

to have endometrial ablation using a thermal balloon technique (Thermachoice II®, Gynecare Ethicon, Johnson and Johnson, New Brunswick, NJ, USA), which was performed as per the manufacturer's specifications under general anaesthesia, were recruited into the study. Ethical committee approval was obtained prior to the study.

The control substance was chosen to be similar in all respects to the intervention substance, to limit bias. The study group received 20 ml of 2% lignocaine gel, whereas the control group received 20 ml of inert KY gel. Gel was injected per vagina into the uterine cavity after the completion of thermal ablation.

All patients received a standard postoperative analgesic regimen consisting of intravenous paracetamol 1 g, rectal diclofenac 100 mg and intravenous fentanyl in increments of 25 µg as required. Pain was assessed by means of two validated pain assessment tools (visual analogue and numerical rating scales) at 15 minutes, after regaining consciousness in the recovery ward and then at one, two and four hours.

Of the 80 subjects recruited, 73 (91%) completed the study, with 36 in the study and 37 in the control group respectively.

Results showed no evidence of pain relief from lignocaine at any assessment time except at 15 minutes post surgery. We concluded that the intrauterine instillation of lignocaine gel after endometrial ablation was not effective in providing clinically important postoperative analgesia.

Any further investigation of this method would need to focus on different approaches, such as the use of a cervical clip or plug to prevent gel leaking out per vagina or intrauterine balloon inflation after the instillation of lignocaine gel, to facilitate uniform dispersion into the endometrial tissue.

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Sugammadex and hypersensitivity

Three articles on sugammadex and anaphylaxis by Savic et al¹, Jeyadoss et al² and Sadleir et al³ in the January 2014 edition of the Journal reflect the ongoing interest in the involvement of this chemically modified cyclodextrin in inducing hypersensitivity reactions—a property that has delayed the approval of sugammadex by the US Food and Drug Administration. In the presentations and interpretations of the findings on four more cases of 'anaphylaxis' to the agent, some aspects of, and omissions in, the reports warrant examination and comment. Three issues in particular deserve scrutiny: the appropriateness of the terminology employed, particularly the term 'anaphylaxis'; the inadequacies and deficiencies of the diagnostic aids currently available and the resultant limitations imposed on reaching correct diagnostic conclusions; and the inadequacy of the literature coverage, with its consequent lack of relevant background for the reader.

'Allergy' and 'hypersensitivity' are much misused terms with no universally accepted definitions within and between disciplines⁴. True allergic, immune-mediated reactions comprise four different hypersensitivity states, types I to IV, in a classification based on reaction latency, humoral or cellular immune involvement, complement involvement and pathophysiological consequences for the host. The word hypersensitivity is often mistakenly applied to reactions that have no immune basis or to cases where the underlying mechanism has not been identified. The terms 'anaphylaxis' and 'anaphylactoid' are used for severe, immediate and often life-threatening reactions that show features of a type I IgE antibody-mediated hypersensitivity. Mechanistically, anaphylactic reactions are true type I hypersensitivities mediated by IgE antibodies, while no immune mechanism can be demonstrated for anaphylactoid responses. Example of the latter reactions include drugs that directly provoke mast cell degranulation, such as opioids, vancomycin and contrast media⁴. In both the Jeyadoss et al² and Sadleir et al³ reports, each of the observed reactions are described as "anaphylaxis". These diagnoses demand close examination of any supporting diagnostic tests employed to supplement the clinical pictures, treatments and outcomes.

In their editorial, Savic et al¹ raise important considerations relevant to the diagnoses, viz the question of non-irritant skin test concentrations of the drug and the possibility of false positive test results. Before proceeding with skin testing with any drug, optimal test concentrations for the drug must

be determined, and this includes establishing non-irritating test concentrations that have the highest possible specificity, and thus high predictive value⁵. In practice, this is the highest concentration that produces no skin reaction in previously non-exposed subjects and in non-allergic patients who have been exposed to the drug but which will produce a positive reaction in patients allergic to the drug⁴. Even with a positive skin test to a non-irritating drug, the test accuracy, i.e. the sensitivity and specificity of the test, remains unknown. Test accuracy cannot be obtained without positive and negative test results and these in turn require provocation testing⁶, a difficult (if not ethically unjustifiable) procedure for many drugs used perioperatively since it involves risk, is often not standardised and is time-consuming^{4,6}. In practice, efforts are often made to determine the non-irritant test concentration with the highest test specificity, usually $\geq 95\%$. In both case reports, Bridion® 100 mg/ml was used to prepare skin test dilutions, but, apart from the claim that sugammadex solutions at 1:77 and 1:770 were previously found not to cause skin irritation or false positive reactions in 11 volunteers⁷, a more thorough skin test verification study is needed to demonstrate that the dilutions used are non-irritant and estimates of the test's sensitivity and specificity are required. In short, the sugammadex skin test remains unvalidated and there is no certainty that the concentrations currently used for skin testing, especially the 1:100 dilution, are not irritant in at least some subjects. Savic et al¹ also point out that the British Society for Allergy and Clinical Immunology Guidelines recommend the employment of skin-prick tests (SPT) prior to intradermal testing (IDT) and, likewise, the French Society for Anaesthesia and Intensive Care recommend that the SPT be used to guide the choice of the first concentration selected for IDT injection. Although the IDT is more sensitive than the SPT, it also produces more false positives; that is, it is less specific but the tendency of the SPT to produce more false negatives may be more than compensated for by its superior specificity and consequent better correlation with specific drug-induced clinical hypersensitivity. In a comparison of both tests in the diagnosis of neuromuscular blocking drug allergic sensitivity, employment of both procedures produced clearer diagnostic outcomes and it was suggested that both should be used when doubt exists over the result of either test⁸.

