References

1. Deschamps A, Lambert J, Couture P, Rochon A, Lebon JS, Ayoub C, Cogan J, Denault A: Reversal of decreases in cerebral saturation in high-risk cardiac surgery. J Cardiothorac Vasc Anesth 2013; 27:1260–6
2. Deschamps A, Hall R, Grocott H, Mazer CD, Choi PT, Turgeon AF, de Medicis E, Bussières JS, Hudson C, Syed S, Seal D, Herd S, Lambert J, Denault A, for the Canadian Perioperative Anesthesia Clinical Trials Group: Cerebral oximetry monitoring to maintain normal cerebral oxygen saturation during high-risk cardiac surgery: A randomized controlled feasibility trial. Anesthesiology 2016; 124:826–36
3. Davie SN, Grocott HP: Impact of extracranial contamination on regional cerebral oxygen saturation: A comparison of three cerebral oximetry technologies. Anesthesiology 2012; 116:834–40
4. Murkin JM, Adams SJ, Novick RJ, Quantz M, Bainbridge D, Iglesias I, Cleland A, Schaefer B, Irwin B, Fox S: Monitoring brain oxygen saturation during coronary bypass surgery: A randomized, prospective study. Anesth Analg 2007; 104:51–8

(Accepted for publication June 21, 2016.)

Underestimated and Modifiable? From Intraoperative Drug Application to Postoperative Infections

To the Editor:

With great interest, we followed the recent publication of Gargiulo *et al.*[1] reporting on perioperative microbiological contamination during drug application. Bacterial contaminants were detected in 6.3% of patients and in 2.4% of sampled syringes. These numbers are alarming, suggesting a potential role of intraoperative management in postoperative infections. The study inherits an interesting design including close-to-real-life conditions. However, there remains some source of bias that is not completely addressable in this setting, and the number of contaminations may even be higher. Especially high contamination rates of propofol are a known problem related to its formulation; consequently, propofol syringes should be prepared directly before application and used propofol syringes should be disposed immediately. Although even the laboratory environment of drug preparation may inherit a, very low, bacterial contamination risk, syringe handling is a key element in this context.[2] Compared to the study by Gargiulo *et al.*,[1] other authors observed higher contamination rates of syringes,[2–4] and as the study was performed unblinded, there is a high probability of a relevant Hawthorne effect. Additionally, some aspects are not completely reported in study description:

- Was there any report or policy on wipe disinfection of glass ampoules or disinfection of the injection port?
- How long in advance were drugs prepared before application to patients?
- How long did it take from sampling to analyzing syringes and filters?

These factors may explain at least some of the observed variability between participating anesthesiologists and are modifiable factors during clinical care.

Finally, we completely agree that microbacterial contamination in the operating room is of high relevance and warrants further investigation. However, the association between contaminated syringes and injection ports and subsequent infection may be difficult to study, *e.g.*, because of infections associated with implants that may be diagnosed only with a delay of months. Immunocompromised patients, those with prosthetic valves,[4] or preterm newborns[5] may be of specifically high risk in this context. Without doubt, measures to increase awareness of aseptic techniques in conjunction with antibiotic stewardship initiatives may reduce the burden of perioperative infections.[6]

Competing Interests

Dr. Spies received funding from Merck Sharp and Dome GmbH (Haar, Bavaria, Germany), Astra Zeneca (Wedel, Schleswig-Holstein, Germany), Bristol-Myers Squibb GmbH (Munich, Bavaria, Germany), Pfizer (Berlin, Berlin, Germany), and Fresenius Kabi (Bad Homburg, Hessen, Germany). The other authors declare no competing interests.

Sascha Tafelski, M.D., Brar Piening, M.D., Claudia Spies, M.D., Irit Nachtigall, M.D. Hospital Waldfriede, Berlin, Germany (I.N.). i.nachtigall@waldfriede.de

References

1. Gargiulo DA, Mitchell SJ, Sheridan J, Short TG, Swift S, Torrie J, Webster CS, Merry AF: Microbiological contamination of drugs during their administration for anesthesia in the operating room. Anesthesiology 2016; 124:785–94
2. van Grafhorst JP, Foudraine NA, Nooteboom F, Crombach WH, Oldenhof NJ, van Doorne H: Unexpected high risk of contamination with staphylococci species attributable to standard preparation of syringes for continuous intravenous drug administration in a simulation model in intensive care units. Crit Care Med 2002; 30:833–6
3. Stucki C, Sautter AM, Favet J, Bonnabry P: Microbial contamination of syringes during preparation: The direct influence of environmental cleanliness and risk manipulations on end-product quality. Am J Health Syst Pharm 2009; 66:2032–6
4. Taylor M, Bourke J, Anderson M, Davey R, Kelly AM, Guthrie B: Titrated intravenous opioids from the same syringe: An infection risk? J Accid Emerg Med 1997; 14:33–5
5. Leistner R, Thürnagel S, Schwab F, Piening B, Gastmeier P, Geffers C: The impact of staffing on central venous catheter-associated bloodstream infections in preterm neonates—Results of nation-wide cohort study in Germany. Antimicrob Resist Infect Control 2013; 2:11
6. Nachtigall I, Tafelski S, Deja M, Halle E, Grebe MC, Tamarkin A, Rothbart A, Uhrig A, Meyer E, Musial-Bright L, Wernecke KD, Spies C: Long-term effect of computer-assisted decision support for antibiotic treatment in critically ill patients: A prospective 'before/after' cohort study. BMJ Open 2014; 4:e005370

(Accepted for publication June 21, 2016.)

