid balance chart can reinforce safer practice by including guidelines for infusion fluid selection; methods for calculating infusion fluid requirements; and a record of essential monitoring data such as a patient's weight and blood electrolyte levels.

5 Promote the reporting of hospital-acquired hyponatraemia incidents via local risk management reporting systems. Implement an audit programme to ensure NPSA recommendations and local procedures are being adhered to.

The incidence of moderate and severe hyponatraemia and associated harm resulting from hospital fluid treatment regimes is difficult to quantify because prospective studies have not been done and, it is suggested, incidents are not recognised or reported.[4]

All NHS staff should report incidents via their local risk management reporting system. This will enable both local and national monitoring of the incidents of hospital-acquired hyponatraemia, and can inform future understanding of the issues.

The NPSA recommends that healthcare organisations should audit infusion therapy in children as part of their annual medicines management audit. This will help to ensure that NPSA recommendations and local procedures are being adhered to. Audit results should be reviewed alongside local patient safety incident data concerning infusion therapy in children. The NPSA has developed a template audit form and this is available at **www.npsa.nhs.uk/health/alerts**

Background information

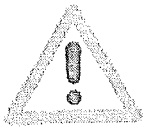
Further information about the content of this patient safety alert can be found at **www.npsa.nhs.uk/health/alerts**

Table 1: features of commonly used intravenous fluids in the UK[1]

Solution	Osmolarity (mOsmol/L)	Sodium content (mequiv/L)	Osmolality (compared to plasma)	Tonicity (with reference to cell membrane)
Sodium chloride 0.9%	308	154	Isosmolar	Isotonic
Sodium chloride 0.45%	154	77	Hyposmolar	Hypotonic
Sodium chloride 0.45% with glucose 5%	432	75	Hyperosmolar	Hypotonic
Glucose 5%	278	–	Isosmolar	Hypotonic
Glucose 10%	555	–	Hyperosmolar	Hypotonic
Sodium chloride 0.9% with glucose 5%	586	150	Hyperosmolar	Isotonic
Sodium chloride 0.45% with glucose 2.5%	293	75	Isosmolar	Hypotonic
Sodium chloride 0.18% with glucose 4%	284	31	Isosmolar	Hypotonic
Hartmann's solution	278	131	Isosmolar	Isotonic
4.5% human albumin solution	275	100-160	Isosmolar	Isotonic

Definition of hyponatraemia

The normal range for plasma sodium varies between different laboratories but is often quoted as 135-145mmol/L. Hyponatraemia is defined as a plasma sodium of less than 135mmol/L. Severe hyponatraemia is defined as a plasma sodium of less than 130mmol/L. Severe acute hyponatraemia is defined as a decrease in plasma sodium from normal to less than 130mmol/L in less than 48 hours.



Mechanism of hyponatraemia

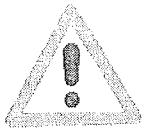
Hyponatraemia has been documented in otherwise healthy children on intravenous fluids and can be due to too much water or too little sodium in extracellular fluid. Most commonly, it indicates an expanded extracellular fluid volume and is rarely caused by sodium (or salt) depletion. The infusion of hypotonic fluids together with the non-osmotic secretion of ADH may result in hyponatraemia. Non-osmotic secretion of ADH can be induced in a variety of clinical situations, including pain, anxiety, the post-operative state, nausea, vomiting, certain drugs, pyrexia, sepsis, reduced circulating volume, respiratory disorders, CNS infections, and metabolic and endocrine disorders.[18]

Mechanism of hyponatraemic encephalopathy

A major consequence of hyponatraemia is an influx of water into the intracellular space resulting in cellular swelling, which can cause cerebral oedema, seizures and brain stem herniation. Hyponatraemic encephalopathy is a serious complication and children are a group of patients particularly susceptible to developing neurological complications.

This is due to the reduced space for brain swelling in the skull and impaired ability of the paediatric brain to adapt to hyponatraemia compared to adults. Acute symptomatic hyponatraemic encephalopathy is considered a medical emergency.

Hospital-acquired hyponatraemic encephalopathy is most often seen in patients with excess ADH secretion, frequently in the post-operative period. Mortality directly attributed to encephalopathy in children with post-operative hyponatraemia is estimated as eight per cent. The most important contributing factors are the failure to recognise that the patient's ability to manage free water may be compromised, and the administration of hypotonic solutions in such situations.[19-22]



Prevention of hyponatraemia

The practice of prescribing hypotonic solutions dates back to the work of Holliday and Segar in the 1950s and hypotonic solutions are still in common use today. Their approach recommended a simple methodology for calculating fluid and energy requirements and the use of an 'ideal' hypotonic solution, glucose 5% and sodium chloride 0.2% (sodium chloride 0.18% and glucose 4% in the UK).[23] These recommendations do not take into account deficits, losses, unusual metabolic demands or the secretion of excess ADH during illness and particularly in the peri-operative period. A number of investigators, including Holliday, have since concurred that the administration of hypotonic parenteral fluids can result in dangerous hyponatraemia.[1,2,23-28]

There is much debate in recent literature about the preferred approach to paediatric fluid management and the prevention of hyponatraemia. However, there are no reports of clinical trials. The literature emphasises that, where possible, oral administration remains the preferred route of choice but it must be remembered that injudicious use of oral fluids can also be life-threatening.[4] In relation to parenteral fluid choice, the differing clinical opinions for prevention include: continued use of hypotonic solutions with fluid restriction,[29] isotonic solutions with fluid restriction,[30] the use of only isotonic solutions[22] or the use of isotonic and hypotonic solutions in specific clinical situations.[1,12]

Whilst there is evidence of harm associated with the use of hypotonic solutions, there is an absence of definitive evidence for clinicians that can help them when choosing a solution. It is against this backdrop that the NPSA is making the recommendations outlined in this patient safety alert.

