Propofol emulsion and bacterial contamination

Gerard J. McHugh MB ChB DipObst,*
Graham M. Roper MB ChB†

Package insert information provided with propofol advises prompt administration following its drawing-up. This study has examined the delays which occur between drawing-up and administration of propofol in clinical practice and the incidence of bacterial contamination occurring under such conditions. Two hundred and fifty-four clinical uses of propofol were examined. Mean elapsed times (range) from drawing-up to induction were 28.8 min (1–172), and 11.6 min (1–65) from induction to culture inoculation. The delay to induction exceeded ten minutes in 68.5% of propofol uses. Sixteen cultures (6.3%) grew bacteria. Delay to induction was not associated with increased chances of bacterial growth in any of the samples. Increasing delay between induction and culture inoculation was associated with greater odds of bacterial growth, which is consistent with contamination occurring at or after induction. Whilst the manufacturers advise prompt administration, our findings show that when inadvertent delays occur, propofol remains bacteriologically safe to use under standard clinical conditions. Microbial contamination can occur at any stage, thus attention to asepsis remains important throughout the administration period.

Le dépliant inséré dans l'emballage du propofol met en garde contre les délais d'administration une fois le produit soutiré. Cette étude porte sur les délais enregistrés entre l'aspiration du propofol et son administration en clinique, et l'incidence de la contamination bactérienne dans ces conditions. Deux cent cinquante-quatre maniements sont étudiés. Les délais entre le soutirage et l'administration sont de 28,8 min (1–172) et de 11,6 min (1–65) entre l'induction et la culture. Le délai jusqu'à l'induction dépasse dix minutes dans 68,5% des maniements. Des bactéries se développent 16 fois dans les milieux de cultures (6,3%). Le délai jusqu'à l'induction n'est pas associé à une plus grande probabilité de croissance bactérienne, ce qui est cohérent avec la contamination qui survient à l'induction ou après celle-ci. Même si les manufacturiers avertissent d'utiliser le propofol sans délai, notre travail montre que lorsque des délai imprévisibles surviennent, le propofol demeure stérile sous des conditions cliniques standards. La contamination bactérienne étant possible à tous les stages du maniement, il est important de maintenir l'asepsie pendant toute la période d'administration.

Key words
ANAESTHETICS, INTRAVENOUS: propofol;
COMPLICATIONS: bacterial contamination.

From the *Department of Anaesthesia, Memorial Hospital, Omahu Road, Hastings, New Zealand, and the †Department of Anaesthesia, Napier Hospital, Napier Terrace, Napier, New Zealand

Address correspondence to: Dr. G.J. McHugh, Department of Anaesthesia, Wellington Hospital, PO Box 7902, Wellington South, Wellington, New Zealand.

Accepted for publication 8th May, 1995.

Propofol (2,6 diisopropylphenol) has established itself as an intravenous agent for the induction and maintenance of general anaesthesia. The drug is available as an aqueous lipid emulsion (Diprivan®, ICI Pharmaceuticals) containing 1% propofol, 10% soyabean oil, 1.2% egg phosphatide and 2.25% glycerol.

Product information provided with propofol states that the preparation should be "... drawn aseptically into a sterile syringe ... immediately after opening the ampoule" and that it should be injected "... without delay." Despite these recommendations, it is often difficult in clinical practice to ensure that there is no delay between drawing-up and administration. Therefore propofol can often be left standing in a sterile syringe for some period of time prior to administration. For some anaesthetists, this delay is on occassion deliberate with several induction doses prepared in advance for an operating list. The problem of clinical practicalities occasionally resulting in divergence from package insert guidelines has been previously identified,[1] but not quantified.

Emulsions of soyabean oil used clinically support bacterial growth.[2–5] More recently, it has been shown that deliberate contamination of propofol emulsion with common pathogens results in microbial proliferation.[6–9] The product insert states this information as one of the precautions in the use of propofol. Adherence to aseptic technique in aspiration and administration of propofol will eliminate any microbial contamination.[10–12] In clinical practice, accidental contamination has resulted in considerable morbidity.[13,14]

This study sought to quantify the delay between drawing-up and injection of propofol, and to find evidence of microbial contamination of propofol emulsion under standard clinical conditions.

