Intravenous 0.18% saline/4% glucose solution (‘hypotonic saline’): do not use in children except in specialist settings under expert supervision

October 2012
PLAIN-LANGUAGE SUMMARY

**KEY MESSAGE:** Intravenous hypotonic saline (0.18% saline/4% glucose solution) can cause dangerously low levels of sodium in children, which in some cases has lead to swelling of the brain and death.

Therefore, 0.18% saline/4% glucose solution must not be used in children aged 16 years or less, unless it is in a specialist setting, such as kidney, heart, liver, high-dependency, or intensive care units, and there is expert medical supervision. The child must be carefully monitored throughout treatment.

**Background**

The Medicines and Healthcare products Regulatory Agency (MHRA) is the UK government agency responsible for regulating medicines and medical devices. We continually review the safety of medicines and vaccines in the UK¹, and inform healthcare professionals and the public of the latest updates through several means, including public assessment reports. This report discusses a medical solution used in hospitals called hypotonic saline (0.18% saline/4% glucose), and its risks and benefits when used in children.

Hypotonic saline is given to patients intravenously² by health professionals in a hospital to maintain or replace their fluid and salt requirements. It has been used for this purpose for since the 1950s in both adults and children. There are several solutions of different compositions available in hospitals for intravenous fluid replacement therapy.

As with any medicine, the use of hypotonic saline (0.18% saline/4% glucose solution) may lead to side effects (adverse drug reactions [ADRs]) in some individuals. A review of the risks and benefits of this solution when used in children was recently undertaken by the MHRA and the Commission on Human Medicines³. The review followed the restart of a public inquiry into the deaths of three children in the UK who died from swelling of the brain caused by dangerously low levels of sodium after receiving intravenous hypotonic saline.

**Results**

The review examined information obtained up until November 2011 from clinical trials, analyses of scientific and medical research, reported cases, and clinical guidelines.

There have been over 50 reported cases worldwide of brain damage or death in children since 1993 resulting from low sodium levels associated with the use of hypotonic saline solution, often in previously healthy children undergoing a routine surgery.

Several clinical trials provided evidence that a much higher proportion of children who were administered 0.18% saline/4% glucose developed low sodium levels (hyponatraemia) compared with children receiving other intravenous fluid regimens.

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¹ Suspected side effects to any drug or vaccine can be reported to the MHRA by both healthcare professionals and members of the public via the YellowCard Scheme ([http://yellowcard.mhra.gov.uk/](http://yellowcard.mhra.gov.uk/))
² Via a drip into a vein
³ An independent committee comprised of health professionals and scientists who give advice to government Ministers on the safety, effectiveness and quality of medicines
Many publications concluded that no single fluid rate or composition is ideal for all children and therefore the optimal fluid therapy must be decided on an individual basis.

The risk of hyponatraemia in children with the use of intravenous hypotonic saline is well recognised in published medical literature and discontinuing use of this solution in children is supported by many authors.

The Royal College of Anaesthetists issued a News Bulletin in 2003 on the possibility of severely low sodium levels developing after the infusion of 0.18% saline/4% glucose\(^1\). In addition, the National Patient Safety Agency\(^2\) issued an alert in 2007 on how to minimise the risk of hyponatraemia when administering intravenous fluids in children\(^3\). The alert advised that 0.18% saline/4% glucose solutions should be removed from stock and general use in areas that treat children.

On the basis of the evidence from this review, the CHM recommended that 0.18% saline/4% glucose should not be used in children except those treated by experts in paediatric specialist settings, such as kidney, heart, liver, high dependency and intensive care units.

In light of the above, the following advice was given for healthcare professionals\(^4\) for intravenous 0.18% saline/4% glucose solution:

**Key advice:**

- Intravenous hypotonic saline (0.18% saline/4% glucose infusion) is now contraindicated in children except when initiated and maintained under expert medical supervision in paediatric specialist settings – such as renal, liver, cardiac, high dependency and intensive care units

- Remove 0.18% saline/4% glucose intravenous infusions from stock and general use in areas that treat children and ensure that suitable alternatives are available (in line with local guidelines). Restrict availability of 0.18% saline/4% glucose intravenous infusions to critical care and specialist wards – according to National Patient Safety Agency’s Alert 22\(^5\).

- If hypotonic intravenous fluids do need to be prescribed to children (according to the strict conditions above), the child’s individual clinical needs and possibility of increased anti-diuretic hormone secretion should be taken into account – fluid balance, plasma and urinary electrolyte concentrations must be carefully monitored during treatment.

- Acute symptomatic hyponatraemic encephalopathy\(^6\) is a medical emergency. Healthcare professionals should be aware and promptly recognize the signs and symptoms of hyponatraemia (headache, nausea\(^7\), seizures, lethargy\(^7\), coma, cerebral oedema\(^8\)) in children receiving hypotonic intravenous fluids.

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2. An agency of the Department of Health which identifies patient safety issues
3. [http://www.nrls.npsa.nhs.uk/resources/?EntryId45=59809](http://www.nrls.npsa.nhs.uk/resources/?EntryId45=59809)
4. Product information for medicines in the UK can be found at [http://www.medicines.org.uk/emc/](http://www.medicines.org.uk/emc/)
5. A term referring to any brain disease that causes brain dysfunction
6. Feeling of sickness
7. Extreme tiredness
8. Brain swelling due to accumulation of excessive water
1. INTRODUCTION

*(See glossary for an explanation of terms used in this report)*

This is a review of the risks and benefits of intravenous hypotonic saline (0.18% sodium chloride / 4% glucose infusion solution) when used in children, prompted by the restart of a public inquiry into the deaths of three children in the UK who died of cerebral oedema secondary to hyponatraemia following administration of intravenous 0.18% saline/4% glucose solution.

One of the above mentioned fatal hyponatraemic events was reported to the MHRA and led to a safety review of hypotonic saline in October 2001. At that time, available data suggested that hyponatraemia in association with hypotonic intravenous fluids administration related more to clinical practice rather than to medicines regulation and an expert working group advised that there should be no changes to product information.