Acknowledgements

The NPSA gratefully acknowledges the contributions of members of the multi-disciplinary working group and the individuals, teams and organisations who contributed to the consultation process. Further information about contributors can be found at **www.npsa.nhs.uk/health/alerts**

Further details

For further information about this patient safety alert, please contact:

Linda Matthew, Senior Pharmacist, Safe Medication Practice
National Patient Safety Agency
4-8 Maple Street
London W1T 5HD
Tel: 020 7927 9500
Email: **paediatric-infusions@npsa.nhs.uk**

For more information on the NPSA, visit **www.npsa.nhs.uk**

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A patient safety alert requires prompt action to address high risk safety problems.

This patient safety alert was written in the following context:

It represents the view of the National Patient Safety Agency, which was arrived at after consideration of the evidence available. It is anticipated that healthcare staff will take it into account when designing services and delivering patient care. This does not, however, override the individual responsibility of healthcare staff to make decisions appropriate to local circumstances and the needs of patients and to take appropriate professional advice where necessary.

28 March 2007
0409

Suggested template for local development of intravenous fluid guidelines

For previously well children aged one mont

diac, diabetic ketoacidosis and acute burns patients)

Hyponatraemia may develop as a complication of any fluid regime.

If shock is present administer 20ml/kg sodium chloride 0.9% (10ml/kg in the setting of trauma). Repeat if necessary and call for senior help immediately.

Symptomatic hyponatraemia is a medical emergency.

Check plasma electrolytes.

Consider the replacement of any pre-existing fluid deficit, the requirement for maintenance fluids and the replacement of any ongoing losses.

Fluid deficit

Estimate any fluid deficit and replace as sodium chloride 0.9% with glucose 5% or sodium chloride 0.9% over a minimum of 24 hours.

Ongoing fluid losses

Reassess ongoing fluid losses every four hours. Fluids used to replace ongoing fluid losses should ideally reflect the electrolyte composition of the fluid being lost. Sodium chloride 0.9% is appropriate in most cases (with or without the addition of potassium chloride).

Those requiring maintenance fluids and replacement of ongoing losses should receive a single isotonic fluid such as sodium chloride 0.9% or sodium chloride 0.9% with glucose 5%.

Monitoring

Check plasma electrolytes before commencing the infusion, except prior to the majority of elective surgery. Monitor plasma glucose if glucose-free solutions are used during surgery.

Check plasma electrolytes every 24 hours whilst intravenous fluids are being administered. If plasma electrolytes are abnormal, consider rechecking every four to six hours, but definitely if plasma sodium concentration is below 130mmol/L.

Check plasma electrolytes if clinical features suggestive of hyponatraemia develop; these features include nausea, vomiting, headache, irritability, altered level of consciousness, seizure and apnoea.

Where possible, all children on intravenous fluids should be weighed prior to the commencement of therapy and be weighed again each day.

Document accurate fluid balance daily. Assess urine output – oliguria may be due to inadequate fluid, renal failure, obstruction or the effect of ADH.

Maintenance fluids

Type of intravenous fluid

The majority of children may be safely administered sodium chloride 0.45% with glucose 5% or sodium chloride 0.45% with glucose 2.5% – although there is little evidence to support the choice of a particular strength of glucose.

In some circumstances, children should only ever be administered isotonic fluids such as sodium chloride 0.9% with glucose 5%, sodium chloride 0.9%, Hartmann's solution or Ringer Lactate solution. Solution choice should be tailored to the patient's needs.

These circumstances include:

- serum sodium at the lower normal reference range and definitely if less than 135mmol/L
- intravascular volume depletion
- post-operative patients
- hypotension
- CNS infection
- head injury
- bronchiolitis
- sepsis
- excessive gastric or diarrhoeal losses
- cystic fibrosis and chronic conditions such as diabetes insipidus and renal tubular defects, and those requiring total parenteral nutrition.

Children with a plasma sodium in excess of 150mmol/L should receive isotonic solutions to reduce the risk of neurological injury associated with correction of plasma sodium.

Volume of intravenous fluid

- Less than 10kg: 100ml/kg/day or 4ml/kg/hour
- 10-20kg: 1000ml plus 50ml/kg/day for each kg over 10kg or 4ml/kg/hour plus 2ml/kg/hour for each kg over 10kg
- Over 20kg: 1500ml plus 20ml/kg/day for each kg over 20kg or 60ml/hour plus 1ml/kg/hour for each kg over 20kg

Up to a maximum of 2.4L/day in males and 2.0L/day in females

Consider adding potassium chloride up to 40mmol/L to maintenance fluids once plasma potassium concentration is known.

Some severely ill children with increased ADH secretion may benefit from restriction of maintenance fluids to 2/3rds of normal recommended volume.

An electronic copy of the template is available at www.npsa.nhs.uk/health/alerts

March 2007