Methods

Approval for the study was gained from the Hawkes' Bay Area Health Board Ethics Committee.

During a two-month period (August, September, 1992) every use of propofol for the induction of general anaesthesia in the operating theatres of the two principal hospitals of the Hawkes' Bay Area Health Board (Memorial Hospital, Hastings and Napier Hospital, Napier) was recorded.

Each time that general anaesthesia was induced with propofol, anaesthetists were asked to record the time that propofol was drawn up, and then to record the time of induction of anaesthesia. They were further requested that as soon as was practicable after induction, two equal sized aliquots (0.5–5.0 ml) of any remaining propofol emulsion be injected into a pair of blood culture bottles (BCB Liquoid; Roche Products Ltd) using a separate sterile needle. The time of this injection was also recorded. The culture bottles were then incubated at 36°C to 37°C for seven days. Any indication of bacterial growth resulted in subculture; all were terminally subcultured. Where bacterial growth occurred, no attempt was made to quantify the magnitude of the initial inoculum. Product sterility prior to ampoule opening has been assumed.

In all other respects, propofol use was according to the individual anaesthetist's usual practice. Specific aspetic measures such as ampoule-neck disinfection or the use of sterile gloves were neither prohibited nor recommended. Any occasions on which no propofol remained after induction were also noted. Similarly the protocol allowed for occasions on which intervening clinical priorities took precedence over completion of study requirements. No record was made of details concerning intravenous access, methods of propofol storage subsequent to induction or the causes of any delays.

Chi-squared and logistic regression were used to analyse the data. A $P < 0.05$ was considered to be significant.

Results

During the study period, there were 301 recorded uses of propofol. Forty-seven were excluded from analysis either for reasons of incompletely recorded information, or where no propofol remained for culture. There were no recorded instances of clinical priorities preventing completion of inoculation. The remaining 254 events were analysed (Hastings: 87, Napier: 167).

There were 16 positive cultures (6.3%) – two from Hastings and the remainder from Napier. This geographical difference was not statistically significant ($\chi^2 = 3.59$, 1 DF, $P = 0.06$). One culture yielded two organisms (a Bacillus sp. and a coagulase negative Staphylococcus) while the remainder each grew a single organism. These were a Diptheroid sp. (6 cultures), coagulase negative Staphylococci (7), and a Micrococcus sp. (2). Indentification of respective individual bacterial species was not pursued.

TABLE I Mean (range) elapsed times (min) for culture inoculation

Interval	*Culture negative (n = 238)*	*Culture positive (n = 16)*	*All cultures (n = 254)*
Drawing-up to induction	29.0 (1–172)	25.7 (1–65)	28.8 (1–172)
Induction to inoculation	11.0 (1–65)	20.9 (4–55)	11.6 (1–65)
Drawing-up to inoculation	40.0 (5–185)	46.6 (15–99)	40.4 (5–185)

TABLE II Time elapsed between drawing up of propofol and induction

Time (min)	*Culture negative (%)*		*Culture positive (%)*		*Total (%)*	
0–10	75 (31.5)		5 (31.25)		80 (31.5)	
11–59	130 (54.6)	(68.5)	10 (62.5)	(68.75)	140 (55.1)	(68.5)
≥60	33 (13.9)		1 (6.25)		34 (13.4)	
	238 (100)		16 (100)		254 (100)	

Table I shows the mean elapsed times for the three intervals: delay to induction; time to inoculation; and the overall time between aspiration and culture inoculation. Table II relates delay in induction to the presence or absence of bacterial growth.

The relationships between the time variables (induction time, inoculation time and time between induction and inoculation) and the outcome (growth of bacteria) were analysed using logistic regression. The regression coefficients estimated by this method can be interpreted as the natural logarithm of the corresponding odds ratio.