The objective of this report is to re-evaluate the safety and current paediatric clinical use of intravenous 0.18% saline solutions in order to identify if any additional advice and recommendations on their use are necessary in the light of further information becoming available since the original safety review.

2. BACKGROUND

**Intravenous fluid therapy in children**

Solutions of electrolytes are given intravenously, to meet normal fluid and electrolyte requirements or to replenish substantial deficits or continuing losses when it is not possible or desirable to use the oral route. In an individual patient the nature and severity of the electrolyte imbalance must be assessed from the history, and a clinical and biochemical examination. Sodium, potassium, chloride, magnesium, phosphate, and water depletion can occur singly and in combination with or without disturbances of acid-base balance.

- **Maintenance fluid requirements** in children are usually derived from the relationship that exists between body-weight and metabolic rate; the figures in Table 1 are widely used in clinical practice as a guide outside the neonatal period. The glucose requirement is that needed to minimise gluconeogenesis from amino acids obtained as substrate from muscle breakdown. Maintenance fluids are intended only to provide hydration for a short period until enteral or parenteral nutrition can be established. It is usual to meet these temporary requirements by using a standard solution of sodium chloride and glucose. Solutions containing 20 mmol/litre of potassium chloride meet the usual potassium requirements when they are given in the suggested volumes; adjustments may be needed if there is an inability to excrete fluids or electrolytes, excessive renal loss or continuing extra-renal losses. The exact requirements depend upon the nature of the clinical situation and types of losses incurred.

| Table 1. Fluid requirements for children over 1 month (reproduced from BNF for Children 2011-2012) |
Body-weight | 24-hour fluid requirement
---|---
Under 10 kg | 100 mL/kg
10–20 kg | 100 mL/kg for the first 10 kg
 | + 50 mL/kg for each 1 kg body-weight over 10 kg
Over 20 kg | 100 mL/kg for the first 10 kg
 | + 50 mL/kg for each 1 kg body-weight between 10–20 kg
 | + 20 mL/kg for each 1 kg body-weight over 20 kg
 | (max. 2 litres in females, 2.5 litres in males)

However, it is important to keep in mind that the baseline fluid requirements shown in Table 1 should be adjusted to take account of factors that reduce water loss (eg, increased antidiuretic hormone (ADH), renal failure, hypothermia, and high ambient humidity) or increase water loss (eg, pyrexia or burns). During parenteral hydration, fluids and electrolytes should be monitored closely and any disturbance should be corrected by slow infusion of an appropriate solution.

- **Replacement therapy**: initial intravenous replacement fluid is generally required if the child is over 10% dehydrated or if 5–10% dehydrated and oral or enteral rehydration is not tolerated or possible. Oral rehydration is adequate, if tolerated, in the majority of those less than 10% dehydrated. Subsequent fluid and electrolyte requirements are determined by clinical assessment of fluid balance.

- **Neonates** lose water through the skin and nose, particularly if preterm or if the skin is damaged. The basic fluid requirement for a full-term baby in average ambient humidity is 40–60 mL/kg/day plus urinary losses. Preterm babies have very high transepidermal fluid losses particularly in the first few days of life; they may need more fluid replacement than full term babies and up to 180 mL/kg/day may be required. Local guidelines for fluid management in the neonatal period should be consulted.

- **Features of commonly used intravenous fluids in the UK** are summarised in Table 2.

**Table 2. Features of commonly used intravenous fluids in the UK**
(reproduced from “Background information for National Patient Safety Alert 22: March 2007”)

1 [http://www.nrls.npsa.nhs.uk/resources/?EntryId45=59809](http://www.nrls.npsa.nhs.uk/resources/?EntryId45=59809)
<table>
<thead>
<tr>
<th>Solution</th>
<th>Osmolality (mOsmol/L)</th>
<th>Sodium content (mequiv/L)</th>
<th>Osmolality (compared to plasma)</th>
<th>Tonicity (with reference to cell membrane)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium chloride 0.9%</td>
<td>308</td>
<td>154</td>
<td>Isosmolar</td>
<td>Isotonic</td>
</tr>
<tr>
<td>Sodium chloride 0.45%</td>
<td>154</td>
<td>77</td>
<td>Hyposmolar</td>
<td>Hypotonic</td>
</tr>
<tr>
<td>Sodium chloride 0.45% and glucose 5%</td>
<td>432</td>
<td>75</td>
<td>Hyperosmolar</td>
<td>Hypotonic</td>
</tr>
<tr>
<td>Glucose 5%</td>
<td>278</td>
<td>-</td>
<td>Isosmolar</td>
<td>Hypotonic</td>
</tr>
<tr>
<td>Glucose 10%</td>
<td>555</td>
<td>-</td>
<td>Hyperosmolar</td>
<td>Hypotonic</td>
</tr>
<tr>
<td>Sodium chloride 0.9% and glucose 5%</td>
<td>586</td>
<td>150</td>
<td>Hyperosmolar</td>
<td>Isotonic</td>
</tr>
<tr>
<td>Sodium chloride 0.45% and glucose 2.5%</td>
<td>293</td>
<td>75</td>
<td>Isosmolar</td>
<td>Hypotonic</td>
</tr>
<tr>
<td>Sodium chloride 0.18% and glucose 4%</td>
<td>284</td>
<td>31</td>
<td>Isosmolar</td>
<td>Hypotonic</td>
</tr>
<tr>
<td>Hartmann's Solution</td>
<td>278</td>
<td>131</td>
<td>Isosmolar</td>
<td>Isotonic</td>
</tr>
<tr>
<td>4.5% Human albumin solution</td>
<td>275</td>
<td>100-160</td>
<td>Isosmolar</td>
<td>Isotonic</td>
</tr>
</tbody>
</table>

**Review of intravenous fluid prescribing practice for children over the past decade**

Up until 2007, intravenous (IV) fluid prescription practices were based upon the original description of maintenance fluid requirements by Holliday and Segar in 1957 (Holliday et al, 1957). Their pioneering work was performed in healthy breastfed children and was based on calorific requirements; that if IV fluid therapy was necessary, hypotonic instead of isotonic fluid should be used at rates based on body weight rather than body surface area. Since then, there has been much debate around how suitable hypotonic fluids are as maintenance therapy in paediatric patients.

