4 February 1986

Dr C A Ludlam
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Dear Dr Ludlam

You asked for information on the osmolality of various commonly used injections to compare them with a new product which the Protein Fractionating Centre hopes to issue, having a maximum osmolality of 500mosmol/kg solvent. This kind of information seems to be available only for TPN infusions and high doses of infused antibiotics, but not for small volumes of IV doses. However, the following data and enclosed paper will be of some help to decide if slow IV infusions of 2-100ml of the proposed new product would be acceptable on a regular basis for haemophilic patients.

In parenteral nutrition, 10% dextrose is the maximum strength which can be safely infused peripherally for any length of time, but after 72 hours (1), it is not unusual for redness to occur, necessitating a change of infusion site. Obviously, if larger veins are used it will minimise the risk of thrombophlebitis. The osmotic values for glucose are:

- 10% glucose - 523mosmol/kg solvent
- 5% glucose - 1250mosmol/kg solvent

An American paper (3), studied the effect of nitrogen and non-nitrogen infusions on peripheral veins, and stated that phlebitis was universal when osmolarity exceeded 600mosmol/l. 40% of the patients in this study developed phlebitis from continuous infusions of solutions with an osmolarity of over 400mosmol/l. The rate of infusion and the site (the forearm or the hand) did not appear to be an important factor, but the authors did emphasise that small veins were more disposed to phlebitis than large.

Another paper (4), examined the osmolality and osmolarity of many antibiotics in small volumes of infusions. The authors took a value of 400mosmol/kg as the cut-off point, above which solutions of the drug in 50ml of normal saline could be considered hyperosmolar, and suggested the use of water or 0-45% saline as an alternative diluent to reduce the osmolality value eg:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Osmolality in Water</th>
<th>Osmolality in 0-9% Saline</th>
<th>Osmolality in 0-45% Saline</th>
<th>Osmolality in 5% Dextrose</th>
</tr>
</thead>
<tbody>
<tr>
<td>2g Ampicillin Sodium in 50ml of IV Fluid</td>
<td>-</td>
<td>463mosmol/kg</td>
<td>302mosmol/kg</td>
<td>439mosmol/kg</td>
</tr>
<tr>
<td>4g Azlocillin Sodium in 100ml of Fluid</td>
<td>157mosmol/kg</td>
<td>451mosmol/kg</td>
<td>236mosmol/kg</td>
<td>576mosmol/kg</td>
</tr>
</tbody>
</table>
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However, consideration of these figures does not necessarily indicate that 20ml of a hyperosmolar solution of 400mosmol/kg or under would be free from hazard, since all these injections reported were given by slow IV infusion over at least 20 minutes, into a peripheral intravenous line, not into the small veins of the hand, as I understand are often used in haemophiles.

Incidentally, has the pH of the proposed solution been considered, since if this should be too far on either side of 7, a buffer may need to be added and this can also increase the osmolality.

I will note that figures in the enclosed paper are stated in terms of mosmol/kg, that is, osmolality as well as mosmol/l is osmolality. The values are not the same, but in this particular context, does not seriously affect the issue since they are close enough for all practical purposes e.g. ampicillin sodium 2g in 50ml of normal saline has a calculated osmolality of 444mosmol/kg, the measured osmolality is 463mosmol/kg, the osmolality is 453mosmol/l.

In conclusion, if the physical characteristics of the solution are such that a final product has an osmolality of over 400mosmol/kg, then it should be administered, if possible, 50% diluted with water, and also very slowly, or I believe there could be a risk of phlebitis developing with constant use.

Yours sincerely

[Signature]

M K A Irvine (Mrs)
Off Pharmacist

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