There was no association between the delay to induction or the overall delay to inoculation and the odds of bacterial growth. For induction time the odds ratio was 1.00 (95% CI: 0.98–1.02; $\chi^2 = 0.18$, $P = 0.67$). For inoculation time the estimated odds ratio was also 1.00 (95% CI: 0.99–1.02; $\chi^2 = 0.66$, $P = 0.42$).

The time between induction and inoculation was positively associated with the odds of bacterial growth. The estimated odds ratio was 1.06 (95% CI: 1.03–1.10; $\chi^2 = 11.24$, $P < 0.001$).

Discussion

The way in which package insert information influences the use of drugs by anaesthetists has been discussed previously,[1] with specific mention of propofol and its recommended infection control measures. The day-to-day

practicalities of clinical anaesthesia dictate that some delay between the aspiration of propofol and its injection into the patient is unavoidable. However, these delays are variable in both duration and causation. We have observed that, despite the manufacturers' recommendations, in our institutions, delay in the administration of propofol is common. In 68.5% of cases (174/254) there was more than ten minutes delay between aspiration and induction. Whether or not ten minutes exceeds the recommendation of injection "... without delay" is open to some interpretation, but delays of an hour or more (34/254; 13.4%) are not. The longest delay was 172 min. These delays did not appear to cause any demonstrable increase in the likelihood of bacterial contamination. Thus, under standard clinical conditions in our institutions, the passage of time, as one would expect, did not result in any compromise of sterility. Our standard clinical conditions did not include any specific additional aseptic measures applied to the preparation and/or use of propofol. This leads one to surmise that with appropriate technique, induction doses of propofol prepared in advance are no more likely to be implicated in clinically relevant infective sequelae than propofol which is aspirated immediately before injection. Whilst some of the delays encountered in our hospitals were undoubtedly deliberate advance preparation, such a practice is difficult to endorse given the manufacturers' recommendations. The reasons for each of the observed delays were not recorded, and so we cannot comment on them further. We conclude that should inadvertent or unavoidable delays occur, carefully aspirated propofol remains bacteriologically safe to use. We are unable to specify a safe limit to these delays. Experimental findings suggest six hours,[9] but it is difficult to imagine circumstances where such a delay was either inadvertent or unavoidable.

Following induction, any propofol remaining in the syringe can become contaminated from contact with whatever type of injection portal is being used,[15,16] and this risk will vary according to whether or not the *iv* access was newly established solely for the induction of anaesthesia. We did not collect this information. The association of a positive culture with increasing time from induction to inoculation is consistent with contamination occurring at or after induction. Culture inoculation prior to, or directly after induction may have allowed us to observe more accurately the rate of contamination at induction, but we wished to interfere with standard clinical practice as little as possible. Thus we chose the method described. In so-doing we have identified an important association between culture-positivity and time elapsed after induction. This has implications for the subsequent administration of residual propofol emulsion during the course of the anaesthetic. If the propofol has become contaminated, then further bolusing from the induction syringe exposes the patient to iatrogenic bacteraemia. The method of storage of any propofol remaining after induction may also contribute to potential microbe introduction. We are unable to speculate upon the possible role of differing types of intravenous access or differing ways of storing propofol subsequent to induction. However, the bacteria that were isolated support the premise that skin contact was the cause of the contamination. Whilst the inoculating samples will have differed in volume, we consider that they have equivalence for our purposes. We sought only to identify the presence or absence of contaminating microbes without quantification. The culture media used are sufficiently sensitive to allow detection of a small bacterial inoculum. We acknowledge that this plus a seven day incubation may overstate the risk, but at the same time it minimises the chances of not detecting contamination, even if the volume of propofol available for inoculation was only 1 ml (i.e., 2 × 0.5 ml). We cannot say if aliquots associated with longer delays between induction and inoculation were of greater or lesser volume than those associated with shorter delays.

