Chapter 1

Crystalloid fluids

Robert G. Hahn

The term *crystalloid fluid* refers to sterile water solutions that contain small molecules, such as salt and glucose, which are able to crystallize. These solutes easily pass through the capillary membrane, which is the thin fenestrated endothelium that divides the plasma volume from the interstitial fluid volume. This process of solute distribution brings along water. Hence, the volume of a crystalloid fluid is spread throughout the extracellular fluid (ECF) space.

Osmolality is the number of particles dissolved in the water solution. The osmolality of the body fluids is approximately 295 mosmol/kg and is a powerful driving force for water distribution. However, it is both the type of dissolved particles and the osmolality of the solution that determine the tonicity, i.e., to what degree the infusion fluid hydrates or dehydrates the intracellular fluid (ICF) space [1].

If the solutes in the infusion fluid remain outside the cells, as is the case for sodium and chloride, the osmolality and the tonicity agree. An iso-osmotic infusion fluid (295 mosmol/kg) is then isotonic. In contrast, osmolality and tonicity are not equivalent in the case where the solutes easily penetrate the cell membrane, which separates the ECF from the ICF. An example is ethanol, which markedly raises the body osmolality but without redistributing water. Therefore, ethanol is said to have low tonicity.

The cell membrane regulates the distribution of many other solutes across the cell membrane in a finely graded manner via energy-consuming pump mechanisms, which then also modify the water distribution. These pumping mechanisms operate slowly (minutes to hours) while changes in osmolality redistribute water within seconds.

The marketed crystalloid infusion fluids are usually isotonic or nearly isotonic. Hence, they expand the ECF volume but not the ICF volume.

Normal saline

A 0.9% solution of saline is isotonic and is therefore called physiological or "normal." The fluid still contains a marked surplus of chloride ions and no buffer (Table 1.1) and, hence, infusion of 2 l or more of the fluid causes hyperchloremic metabolic acidosis [2].

In adults, normal saline should be reserved for patients with hypochloremic metabolic alkalosis, as in disease states associated with vomiting. The fluid has a more accepted role for perioperative fluid therapy in children where the risk of subacute hyponatremia is a more serious concern than in adults (see Chapter 8 – Pediatrics).

Clinical Fluid Therapy in the Perioperative Setting, ed. Robert G. Hahn. Published by Cambridge University Press.

Table 1.1. Composition of plasma and the most common crystalloid solutions.

	Osmolality (mosmol/kg)	pH	Na^+ (mmol/l)	K^+ (mmol/l)	HCO_3^- (mmol/l) equivalent	Cl^- (mmol/l)	Glucose (mmol/l)
Plasma	295	7.40	140	3.6–5.1	30	100	5
0.9% saline	308	5.0	154	0	0	154	0
7.5% saline	2400	3.5–7.0	1250	0	0	1250	0
Lactated Ringer's	274	6.5	130	4	30	110	0
Acetated Ringer's	270	6.0	130	4	30	110	0
Plasma-Lyte A[a]	294	7.4	140	5	27	98	0
Glucose (5%)	278	5.0	0	0	0	0	278
Glucose (2.5%) + electrolytes	280	6.0	70	0	25	45	139

[a] Plasma-Lyte A also contains 23 mmol/l of gluconate.
All infusion fluids may contain small amounts of electrolytes like magnesium and calcium.

When infused in healthy volunteers normal saline might cause abdominal pain, which is not the case for lactated Ringer's [3]. The fluid also has more undesired effects, including acidosis, when used during surgery [4].

Normal saline is excreted more slowly than both lactated and acetated Ringer's solution [5,6], increasing the volume effect ("efficiency") of the fluid to be about 10% greater compared with the Ringer's solutions [5].

Saline may also be marketed as hypertonic solutions at strengths of 3% and 7.5% solution. The first is mainly intended as a means of raising the serum sodium concentration in in-hospital patients, whereas the latter is used for plasma volume expansion in emergency care. In volunteers, 7.5% saline is four times more effective as a plasma volume expander than normal saline [5].

Ringer's solutions

Ringer's solution is a composition created by Sydney Ringer in the 1880s to be as similar as possible to the ECF. Alexis Hartmann later added a lactate buffer to the fluid and made it Hartmann's solution, or "lactated" Ringer's solution.

