

Chlorhexidine anaphylaxis: Again and again

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This issue of the journal contains two reports of clusters of perioperative allergic reactions to chlorhexidine,^{1,2} and follows a case report two issues prior.³ This cluster of cases, and the recent 6th National Audit Project on perioperative anaphylaxis report,⁴ which identified chlorhexidine as the third most common cause of perioperative anaphylaxis in the UK, may require us to re-examine the risk–benefit profile of this antiseptic, and particularly the manner in which this pharmaceutical has become so ubiquitous in anaesthetic practice.

The authors of the two reports in this issue summarise the evidence for the use of chlorhexidine concisely. The importance of preventing healthcare-associated infections is acknowledged, but it is cogently argued that chlorhexidine should not be used prior to short-term intravenous (IV) cannulation, or for disinfecting needleless connector access points, or in impregnated central venous catheters used for routine cardiac surgery where the expected dwell time is less than seven days.

There will be barriers to anaesthetists following their recommendations. Stocking two alternative products is more complicated than one, and many environments in which anaesthesia is conducted have only chlorhexidine-containing wipes available for the process of IV cannulation. The managers of these environments do so not without justification, as the National Health and Medical Research Council, Australian Commission on Safety and Quality in Health Care (ACSQHC) stated in 2010 that prior to insertion of an intravascular device, skin preparation with ‘at least 0.5% chlorhexidine (is) recommended for procedures penetrating skin’.⁵

This ACSQHC recommendation was challenged by representatives of the Australian and New Zealand Anaesthetic Allergy Group, and submissions made by the Australian and New Zealand College of Anaesthetists in 2013 argued that ‘exposure to chlorhexidine for day-stay and other short-term peripheral cannulation is currently not justifiable’. An update of the 2010 guidelines was due at the end of 2018, and a Technical Report ‘What is the impact of chlorhexidine

use on the incidence of anaphylaxis?’ was commissioned by the National Health and Medical Research Council in 2017 to inform this update.^{5,6} Surprisingly, they concluded that ‘research in the area of chlorhexidine-related anaphylaxis (is) quite limited’.

Research is a process of systematic investigation in order to establish the truth. It may be true that publication of manuscripts related to this topic is unrepresentative, but that is another matter entirely. Publication of research depends on the interest of the audience, but what if the topic is uncontroversial? Case reports of chlorhexidine allergy exist from over half a century ago and warnings about its use on mucous membranes by Japanese authorities were made in the 1980s. Impregnated chlorhexidine central venous catheters (CVCs) were withdrawn from that country 20 years ago, followed by a US Food and Drug Administration (FDA) Public Health Notice warning in 1998,⁷ and belatedly by the Australian Therapeutic Goods Administration (TGA) in 2012.⁸ The routine use of chlorhexidine in lignocaine gel as a lubricant for urological procedures decreased significantly after a 2009 TGA report described 19 cases over 19 years⁹ (although two cases were reported in this journal 15 years prior¹⁰), and last year the US FDA issued a safety communication in response to the increasing incidence of serious anaphylactic reactions with topical use,¹¹ years after the New Zealand Medicines and Medical Devices Safety Authority reported a similar remarkable rise in the rate of reported reactions.¹² Once a phenomenon is described and accepted, the publication of subsequent cases is unnecessary unless they demonstrate unusual characteristics. Concerned clinicians have continued to conduct research, discuss and form expert opinions, make submissions and press releases to the media and

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educate fellow practitioners, but not necessarily in print. A comparable failure has been the inability of the TGA to act when counselled about the risks of pholcodine sales in Australia. Perhaps the problem is that government organisations just do not listen?

Central-line-associated bloodstream infections (CLABSI) are an important clinical problem in intensive care units, although the cost-effectiveness of chlorhexidine-impregnated catheters in preventing these is highly uncertain.¹³ Nonetheless, an economic pressure now exists to use them. If a clinician chooses a 20 cm 5-lumen CVC for patients undergoing cardiac surgery, they may choose either a chlorhexidine-sulfadiazine impregnated catheter (Arrowg+ard CS-25855, Teleflex, Morrisville, NC, USA) or an uncoated catheter (Arrow CS-15955). The ability to freely make this choice is limited in Australia by the unusual circumstances where the uncoated catheter will incur an additional AUD\$122 cost to the hospital compared with the impregnated catheter, as the former is fully rebatable, while the latter attracts no health fund rebate. If a clinician chooses a 16 cm 5-lumen catheter, the manufacturer does not even produce an uncoated alternative, although it is the user responsible for creating demand. It is interesting to note that recent simulation-based laboratory research demonstrated that these catheters lose their antimicrobial function after 48 hours of simulated use due to loss of the antimicrobial coating,¹⁴ calling into question their efficacy for patients requiring longer-term central venous access.

Anaphylaxis is one of the most common causes of unanticipated sudden catastrophe during anaesthesia and although it is always a surprise when it does occur, the current burden of disease can be considered to some extent to be both predictable and reducible. Rational anaesthetists must make choices based on the weighted averages of the utilities of possible outcomes to maximise expected utility. They should consider their patients' risk of CLABSI, and that the Cochrane Collaboration's 2016 update of their systematic review found that antimicrobial impregnation, coating or bonding of CVCs does not reduce clinically diagnosed sepsis or mortality.¹⁵ They should consider the likelihood of their patient requiring a CVC for more than seven days, but also that the Arrowg+ard chlorhexidine CVC may lose its antimicrobial function after only two. Finally, they must consider the rare risk of anaphylaxis and the likelihood of the particular patient suffering harm from it, which depends on their physiological reserve. For most patients the expected utility of placing a chlorhexidine-impregnated CVC would be low, but the hazard is rarely converted to harm because anaphylaxis is rare. And yet it is not logical that these choices would be

criticised only if bad fortune results in harm, because the unnecessary hazard is there in every instance. The law of large numbers means that over a long enough period the consequences of these choices will approach expected values. This is easier to appreciate in a population of anaesthetists. For example, anaesthetists in Western Australia currently report a total of about 50 cases of intraoperative anaphylaxis a year (West Australian Anaesthetic Allergy Service, unpublished observations). If they were to immediately change from using rocuronium to using vecuronium, sugammadex to neostigmine, and chlorhexidine to isopropyl alcohol or povidone iodine, this annual number with its substantial morbidity and potential mortality would most likely be halved. The same would be likely for any group of anaesthetists. Would this produce the maximal expected utility?

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