Several studies have demonstrated hyponatraemia after administration of hypotonic IV fluids (see results section, pg 9). Worldwide, there have been over 50 reports of permanent neurological injuries or deaths in children as a result of iatrogenic hyponatraemia associated with the use of hypotonic IV fluids, often in previously healthy children undergoing routine elective surgery. These include four deaths and one ‘near-miss’ event in the UK since 2000.

Following one of the above-mentioned hyponatraemic fatal events in the UK, the Royal College of Paediatrics and Child Health (RCPCH) and Royal College of Anaesthetists (RCoA) disseminated a warning about the possibility of water overload with severe hyponatraemia developing after the infusion of 0.18% saline/4% glucose in November 2003. RCPCH and RCoA recommended that intravenous fluids, particularly 0.18% saline/4% glucose should be prescribed carefully, especially to children in the post-operative period. Furthermore, they advised that after surgery, fluid balance and serum electrolytes should be carefully monitored and clinicians should ensure that the fluid used to replace losses matches the losses (The Royal College of Anaesthetists News Bulletin, Nov 2003).

Three years later a survey was carried out by Way et al. to assess practice of postoperative intravenous fluid prescription by paediatric anaesthetists (Way et al
2006). The results showed that 75.2% of anaesthetists prescribed hypotonic glucose saline solutions in the postoperative period. 58.1% were unaware of the concerns of RCPCH and 67.7% did not have a local departmental policy for fluid prescription. The authors suggested that national guidance was required.

To reduce the risk of iatrogenic hyponatraemia, the National Patient Safety Agency (NPSA) issued an alert on this concern in March 2007 (Alert 22). The alert recommended that 0.18% saline/4% glucose should be removed completely from general paediatric wards and restricted to intensive care and specialist wards. When treating conditions considered to be at high risk of hyponatraemia (including serum sodium level in the lower normal reference range, intravascular volume depletion, hypotension, central nervous system infection, head injury, bronchiolitis, sepsis, excessive gastrointestinal losses, salt wasting syndromes and chronic conditions such as cystic fibrosis and diabetes), the alert advised the use of isotonic solutions (eg, 0.9% saline with or without glucose).

The alert also recommended improving clinical guidelines for the administration of IV fluids, improving IV fluid prescription and fluid balance charts and providing better training, supervision and risk management system. In addition to the Patient Safety Alert, a Workforce competence statement, access to an E-learning module (BMJ) to support staff training, a paediatric audit checklist and background information on hyponatraemia were also published on the NPSA website (www.nrls.npsa.nhs.uk).

A study auditing the impact of the NPSA alert on clinical practice at King’s College Hospital in London was published in 2009 (Drysdale et al, 2009). The audit found that implementation of a new IV fluid guideline based on Alert 22 has been associated with less use of IV fluids not recommended by NPSA, resulting in less serum sodium level reduction. The only children who became hyponatraemic received IV fluids not recommended by NPSA Alert 22. However, despite the alert and guideline implementation, fewer children had electrolyte levels checked while receiving IV fluid therapy (Drysdale et al, 2009)

Furthermore, related guidance from the National Institute for Health and Clinical Excellence (NICE) was published in June 2010 (http://guidance.nice.org.uk/CG102). NICE provided recommendations on the management of bacterial meningitis in children, including the use of intravenous fluids in children with raised intracranial pressure and increased ADH secretion. The recommended types of maintenance fluid are isotonic, sodium chloride 0.9% with glucose 5% or sodium chloride 0.9% with glucose 5%. In neonates glucose 10% and added sodium chloride for maintenance is advised.

In summary, as a result of the above mentioned safety warnings and guidance, clinical practice in prescribing IV fluids for children has significantly changed in the UK over the past decade.

**Mechanism of hyponatraemia**

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

Hyponatraemia has been documented in otherwise healthy children receiving 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.

A major consequence of hyponatraemia is the 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 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 8%. 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.
3. RESULTS

Reports of hyponatraemia and 0.18% sodium chloride/4% glucose
There have been over 50 worldwide reports of permanent neurological injuries or
deaths in children as a result of iatrogenic hyponatraemia associated with the use of
hypotonic IV fluids, often in previously healthy children undergoing routine elective
surgery. These include four deaths and one ‘near-miss’ event in the UK since 2000.

Literature review

There are close to a hundred publications on finding the appropriate type of
maintenance fluid for children; the most relevant ones have been selected and are
summarised here:

- **Duke et al.: Hypotonic vs isotonic saline solutions for intravenous fluid
  management of acute infections.** Cochrane Database of Systematic Reviews

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

- **Moritz et al.: Prevention of hospital-acquired hyponatraemia: A case for
  using isotonic saline.** Pediatrics 2003;111;227-230

Common childhood conditions requiring parenteral fluids, such as pulmonary and
central nervous system infections, dehydration, and the postoperative state, are
associated with a non-osmotic stimulus for ADH production, which can lead to free
water retention and hyponatraemia. The authors conclude that the administration of
isotonic saline in maintenance parenteral fluids is the most important prophylactic
measure that can be taken to prevent the development of hyponatraemia in children
who receive parenteral fluids.

