Hazards of parenteral treatment: do particles count?

J W L Puntis, K M Wilkins, P A Ball, D I Rushton, I W Booth

Abstract

After prolonged parenteral nutrition a 12 month old infant died with pulmonary hypertension and granulomatous pulmonary arteritis. A review of necropsy findings in 41 infants who had been fed parenterally showed that two of these also had pulmonary artery granulomata, while none of 32 control patients who died from sudden infant death syndrome had similar findings. Particulate contaminants have been implicated in the pathogenesis of such lesions and these were quantified in amino acid/dextrose solutions and fat emulsions using automated particle counting and optical microscopy counting respectively. Parenteral feed infusions compounded for a 3000 g infant according to standard nutritional regimens were found to include approximately 37 000 particles between 2 and 100 μm in size in one day's feed, of which 80% were derived from the fat emulsion. In-line end filtration of intravenous infusions may reduce the risk of particle associated complications. A suitable particle filter is required for use with lipid.

Subjects and methods

Necropsy study

Subjects

Postmortem material from all parenterally fed infants from a regional neonatal intensive care unit who had died between 1980 and 1989 were reviewed. Forty one such patients were identified, with a median (range) gestational age of 28 weeks (25–40) and weight 880 g (450–2820). The most common indication for parenteral nutrition was prematurity and failure to tolerate enteral feeding in association with respiratory distress requiring ventilatory support (n=38); indications in the three remaining patients were necrotising enterocolitis, ischaemic colitis, and ileal atresia. Parenteral nutrition was prescribed according to a standard protocol1 with a fluid intake of 150 ml/kg. The median (range) duration of parenteral feeding was 14 days (1–46).

Controls

Necropsy findings in 32 infants who had died over the same period from sudden infant death syndrome (SIDS) were reviewed. None had received intravenous treatment of any sort.

Although not a double blind study, all postmortem examinations were performed by the same person (DIR). Tissue sections from each lobe of each lung were routinely examined for particulate matter, such as glass or cotton fibres, and for pulmonary vascular granulomata.

Particle study

Six amino acid/dextrose feeds (Vamin 9 glucose, Kabi Pharmacia; 250 ml in plastic bags) and eight 35 ml aliquots of lipid emulsion (Intralipid 10%, Kabi Pharmacia; in plastic syringes) were constituted according to a standard prescription for neonatal parenteral nutrition,5 including addition of trace elements, micronutrients, and vitamins. Particles in the feeds were counted in glassware precleaned by washing in laboratory detergent (Decon 90), water, propan-2-ol, trichlorotrifluoroethane, propan-2-ol, and finally water. All washing solutions (except the detergent) were terminally filtered through 0.2 μm rated filters fitted to pressurised dispensers.

Automated particle counting

Approximately 100 ml samples of Vamin dextrose solution were run into precleaned bottles (which
registered <20 particles >2 µm in size per 10 ml sample volume when filled with filtered water). Numbers of particles in the ranges 2–5 µm, 5–10 µm, 10–25 µm, 25–40 µm, and 40–100 µm were determined in 10 ml aliquots of these samples using a Hiac PC-320 automated particle counter with attached D2–60 automatic bottle sampler.

OPTICAL MICROSCOPE COUNTING
Samples of Intralipid 10% (35 ml) were filtered through precleaned 0·8 µm membranes contained in precleaned filter funnels. The membranes were dried, made transparent, and particles in the range 2–5 µm, 5–10 µm, 10–25 µm, 25–40 µm, and 40–100 µm were counted using a Vickers M17 optical microscope (so that lipid droplets were not counted).

Results
Necropsy Study
Postmortem examination of the 41 parenterally fed infants showed two cases of widespread pulmonary granulomata (figure), which had also been identified at the original necropsy. These were located throughout the pulmonary arterial system and showed characteristic features of intimal fibrosis associated with foreign body giant cells with or without associated thrombus formation. In most granulomata it was not possible to identify specific foreign material within the giant cells, but occasionally glass fragments and cotton fibres were easily visible under polarised light. No granulomata or foreign bodies could be found in those patients who died from SIDS.

Particle Study
Particle counts recorded are shown in the table. In one day's parenteral feeding for a 3000 g infant, there were approximately 37 000 particles between 2 and 100 µm, with the majority (70%) being less than 5 µm size and only 4% being above 25 µm.

Discussion
Our findings confirm that pulmonary granulomata can be found in a small proportion of patients who have received parenteral fluids. Such granulomata formation has been convincingly related to both particulate contamination of intravenous solutions and the development of severe cardiovascular disease, and has been described in infants as well as adults. We estimate that our index patient with pulmonary hypertension and right heart failure would have received approximately 5 million particles between 2 and 100 µm in size from parenteral feed solutions alone.