Lactate and acetate

Today Ringer's solution is used with the addition of buffer in the form of *lactate* or *acetate*, of which the former is most common. Both ions are metabolized to bicarbonate in the body, albeit with certain differences. Lactate is metabolized in the liver and the kidneys with the aid of oxygen and under production of bicarbonate and carbon dioxide. Acetate is metabolized faster and in most tissues, and it consumes only half as much oxygen per mole of produced bicarbonate compared with lactate. Hence, lactate slightly increases the oxygen consumption [7] and might also raise plasma glucose, particularly in diabetic patients [7,8]. Large amounts of lactated Ringer's confuse assays used to monitor lactic acidosis.

Both lactate and acetate are vasodilatators. Rapid administration aggravates the reduction of the systemic vascular resistance that normally occurs in response to volume loading. Both lactate and acetate are also fuels, although the calorific content in 1 l of any Ringer's solution is quite low (approximately 5 kcal).

Although the differences between lactate and acetate are usually negligible, several factors suggest that acetate is the better buffer in the presence of a compromised circulation and in shock.

Pharmacokinetics

During intravenous infusion the Ringer's solutions distribute from the plasma to the interstitial fluid space in a process that requires 25–30 min for completion. The distribution half-life is approximately 8 min [5,9].

The elimination (by voiding) in volunteers is so rapid that the fluid may exhibit one-compartment kinetics, which has been interpreted to imply that the fluid is distributed from the plasma to well-perfused areas of the interstitial fluid space only. In contrast, elimination is greatly retarded during surgery where Ringer's always exhibits two-compartment kinetics [10] (see Chapter 15 – Body volumes and fluid kinetics). Infusion of 2 l of Ringer's in volunteers is followed by elimination of 50–80% of the fluid within 2 h, whereas the corresponding figure in anesthetized patients is only 10–20%. Lowered blood pressure, vasodilatation and activation of the renin–aldosterone axis are factors thought to be responsible for the slow

turnover of Ringer's during anesthesia and surgery [11]. Naturally, the retarded elimination makes it easier to cause edema by overhydration in a patient than in a volunteer.

For the infusion rates normally used during surgery, the ratio of the plasma to the expandable parts of the interstitial fluid space is 1:3, which means that 30% of the infused fluid is retained in the plasma (if we disregard elimination) [9]. However, one can count on the effect of distribution resulting in much stronger plasma volume expansion than offered by this relationship as long as the infusion continues (see Chapter 15).

The fluid distributed to the interstitial fluid space in the course of crystalloid volume loading is bound in the interstitial gel. However, free fluid can accumulate rapidly in the tissue spaces if an infusion of crystalloid fluid is provided so fast that the normally negative interstitial fluid pressure becomes positive [1]. This creates *pitting edema*, by which we can expect that the ratio of 1:2 has been abruptly reduced.

Clinical use

The pharmacodynamics of the Ringer's solutions is strongly related to their capacity to expand the ECF volume.

These fluids may be used to replace preoperative losses of fluid due to diarrhea. In contrast, vomiting should be replaced by normal saline.

The Ringer's solutions are commonly used (in a volume of approximately 500 ml) to compensate the blood volume for the expansion of the vascular tree that occurs from induction of both regional and general anesthesia.

The Ringer's solutions reverse the compensatory changes in blood pressure and sympathetic tone resulting from hypovolemia. There are numerous reports confirming that rapid infusion of Ringer's is a life-saving treatment in excessive hemorrhage due to the resulting expansion of the plasma volume.

In contrast, crystalloid fluid cannot reverse drug-induced hypotension [11]. If a crystalloid bolus has no effect in reversing hypotension during surgery, the anesthetist should change strategy and lighten the anesthesia, or else institute treatment with an adrenergic drug, rather than providing several liters of crystalloid fluid.

As crystalloids are inexpensive and carry no risk of allergic reactions, a Ringer's solution is often used to replace smaller blood losses while colloids are withheld until 10–15% of the blood volume has been lost. The commonly recommended dosage is to infuse three times as much Ringer's as the amount of blood lost (3:1 principle). If the patient's legs are placed in stirrups, a 2:1 replacement scheme can be used, with the last third given as a bolus infusion when the legs are lowered from the stirrups [12].

Dosing

The rate and volume of infused Ringer's solutions vary considerably during surgery.

