Do infusions of midazolam and propofol pose an infection risk to critically ill patients?

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SUMMARY

In order to investigate bacterial contamination of i.v. anaesthetic agents, given by infusion to critically ill patients, we have cultured residual infusion fluid from infusion syringes, 50 containing midazolam and 50 propofol. The infusions had been prepared with routine aseptic precautions and had been running for between 0.75 and 21.25 h. Only scanty growths of Staphylococcus epidermidis were isolated from seven syringes (four midazolam and three propofol). Small volume samples were more likely to produce bacterial growth than large volume specimens. Midazolam infusions made up in 5% glucose were more likely to be contaminated than those made up in 0.9% saline. Antibacterial activity was detected in 18 midazolam and one propofol filtrate. Midazolam infusions inhibited the growth of all seven of the S. epidermidis isolates, whereas propofol supported similar rates of multiplication to that obtained with control broth medium. The results of this study imply that contamination of the infusions probably occurred after they were disconnected from the patient. Despite the ability of propofol to support microbial multiplication, we have no evidence to suggest that this is clinically significant when infusions are prepared with conventional aseptic precautions. (Br. J. Anaesth. 1994; 72: 415-417)

KEY WORDS


I.v. fluids may become contaminated by various microorganisms during manufacture, preparation for infusion and infusion itself [1]. Attention has focused recently on the possible clinical significance of bacterial and fungal contamination of i.v. anaesthetic agents given by continuous infusion.

Midazolam and propofol are used widely for sedating critically ill patients. Nursing staff make up solutions of these agents and put them into infusion syringes, where they may remain for many hours at room temperature. Midazolam is a water-soluble benzodiazepine with a pH of 3-4 and is supplied containing antimicrobial preservative agents. It is usually diluted for infusion to critically ill patients in 5% glucose or 0.9% saline, in which case it has the pH of that solution. Propofol is a short-acting induction agent that is insoluble in water (hence it is used emulsified in soya bean extract and glycerol with a pH of 3.5) and contains no preservatives. It is not diluted before use.

Several studies have shown that propofol supports rapid growth of microorganisms inoculated into it in vitro. These microbes include Escherichia coli, Pseudomonas aeruginosa, Enterobacter cloacae, Moraxella osloensis, Acinetobacter sp, Staphylococcus aureus, Staphylococcus epidermidis, Enterococcus faecalis and Candida albicans [2, 3]. However, only one limited microbiological assessment of extrinsic contamination of propofol infusions in syringes has been carried out [3] and no comparisons with solutions of other anaesthetic agents have been reported. Epidemiological studies have implicated extrinsic contamination of propofol infusions in outbreaks of infection with S. aureus, C. albicans and M. osloensis [4]. However, only in the case of the M. osloensis outbreak was the causative agent isolated from a propofol infusion. Aseptic precautions were apparently primitive in all units where the reported outbreaks occurred and no prospective microbiological studies have been reported during in-use conditions.

We have performed, therefore, a study of in-use contamination of midazolam and propofol infusion syringes in our eight-bedded intensive care unit (ICU) and assessed the abilities of midazolam and propofol to support multiplication of the bacteria isolated.

MATERIALS AND METHODS

We planned to collect syringes at the end of 50 midazolam (25 diluted in 5% glucose, 25 in 0.9% saline) and 50 propofol infusions. Syringes and infusion tubing were changed before starting each infusion. Infusions were stopped when about 5 ml of fluid was left in each or when sedation was no longer needed. Syringes were removed from their drivers and then sent complete to the microbiology laboratory. Samples arriving at the laboratory outside normal working hours were refrigerated at 4 °C.

Records were kept of the times (to the nearest 15 min) of making up each solution, of ending the infusion and of processing the solution in the microbiology department.

In the laboratory, the approximate volume of fluid in each syringe was recorded and passed by gentle positive pressure through a sterile 0.45-µm filter (Sartorius SM16517), which was transferred aseptically to a blood agar plate and incubated for 5 days at 37 °C with 5% carbon dioxide added. Twenty control infusions containing saline alone were made up in syringes under aseptic conditions in the laboratory in a laminar flow cabinet. These were also filtered and cultured. Resulting colonies were identified by standard bacteriological methods.

To detect the presence of antibacterial activity (ABA), filtrates from the 100 infusion syringes were placed within wells cut in nutrient agar plates prepared with *S. aureus* (NCTC 6571) and *E. coli* (NCTC 10418). Any zone of inhibition after 48 h incubation at 37 °C in air was taken to indicate a positive result.

To assess the abilities of bacteria grown from the infusates to multiply within midazolam or propofol, standard suspensions of each, together with *S. aureus* (NCTC 6571) as a control, were prepared after overnight growth in brain heart broth (Oxoid, U.K.) by dilution against a turbidometric standard. Each suspension (20 µl) was inoculated to sterile glass bottles containing propofol 5 ml (at supplied concentration), 1% midazolam in 5% glucose or brain heart broth (as control). The test suspensions were incubated for 48 h at 37 °C in air with 5% carbon dioxide added. Samples (200 µl) were obtained at time 0 and after 5, 24 and 48 h, and inoculated neat and after serial 10-fold dilution to blood agar plates which were incubated for 48 h at 37 °C in air with 5% carbon dioxide added. Resulting colonies were counted and the numbers of viable bacteria in the original suspension calculated.

