Glass Particle Contamination: Influence of Aspiration Methods and Ampule Types

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Glass particle contamination of the contents of single-dose glass ampules can occur upon opening. In our study we determined if different aspirating techniques or different ampule types had any effect on glass particle contamination. In part 1 of this study different aspiration techniques were evaluated. The four groups included a control group of 3-mm tubing, an 18-g 1.5-inch needle, a filter needle, and an in-line filter. A significant reduction in glass particle contamination was found when using either an in-line filter or a filter needle compared with the control group or when aspirating through an 18-g needle. The average number of glass particles found per ampule for each group was 100.8 ± 16.3, 65.6 ± 18.7, 1.3 ± 0.3, and 1.2 ± 0.3, respectively, for the control group, 18-g needle, filter needle, and in-line filter. In part 2 we examined four types of glass ampules: transparent metal etched, transparent chemically etched, amber metal etched, and amber chemically etched. There was a significantly greater number of glass particles found in the transparent metal etched ampules compared with that found in the other three ampule types. Transparent metal etched ampules yielded an average total number of particles per ampule of 45.9 ± 15.4 compared with 3.2 ± 0.9, 6.0 ± 1.7, and 3.1 ± 0.6, in the transparent chemically etched, amber metal etched, and amber chemically etched ampule types, respectively. This study demonstrates that using drugs supplied in ampules other than transparent metal etched type and by using filters will decrease the risk of parenteral injection of glass particles. (Key words: Equipment, ampules; glass particle contamination.)

Many drugs are supplied in glass ampules. Glass particle contamination of the contents of single-dose glass ampules can occur upon opening.1-8 The iv administration of glass particles in animals has been shown to cause inflammatory reactions and granuloma formation in pulmonary, hepatic, splenic, renal, and intestinal distribution.9,10 Therefore, it is clinically important to determine quantitatively the degree of glass particle contamination of ampule contents and to identify potential remedies. To date no randomized, blinded, controlled study has found a reduction in ampule contamination by altering the method of aspiration. In addition, no study has considered that different types of ampules themselves may influence the degree of glass particle contamination.

Our study consisted of two parts. The purpose of part 1 was twofold: 1) to quantitate the specific size and number of glass particles contaminating single-dose glass ampules after opening, and 2) to determine if different methods of aspiration could reduce or eliminate the glass particle contamination. The purpose of part 2 was to determine if the type of glass or method of scoring technique influenced the amount of glass particle contamination.

Materials and Methods

Part 1

Eighty transparent metal etched, 10 ml, single-dose glass ampules from the same manufacture lot number were randomized to four groups of 20 ampules each: group 1 (control), aspiration through a 7-cm length of 3 mm plastic tubing; group 2, aspiration through an 18-g, 3.8-cm needle; group 3, aspiration through a 19-g 3.8-cm, 5-μm filter needle; and group 4, aspiration through a 0.22-μm in-line filter.

Each ampule was opened by hand while in an upright position. The contents of each ampule were aspirated as described above into a prewashed 10-ml syringe. The syringe contents were then emptied directly into a Buchner funnel® and filtered through a 0.45-μm, 25-mm nylon filter, attached to a vacuum flask apparatus. The Buchner funnel® was then rinsed with 10 ml of sterile water along the edges. The microscopist, blinded to the method of aspiration, immediately examined the wet filter under a light microscope with ×10 power. Using a calibrated ocular micrometer, the number and size of the glass particles observed were recorded.

Part 2

Eighty 10-ml, single-dose glass ampules were divided into four groups of 20 ampules each based upon their color and method of scoring: group 1, transparent, metal etched; group 2, transparent, chemical scored; group 3, amber, metal etched; and group 4, amber, chemical scored. Each group of ampules was from the same man-

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ufacture lot number. The ampules were randomized and then opened as in part 1. Aspiration was through an 18-g needle, into a prewashed 10-ml syringe and filtered the same as in part 1. The microscopist was blind to the type of ampule.

Results from part 1 were analyzed by one-way analysis of variance (ANOVA). The data from part 2 were analyzed by two-way ANOVA. A Student’s t test was used to determine significance within each size group. Significant differences between ampule groups were determined by Tukey’s HSD test, the a posteriori procedure for evaluating all pairwise comparisons for equal size sample groups. All results are reported as mean ± SEM.