In healthy adult females very rapid infusions of Ringer's (2 l over 15 min) caused swelling sensations, dyspnea and headache [13]. No symptoms were observed after infusing the same volume more slowly. This rate (133 ml/min) should not be exceeded in the absence of blunt hypovolemia.

In elderly and debilitated patients the rate of infusion of crystalloid fluid should be further reduced and adjusted according to the patient´s *cardiovascular status*.

Too rapid volume loading might be complicated by instant *pulmonary edema*. Both the dilution of the plasma proteins and the increased cardiac pressures promote such edema,

which should be treated with acute vasodilatation, administration of loop diuretics and application of continuous positive airway pressure (or positive end-expiratory pressure if the patient is mechanically ventilated).

There is a risk of pulmonary edema developing also in the postoperative period if the total volume infused during the day of surgery amounts to 10 l or more. Arieff [14] reported development of pulmonary edema in 7.6% of 8195 patients who underwent major surgery. The mortality in this group was 11.9%.

Volume loading with 3 l of lactated Ringer's in volunteers (mean age 63 years) reduced the forced expiratory capacity and the peak flow rate [15].

Outcome studies using prospective registration of postoperative adverse events have demonstrated that crystalloid fluid administration during colonic surgery should be closer to 4 ml/(kg h) than 12 ml/(kg h) [16]. Many similar outcome studies will be discussed later in this book that advise the anesthestist about the optimal infusion rates during various surgeries.

There are concerns about the use of Ringer's in *brain injury*, because the fluid is slightly hypotonic (270 mosmol/kg) and increases brain cell mass when the central nervous system is traumatized. Normal saline is likely to be a better choice during neurosurgery. However, in volunteers acetated Ringer's did not increase the ICF volume because the urinary sodium concentration was only half as high as that of the plasma [16].

All Ringer's should also be infused cautiously in patients with *renal insufficiency* since these patients may not be able to excrete an excess amount of crystalloid fluid.

Plasma-Lyte

The infusion fluid Plasma-Lyte A is constructed to further refine the "balanced" composition of acetated Ringer's solution. Here, the sodium and chloride concentrations are virtually identical to those of human plasma (Table 1.1).

To make up for the increase in cation and decrease of anion concentration the solution also contains the negatively charged ion gluconate, which is also metabolized to carbon dioxide and water but still has only a weak alkalinizing effect.

Glucose solutions

Glucose (dextrose) solutions are used to administer calories to prevent starvation, and also to provide body water. They are the only available infusion fluids that add volume to both the ECF and the ICF volumes. However, the volume component of the glucose solutions is distributed throughout the total body water only after the glucose added to the sterile water has been metabolized to carbon dioxide, which needs to be removed by ventilation, and water.

Pharmacokinetics

Infused *glucose* distributes rapidly over two-thirds of the expected ECF space. Elimination occurs by insulin-dependent uptake by the body cells. The half-life is approximately 15 min in healthy volunteers [17] but twice as long during laparoscopic cholecystectomy [18]. Elimination apparently occurs even more slowly in the presence of diabetes.

The *volume* component of isotonic glucose 2.5% with electrolytes and plain glucose 5% (the latter fluid is sometimes abbreviated to D5W) initially expands the plasma volume as effectively as acetated Ringer's solution [17]. The fluids show no distribution phase,

which means that they do not significantly expand the interstitial fluid space. Instead, fluid leaving the plasma volume enters the ICF space due to the osmotic strength of the "eliminated" glucose molecules. Hence, the kinetics of the fluid component of glucose solutions is coupled with the glucose metabolism. A slow redistribution of volume to the total body water then begins because the osmotic strength of glucose fades away when being incorporated into large glycogen molecules, and later when being the subject of metabolism.

Glucose 2.5% with electrolytes and plain glucose 5% are almost entirely eliminated within 2.5 h in volunteers (which is faster than Ringer's) [17]. Some of the volume component of glucose 5% still resides in the ICF space at that time.

Glucose solutions of 10% and 20% are hypertonic and withdraw fluid from the ICF to the ECF by virtue of osmosis. This volume returns to the cells when the glucose is metabolized.

Clinical use

Glucose solutions are widely used to treat debilitated hospital patients. Besides preventing starvation, glucose solutions hydrate the ICF volume in those who cannot be fed orally.

In the perioperative period, infusing a glucose solution with little or no electrolytes is the most logical way to provide free water to compensate for vaporization from airways and surgical wounds.

