British Journal of Anaesthesia **105** (5): 635–9 (2010)
Advance Access publication 6 August 2010 · doi:10.1093/bja/aeq204

BJA

Safety of glucose-containing solutions during accidental hyperinfusion in piglets

L. Witt[1*†], W. A. Osthaus[1†], T. Lücke[2,4], B. Jüttner[1], N. Teich[1], S. Jänisch[3], A. S. Debertin[3] and R. Sümpelmann[1]

[1] Department of Anaesthesiology, [2] Clinic for Paediatric Nephrology, Hepatology and Metabolic Disorders and [3] Institute for Forensic Medicine, Hannover Medical School, Carl-Neuberg-Str.1, 30625 Hannover, Germany
[4] Clinic for Neuropaediatrics, Ruhr-Universität Bochum, Universitätsstraße 150, 44801 Bochum, Germany

* Corresponding author. E-mail: witt.lars-henrik@mh-hannover.de

Key points

- Hypotonic glucose-containing i.v. solutions in infants has been questioned due to possible hyponatraemia and hyperglycaemia.
- Alternatively, co-infusion of isotonic electrolytes and concentrated glucose solutions could be harmful with accidental hyperinfusion.
- In piglets, high glucose-containing solutions cause potentially hazardous changes in blood electrolytes, glucose, and osmolality.
- These experimental findings challenge the safety of concentrated glucose solutions in paediatric anaesthesia.

Background. Errors in fluid management can lead to significant morbidity in children. We conducted an experimental animal study to determine the margin of safety in accidental hyperinfusion of different glucose and electrolyte containing solutions.

Methods. Fifteen piglets [bodyweight 12.1 (SD 2.0) kg] were randomly assigned to receive either 100 ml kg^{-1} of balanced electrolyte solution with glucose 1% (BS-G1), hypotonic electrolyte solution with glucose 5% (HE-G5), or glucose 40% solution (G40) over 1 h. Blood electrolytes, glucose, and osmolality and intracranial pressure (ICP) were measured before, during, and after fluid administration.

Results. Hyperinfusion of BS-G1 led to moderate hyperglycaemia [baseline 3.4 (SD 1.3) mmol $litre^{-1}$, study end 12.6 (1.8) mmol $litre^{-1}$], but no other relevant pathophysiological alterations. Hyperinfusion of HE-G5 produced marked hyperglycaemia [baseline 3.9 (1.2) mmol $litre^{-1}$, study end 48.6 (4.3) mmol $litre^{-1}$, $P<0.05$] and hyponatraemia [baseline 136.4 (1.3) mmol $litre^{-1}$, study end 119.6 (2.1) mmol $litre^{-1}$, $P<0.05$], whereas osmolality remained stable during the course of the study. Hyperinfusion of G40 induced acute hyperglycaemic/hyperosmolar decompensation with an extreme decrease in serum electrolytes [e.g. sodium baseline 138 (1.1) mmol $litre^{-1}$, 30 min 87.8 (6.4) mmol $litre^{-1}$, $P<0.01$], leading to cardiac arrest after infusion of 50–75 ml kg^{-1}. ICP remained within a physiological range in all groups.

Conclusions. In an animal model of accidental hyperinfusion, BS-G1 showed the widest margin of safety and can therefore be expected to enhance patient safety in perioperative fluid management in children; HE-G5 proved significantly less safe; and G40 was found to be outright hazardous.

Keywords: blood glucose; critical incident; hyperglycaemia; i.v. infusions

Accepted for publication: 7 June 2010

In 1957, Holliday and Segar[1] first presented a practical method for clinicians to prescribe i.v. fluids in children. The authors first estimated the daily fluid requirements by the metabolic rate and secondly defined the daily electrolyte requirements by considering the electrolyte composition of human and cow's milk. These recommendations have resulted in the widespread use of hypotonic fluids with glucose 5% in paediatric patients for nearly half a century.[2–4] Recently, the safety of this practice has been questioned as hyperglycaemia and hyponatremia leading to hyponatraemic encephalopathy have been reported in association with the use of these hypotonic fluids.[5 6] As a consequence, recent guidelines of several associations of paediatric anaesthesiologists have recommended the perioperative use of isotonic instead of hypotonic electrolyte solutions with or without glucose 1–2.5%.[7 8]

Isotonic solutions with a reduced glucose concentration are currently not available commercially in most European countries and the USA.[2 9] Therefore, the use of concentrated glucose solutions (e.g. glucose 40%), infused via a separate infusion (bypass) to an isotonic electrolyte solution, is clinical practice in some hospitals during anaesthesia in newborns and infants. However, several case reports have shown that in the case of accidental hyperinfusion of these concentrated glucose solutions, this practice may lead to potentially fatal brain damage.[10–12] We conducted an experimental study in

† L. W. and W. A. O. contributed equally to the study and share responsibility as first author.

order to determine the margin of safety of different glucose and electrolyte containing solutions mimicking accidental hyperinfusion in an approved infant animal model.[13 14] We hypothesized that hyperinfusion of a hypotonic electrolyte solution with glucose 5% and of a glucose 40% solution will cause significant hyperglycaemia, hyponatraemia, and cerebral oedema compared with an isotonic balanced electrolyte solution with glucose 1%.