- **Playfor et al.: Hypotonic intravenous solutions in children.** Expert Opin.
  Drug Saf 3 (1); 67-73 2004

The use of hypotonic intravenous solutions, especially 0.18% saline/4% glucose
(originally referred to as ‘dextrose’) solution, remains standard practice in many
paediatric units in the UK. The practice of prescribing hypotonic intravenous fluids
derives from the work of investigators in the 1950s, who produced arbitrarily-derived
formulae for calculating the maintenance requirements for water and electrolytes in
hospitalised patients. Combining these values led to the widespread acceptance of
hypotonic solutions such as 0.18% saline/4% glucose as ‘standard maintenance’
parenteral fluids. Unfortunately, these calculations do not account for the effects of
ADH, the secretion of which is stimulated by many factors encountered during acute
illness and especially in the perioperative period. In this setting, the administration of
hypotonic intravenous fluids results in the retention of free water and the
development of hyponatraemia. The routine administration of hypotonic intravenous
fluids has been shown to be associated with severe morbidity and the deaths of many previously healthy children. The problem is compounded by the fact that 0.18% saline/4% glucose is labelled as 'isotonic'. Whilst this solution is isosmolar compared to plasma, lack of osmotically-effective solutes means that it is hypotonic with reference to the cell membrane. There is no justification for the routine administration of hypotonic intravenous fluids.

- **Holliday:** Isotonic saline expands extracellular fluid and is inappropriate for maintenance therapy. Paediatrics 2005; 115: 193-194

The authors state that rapid and generous expansion of extracellular fluid (ECF) suppresses ADH in acutely ill children with subtle hypovolaemia, which is similar to that seen in severe dehydration, burn shock, and septic shock, although much less intense. Once ECF is expanded, IV maintenance therapy can be given safely in the recommended amounts using hypotonic saline.

The authors concluded that the key to preventing hyponatraemia is suppressing ADH before undertaking maintenance therapy. This approach differs from the authors and that of Moritz and Ayus (2003), who recommend using isotonic saline as generic maintenance fluid. Although initially accomplishing the same goal, the Holliday recommendations needlessly distort the meaning of the term "maintenance" therapy and confuse follow-up planning.

On the other hand, the authors suggest that using isotonic saline as generic maintenance therapy imposes an IV sodium-chloride load that substantially increases when IV maintenance therapy is extended beyond the first day. This can cause hypernatraemia, which, similar to hyponatraemia, results in brain injury or death. To restore ECF before maintenance therapy is begun, many emergency departments initially give isotonic saline, 5 mL/kg/hour for 6 to 12 hours. After this, maintenance needs often can be met by oral fluids, but they will be safely met by IV maintenance therapy when given in recommended amounts. The authors proposed the more robust response of giving isotonic saline at a rate of 10 mL/kg/hour for 2 to 4 hours. This rapidly and safely expands ECF, suppresses ADH if elevated, and initiates normal urine flow.

- **Neville et al:** High antidiuretic hormone levels and hyponatraemia in children with gastroenteritis. Paediatrics 116(6):1401-1407 2005

In this prospective observational study, plasma ADH, electrolytes, osmolality, and glucose were measured in 52 subjects before (T-0) and 4 hours after (T-4) starting 0.45% saline/2.5% glucose, and subsequently when indicated. Hormonal markers of stress were measured at T-0. Urine samples were collected to measure electrolytes and osmolality. The non-osmotic stimuli of ADH secretion that were identified: vomiting (n=50), dehydration (median: 5%; range: 3-8%), hypoglycemia (n=2), and raised hormonal markers of stress (mean +/- SD: cortisol, 1094 +/- 589 nmol/L; reverse triiodothyronine, 792 +/- 293 pmol/L).

At T-0, around 50% of the children were hyponatraemic (plasma sodium concentration of < 135 mmol/L; n = 27). The median plasma ADH concentration at T-0 was significantly elevated (median: 7.4 pg/mL; range: <1.9 – 85.6 pg/mL). ADH was high in both hyponatraemic and normonatraemic children and remained high at T-4 in 33 of the 52 children, 22 of whom were concurrently hyponatraemic.
At T4, mean plasma sodium concentration was unchanged in the hyponatraemic children but was 2.6 mmol/L (+/- 2.0) lower in those who were initially normonatraemic. Urine tonicity was high compared with 0.45% saline in 16 out of 19 children at baseline and in 20 out of 37 children after 3 to 12 hours of IV fluids. It was concluded that non-osmotic stimuli of ADH secretion are frequent in children with gastroenteritis. The persistence of elevated ADH during IV fluid administration predisposes to dilutional hyponatraemia. The authors are of the view that the use of hypotonic saline for deficit replacement needs to be reassessed.

- **Choong et al.: Hypotonic versus isotonic saline in hospitalised children: a systematic review** Arch Dis Child 2006;91:828-835

The traditional recommendations which suggest that hypotonic IV maintenance fluids are the solutions of choice in paediatric patients have not been rigorously tested in clinical trials, and may not be appropriate for all children. The aims of this study were to systematically review the evidence from studies evaluating the safety of administering hypotonic versus isotonic IV maintenance fluids in hospitalised children. Data sources were Medline (1966 - 2006), Embase (1980 - 2006), the Cochrane Library, abstract proceedings, personal files, and reference lists. Studies that compared hypotonic to isotonic maintenance solutions in children were selected. Case reports and studies in neonates or patients with a pre-existing history of hyponatraemia were excluded. Six studies met the selection criteria. A meta-analysis combining these studies showed that hypotonic solutions significantly increased the risk of developing acute hyponatraemia (OR 17.22; 95% CI 8.67 to 34.2), and resulted in greater patient morbidity. The authors concluded that the current practice of prescribing IV maintenance fluids in children is based on limited clinical experimental evidence from poorly and differently designed studies, where bias could possibly raise doubt about the results. They do not provide evidence for optimal fluid and electrolyte homeostasis in hospitalised children.

This systematic review indicates potential harm with hypotonic solutions in children, which can be anticipated and avoided with isotonic solutions. No single fluid rate or composition is ideal for all children. However, isotonic or near-isotonic solutions may be more physiological, and therefore a safer choice in the acute phase of illness and peri-operative period.