The glucose component of the fluid is indicated in patients at risk of developing hypoglycemia, such as in diabetes, alcohol dependency, hepatomas and pancreatic islet cell tumors. Certain drugs, like propranolol, increase the risk of hypoglycemia.

Alternatively, there seems to be little reason to routinely administer glucose perioperatively. In the vast majority of patients hormonal changes associated with surgery raise the blood glucose level sufficiently (by stimulating glycogenolysis and gluconeogenesis) to maintain normoglycemia, or even to reach mild hyperglycemia. The stress response, in turn, makes it difficult for the body to adequately use exogenous glucose to limit gluconeogenesis and protein catabolism ("protein-sparing effect").

Another argument to refrain from glucose administration perioperatively is that a very high glucose concentration worsens the *cerebral damage* that develops in association with cardiac arrest [19,20]. Therefore, glucose solution is contraindicated in acute stroke and not recommended in operations associated with a high risk of perioperative cerebral ischema, such as carotid artery and cardiopulmonary bypass surgery.

If used, plain glucose must be infused quite slowly (alongside other fluids) as there is otherwise a risk of blunt hyperglycemia developing [21].

Hypertonic glucose solutions (10% and 20%) must be monitored by measurements of the plasma glucose concentration. These fluids are used for more ambitious supplementation of calories in postoperative care and also in the intensive care unit.

In the past decade, modifying the plasma glucose level by glucose infusions and insulin has become a tool to reduce complications and improve survival after intensive care and cardiac surgery [22,23]. Cardiac function may even be improved in patients undergoing cardiac surgery by infusing a solution containing glucose, insulin and potassium [24].

In Europe "glucose loading" by mouth is sometimes performed in the evening and morning before abdominal operations, the purpose being to reduce nausea and insulin resistance [25].

Dosing

The basic need for glucose in an adult corresponds to 4 l of glucose 5% per 24 h (800 kcal), which prevents blunt starvation while not providing adequate nutrition. However, the amount administered to hospital patients is more often guided by the need for "free" body water, which is 2–3 l per 24 h. Although the commonly infused amount provides less glucose than the body utilizes, the glucose supplementation reduces muscle wasting [21]. As stated previously, this "nitrogen-sparing effect" of glucose is poorer in association with surgery due to the accompanying physiological stress response.

The rate of glucose infusion should not increase plasma glucose concentrations above the *renal threshold*, which is 12–15 mmol/l. Higher levels induce *osmotic diuresis* in which water and electrolytes losses are poorly controlled. This limit is reached by infusing 1 l of glucose 5% over 1 h in healthy volunteers [17].

Due to the ease by which plasma glucose becomes elevated during surgery, most anesthetists prefer to use glucose 2.5% with electrolytes in the perioperative setting. During laparoscopic cholecystectomy 1.4 l of glucose 2.5% with electrolytes over 60 min raised plasma glucose from normal to the renal threshold for osmotic diuresis (16 mmol/l) [18]. The limitations set to the infusion rate due to the risk of hyperglycemia make both glucose 2.5% and 5% unsuitable for use as plasma volume expanders.

Glucose metabolism yields CO_2, and the accompanying increased breathing might be a problem in debilitated patients with impaired lung function.

Hyponatremia

Repeated infusion of electrolyte-free glucose solution (usually plain 5%) might induce *subacute hyponatremia* [26]. This complication usually develops 2–3 days after surgery and is characterized by neurological disturbances, nausea and vomiting [27]. When symptoms appear, serum sodium is usually between 120 and 130 mmol/l (normal level 138–140 mmol/l).

Hyponatremia might cause permanent brain damage if left untreated. Menstruating women are most prone to develop such sequelae [28]. The surgery might be trivial but has often (at some stage) been complicated by sudden hypotension, which boosts the vasopressin concentration. Impaired renal function and liberal postoperative ingestion of soft juice drinks devoid of salt are other risk factors [26,29].

Treatment in symptomatic patients consists of hypertonic saline, which should be monitored so as to increase serum sodium no faster than 1–2 mmol/(l h). If hyponatremia has not appeared after surgery the development has probably been more gradual, and serum sodium in such *chronic hyponatremia* should be raised even more slowly (0.5 mmol/[l h]). The reason for the caution is that the brain gradually adapts to the lower osmolality and damage might occur if the normal concentration is attained fast.