Early studies of intravenous fluids showed that components of rubber bungs, glass from bottles, and fungal spores were common particulate contaminants together with more exotic finds such as fragments of crustacean. More recently the hazards of glass fragments and cotton fibres from alcohol impregnated swabs have been highlighted. Many particles appear to be organic in nature and generated by chemical interactions when mixing solutions. Some undoubtedly come from within plastic infusion systems, arising during the process of manufacture. Although there are accepted standards for particle counts in large and small volume parenterals, no such standards exist for infusion systems.

As pulmonary capillaries vary between 8 and 12 µm in size, any particle larger than this is likely to be filtered out and retained in the pulmonary vascular bed. Animal experiments with intravenous injection of microspheres indicate that small particles enter the systemic circulation and end up in organs including liver and spleen. The clinical significance of particles too small to be retained in the lungs is uncertain, although some haemodialysis patients have developed abnormal liver function thought to be a result of silicone particles in the liver derived from siliconised peristaltic blood pumps.

Particulate contamination is known to cause phlebitis in peripheral vessels, a complication significantly reduced by filtration. Perhaps such physicochemical interaction between particles and vessel walls involves very small as well as large particles. Certainly it is not simply particles large enough to get trapped in vessel lumens that trigger granulomata formulation, as often it is impossible to see any foreign body within the granulomata, while when glass

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**Table:**

<table>
<thead>
<tr>
<th>Feed</th>
<th>No of samples</th>
<th>Particulate size (µm)</th>
<th>2–5</th>
<th>5–10</th>
<th>10–25</th>
<th>25–40</th>
<th>40–100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amino acid/dextrose</td>
<td>6</td>
<td>151 (24)</td>
<td>44</td>
<td>(13)</td>
<td>13</td>
<td>(5)</td>
<td>4</td>
</tr>
<tr>
<td>Lipid emulsion</td>
<td>8</td>
<td>5881 (1538)</td>
<td>766</td>
<td>(317)</td>
<td>729</td>
<td>(406)</td>
<td>418</td>
</tr>
</tbody>
</table>

Mean (SD) particle count (by size) per 10 ml of amino acid/dextrose solution and per 35 ml of Intralipid 10%, with additives compounded according to standard regimen for infant <10 kg, and dispensed from plastic bags and plastic syringes respectively.

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**Figure:**

Section of neonatal lung showing granuloma with giant cells in the wall of a pulmonary artery. (Haematoxylin and eosin×300.)

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particles can be identified they may be smaller than the vessel lumen itself. There is increasing
evidence that interaction between particles and
damaged endothelium may be implicated in
microcirculatory disturbance which appears to
be a key feature of adult respiratory distress
syndrome and multiple organ failure in adult
intensive care patients.14

In-line filtration of amino acid/dextrose mix-
tures is commonly performed using a 0.2 µm
rated filter. This type of filter has been
developed to retain any microbiological organisms con-
taminating feeds,15 but its usefulness has been
questioned16 perhaps without consideration of
its additional role as particle filter. Any hazards
of particulate matter are more likely to occur in
patients on long term intravenous treatment.
Small infants who have a high fluid intake
relative to their weight might be at particular
risk. Since Intralipid droplets are similar in size
to natural chylomicrons (0.6–1.6 µm) and also
highly charged they cannot be filtered through a
0.2 µm membrane. This means that in our
patients, even when the amino acid/dextrose
mixture is filtered, four fifths of the particle
load within the day's parenteral nutrition fluids
is not retained.

Although we have focused attention on
parenteral nutrition fluids, it has been estimated
that the majority of particles delivered to a
patient come from medications together with
infusion solutions, ampoules, injection sites,
and syringes.17 Whereas in-line filtration of
parenteral nutrition fluids seems desirable in
patients on long term parenteral nutrition, any
attempt to reduce the particle load delivered
must take account of these other sources.

Increasing recognition that particulate con-
taminants may cause serious disease provides a
persuasive argument for in-line end filtration of
all intravenous fluids and injections given to
patients needing intensive care. Such a policy
could be cost effective through reducing phlebitis
associated with peripheral infusions13 or in
prolonging intravenous administration set life.18,19
Alternatives to glass ampoules20 have
already been developed and are associated with
fewer particles than glass ampoules. The use of
dropdromic needles with in-built 5 µm filters
for drawing up solutions effectively removes
many of the glass fragments seen with glass
ampoules.

While the precise risks associated with parti-
culate contaminants of intravenous treatment
remain uncertain, it is clear that particles
themselves are unwanted and unnecessary.
There is mounting evidence that they may cause
serious disease, particularly in sick patients.
Standards for manufacture of administration
systems are urgently required. As the manufac-
turing of small and large volume parenteral
nutrition solutions is likely to remain associated
with at least some level of particulate con-
tamination, effective filtration will be the only
way of preventing adverse clinical consequences.
Future developments should include filters
suitable for use with lipid emulsions.

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