- **The Royal College of Anaesthetists News Bulletin: Possibility of water overload with severe hyponatraemia developing after the infusion of 4% dextrose/0.18% saline, November 2003**

The College warned that there is a possibility of water overload with severe hyponatraemia developing after the infusion of 4% glucose/0.18% saline. However, a review of the literature shows that acute hyponatraemia in children following the administration of hypotonic fluids, intravenously or orally, is documented from the late 1960's. None of the published reports relates specifically to 0.18% saline/4% glucose but rather refer to hypotonic fluids. In contrast, 0.18% saline/4% glucose is isotonic before being administered but is effectively hypotonic in the sick child once the glucose has metabolised. Children in the post-operative period are particularly susceptible to serious and occasionally fatal neurological complications of acute hyponatraemia and sick children in other 'stressful' situations may also be at additional risk. The most recent case suggests that although this phenomenon is not new, the administration of hypotonic post-operative intravenous fluids (or fluids which...
are isotonic in vitro but hypotonic in vivo) is still occurring with potentially serious consequences.

- **National Patient Safety Agency: Patient Safety Alert – Reducing the risk of hyponatraemia when administering intravenous infusions to children**
  28th March 2007

**Actions for the NHS**
The NPSA recommended that healthcare organisations and local health boards in England and Wales should take the following actions by 30 September 2007 to minimise the risk of hyponatraemia with IV fluid administration 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 training and supervision for all healthcare 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.


Practice and outcome was audited in children receiving maintenance IV fluid therapy at King’s College Hospital in London in June 2007 (before NPSA guideline implementation) and June 2008 (after NPSA guideline implementation). In June 2007, 44 (30%) children were prescribed IV fluids in the hospital’s paediatric departments (excluding paediatric and neonatal intensive care and paediatric hepatology units), six received IV fluids not recommended by NPSA alert 22 and one became hyponatraemic. In June 2008, 56 (30%) children received IV fluids; one received IV fluid not recommended by NPSA alert 22 and became hyponatraemic. The median change in serum sodium levels for all children who received IV fluids not recommended by NPSA alert 22 [-5 (-15 to 0) mmol/l] was significantly greater than those who received IV fluids recommended by NPSA alert 22 [0 (-13 to +7) mmol/l, p = 0.002]. In addition, there was a significant (p = 0.04) reduction in the number of children who had electrolytes checked, while on IV fluids after implementation of the guideline. Implementation of a new IV fluid guideline has been associated with less use of IV fluids not recommended by NPSA alert 22, resulting in less serum sodium level reduction. The only children who became hyponatraemic received IV fluid therapy not recommended by NPSA alert 22. Despite the NPSA alert and guideline implementation, fewer children had electrolyte levels checked while receiving IV fluids.
• **Coulthard:** Will changing maintenance intravenous fluid from 0.18% to 0.45% saline do more harm than good? Arch Dis Child 2008;93:335-340

The author suggests that the recommended change in maintenance intravenous fluid in children from 0.18% to 0.45% saline by the NPSA might cause more children to develop hypernatraemia than it would prevent children from developing hyponatraemia, and thus could do more harm than good. There is no simple formula that will guarantee to prevent either hyponatraemia or hypernatraemia in all children, and it is impossible to decide on a safe fluid regimen merely by knowing the plasma sodium concentration and estimating the degree of dehydration, as is often done. Changing which fluid is used for routine maintenance therapy will not compensate for using a too-simple approach to fluid replacement. Instead, it is necessary to base the fluid regimen on an assessment of the child’s physiology. A vital part of that assessment includes measuring the urinary volume, sodium and creatinine, and using them to calculate the fractional excretion of water and sodium. This enables fluid replacement to be decided using a logical approach in which plasma sodium measurements are just used for fine-tuning. Also, 0.18% saline provides a more physiological standard replacement than 0.45% saline, equivalent to normal oral intakes, and should remain the basic maintenance fluid.


This study intended to determine whether the use of isotonic fluids prevents hyponatraemia and secondly, whether these fluids increase the incidence of adverse events. One hundred twenty-two paediatric patients hospitalized in intensive care unit requiring maintenance fluid therapy were randomized to receive isotonic fluids (isotonic group, NaCl = 140 mEq/L) or hypotonic fluids (hypotonic group, NaCl <100 mEq/L). Electrolyte blood concentration, glycaemia, and blood pressure were measured at 0, 6, and 24 hrs after the beginning of fluid therapy. Plasma creatinine, urine specific gravity, and urine electrolyte concentration were measured at 6 hrs.

At 24 hrs, the percentage of hyponatraemia in the hypotonic group was significantly higher: 20.6%, as opposed to 5.1% in the isotonic group (p = 0.02). No differences in the number of adverse events other than hyponatraemia were observed between groups.

The use of hypotonic fluids increases the risk of hyponatraemia when compared with isotonic fluids at 24 hrs following infusion (number needed to harm [confidence interval 95%] = 7[4;25]). In this sample, the use of isotonic fluids did not increase the incidence of adverse events compared with hypotonic fluids.

• **Yung et al:** Randomized controlled trial of intravenous maintenance fluids. J Paediatr Child Health 2009; 49:9-14, Paediatric Intensive Care Unit, Women’s and Children’s Hospital, North Adelaide, South Australia, Australia

A factorial-design, double-blind, randomised controlled trial was used. 50 children with normal electrolytes without hypoglycaemia who needed intravenous maintenance fluids for more than 12 hours were randomised to 0.9% saline (normal saline) or 4% glucose/ and 0.18% saline (glucose saline), at either the traditional maintenance fluid rate or 2/3 of that rate were randomised. The main outcome measure was change in plasma sodium from admission to 12–24 hours later. Fifty patients (37 surgical) were enrolled. Plasma sodium fell in all groups: mean fall 2.3
Fluid type ($P = 0.0063$) but not rate ($P = 0.12$) was significantly associated with fall in plasma sodium. Glucose saline produced a greater fall in plasma sodium than normal saline: difference 3.0, 95% confidence interval 0.8–5.1 mmol/L. Full maintenance rate produced a greater fall in plasma sodium than restricted rate, but the difference was small and non-significant: 1.6 (-0.7, 3.9) mmol/L. Fluid type, but not rate, remained significant after adjustment for surgical status. One patient, receiving normal saline at restricted rate, developed asymptomatic hypoglycaemia. The authors concluded that sick and post-operative children given glucose saline at traditional maintenance rates are at risk of hyponatraemia.