When bacterial contamination does occur, the potential for severe morbidity (e.g., pyrexia, surgical wound infection, septic shock, respiratory distress syndrome, multiorgan failure) associated with the use of propofol tainted in such a way is clear.[13,14] The paucity of reported cases of propofol-associated sepsis may reflect difficulty in identifying propofol as the cause of the sepsis. Alternatively, one might consider that it highlights the low risk of developing a systemic infection following the injection of bacterially contaminated propofol. This issue remains unresolved. We are unaware of any septic events related to propofol use during the study period. In light of the 6.3% incidence of contamination, participants in our study have been circularised, restating the manufacturer's recommendations for use, and re-emphasising the importance of careful technique.

In conclusion, we have found that delays in administration of propofol are common in our institutions. Further, we conclude that under standard clinical conditions, such delays do not appear to result in an increase in the likelihood of bacterial contamination. Additionally, care must be taken to avoid contamination during and after induction if further portions of the syringe contents are to be administered safely.

Acknowledgments

Provision of funding by the Hawkes' Bay Medical Research Foundation is gratefully acknowledged. Thanks to Mr. I. Christie, Charge Microbiology Technician, Hastings. Statistical analysis kindly provided by Dr. R. Fright and Mr. P. Graham, Christchurch School of Medicine.

References

1 *White PF, Watcha MF.* The practice of anesthesiology and the package insert: decision-making regarding drug use in anesthesiology. Anesth Analg 1993; 76: 928–30.

2 *Deitel M, Kaminsky VM, Fuska M.* Growth of common bacteria and Candida albicans in 10% soybean oil emulsion. Can J Surg 1975; 18: 531–5.

3 *Deitel M, Fuska M, Kaminsky VM, Vasic V.* Growth of micro-organisms in soybean oil emulsion and clinical implications. Int Surg 1979; 64: 27–32.

4 *Keammerer D, Mayhall CG, Hall GO, Pesko LJ, Thomas RB.* Microbial growth patterns in intravenous fat emulsions. Am J Hosp Pharm 1983; 40: 1650–3.

5 *Garcia-Cabellero J, Herruzo-Cabrera H, Vera-Cortes ML, et al.* The growth of micro-organisms in intravenous fluids. J Hosp Infect 1985; 6: 154–7.

6 *Arduino MJ, Bland LA, McAlister SK, et al.* Microbial growth and endotoxin production in the intravenous anesthetic propofol. Infect Control Hosp Epidemiol 1991; 12: 535–9.

7 *Tessler M, Dascal A, Gioseffini S, Miller M, Mendelson J.* Growth curves of Staphylococcus aureus, Candida albicans, and Moraxella osloensis in propofol and other media. Can J Anaesth 1992; 39: 509–11.

8 *Berry CB, Gillespie T, Hood J, Scott NB.* Growth of micro-organisms in solutions of intravenous anaesthetic agents. Anaesthesia 1993; 48: 30–2.

9 *Sosis MB, Braverman B.* Growth of Staphylococcus aureus in four intravenous anesthetics. Anesth Analg 1993; 77: 766–8.

10 *Downs GJ, Haley PR, Parent JB.* Propofol: can a single ampule be used for multiple patients? (Letter). Anesthesiology 1991; 74: 1156.

11 *Goodale DB.* Propofol: can a single ampule be used for multiple patients? (Letter). Anesthesiology 1991; 74: 1156–7.

12 *McLeod GA, Pace N, Inglis MD.* Bacterial growth in propofol (Letter). Br J Anaesth 1991; 67: 665–6.

13 *Center for Disease Control.* Postsurgical infections associated with extrinsically contaminated intravenous anesthetic agent – California, Illinois, Maine, and Michigan. MMWR Morb Mortal Wkly Rep 1990; 39: 426–7,433.

14 *Veber B, Gachot B, Bedos JP, Wolff M.* Severe sepsis after intravenous injection of contaminated propofol. (Letter). Anesthesiology 1994; 80: 712.

15 *Oberhammer EP.* Contamination of injection ports on intravenous cannula (Letter). Lancet 1980; 2: 1027–8.

16 *Cheesborough JS, Finch R.* Side-ports – an infection hazard? British Journal of Parenteral Therapy 1984; 155–7.