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## FOCUS ON: PAEDIATRIC ANAESTHESIA

### Fluid prescription in children. Where are we now?

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#### A B S T R A C T

Fluid prescription in children has, for many years, been based on calculations derived from energy expenditure in healthy children and the solute load that arises from ingesting cows' milk. In the per-operative period, reduced energy expenditure and non-osmotic stimuli for antidiuretic hormone secretion render children acutely susceptible to hyponatramia if 'conventional' fluid prescribing guidelines are followed. This article reviews the recently issued safety guidelines on type and volume of fluids that are appropriate for fluid maintenance and resuscitation in the per-operative period.

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#### 1. Introduction

Prescription of fluid therapy in children, both maintenance and replacement has generated endless discussion over the past 30 years. Though there is a wealth of information outlining the dangers of hypotonic fluids, and reports of morbidity and mortality associated with the prescription of hypotonic fluid in children,<sup>1,2</sup> there is a deficiency of good evidence to support assertions of what is the best fluid prescription.

Recently, specific guidance for prescribing fluids in children became available. The National Patient Safety Agency (NPSA) published guidance for physicians prescribing fluid therapy in children, in March 2007. An accompanying Alert document was circulated on 28th March 2007.<sup>3</sup> This document provides detailed explanatory notes for the safe prescription of resuscitation, deficit and maintenance fluid in children.

When deciding fluid therapy in children, there are two main questions; what type and what volume? As anaesthetists looking after children in the per-operative period, we are most commonly interested in the prescription of maintenance and resuscitation fluid. Paediatric anaesthetists do also come across children with much more complex deficits, for example pyloric stenosis, in whom the fluid management is specifically tailored to their pre-existing losses. Initial anaesthetic assessment of any child prior to their surgery should include an appreciation of hydration state, pre-existing and ongoing fluid loss, including blood, third space loss and insensible losses. Resuscitation fluid may well be required at this stage to optimize intravascular volume and organ perfusion prior to induction of anesthesia.

#### 1.1. Fluid volume

##### 1.1.1. Maintenance

The '4:2:1 rule', frequently quoted for maintenance fluid prescription purposes is derived from work carried out by Holliday and Segar.<sup>4</sup> The rule is based on earlier research relating maintenance fluid requirement to the body surface area.<sup>5</sup> Maintenance requirement for water is determined by calorific expenditure, approximately equating to 1 ml/kcal spent. For weights ranging from 0 to 10 kg, the caloric expenditure is approximately 100 kcal/kg/day; >10–20 kg the expenditure is 1000 kcal + 50 kcal/kg/day for each kg over 10; >20–30 kg the expenditure is 1500 kcal + 20 kcal/kg/day for each kg over 20. This formula for maintenance has served the paediatric population well since its development 50 years ago. The argument for this regimen being an overestimation of maintenance fluid requirement in the hospital setting was outlined by Taylor and Durward.<sup>6</sup> Energy expenditure predominates in the major metabolic organs (heart, liver, kidneys and brain) which make up only 7% of body mass, so relating fluid requirement to mass will frequently produce an overestimation. They also point out that children who are unwell tend to be less physically active and should, therefore, require less water. Other factors reducing maintenance requirement include protection against insensible water loss from the respiratory tract by using humidification devices, and pharmacological sedation in the intensive care environment. For this reason, arbitrary modifications of the original '4:2:1' rule have been used in clinical situations, e.g., 60% or 2/3 maintenance.

##### 1.1.2. Resuscitation

Prescribing resuscitation fluid relies on clinical estimates of intra-operative fluid losses. We are guided using a number of clinical

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prompts which vary in their accuracy, e.g., weighing swabs, suction volumes, clinical assessment of patient cardiovascular parameters, urine output, invasive monitoring and assessing haemoglobin intra-operatively with bedside testing or arterial blood gas analysis. In general, combinations of some or all of the above allow clinicians to make reasonably accurate assessment of losses and resuscitation requirements. A fluid challenge of 20 ml/kg is the standard amount accepted for resuscitation of significant hypovolaemia.