Results

PART 1

Results are summarized in table 1. The mean number of particles found in ampules in the control group was 100.6 ± 16.3 with particle size ranging from 10 to 1,000 µm. Aspiration through an 18-g needle reduced the mean number of particles to 65.6 ± 18.7 and decreased the maximum particle size to less than 400 µm. Aspiration through a 19-g, 5-µm filter needle and a 0.22-µm in-line filter decreased the mean total number of particles to 1.3 ± 0.3 and 1.2 ± 0.3, respectively. These decreases were significantly different (P < 0.01) compared with both the control and the 18-g needle groups. The mean number of particles in the 0–50, 51–100, 101–200, and 201–400 µm size categories were significantly decreased (P < 0.01) in the filter groups compared with those using the control method of aspiration. Aspirating ampule contents through a filter needle or in-line filter decreased the number of particles in the 0–50, 51–100, and 101–200 µm range (P < 0.01) when compared with aspirating through an 18-g needle. No particles larger than 200 µm were found.

PART 2

Results are summarized in table 2. The mean number of particles found in each transparent, metal etched ampule was 45.9 ± 15.4. This value was significantly greater (P < 0.01) than the other three ampule types. Transparent and amber chemically scored ampules and amber, metal etched ampules produced mean numbers of particles of 3.2 ± 0.9, 3.1 ± 0.6, and 6.0 ± 1.7, respectively. Only the transparent, metal etched group had glass particles larger than 200 µm. Transparent, metal etched ampules produced a significantly greater (P < 0.05) number of particles in the 0–50 and 101–200 µm size categories when compared with the other three ampule types.

Discussion

Patients in the operating room and in intensive care units receive medications almost exclusively in parenteral

<table>
<thead>
<tr>
<th>Group</th>
<th>0–50 µm</th>
<th>51–100 µm</th>
<th>101–200 µm</th>
<th>201–400 µm</th>
<th>&gt;400 µm</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td>Transparent metal</td>
<td>36.9 ± 11.9</td>
<td>7.8 ± 3.6</td>
<td>1.1 ± 0.4</td>
<td>0.2 ± 0.1</td>
<td>0.1 ± 0.1</td>
<td>45.9 ± 15.4</td>
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<td>(n = 20)</td>
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<tr>
<td>Transparent chemical</td>
<td>2.9 ± 0.8*</td>
<td>0.3 ± 0.2*</td>
<td>0.1 ± 0.1*</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
<td>3.2 ± 0.9*</td>
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<td>(n = 20)</td>
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<tr>
<td>Amber metal</td>
<td>4.6 ± 1.3*</td>
<td>1.3 ± 0.4</td>
<td>0.2 ± 0.1*</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
<td>6.0 ± 1.7*</td>
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<td>(n = 20)</td>
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<tr>
<td>Amber chemical</td>
<td>2.6 ± 0.5*</td>
<td>0.5 ± 0.2</td>
<td>0.0 ± 0.0*</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
<td>3.1 ± 0.6*</td>
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<td>(n = 20)</td>
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All values are expressed as mean ± SEM.
* P < 0.05 compared with transparent, metal etched.
† P < 0.01 compared with transparent, metal etched.
form through epidural, subarachnoid, subcutaneous, intramuscular, and intravenous routes. Many of the medications used are contained in single-dose glass ampules; thus, the risk of glass particle exposure in this group of patients is potentially high.

Intravenous infusion of nonglass particulates has been shown to cause pathologic changes in both animal and human studies.\textsuperscript{11-14} Administration of ground filter paper and ground plastic material intravenously to beagles caused nonsuppurative granulomatous lesions in the lungs as early as 5 days after the particulate administration.\textsuperscript{1} The intravenous infusion of normal saline contaminated with cellulose, chemical, and rubber particles to rabbits produced pulmonary granulomas on postmortem examination as early as 8 days following the infusion.\textsuperscript{15} Similarly contaminated intravenous fluid has been linked to infusion phlebitis in humans.\textsuperscript{16}

The intravenous administration of glass particles is associated more with chronic than acute changes. Brewer and Dunning\textsuperscript{17} reported that after 32 days of daily glass infusions in rabbits, glass particles were found within pulmonary capillaries along with occasional thrombi, engorgement of the pulmonary capillaries and venules, and a variable degree of atelectasis. No pathology was apparent in any other organs. In a second group, after intermittent glass particle infusions for 334 days, postmortem examination of the lungs revealed large, discrete tubercle-like lesions similar to those seen in chronic siliconosis. Capillaries were filled with glass particles. Alveolar septae contained glass particles associated with foreign body giant cells that occasionally occluded the alveolar spaces. Examination of the liver revealed many small glass particles throughout, along with multinucleated giant cells filling the portal triads. Giant cells were also studded throughout the kidneys, spleen, and intestinal walls.