Subacaute hyponatremia can be prevented by limiting the amount of plain glucose 5% to 1 l only. All other glucose solutions should contain sodium.

Rebound hypoglycemia

Moderate hypoglycemia and hypovolemia are likely to develop 30 min after a glucose infusion has been stopped abruptly in subjects with a strong insulin response to glucose, or when glucose is infused together with insulin [30]. This complication is called "rebound hypoglycemia" and is an issue when, for example, parenteral nutrition is turned off.

This complication may also occur during *labor*. Glucose from the mother passes the placenta and induces an insulin response in the fetus. At birth a strong insulin effect remains in the newborn, whose capacity to increase endogenous glucose production is limited [31]. Dangerous hypoglycemia develops, which might result in convulsions and brain damage. The "rebound" effect can be avoided by infusing the glucose no faster than required to prevent blunt starvation, which is 1 l glucose 5% over 6 h. A practical rule is to slow the rate of infusion of the glucose solution at the end of delivery.

The same critical situation for the newborn might develop if maternal volume loading is provided with glucose-containing fluid just before Cesarean section [32].

Mannitol

Mannitol is an isomer of glucose that is not metabolized in the body but is eliminated by renal excretion. The molecule remains essentially in the ECF fluid. The half-life is approximately 130 min but can be twice as long in the presence of impaired kidney function [33].

The isotonic concentration of mannitol is the same as for 5% glucose, which is sometimes used as an irrigating solution in endoscopic surgery. The clinical use of mannitol for intravenous administration is restricted to a plain 10% or 20% solution (in some countries only 15%), which induces diuresis in failing, oliguric kidneys. The mechanism is that the renal excretion of mannitol occurs by virtue of osmotic diuresis, by which the body loses water.

The hypertonic nature of 15% mannitol has made it a means of acutely reducing the intracranial pressure in patients with head trauma. The volume used is then 500–750 ml, of which half is given as a bolus infusion. Despite a long history, mannitol treatment remains poorly evaluated in outcome studies. As the fluid contains no electrolytes, users should be aware the osmotic diuresis creates an absolute loss of sodium and other electrolytes from the body that may need to be replaced.

The marked increase in ECF volume makes infusion of hypertonic mannitol contraindicated in congestive heart failure.

Like all hypertonic fluids, mannitol 15% should not be administered together with erythrocyte transfusions.

References

1. Guyton AC, Hall JE. *Textbook of Medical Physiology*, 9th edn. Philadelphia: WB Saunders Company, 1996; 185–6, 298–313.
2. Scheingraber S, Rehm M, Sehmisch C, Finisterer U. Rapid saline infusion produces hyperchloremic acidocis in patients undergoing gynecologic surgery. *Anesthesiology* 1999; **90**: 1265–70.
3. Williams EL, Hildebrand KL, McCormick SA, Bedel MJ. The effect of intravenous lactated Ringer´s solution vs. 0.9% sodium chloride solution on serum osmolality in human volunteers. *Anesth Analg* 1999; **88**: 999–1003.
4. Wilkes NJ, Woolf R, Mutch M, *et al*. The effects of balanced versus saline-based hetastarch and crystalloid solutions on acid-base and electrolyte status and gastric mucosal perfusion in elderly surgical patients. *Anesth Analg* 2001; **93**: 811–16.
5. Drobin D, Hahn RG. Kinetics of isotonic and hypertonic plasma volume expanders. *Anesthesiology* 2002; **96**: 1371–80.
6. Reid F, Lobo DN, Williams RN, Rowlands BJ, Allison SP. (Ab)normal saline and physiological Hartmann's solution: a randomized double-blind crossover study. *Clin Sci* 2003; **104**: 17–24.

