Expert Advisors Report: SOLUTION 18 (Dextrose 4% saline 0.18%)

Q1. What is the likelihood, if any, of a connection between the manufacturers of Solution 18 and hospitals/trusts/medical personnel that might have affected, or improperly affected, any decision on appropriate fluid administration?

The decision regarding which particular intravenous fluid to administer to a patient, whatever their age, is made by a clinician with due regard to the needs of that patient at that time. However, the range of different intravenous fluids available to the clinician to prescribe is somewhat constrained by hospital/Trust pharmacy purchasing policies. For more expensive fluid preparations, particularly colloid blood substitutes, there is the potential for purchasing decisions to be heavily influenced by cost and not, solely, by the particular merits or demerits of any particular fluid preparation.

Within certain financial limits, buyers in NHS Supplies purchase what clinicians think is necessary. Crystalloid fluids (such as dextrose saline and saline) are relatively cheap (see below). Buyers search for economies if there is more than one company producing the same product, rather than suggesting a change to the product itself. All the major manufacturers provide a range of crystalloid fluids, all at similar cost: there would be no logical reason for the Trust not to stock at least three different types of crystalloid fluid.

There is one aspect of this purchasing decision that has the potential to influence clinicians' prescription of intravenous fluids. When administering intravenous fluids to replace blood volume, there is always a choice to be made between crystalloid and colloid. The argument as to which is 'better' has been raging for decades.[1] There is one undisputed fact in this argument, however; crystalloids are significantly cheaper than colloids. Hence, Trusts always prefer clinicians use crystalloids rather than colloids. (Colloids contain either protein or other long chain molecules that stay in the circulation for hours; crystalloid solutions only stay in the circulation for minutes). There are particularly expensive colloids and much cheaper colloids. Understandably, Trusts are often reluctant to stock the more expensive colloids. However, in this particular case, the issue is not about choice of colloids but about the decision to use one particular crystalloid solution, rather than another.

Hence, we think it is highly improbable that Trust purchasing policies could influence, in any way, prescribing choice of crystalloid.

Q2. *Are there are any commercial benefits from using a Solution 18 product in preference to a less hypotonic intravenous solution, such as half-normal saline (0.45% saline + 5% glucose), or to an isotonic solution such as normal saline (0.9% saline).*

The relative costs of these three solutions are given below; they are not significantly different. Hence, we doubt whether companies would deliberately promote one

particular crystalloid fluid on profitability grounds, particularly if they were aware of any clinically contentious issues. Nevertheless, we suggest:

- The relevant manufacturers should be asked if they were aware of these issues and what was their reaction to it (e.g. did they change their product information leaflet?).
- The relevant manufacturers should be asked if the relative production costs of the various crystalloid fluids were reflected in their relative cost to the NHS

(3) *Are there are any commercial benefits from using a particular Solution 18 product from one manufacturer in preference to using another Solution 18 product from a different manufacturer?*

- The manufacturers should be asked for their price list of these three different solutions at the relevant times.

(4) *What are the relative costs of Solution 18, half-normal saline and normal saline solutions?*

These are current list prices (in the public domain; obtained from the manufacturers' websites, or by telephoning the relevant customer care department). **Please be aware that locally negotiated hospital contract prices may be very different – but are always *cheaper* than list prices.**

Baxter

Sodium chloride 0.18% and glucose 4% - 500 ml viaflow:	£1.15
Sodium chloride 0.45% and glucose 5% - 500 ml viaflex:	£1.15
Sodium chloride 0.9% - 500 ml viaflow:	£1.15

Fresenuis kabi

Sodium chloride 0.18% and glucose 4% - 500 ml polyfusor:	£1.98
Sodium chloride 0.45% and glucose 5% - 500 ml steriflex:	£1.66
Sodium chloride 0.9% - 500 ml viaflow:	£1.74

Braun

Sodium chloride 0.9% - 500ml:	£0.64
*Gelofusine - 500ml:	£5.68

(Gelofusine put in for the sake of comparison. It is one of the 'cheaper' colloids.)

(5) *What is the procedure and effectiveness of reporting of adverse effects from medication or solutions to the MHRA through ADROIT (Adverse Drug Reactions Online Information Tracking)?*

The Medicines Act of 1968 provided the legal framework for the control of medicines in the UK. The Act required medicines to be licensed before being allowed onto the UK market. However, many of the provisions of the Act have now been superseded by regulations implementing European legislation on medicines.

The recognition of the effects of chloramphenicol on the newborn infant and thalidomide on the developing fetus led to the setting up of the Yellow Card Scheme (YCS) in 1964. The YCS is a *voluntary* scheme whereby doctors, dentists, coroners and pharmacists can report *suspected* adverse drug reactions (ADRs). As from November 2002, nurses were able to report suspected ADRs through the YCS, and from 2005, patients themselves have been able to submit yellow card reports. Pharmaceutical companies have to report through the YCS under statutory obligations.