## 1.2. Fluid type

### 1.2.1. Maintenance

Historically, the traditional maintenance fluid of choice for children in hospital has been 0.18% NaCl in 4% dextrose. The rationale for this originates from the calculated sodium requirements of infants of 3 mmol/kg/24 h.<sup>4,5</sup> This requirement is met using a concentration of 0.18% NaCl (30.8 mmol/L). For example, a 10 kg infant would receive 100 ml/kg/day, equal to 1 L. One litre contains 30.8 mmol, giving a sodium intake of 3.08 mmol/kg. The glucose provided in the solution is not adequate to supply calorific needs; it is included to prevent hypoglycaemia and subsequent ketosis. Potassium requirements are 2 mmol/kg/day and can be met by adding 20 mmol of potassium to maintenance fluid. Chloride requirements are also 2 mmol/kg/day, so it is clear that this maintenance will supply more than the necessary chloride requirements. The danger of prescribing such a solution as intravenous therapy lies in the fact that the solution is hypotonic, creating the potential for water overload and intracellular volume expansion. This is particularly true of the hospital paediatric populations who often have multiple non-osmotic triggers for ADH secretion as part of their ongoing illness. For this reason the safety of prescribing such hypotonic solutions has been questioned and the guidance set out by the NPSA specifically states that all sodium chloride 0.18% with glucose 4% should be removed from stock and general use in areas that treat children. This being said, to date there is insufficient evidence to suggest the best alternative for maintenance solutions. As a general recommendation 0.45% sodium chloride with glucose (2.5% or 5%) may be safely administered to the majority of children for maintenance therapy. Those children who are at high risk of hyponatraemia should only be given isotonic solutions. *This includes children in the per-operative period.*<sup>3</sup> Choice of solution depends on clinical assessment of the patients needs, and is limited by commercial availability. Despite ongoing efforts, there is no ideal physiological crystalloid for maintenance prescription. Of the solutions available each has its own potential problems when given in excess.

The addition of glucose to maintenance fluid was initially intended to render the solution isosmolar and to prevent hypoglycaemia. It is now acknowledged that the risk of hypoglycaemia in children is low, unless they are less than 48 h old or have been receiving TPN or glucose infusions. Excluding these high-risk groups, the tendency is for glucose levels to be maintained or increased secondary to the stress response to surgery. Adding glucose in these situations may cause relative hyperglycaemia.<sup>6</sup>

### 1.2.2. Resuscitation

The type of resuscitation fluid is based on an assessment of the nature of losses. Standard choices in the UK include isotonic crystalloid for dehydration and 3rd space losses, e.g., Hartmann's solution or 0.9% NaCl. On a background of significant blood loss crystalloids or colloids can be used for initial plasma expansion. When using isotonic crystalloid it is important to remember that 100% of the volume given will remain extracellular and 1/4 of this volume will remain within the plasma. Blood products are added as clinical need arises. In the smaller infant and neonate

blood products are generally used sooner to expand a much smaller circulating volume, as the dilution caused by crystalloids and colloids is potentially much more significant. It is universally accepted that rapid large volume resuscitation fluid should be administered as isotonic or hypertonic solutions because of the risks of intracellular volume expansion with hypotonic solutions.

## 1.3. Osmolarity, osmolality, tonicity

When discussing fluids it is important for every clinician to have a good understanding of the differences between osmolarity and tonicity.

**Osmolality:** the number of osmoles per kilogram solvent. The osmolality of plasma is maintained at 280–305 mosmol/kg. It may be estimated by  $\text{mosmol/kg} = \text{glucose} + \text{urea} + (2 \times \text{sodium})$  (mmol/L).

**Osmolarity:** the number of osmoles per litre solution.

**Osmoles:** the molecular weight of a substance divided by the number of freely moving particles liberated in solution.

**Tonicity:** this is the effective osmolarity of a solution. It is a measure of those particles that are capable of exerting an osmotic force across the cell membrane *in vivo*.

So to take 0.18% NaCl with glucose 4%, this solution is isosmolar in comparison to plasma, with an osmolality of 284. However, the glucose component of the solution is a permeant and an ineffective solute, which readily enters cells and is metabolised. Thus the *tonicity* of the solution depends on the effects of the sodium chloride content, which in this case is 31 + 31 mequiv/L making the solution hypotonic (Table 1).

## 1.4. Mechanisms of hyponatraemia

Hyponatraemia in the paediatric population is complex and multifactorial. Ongoing debate of the ideal maintenance prescription fluid and volume relates to the various factors involved.<sup>7–9</sup> Prescription of hypotonic fluids increases the risks of developing hyponatraemia, secondary to the high electrolyte-free water content. Antidiuretic hormone (ADH) also plays a major role. The most important physiological trigger of ADH secretion in health is increased plasma osmolality. In disease states and per-operatively there are multiple non-osmotic triggers of ADH release. These include stress, starvation, haemorrhage, opiates, pain and nausea. ADH acts on the renal collecting ducts to increase the permeability of the cell membranes to water. It does this by activating adenylate cyclase in the lining of the epithelial cells, leading to cyclic adenosine monophosphate production and increased permeability of these cell membranes to water. As a result water is passively reabsorbed from renal collecting ducts into extracellular fluid and returned to peritubular capillaries.<sup>10</sup> Hyponatraemia in this situation is secondary to the dilutional effects of retained water. This hyponatraemia may be secondarily compounded by the effects of reduced aldosterone and increased atrial natriuretic peptide secretion in response to overloading of the circulatory volume. Fluid challenges given in response to dehydration or hypovolaemia temporarily expand the circulating volume. Atrial stretch receptors secrete atrial natriuretic peptide (ANP) in response to local stretching of the atrial wall. ANP induces hyperfiltration and natriuresis by binding to specific cell surface receptors which in turn activate plasma membrane associated guanylate cyclase to produce cGMP.<sup>11</sup> Accompanying the natriuresis one would normally expect an increased diuresis, but in the presence of ADH this is reduced. Prescription of isotonic