7. Ahlborg G, Hagenfeldt L, Wahren J. Influence of lactate infusion on glucose and FFA metabolism in man. *Scand J Clin Lab Invest* 1976; **36**: 193–201.
8. Thomas DJB, Albertini KGMM. Hyperglycaemic effects of Hartmann's solution during surgery in patients with maturity onset diabetes. *Br J Anaesth* 1978; **50**: 185–8.
9. Ewaldsson C-A, Hahn RG. Kinetics and extravascular retention of acetated Ringer's solution during isoflurane and propofol anesthesia for thyroid surgery. *Anesthesiology* 2005; **103**: 460–9.
10. Hahn RG. Volume kinetics of infusion fluids (review). *Anesthesiology* 2010; **113**: 470–81.
11. Norberg Å, Hahn RG, Husong Li, *et al.*, Population volume kinetics predicts retention of 0.9% saline infused in awake and isoflurane-anesthetized volunteers. *Anesthesiology* 2007; **107**: 24–32.
12. Hahn RG. Blood volume at the onset of hypotension in TURP performed during epidural anaesthesia. *Eur J Anaesth* 1993; **10**: 219–25.
13. Hahn RG, Drobin D, Ståhle L. Volume kinetics of Ringer´s solution in female volunteers. *Br J Anaesth* 1997; **78**: 144–8.
14. Arieff AI. Fatal postoperative pulmonary edema. Pathogenesis and literature review. *Chest* 1999; **115**: 1371–7.
15. Holte K, Jensen P, Kehlet H. Physiologic effects of intravenous fluid administration in healthy volunteers. *Anesth Analg* 2003; **96**: 1504–9.
16. Hahn RG, Drobin D. Rapid water and slow sodium excretion of Ringer´s solution dehydrates cells. *Anesth Analg* 2003; **97**: 1590–4.
17. Sjöstrand F, Edsberg L, Hahn RG. Volume kinetics of glucose solutions given by intravenous infusion. *Br J Anaesth* 2001; **87**: 834–43.
18. Sjöstrand F, Hahn RG. Volume kinetics of 2.5% glucose solution during laparoscopic cholecystectomy. *Br J Anaesth* 2004; **92**: 485–92.
19. Myers RE, Yamaguchi S. Nervous system effects of cardiac arrest in monkeys. *Arch Neurol* 1977; **34**: 65–74.
20. Siemkowicz E. The effect of glucose upon restitution after transient cerebral ischemia: a summary. *Acta Neurol Scand* 1985; **71**: 417–27.
21. Sieber FE, Smith DS, Traystman RJ, Wollman H. Glucose: a reevaluation of its intraoperative use (review). *Anesthesiology* 1987; **67**: 72–81.
22. Van der Berghe G, Wouters P, Weekers F, *et al.* Intensive insulin therapy in critically ill patients. *New Engl J Med* 2001; **345**: 1359–67.
23. Lebowitz G, Raizman E, Brezis M, *et al.* Effects of moderate intensity glycemic control after cardiac surgery. *Ann Thorac Surg* 2010; **90**: 1825–32.
24. Gradinac S, Coleman GM, Taegtmeyer H, Sweeney MS, Frazier OH. Improved cardiac function with glucose-insulin-potassium after aortocoronary bypass grafting. *Ann Thorac Surg* 1989; **48**: 484–9.
25. Nygren J, Soop M, Thorell A, *et al.* Preoperative oral carbohydrate administration reduces postoperative insulin resistance. *Clin Nutr* 1998; **17**: 65–71.
26. Chung HM, Kluge R, Schrier RH, Anderson RJ. Postoperative hyponatremia: A prospective study. *Arch Intern Med* 1986; **146**: 333–6.
27. Arieff AI. Hyponatremia, convulsions, respiratory arrest, and permanent brain damage after elective surgery in healthy women. *New Engl J Med* 1986; **314**: 1529–35.
28. Ayus JC, Wheeler JM, Arieff AI. Postoperative hyponatremic encephalopathy in menstruant women. *Ann Intern Med* 1992; **117**: 891–7.
29. Häggström J, Hedlund M, Hahn RG. Subacute hyponatraemia after transurethral resection of the prostate. *Scand J Urol Nephrol* 2001; **35**: 250–1.
30. Berndtson D, Olsson J, Hahn RG. Hypovolaemia after glucose-insulin infusions in volunteers. *Clin Sci* 2008; **115**: 371–8.

31. Philipson EH, Kalham SC, Riha MM, Pimentel R. Effects of maternal glucose infusion on fetal acid-base status in human pregnancy. *Am J Obstet Gynecol* 1987; **157**: 866–73.

32. Kenepp NB, Shelley WC, Gabbe SG, *et al.* Neonatal hazards of maternal hydration with 5% dextrose before caesarean section. *Lancet* 1982; **1**: 1150–2.

33. Anderson P, Boréus L, Gordon E, *et al.* Use of mannitol during neurosurgery: interpatient variability in the plasma and CSF levels. *Eur J Clin Pharmacol* 1988; **35**: 643–9.