- **Moritz et al.: Improving intravenous fluid therapy in children with gastroenteritis.** Paediatric Nephrology 25(8):1383-1384, 2010

Gastroenteritis is one of the most common medical conditions seen by paediatricians. The standard approach to intravenous fluid therapy for these children has been to administer a 0.9% sodium chloride (NaCl) bolus followed by a hypotonic solution ranging from 0.2-0.45% NaCl to replace the remaining deficit plus maintenance. The authors have questioned the safety of this approach as there have been reports of death or permanent neurologic impairment from hyponatraemic encephalopathy. Hanna and Saberi (Pediatr Nephrol. doi:10.1007/s00467-009-1428-y) found the incidence of hospital-acquired hyponatremia (sodium < 135 mEq/L) to be 18.5% for patients presenting with isonatraemic dehydration from gastroenteritis. This confirms that the current approach of using hypotonic fluids results in a high incidence of hyponatraemia. Hypotonic fluids are not appropriate for rehydration in patients with gastroenteritis as it is a state of arginine vasopressin (AVP) excess due to both hemodynamic stimuli from volume depletion and non-hemodynamic stimuli such as nausea and vomiting. Free water will be retained until the volume deficit is corrected and the hemodynamic stimulus for AVP production abates. The authors claim that a safer and more effective approach is the administration of 0.9% NaCl in a continuous infusion following bolus therapy. 0.9% NaCl not only serves as prophylaxis against hyponatraemia, but it is superior to hypotonic fluids as an extracellular volume expander and corrects the volume deficit more rapidly.

- **Eulmesekian et al.: Hospital acquired hyponatraemia in postoperative paediatric patients: Prospective observational study.** (Pediatr Crit Care Med 2010;11:479-483)

This was a prospective, observational, cohort study to establish the incidence and factors associated with hospital-acquired hyponatraemia in paediatric surgical patients who received hypotonic saline (sodium 40 mmol/L plus potassium 20 mmol/L) at the rate suggested by the Holliday and Segar’s formula for calculations of maintenance fluids. Eighty-one patients were included in the study. The incidence of hyponatraemia at 12 hrs was 17 (21%) of 81 (95% confidence interval, 3.7-38.3); at 24 hrs, it was was 15 (31%) of 48 (95% confidence interval, 11.4-50.6). Univariate analysis at 12 hrs showed that hyponatremic patients had a higher sodium loss (0.62 mmol/kg/hr vs. 0.34 mmol/kg/hr, $p = .0001$), a more negative sodium balance (0.39 mmol/kg/hr vs. 0.13 mmol/kg/hr, $p<.0001$), and a higher diuresis (3.08 mL/kg/hr vs. 2.2 mL/kg/hr, $p = .0026$); relative risks were 11.55 (95% confidence interval, 2.99-44.63; $p = .0004$) for a sodium loss >0.5 mmol/kg/hr; 10 (95% confidence interval, 2.55-39.15; $p = .0009$) for a negative sodium balance >0.3 mmol/kg/hr; and 4.25 (95% confidence interval, 1.99-9.08; $p = .0002$) for a diuresis >3.4 mL/kg/hr. At 24 hrs, hyponatraemic patients were in more positive fluid balance (0.65 mL/kg/hr vs. 0.10 mL/kg/hr, $p = .0396$); relative risk was 3.25 (95% confidence interval, 1.2-8.77; $p$
for a positive fluid balance >0.2 mL/kg/hr. The incidence of hyponatraemia in this population was high and progressive over time. It was concluded that negative sodium balance in the first 12 postoperative hours and then a positive fluid balance could be associated with the development of postoperative hyponatraemia.


The aim of this study was to compare the effect of three different IV fluid regimes on the incidence of hyponatraemia in hospitalised children ranging in age from 3 months to 12 years. Children who required IV maintenance fluid for at least 24 hours following hospitalisation were eligible for inclusion. The children were randomized to three IV fluid groups: Group A: 0.9% saline in 5% glucose at the standard maintenance rate; Group B: 0.18% saline in 5% glucose at the standard maintenance rate; Group C: 0.18% saline in 5% glucose at two-thirds of the standard maintenance rate. The primary outcome measure was incidence of hyponatraemia (plasma sodium < 130 mEq/L). Of the 167 patients enrolled, 58, 56 and 53 patients were randomized to Group A, B and C, respectively.

The authors observed that 14.3% (8/56) of the children administered 0.18% saline in 5% glucose at the standard maintenance rate (Group B) developed hyponatraemia compared with 1.72% of the children in Group A and 3.8% of those in Group C. Based on these results, the study concluded that using 0.9% saline in 5% glucose as IV maintenance fluid helps to reduce the incidence of hospital-acquired hyponatraemia among children.

- **Saba et al: A randomized controlled trial of isotonic versus hypotonic maintenance intravenous fluids in hospitalized children.** BMC Pediatr. 2011 Sep 23; 11:82. Dept, of Pediatrics, Montreal Children's Hospital, McGill University, Montreal, QC, Canada.

The objective of this study was to estimate and compare the rates of change in serum sodium for patients administered either hypotonic or isotonic IV fluids for maintenance needs. 16 children were randomised to 0.9% saline and 21 children were randomised to 0.45% saline. Baseline characteristics, duration (average of 12 hours) and rate of study fluid infusion, and the volume of additional isotonic fluids given were similar for the two groups. [Na] increased significantly in the 0.9% group (+0.20 mmol/L/h [IQR +0.03, +0.4]; P = 0.02) and increased, but not significantly, in the 0.45% group (+0.08 mmol/L/h [IQR -0.15, +0). When administered at the appropriate maintenance rate and accompanied by adequate volume expansion with isotonic fluids, 0.45% saline did not result in a drop in serum sodium during the first 12 hours of fluid therapy in children without severe baseline hyponatraemia. However, the authors state that confirmation of this result in a larger study is strongly recommended.