With the aforementioned comments in mind, it is difficult to be confident of an unequivocal diagnosis of anaphylaxis in all four cases reported, although reactions may well have been true type I

hypersensitivity responses in the Adelaide case² and patient 1 in the Sadleir et al³ study where positive serum tryptase levels were detected. The four cases are similar to other reports where, in every case, the absence of confirmatory diagnostic tests to supplement the clinical findings makes it difficult to be confident of a true type I IgE antibody-mediated anaphylactic reaction to sugammadex. In addition to a meticulously gathered and recorded history of a reaction to sugammadex and expert clinical assessment of the signs and symptoms, the following 'best combination' of investigative procedures is suggested:

1. the tryptase test (preferably mature tryptase) performed on the patient's preoperative serum sample and at least one or two samples after the onset of symptoms (e.g. at 30 minutes up to four to six hours)
2. employment of validated sugammadex skin tests—percutaneous, intradermal or both
3. development and application of a specific immunoassay for the detection of sugammadex-reactive IgE antibodies. Such an assay should be used to demonstrate specific serum antibodies in both direct binding and dose-dependent inhibition examinations⁴. Given the carbohydrate nature of sugammadex with its 16 free hydroxyls attached at the secondary rim of the cyclodextrin and the eight terminal carboxylate groups on the side-chains attached at C-6 at the primary rim⁹, preparation of a suitable drug-solid phase⁴ should not be difficult. As a further diagnostic aid, research should also be directed at the development of a basophil activation test.

There are now at least 20 cases of suspected hypersensitivity to sugammadex (for references contact the author at babaldo@iinet.net.au). In every case study, the same absence of definitive proof of an immune-mediated basis for the observed reaction prevents an unequivocal conclusion that the reaction is truly allergic; that is, one stops short of designating the responses 'hypersensitivities' or 'anaphylactic'. A number of the reactions (e.g. cases two and three in the Perth report³) may well be anaphylactoid responses raising the possibility of a type B, non-immune, pseudoallergic reaction. Although there is a dearth of information on the histamine (or other mediator) releasing effects of sugammadex, the European Medicines Agency lists flushing, urticaria, erythematous rash, hypotension, tachycardia and bronchospasm amongst the drug's undesirable effects.

Space constraints may have prevented all three papers conveying the full extent of the accumulating

number of reports of a suspicion of 'hypersensitivity' reactions to sugammadex. Likewise, Savic et al¹ quote a solitary case where sugammadex dramatically reversed an ongoing and difficult to manage anaphylactic reaction to rocuronium. As there are now 12 such reports (for references contact the author) from seven different countries, this again raises the intriguing and difficult question of a possible explanation; that is, what could be the mechanism(s) of such a seemingly unlikely effect?

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In response to Baldo

We read the comments by Baldo on our case of sugammadex anaphylaxis with interest. We appreciate his thorough and concise overview of a state-of-the-art approach in diagnosing sugammadex anaphylaxis. We would like to reiterate that the diagnosis of anaphylaxis is primarily based on history and clinical presentation¹. Additional diagnostic tests such as elevated mast cell tryptase, skin allergy testing and immune assay may be supportive in establishing the diagnosis¹⁻³. We agree with Baldo regarding the current deficiencies, particularly relating to the precision, accuracy and validity of diagnostic tools in detecting sugammadex anaphylaxis. These are not

new and apply to most diagnostic tools in clinical practice. Therefore, good clinical judgement is imperative in interpreting the available investigations in the context of the clinical history.

In our case⁴, there was a clear clinical manifestation of severe circulatory collapse immediately after administration of sugammadex. Anaphylaxis was supported by a marked elevation of mast cell tryptase one hour post event that had resolved 24 hours later. Further confirmation was obtained by a positive intradermal allergy test to sugammadex even at a 1 in 1000 dilution². Based on the current best clinical practice^{2,3}, all these put together would confirm a type I immunoglobulin E (IgE)-mediated reaction to sugammadex beyond all reasonable doubts. Provocative testing on the above background would be unjustifiable in our opinion and clearly puts the patient at risk. The specific immunoassay for the detection of sugammadex-reactive IgE antibodies suggested by Baldo may further add to the diagnosis. However, at the time of this case, such specific immune assay to sugammadex was neither available in Australia nor felt required to establish the diagnosis.

While we cannot confidently exclude a non-IgE mediated allergic reaction in the absence of immune assay, the temporal relationship, markedly elevated tryptase level and positive skin test suggest an anaphylactic rather than an anaphylactoid reaction^{2,3}. From a clinical perspective, regardless of the type of reaction, these are life-threatening events which require similar management with the same precipitating agent. Hence, it still highlights the main message of our case report: that administration of sugammadex is not without risks.

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