The size of the glass particles infused greatly influences their ultimate location and thus the harm they may render the recipient. Gardner and Cummings\textsuperscript{18} infused rabbits with silica particles ranging in size from 1 to 12 μm in diameter. The animals were then examined up to almost 3 yr after the infusions. Larger silica particles of 10-12 μm were usually trapped in the pulmonary capillaries and elicited a foreign body type reaction with granuloma formation. Smaller silica particles were able to pass through the lung and eventually resided in the spleen, liver, and hepatic lymph nodes. In the liver, a progressive nodular cirrhosis developed as a result of the silicotic fibrosis originating in the portal connective tissue.

From these results, it is apparent that the intravenous administration of glass particles is associated with pathologic responses. The fact that glass particle sequelae require a considerable time to develop is not unexpected. Chronic siliconosis from the inhalation of silica particles takes an average of 10 yr for the development of physical signs and symptoms.

Ampules for medical use are made of type 1 grade, borosilicate glass. Glass ampules are found in amber or transparent colors and can be scored either chemically or by metal etching. Thus, there are four different types of ampules available. The most common type are the transparent, metal etched ampules.

In part 1 we determined that glass particle contamination in transparent, metal etched ampules is present and may be significantly reduced by aspirating through a 5-μm filter needle or 0.22-μm in-line filter. The methodology used was designed so that the amount of glass particles found would be representative of what may actually be injected parenterally in clinical practice. Specifically, the ampules and syringes were not rinsed after aspiration or evacuation. However, the sides of the Buchner funnel\textsuperscript{19} were rinsed after each sample to collect any glass particles that might adhere to the sides of the funnel.

Although aspiration through an 18-g needle decreased both the number and size of glass particles compared with those found using control method of aspiration, a large number of particles were still found. Aspiration through either the 19-g, 5-μm filter needle or the 0.22-μm in-line filter removed nearly all glass particles. The particles that did make it through the filter were almost exclusively smaller than 50 μm in size. In contrast to the study of Carbone-Traber and Shanks,\textsuperscript{5} our results indicate that filtration is an effective means of reducing glass particle contamination. The reason for this disparity in results is not readily apparent; possibly aspiration through a filter with a high pressure gradient permitted particles to penetrate the filter. Consistent with our results, Pinnock\textsuperscript{20} in a nonrandomized, open study, demonstrated complete removal of glass particles aspirated through a 5-μm filter needle.

In part 2 of our study, the degree of glass ampule contamination was determined for each type of glass ampule. Aspiration was through an 18-g needle, which most closely simulates clinical practice. The transparent, metal etched ampules produced a significantly greater number and size of glass particles than the other types of ampules. This is an important finding because transparent, metal etched ampules are the most common ampules in clinical use.

The data from this study clearly demonstrate that medications contained in single-dose glass ampules are contaminated with glass particles when opened, especially in transparent metal etched ampules. If medications contained in glass ampules are used, filtration is an effective means of removing glass particle contamination. Because the two methods of filtration tested were of equal efficacy,

either the filter needle or the in-line filter can be recommended. However, because in-line filters cost more and can restrict the flow of certain fluids, aspiration with a filter needle may be the method of choice. In addition, drug manufacturers could reduce the number of glass particles to be filtered by using ampoules other than the transparent, metal etched type.

It may be preferable to use medications in containers other than single-dose glass ampules that do not require the breakage of glass. However, these containers may produce rubber, chemical, or other particulate contamination that may be as harmful as glass particles. Therefore, before recommending replacing single-dose glass ampules with other container types, this area deserves to be studied.

Until more is known, filtration would appear to be the safest technique to use, especially with single-dose glass ampules. Infusion of the contents of single-dose glass ampules without filtration represents an unnecessary and readily preventable patient hazard.

References