**Summary discussion of literature findings:**

There is significantly more information available now in the literature about the use of hypotonic saline infusions in children compared to the MHRA’s previous safety review in 2001. Several of the more recent publications refer specifically to the use of 0.18% saline/4% glucose (Yung et al, 2009, Playfor et al, 2004) whereas in 2001 none of the safety review’s referenced literature did. Furthermore, several
randomised controlled trials have become available which are of great value in finding an optimal intravenous maintenance fluid therapy for children.

Kannan et al. (2010) provided evidence that a much higher proportion of children administered 0.18% saline / 5% dextrose at the standard maintenance rate developed hyponatraemia compared with the children receiving other intravenous fluid regimens (0.9% saline/5% glucose or 0.18% saline/5% glucose at 2/3 maintenance rate). In addition, Yung et al. (2009) reported that fluid type but not rate was significantly associated with fall in plasma sodium when 0.9% saline was compared to 0.18% saline/4% glucose at maintenance rate or 2/3 maintenance rate in a double-blind randomised controlled trial. Glucose saline produced a greater fall in plasma sodium than normal saline: difference 3.0, 95% CI 0.8-5.1 mmol/L.

Saba et al (2011) compared the rates of change in serum sodium for patients administered either hypotonic (0.45% saline/5% glucose) or isotonic (0.9% saline/5% glucose) IV fluids. The authors concluded that when administered at the appropriate maintenance rate and accompanied by adequate volume expansion with isotonic fluids, 0.45% saline did not result in a drop in serum sodium during the first 12 hours of fluid therapy in children without severe baseline hyponatraemia.

NPSA’s recommendation to change maintenance IV fluids to 0.45% or 0.9% saline was not agreed by everyone. For example, Coulthard suggests that it might cause more children to develop hypernatraemia than it would prevent children from developing hyponatraemia (Coulthard 2008). Instead of changing the type of fluid used he advises that the fluid regimen should be based on the assessment of the child’s physiology. Other authors also share his view that no single fluid rate or composition is ideal for all children and it should be evaluated based on the individual child’s clinical scenario (Choong et al. 2006).

However, the risk of hyponatraemia with the use of 0.18% saline/4% glucose IV solution is well recognised in the literature and therefore discontinuation of 0.18% saline is supported by many authors. Furthermore, the phenomenon of increased ADH secretion in the postoperative period (Paut et al. 2006, Eulmesekian et al 2010) and in children with gastroenteritis (Neville et al. 2005, Moritz et al 2010) has been well documented in the literature and its predisposition to dilutional hyponatraemia has been also highlighted.

In 2003, Moritz et al introduced the concept of using 0.9% saline as maintenance parenteral fluid for the prevention of hospital acquired hyponatraemia in children. This initiated the continuing debate on the most appropriate fluid for maintenance therapy in children (Playfor et al. 2004, Holliday 2005, Choong et al. 2006).

It is noted that no further adverse drug reactions with 0.18% saline/4% glucose have been reported in the UK since shortly after publication of the Royal College of Anaesthetists News Bulletin warning in 2003 about the risk of water overload with severe hyponatraemia after infusion of this solution.
4. DISCUSSION

Clinical practice in prescribing intravenous fluid therapy has changed significantly over the past decade. The evolution of change in clinical practice to replace 0.18% saline-containing IV solutions with 0.45% and 0.9% sodium chloride-containing fluids instead in paediatric fluid therapy is detailed in the background section of this report (pg 4). The NPSA alert issued in 2007 played a significant role in this change, however very limited data is available in the literature to describe clinical practice since the publication of the alert.

The literature review reflects that each patient’s physiology needs to be individually assessed and their fluid therapy should be planned accordingly with careful fluid balance, serum/urinary electrolyte monitoring and special attention to conditions where increased ADH secretion may be a factor (see background section ‘mechanism of hyponatraemia’, pg 8).

Furthermore, according to the literature review performed, the use of 0.9% saline solution as replacement therapy, and the use of 0.45% saline/5% glucose or 0.9%saline/5% glucose solutions as maintenance therapy can be supported with the infusion rate adjusted to the patients individual needs (based on urinary/serum electrolytes and fluid balance). The composition of fluid used for ongoing losses depends on the type of fluid being lost.

In conclusion, significant achievements have been reached in improving the safety of intravenous fluid therapy in children over the past decade. However, as these changes are part of an ongoing cycle of continuous improvement, the current safety review was initiated to explore further areas of facilitating safe use of 0.18% saline/4% glucose intravenous solutions.

5. NEW ADVICE

After reviewing all available data on this issue, the CHM concluded that the use of 0.18% saline/4% glucose should be contraindicated in all but a limited number of children treated by experts in paediatric specialist settings, such as renal, cardiac, liver, high dependency, and intensive care units. The following advice is recommended for healthcare professionals:

- Intravenous 0.18% saline/4% glucose infusion is now contraindicated in children except when initiated and maintained under expert medical supervision in paediatric specialist settings – such as renal, liver, cardiac, high dependency and intensive care units

- Remove 0.18% saline/4% glucose intravenous infusions from stock and general use in areas that treat children and ensure that suitable alternatives are available (in line with local guidelines). Restrict availability of 0.18% saline/4% glucose intravenous infusions to critical care and specialist wards – according to National Patient Safety Agency’s Alert 22.

- If hypotonic intravenous fluids do need to be prescribed to children (according to the strict conditions above), the child’s individual clinical needs and possibility of increased anti-diuretic hormone secretion should be taken into account - fluid balance, plasma and urinary electrolyte concentrations must be carefully monitored during treatment.
• Acute symptomatic hyponatraemic encephalopathy is a medical emergency. Healthcare professionals should be aware and promptly recognize the signs and symptoms of hyponatraemia (headache, nausea, seizures, lethargy, coma, cerebral oedema) in children receiving hypotonic intravenous fluids.
6. REFERENCES


Coulthard (2008). Will changing maintenance intravenous fluid from 0.18% to 0.45% saline do more harm than good? *Arch Dis Child;* 93: 335-340


NICE guideline 102: Management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care (http://guidance.nice.org.uk/CG102)


Saba et al (2011): A randomized controlled trial of isotonic versus hypotonic maintenance intravenous fluids in hospitalized children. *BMC Pediatr*; **11**: 82. Dept, of Pediatrics, Montreal Children's Hospital, McGill University, Montreal, QC, Canada.