**RESULTS**

There was considerable variation in the running time of infusions sent for culture and a wide range of infusion volumes was received in the laboratory. Table I shows the mean (range) of sample volumes, duration of infusions and time before culture for subgroups defined by culture result and infused agent. The mean volume of suspensions that produced positive culture results was less than that of infusions that were sterile (2.66 vs 7.07 ml). There were no other differences that might have been associated with bias.

Scant growths of *S. epidermidis* were isolated from seven syringes (7%); four midazolam (1, 1, 3 and 9 colony forming units (cfu)) and three propofol (all 1 cfu). All 20 control cultures were negative. Positive infusion fluids produced mean 2.4 colonies, which corresponds to about 5 cfu ml⁻¹ of test fluid. All four isolates from syringes containing midazolam came from infusions made up with 5% glucose.

Eighteen midazolam (12 in glucose and six in saline) and one propofol filtrate showed antibacterial activity.

**DISCUSSION**

We have found that propofol supported multiplication of those few bacteria that were introduced during in-use conditions. However, when anaesthetic agents were loaded into syringes with aseptic precautions used routinely in our ICU, we did not find that contamination was heavy, or that it was more likely with propofol. There is therefore no evidence to support suggestions that propofol in-

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**TABLE I. Mean (range) distribution of sample volumes, duration of infusion and time before culture among sample groups**

<table>
<thead>
<tr>
<th>Samples</th>
<th>Volume (ml)</th>
<th>Infusion duration (h)</th>
<th>Delay before culture (h)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>6.76</td>
<td>(0.05-50)</td>
<td>(0.75-21.25)</td>
<td>100</td>
</tr>
<tr>
<td>Culture positive</td>
<td>2.66</td>
<td>(0.1-4)</td>
<td>(4-11.5)</td>
<td>7</td>
</tr>
<tr>
<td>Culture negative</td>
<td>7.07</td>
<td>(0.05-50)</td>
<td>(0.75-21.25)</td>
<td>93</td>
</tr>
<tr>
<td>Propofol</td>
<td>6.95</td>
<td>(0.1-50)</td>
<td>(1-15)</td>
<td>50</td>
</tr>
<tr>
<td>Midazolam</td>
<td>6.57</td>
<td>(0.05-50)</td>
<td>(0.75-21.25)</td>
<td>50</td>
</tr>
</tbody>
</table>

No differences were seen between the abilities of *S. epidermidis* isolates from midazolam or propofol syringes to multiply in either agent. Figure 1 shows the mean number of cfu (log (cfu)) after 0, 5, 24 and 48 h for the seven isolates and the Oxford staphylococcus in the control (■), midazolam (●) and propofol (■) media. From the 5-h assessment onwards, the numbers of colonies in midazolam were below the sensitivity of the method of detection (< 5 cfu per tube), whereas multiplication occurred nearly as rapidly in propofol as in the control medium.
INFECTION RISK OF I.V. ANAESTHETICS

infusions should be made up under stringent aseptic conditions, such as within a HEPA-filtered, laminar airflow cabinet.

We were unable to determine at what stage contamination with the S. epidermidis isolates occurred and this could have been at any time between making up the infusions in the ICU and filtering in the laboratory. Contamination was not more likely, or heavier, in propofol syringes than in those containing midazolam. The small concentrations of bacteria isolated from both media argue against contamination having occurred at the time during making up of the infusions. However, it is likely that multiplication rates may be smaller at ambient temperatures (20–24 °C) maintained in the ICU during this study compared with the 37 °C we used for the in vitro experiments. In the study of Arduino and colleagues [5], cultures were performed at 30 °C and multiplication of gram-negative bacteria in propofol was more rapid than that of gram-positive isolates, for which 10-fold multiplication took about 10 h. In our study, only gram-positive bacteria were isolated and infusions had been stopped after a mean of 6.86 h (in addition to multiplication during the mean 5.14 h transport and cold storage time). Thus contamination could have occurred during preparation, but only if little subsequent multiplication had occurred. This possibility, however, provides further support for administering propofol according to standard preparation techniques in the ICU.

These results, together with the failure to isolate any bacteria from control infusions made up in the laboratory, suggest that it is more likely that contamination occurred after the infusion ended. In contrast with the small and variable volumes received from the ICU, 50-ml volumes of saline were used for the control solutions, and 5-ml aliquots were filtered. Larger, standardized volumes are much easier to handle aseptically and it is noteworthy that culture positive fluids had a smaller mean volume than sterile fluids (table I).

Midazolam made up with 5% glucose was more likely to be contaminated during in-use conditions than when it was made up with 0.9% saline, but neither solution was able to support bacterial multiplication in vitro and infusions in glucose more commonly showed antibacterial activity.

ACKNOWLEDGEMENT

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REFERENCES