**Table 1**

Table reproduced from National Patient Safety Agency, reducing the risk of hyponatraemia when administering intravenous infusions to children.<sup>3</sup>

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

NaCl = sodium chloride.

fluids does not provide a complete solution to the problem. Hyponatraemia was demonstrated in adult women having uncomplicated gynaecological surgery, all of whom received only near-isotonic infusions.<sup>12</sup>

### 1.5. Hyponatraemia and cerebral oedema

In hyponatraemic states there is a reduction in the extracellular tonicity, sodium being a predominantly extracellular cation. This leads to movement of water across cell membranes, expanding the intracellular volume. This process can have potentially devastating effects on the brain, where the skull limits volume expansion. Rises in intracranial pressure (ICP) are thought to occur much more readily in children due to the larger brain: intracranial volume ratio.<sup>13</sup> Added to this, evidence from mammals suggests that coping mechanisms, related to extrusion of sodium from cells may not be matured in the pre-pubertal age group.<sup>14</sup> The consequence of these rises in ICP range from headache and nausea to decreased conscious level, seizures, respiratory arrest and death. The incidence of hyponatraemia in hospitalised children can be alarmingly high: 45% in children with pneumonia and 50% in bacterial meningitis.<sup>15</sup> In bronchiolitis patients, rates have been recorded as 30% at hospital admission with 13% of these going on to suffer seizures.<sup>16</sup>

## 2. Summary

We still do not have robust scientific evidence to suggest the best choice of maintenance fluid in children and the ideal rate of volume infusion. Some advocate a wholesale move to the use of isotonic maintenance fluids, arguing that the use of hypotonic solutions, in the scenario of non-osmotic ADH release, puts children at an unacceptably increased risk of hyponatraemia<sup>7</sup>; this in a population more susceptible to cerebral oedema and less able to compensate against intracellular volume expansion.<sup>14</sup> Concerns regarding the development of hypernatraemia following isotonic infusions in adults have not been proven and work showing a rise in sodium levels only when using hypertonic 3% sodium chloride disputes this fear.<sup>17</sup> Others argue that the problem is not the tonicity of the solution, more so the use of inappropriate maintenance volume prescriptions.<sup>9</sup> Volumes calculated on a weight

basis overestimate actual requirements from body surface area calculations in infants by 14%.<sup>4</sup> Reductions in metabolic activity and insensible water loss in hospitalised children compound the issue and renal generation of electrolyte-free water secondary to non-osmotic ADH secretion contributes to the prescription being over-zealous. Recommendations for 60% maintenance of hypotonic solutions have been suggested.<sup>9</sup> This approach requires attention to detail such that all other additional ongoing losses are accounted for separately.<sup>13</sup>

Ideally, we should be conducting a large randomised controlled trial to investigate which fluid type and volume is best. However, it would be difficult to justify exposing large numbers of children to hypotonic fluid at standard and reduced maintenance rates, or isotonic fluids at standard or reduced maintenance rates, in view of previous experiences. We are left without a full answer to the problem. To assist in avoiding iatrogenic injury secondary to fluid prescriptions in the future, we should use the guidelines set out by the National Patient Safety Advisory Committee. These include the advice to remove all sodium chloride 0.18% in dextrose 4% from general use areas, replacing with suitable alternatives. It emphasises the need to disseminate guidelines on fluid prescription and laboratory monitoring, and the importance of ensuring adequate training of those staff involved in the prescription of intravenous fluids in children.<sup>3</sup> Reporting of hyponatraemic episodes should be encouraged, to allow review of individual cases for contributory factors. The NPSA Committee encourages the review of fluid prescription charts and fluid balance charts and it helpfully provides example templates for departmental guidance. Audit of current practices will of course be required, to assess compliance with guidelines and allow future improvements in practice. Hopefully we will be able to avoid tragic iatrogenic injury by fluid prescription in the future.<sup>2</sup>

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