Yung et al (2009). Randomized controlled trial of intravenous maintenance fluids. *J Paediatr Child Health; 49*: 9-14, Paediatric Intensive Care Unit, Women's and Children's Hospital, North Adelaide, South Australia, Australia
7. GLOSSARY

**ADH (see Antidiuretic hormone)**

**Amino acids**
A group of 20 substances that are combined to form proteins in living things

**Antidiuretic hormone (ADH)**
A chemical substance produced in the body that is responsible for regulation of water reabsorption in the kidney

**Arginine vasopressin**
A chemical substance produced in the body that is responsible for regulating the body’s retention of water

**Bacterial meningitis**
Meningitis is an inflammation of the membranes (meninges) surrounding the brain and spinal cord, usually due to the spread of an infection. Most cases of meningitis are caused by a viral infection, but bacterial and fungal infections also can lead to meningitis.

**Bronchiolitis**
Bronchiolitis is an viral infection of the small air passages of the lungs called the bronchioles.

**Cardiac**
Related to the heart

**Cerebral oedema**
Accumulation of fluid in the brain and resultant swelling that occur from different causes, such as trauma, a tumour, or exposure to toxic substances

**Clinical study**
A research study that tests the effectiveness and safety of medicines in humans

**Commission on Human Medicine**
(CHM): An independent committee comprised of health professionals and scientists who give advice to government Ministers on the safety, effectiveness and quality of medicines

**Cortisol**
A substance produced in the body that affects the metabolism of glucose, protein, and fats

**Creatinine**
A by-product produced in the body when muscles expend energy.

**Cystic fibrosis**
An inherited disease that affects the lungs, digestive system, sweat glands, and male fertility

**Diabetes**
A medical condition in which the body does not produce enough insulin, or when insulin does not work properly. Insulin controls the level of sugar in the blood

**Electrolytes**
Salts and minerals that can conduct electrical impulses in the body. Common human electrolytes are sodium chloride, potassium, and calcium. Electrolytes help to regulate metabolism and total body fluid levels.

**Encephalopathy**
Temporary or permanent damage to the brain

**Endocrine**
Of, relating to, or denoting glands that secrete hormones or other products directly into the blood.

**Enteral nutrition**
A way to provide food through a tube placed in the nose, the stomach, or the small intestine.

**Extracellular**
Located or occurring outside a cell or cells.

**Fluid replacement therapy**
Administration of fluids to a patient as a treatment for dehydration.

**Gastrointestinal**
Related to the stomach and intestines.

**Gluconeogenesis**
The process by which glucose is made, primarily in the liver, from non-carbohydrate sources.

**Glucose**
The main type of sugar in the blood and is the major source of energy for the body's cells.

**Glycaemia**
The presence of glucose in the blood. Too-low levels of glucose is known as hypoglycaemia; too-high levels is known as hyperglycaemia.

**Herniation**
Abnormal protrusion of an organ or other body structure through a defect or natural opening.

**High-dependency unit**
A unit in a hospital that offers specialist nursing care and monitoring to seriously ill patients. It provides greater care than is available on general wards but less than is given to patients in intensive care.

**Hyponatraemia**
Abnormally low level of sodium in the blood.

**Hypotension**
The medical term for low blood pressure.

**Hypothermia**
Abnormally low body temperature.

**Hypotonic saline**
A solution with a lower salt concentration than in normal cells of the body and the blood.

**Iatrogenic**
Resulting from the activity of physicians (doctors)

**Infusion**
Introduction of a solution into the body through a vein for therapeutic purposes

**Intensive-care unit**
A hospital unit with concentrated special equipment and specially trained personnel for the care of seriously ill patients requiring immediate and continuous attention.

**Intracranial**
Located within or on the surface of the brain

**Intravascular**
Within one or more blood vessels

**Intravenous**
Into, or within a vein

**Isotonic fluid**
A solution containing the same salt concentration as mammalian blood

**IV**
Intravenous

**Lethargy**
A state of sluggishness, inactivity, and apathy

**Median**
A statistical average: the middle value in a range of values in a sample

**Medicines and Healthcare products Regulatory Agency (MHRA):**
The UK government agency responsible for ensuring that medicines and medical devices work, and are acceptably safe

**Metabolism**
The chemical processes or changes that occur in the body in order to maintain life. This involves either breaking down substances or making new ones

**MHRA (see Medicines and Healthcare products Regulatory Agency)**

**Mortality**
The incidence of death (or death rate) in a group or population over a given

**National Patient Safety Agency (NPSA)**
An Arm's Length Body of the Department of Health that identifies and reduces risks to patients receiving NHS care

**Nausea**
Feeling of sickness or an urge to vomit

**Neonate**
Newborn infant aged 0–28 days

**NPSA** (see *National Patient Safety Agency*)

**Observational study**
A type of *clinical study* where the investigators observe the patients’ response to a treatment and measure their outcomes, but do not actively manage the study.

**Paediatric**
Occurring in, or relating to, children

**Parenteral nutrition**
Given to, or taken into the body through a route outside the digestive system, eg, by injection

**Physiology**
The study of how living organisms and their separate parts function

**Pulmonary**
Related to the lung

**Pyrexia**
Fever

**Renal**
Related to the kidney

**Respiratory**
Related to breathing

**Saline**
Consisting of or containing salt (sodium chloride)

**Seizures**
Uncontrolled electrical activity in the brain that produces fits or convulsions of the body

**Sepsis**
A bacterial infection in the bloodstream or body tissues

**Sodium levels** (in the body)
Sodium is a mineral that exists in the body and is acquired through diet, mainly in the form of salt (sodium chloride, NaCl). Regulating the amount of sodium in the body is critical to life and health

**Transepidermal**
Through the surface of the skin

**Triiodothyronin**
A hormone secreted by the thyroid gland