The Adverse Drug Reactions On-line Information Tracking (ADROIT) database, established in 1991, is the national database of the UK Medicines Control Agency (MCA), which was created in 1989; it merged with the Medical Devices Agency to become the Medicines and Health Care Products Regulatory Agency (MHRA) in 2003. It contains details of reports of ADRs that have been reported to the MCA/MHRA since 1964 via the YCS. In assessing the safety of medicines, the MHRA is advised by the Commission on Human Medicines (CHM), which is the Government's independent scientific advisory body on medicines safety. The CHM is made up of experts from a range of health professions and includes lay representatives. (The Commission on Human Medicines was established in 2005; it combines the functions of the Committee on Safety of Medicines (CSM – see below) and the Medicines Commission).

The YCS has a proven track record in detecting signals of drug safety but cannot reliably be used to assess causality.[2] In other words, a Yellow Card report can only reflect the opinion of the reporter that there might be a connection between an administered drug and an adverse event; this is substantially short of proof of cause and effect. Instead, the YCS acts largely as an early warning system generating hypotheses of previously unrecognised adverse reactions, as well as identifying increases in the frequencies or severity of previously recognised reactions. Limitations of the YCS include under-reporting of reactions, lack of a denominator (i.e. total population exposure to particular medicines), reporting rates being affected by factors such as time that the drug has been on the market, any media attention, and the variable quality of the data received.

Although the YCS remains important for post-marketing surveillance, it is generally accepted that it under-reports ADRs.[3,4] Awareness and encouragement to use the YCS improves the reporting rate, as does an active prompting system.[4] Nevertheless, in hospital it relies on staff recollecting cases after they have

completed their normal clinical duties and taking the time either to complete a form on-line or return a yellow card by post. Under-reporting may be compounded by fears of litigation following unlicensed or off-license prescribing: many medicines used in children (and nearly all in neonates) are unlicensed; ADRs may be more likely with unlicensed drugs. About 10% of hospitalised children have an ADR.[5] ('Off-license' means the drug does have a license for use but not for the condition to be treated and/or for the age of the child concerned)

The YCS receives more than 20,000 reports of possible ADRs each year. Half a million reports were received in the scheme's first 40 years. [MHRA website, accessed April 2011] About 8% of these reports were for those aged under 18 years.[6] About 0.8% of yellow card reports for children have a fatal outcome.[2]

(6) *Is there any significance or investigation required into the Yellow Card Scheme report of January 1999?*

There have been two yellow card reports of possible ADRs related to dextrose 4% saline 0.18% up until 2010.[7] One was a report of the Raychel Ferguson case by Dr Taylor of RBHSC in 2001.

The other report concerns a female of unknown age who underwent abdominoplasty and died on 28th January 1999. (The nature of the surgery suggests that this was an adult). Apparently this woman had been infused with 3000 ml of dextrose/saline and 500 ml Haemaccel (an isotonic colloid containing sodium 145 mmol/L). When the 'batch' was tested by the hospital, results indicated the 'batch' did not contain sodium. It was indicated that this individual died as a result of cerebral oedema caused by a post-operative infusion.

We do not think that because this case was reported via the YCS it is imparted with any special relevance. There are many paediatric reports in the literature that are more comparable with our cases.[8,9]

The minutes of a CSM Working Group on Paediatric Medicines (advising the MCA, now the MHRA), meeting in 2001, considered a review of the use of dextrose 4% saline 0.18% in children.[10] This review, by Dr Cheng in 2001, was written subsequent to Dr Taylor's report. In her review, Dr Cheng stated that there were no other spontaneous reports, in any age group, on the ADROIT database, of hyponatraemia associated specifically with the use of dextrose 4% saline 0.18%, (despite the case mentioned above from 1999). This anomaly raises some questions as to the reliability of their searching algorithm.

We disagree with the Working Group that "there is a risk of hyponatraemia and electrolyte imbalance with the use of all intravenous fluids". We would substitute instead the phrase "there is a risk of electrolyte imbalance with the use of all intravenous fluids". (It would be difficult, for instance, to develop hyponatraemia secondary to receiving an infusion of 0.9% saline).

(7) *Does the Inquiry require further information in order to answer the above issues effectively?*

No, other than the questions we suggest putting to the three manufacturers (see above).

(8) *Whether any of these issues should be included in the work of the Inquiry*

No. We agree with the CSM Working Group on Paediatric Medicines that the issue of hyponatraemia relates more to clinical practice rather than to medicines regulation.

References

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