Particulate Contamination of an Intact Glass Ampule

To the Editor—The contamination of single-dose glass ampules by glass fragments upon opening has been well documented.2-11 Intravenous infusion of these particles has been associated with a break in sterility,1,5,11 thrombophlebitis,4,8,12 thromboembolism,8 and the formation of large mono- and multinucleated foreign body giant cells.9 A Medline literature search in the English language literature of the medical subject headings "glass," "ampule," and "drug packaging" from 1966 to the present as well as a review of all references cited in this bibliography failed to document any report of glass particles contaminating an unopened glass ampule. We report the occurrence of an intact propofol ampule containing particulate matter.

Propofol (Diprivan®, Stuart Pharmaceuticals), an intravenous hypnotic agent, recently was introduced in the United States for anesthetic induction and maintenance. It is formulated as an emulsion containing soybean oil, glycerol, and egg lecithin. Routine shaking of a 20-ml ampule revealed a rattling sound suggestive of particulate matter within.

A radiograph taken at 25 mA, 55 kV, for 1/15 s showed four distinct, irregularly shaped particles (presumably glass) ranging in length from approximately 2.5 to 17 mm measured radiographically. Their presence was confirmed with multiple views (fig. 1).

The characteristic milky, opaque appearance of propofol can hide from view macroparticles that would be noticed easily in the other clear, transparent induction and maintenance agents currently in use. The presence of macroparticles in this case strongly suggests the presence of undetected microparticles.

Many risk factors for glass contamination have been identified including a positive correlation with ampule size,6 ampule type (transparent metal etched),7 the lack of in-line filtration,8,12 and immediate (versus delayed) aspiration after opening.8 External glass particles falling into the ampule upon opening clearly represents a break in sterility.1,8,10,11 Falck et al.13 demonstrated a statistically significant decrease in the incidence of infusion related phlebitis with an in-line filter.

Although direct evidence linking intravascular injection of glass particles to significant injury in humans is lacking, we believe all measures should be taken to limit such exposure. The use of in-line filters has been associated with reduced glass particle injection or its sequence.2,4 Although Butler et al.15 demonstrated a reduction in potency of certain drugs administered in low dosages through an in-line filter, propofol is given typically in a large bolus dose and titrated to effect, thereby obviating this potential problem. Propofol can not be aspirated through a 0.22-μm in-line filter, but can be injected through such a filter with moderate force.

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In Reply—Dr. Finkelstein and colleagues raise a number of important issues related to the intravenous administration of fluids and drugs. They indicate that glass particles may be found in ampules, either before opening or as a result of mapping open the ampule. A further search of the literature indicates that particulate matter or glass has been found in administration sets, plastic bags, iv solutions, drug solutions, syringes, glass containers, and powders for reconstitution. Clear drug solutions have been found to contain both macroscopic and microscopic particles upon opening of the ampules. These microscopic particles can be aspirated, and many of them are too small to be visible under normal lighting conditions, even in clear drug solutions. Macroscopic fragments such as those identified by Dr. Finkelstein and co-workers would be too large to be aspirated through a needle.

Quality assurance is of the highest priority for Stuart Pharmaceuticals, and we are working with the ampule manufacturer as an ongoing process to ensure that Dipirvan® (propofol) is of the highest possible quality. Currently, every filled ampule of Dipirvan® is inspected during production, consistent with our approved quality-assurance procedures. We have recently instituted an additional inspection prior to filing, for further assurance.

A thorough review of the safety data base for Dipirvan®, based on an estimated exposure of ten million patients worldwide and over 80 controlled clinical trials in North America, has not revealed any clinical events that appear to be related to the injection of particulate matter.

Should an anesthesiologist choose to filter intravenous agents, filters with a pore size of 0.22 μm are not appropriate for use with Dipirvan®. Filters of less than 5 μm could restrict the flow of Dipirvan® and may cause breakdown of the emulsion. Although we are currently conducting studies to determine the performance and compatibility of different filter types with Dipirvan®, evidence has been presented that a 5 μm filter does not affect the integrity of a more concentrated emulsion.

In summary: review of the international safety database for Dipirvan® has not revealed evidence of clinical events due to injection of particulate matter to date.

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