In Reply:

We thank Tafelski *et al.* for making some interesting points about our recent study[1] and asking for clarification of some issues.

We agree that for various reasons, our results may be an underestimate, and we discussed these in some length in our article.

With respect to the Hawthorne effect, we agree that our findings may reflect an underestimation of the actual rate of syringe contamination. Indeed, in the article, we indicated that "anesthesiologists were encouraged to behave 'normally' in respect of their aseptic practice," but that "the open-label nature of the study may have influenced them to be more fastidious."

We also agree that the exclusion of propofol from drugs injected through the filter unit in our study may have contributed to an underestimation of the rate at which microorganisms were injected into patients, and this too was mentioned. On the other hand, the used propofol syringes were included in the analysis of syringe contamination.

Our institution has no formal policy concerning disinfection of vial septa with alcohol in the context of anesthetic practice, although guidelines from the Australian and New Zealand College of Anaesthetists[2] are considered applicable, and these guidelines recommend this practice. We made no attempt to evaluate compliance with any aspect of the safe injection of intravenous medications in this study, but in a previous study[3] in a highly realistic simulated anesthetic environment, none of our participants wiped the vial septa.

We did not measure the time taken between drug preparation and injection into the intravenous lines, and so cannot comment on this. However, we believe that these times were reflective of the normal clinical practice of the participants.

The mean (range) time taken from collecting to analyzing our syringes was 3.6 h (0.75 to 22.5 h). We could find no apparent relationship between length of time and the number of microorganisms found.

We appreciate this interest in our work because we believe that more reflection and research is warranted to inform effective initiatives to improve this aspect of patient care in anesthesia.

Competing Interests

The authors declare no competing interests.

Derryn A. Gargiulo, M.Pharm.Clin., Reg.Pharm.N.Z., Simon J. Mitchell, Ph.D., F.A.N.Z.C.A., Janie Sheridan, Ph.D., F.R.Pharm.S., Timothy G. Short, M.B.Ch.B., M.D., F.A.N.Z.C.A., Simon Swift, Ph.D., Jane Torrie, M.B.Ch.B., F.A.N.Z.C.A., Craig S. Webster, Ph.D., Alan F. Merry, M.B.Ch.B., F.F.P.M.A.N.Z.C.A., F.R.C.A., F.A.N.Z.C.A. University of Auckland, Auckland City Hospital, Auckland, New Zealand (A.F.M.). a.merry@auckland.ac.nz

References

1. Gargiulo DA, Mitchell SJ, Sheridan J, Short TG, Swift S, Torrie J, Webster CS, Merry AF: Microbiological contamination of drugs during their administration for anesthesia in the operating room. Anesthesiology 2016; 124:785–94
2. Australian and New Zealand College of Anaesthetists: PS28 Guidelines on Infection Control in Anaesthesia 2015. Available at: http://www.anzca.edu.au/resources/professional-documents/pdfs/ps28-2015-guidelines-on-infection-control-in-anaesthesia.pdf. Accessed August, 2014
3. Gargiulo DA, Sheridan J, Webster CS, Swift S, Torrie J, Weller J, Henderson K, Hannam J, Merry AF: Anaesthetic drug administration as a potential contributor to healthcare-associated infections: A prospective simulation-based evaluation of aseptic techniques in the administration of anaesthetic drugs. BMJ Qual Saf 2012; 21:826–34

(Accepted for publication June 21, 2016.)

Relevance of Clinical Relevance

To the Editor:

We are concerned by an article published in the April 2016 issue of Anesthesiology by Han *et al.*[1] entitled "Propofol-induced Inhibition of Catecholamine Release Is Reversed by Maintaining Calcium Influx." The authors addressed the molecular mechanisms underlying propofol-induced hypotension and describe a number of proposed molecular mechanisms thought to underlie this clinical effect. They focus their study on one such mechanism: the effect of propofol on catecholamine release from rat PC12 neuroendocrine cells and isolated cortical nerve terminals. In contrast to a number of previous studies showing that propofol inhibits catecholamine release,[2,3] the authors report that when intracellular calcium concentration was maintained constant, catecholamine release was enhanced by propofol. Our principal concern is that enhanced catechoamine release was observed only at propofol concentrations greater than 10 μM, a value that the authors suggest represents a "*clinically relevant concentration.*"

The total plasma concentration of propofol required to produce loss of consciousness in 50% of subjects is 4.4 μg/ml (25 μM), while the concentration for preventing response to intubation in 50% of subjects is 17 μg/ml (98 μM).[4] Importantly, studies of the total compared to free propofol concentrations in human blood show that more than 97% of total propofol is bound to blood constituents, largely to plasma proteins, and thus is pharmacologically sequestered.[5,6] While in principle a continuous propofol infusion at a standard rate of 100 μg kg^{-1} min^{-1} could produce a total blood propofol concentration of approximately 10 μM, the combined effects of metabolism, redistribution, and binding to plasma proteins and erythrocytes significantly reduce free blood propofol concentrations *in vivo*. The clinically relevant free propofol concentration is in the submicromolar range, with the most commonly cited value of 0.4 μM based on a widely cited and influential review by Franks and Lieb.[7] They and others[8] have called attention to the critical importance of using free anesthetic concentrations, which more accurately reflect effect-site concentration, in designing and interpreting experiments performed *in vitro*.

It is unlikely that a free blood propofol concentration of 10 to 100 μM will ever be encountered in clinical practice, an important detail when weighing the clinical applicability and relevance of an *ex vivo* study. The pharmacology of propofol, and other common anesthetic agents, has been