Methods

After approval by the local animal experimentation committee (Protocol no. 42502-04-08/1555), 15 4-week-old female German landrace piglets were studied. After a water-only overnight fast, they received i.m. premedication with azaperone and atropine. The piglets were then anaesthetized with i.v. propofol and fentanyl, orotracheally intubated, and mechanically ventilated with isoflurane 1.5% in oxygen/air ($F_{I_{O_2}}$ 0.5). The tidal volume was adjusted to maintain an end-tidal carbon dioxide tension of 5.3 kPa. All animals received fentanyl 20 μg kg^{-1} h^{-1} and rocuronium 0.5 mg kg^{-1} h^{-1} during the surgical interventions. Body temperature was maintained using an infrared lamp (LP1, Lister, Germany) and a circulating water mattress (HICO Aquatherm 650, Hirtz, Cologne, Germany). Heart rate, body temperature, and end-tidal carbon dioxide were measured using a patient monitoring system (Cardiocap 5, Datex-Ohmeda, Freiburg, Germany). Using standard cut-down techniques, 5 F percutaneous sheath introducer sets (Arrow, Reading, PA, USA) were inserted into the right jugular vein and the right common carotid artery. Through the venous introducer set, a 4 F two-lumen central venous catheter (Arrow) was placed in the superior vena cava for central venous pressure (CVP) recording. Through the arterial introducer set, a 4 F thermodilution catheter (Pulsiocath, 4 F PV 2024L; Pulsion, Munich, Germany) was inserted to determine mean arterial pressure (MAP) and cardiac output (CO) with a standard haemodynamic monitor system (PiCCO plus, Pulsion). Cardiac index (CI) adapted to the piglets body surface was calculated using the formula of Mack (*K* equals the piglets' body surface area constant): $CI = CO/K \times \sqrt[3]{\text{bodyweight}^2}$.[15]

A 20 G cannula was placed in the right saphenous vein to facilitate fluid administration. In addition, animals underwent burr hole craniotomy (9 mm) 1 cm paramedian to the sagittal suture over the right cortex in order to fix a 1.65 mm precision pressure catheter (Neurovent P, Raumedic, Helmbrechts, Germany) for intracranial pressure (ICP) measurements. Continuous ICP was monitored by transduction of the cortex tissue with pressure lines set to zero at the external auditory meatus.

After catheter placement and burr hole craniotomy, the first blood samples for blood gas analysis using a standard blood gas oximetry system (ABL 735, Radiometer, Copenhagen, Denmark) were collected into heparinized syringes. In each sample, pH, Pa_{O_2}, Pa_{CO_2}, actual base excess, actual bicarbonate, sodium, chloride, potassium, lactate, haemoglobin, and haematocrit were measured. Additionally, a further blood sample was drawn to measure serum osmolality using standard laboratory techniques. Piglets were then randomly assigned to receive either 100 ml kg^{-1} balanced electrolyte solution with glucose 1% (BS-G1, Table 1, E148 G1 PÄD, Serumwerk Bernburg, Bernburg, Germany), hypotonic electrolyte solution with glucose 5% (HE-G5, Table 1, Sterofundin HEG-5, B. Braun Melsungen, Melsungen, Germany) or glucose 40% (G40, Table 1, Glucose-Lösung 40%, Delta Select, Dreieich, Germany) over 1 h. During fluid administration, blood samples were collected every 15 min. When the infusion was stopped, the last blood sample was collected and the piglets were euthanized by i.v. injection of pentobarbital. Brain tissue samples for gross and microscopic examination were collected from each piglet after postmortem examination. Tissues for histopathology were fixed in 4% neutral buffered formalin, processed routinely, and embedded in paraffin. Sections (4 mm) were stained with haematoxylin and eosin (HE).

Table 1 Composition of piglet blood at baseline [expressed as mean (SD)], BS-G1, HE-G5, and G40

	Serum at baseline ($n=15$)	BS-G1	HE-G5	G40
Sodium (mmol $litre^{-1}$)	137 (2.5)	140	70	—
Potassium (mmol $litre^{-1}$)	3.7 (0.3)	4	2	—
Calcium (mmol $litre^{-1}$)	1.4 (0.1)	2	1.3	—
Chloride (mmol $litre^{-1}$)	102 (2.2)	118	66	—
Actual bicarbonate (mmol $litre^{-1}$)	26.3 (1.5)	—	—	—
Acetate (mmol $litre^{-1}$)	—	30	—	—
Lactate (mmol $litre^{-1}$)	1,1	—	—	—
Malate (mmol $litre^{-1}$)	—	—	10	—
Glucose (mmol $litre^{-1}$)	3.6 (1.4)	55.5	278	2220

Statistical analyses

The power calculation was carried out using the nQuery Advisor software 6.0 (Statistical solutions, Cork, Ireland) with a power of 90% and a significance level (α) of 0.05. This showed that a sample size of five piglets per group would allow detection of a difference of 10% in the sodium, chloride, and osmolality values in each infusion group. For data measured before, during, and after hyperinfusion, non-parametric statistical tests were performed. The Kruskal–Wallis test (*H* test) was used to determine differences between the groups at baseline and 15 and 30 min after the start of the infusion. Wilcoxon's test and the Mann–Whitney *U*-test were used as appropriate to compare within-group and between-group differences. The level of statistical significance was set at $P<0.05$. Values are expressed as means (SD). Recorded data were analysed using SPSS 15.0 software for Windows (SPSS Software, Munich, Germany).