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Editorial

Anaphylaxis to sugammadex

Sugammadex is a synthetic, modified gamma-cyclodextrin which binds specifically to non-depolarising neuromuscular blocking agents (affinity for rocuronium > vecuronium > pancuronium). It encapsulates the neuromuscular blocking agent molecule on a 1:1 basis, and causes a concentration gradient down which remaining neuromuscular blocking agent moves away from the neuromuscular junction, resulting in rapid reversal of neuromuscular block[1]. Cyclodextrins are used widely in drug carriage systems[2]; typically the drug-cyclodextrin complex is formed outside the body and after administration dissociates, releasing the drug. Episodes of allergic reaction to the carrier molecule appear to be rare.

In this issue, two articles[3,4] report a total of four cases of anaphylaxis ascribed to sugammadex. Several cases of presumed sugammadex anaphylaxis have been reported previously, predominantly from Japan[5–9]. The new cases from Australia highlight not only the potential for serious adverse effects when using sugammadex but also some of the difficulties in establishing a diagnosis of anaphylaxis to sugammadex. Interesting questions are raised about the mechanism of sugammadex-mediated anaphylaxis, the immunological consequences of the interaction between rocuronium and sugammadex, and the potential implications for expanding the therapeutic use of cyclodextrins.

The diagnosis of anaphylaxis associated with any anaesthetic agent requires demonstration of a temporal relationship between drug administration and the signs and symptoms of anaphylaxis, objective evidence of mast cell degranulation, and evidence of IgE-mediated mast cell activation where IgE-mediated anaphylaxis is suspected[10,11]. For reactions occurring during anaesthesia, the patient clearly cannot report symptoms, while urticaria and angioedema, which are usually the most obvious signs of anaphylaxis, are frequently absent even in the more severe forms of reaction or obscured by surgical drapes. Unexplained cardiovascular collapse and severe respiratory compromise are often the only features reported in anaphylaxis associated with general anaesthesia.

Other factors of interest in the history include the preoperative use of angiotensin converting enzyme inhibitors and perioperative use of non-steroidal anti-inflammatory drugs, both of which act as mast cell destabilisers[12] and can provoke non-specific mast cell degranulation, while the former also exacerbates the hypotensive effects of general anaesthesia. Evidence of use of a sensitising agent should be sought when considering IgE-mediated anaphylaxis.

A rise in serum mast cell tryptase concentration shortly after the event is strongly indicative of systemic mast cell degranulation, although baseline levels are needed to exclude causes of persistently elevated mast cell tryptase such as mastocytosis. Without any gold standard for the diagnosis of anaphylaxis, it is difficult to determine the sensitivity of an increase in mast cell tryptase for the detection of anaesthetic anaphylaxis, although data from a venom anaphylaxis trial found a sensitivity of only 36% using a concentration of $>12.0\,\mu g/l$ as the upper limit of normal[13]. The rationale for skin tests (intradermal or skin prick tests) is that a positive test confirms IgE-mediated anaphylaxis. A negative test may reflect a lack of sensitivity of the test, a non-IgE–mediated anaphylaxis or an erroneous clinical diagnosis of anaphylaxis. For many anaesthetic drugs, including sugammadex, the non-irritant concentration of the drug for skin testing is not known, raising the possibility of false positive test results. The sensitivity and specificity of such tests remains to be verified.

On the basis of available clinical information, the patient described by Jeyadoss et al[3] had a reaction that was temporally related to the administration of sugammadex, with profound, isolated cardiovascular collapse and grossly elevated mast cell tryptase concentration in the acute phase although no baseline level was reported. Similarly, patient 1 in the series of Sadleir et al[4] had isolated hypotension temporally related to sugammadex administration with generalised oedema apparent later. The acute rise in serum mast cell tryptase concentration returned to normal within 18 hours of the event. Patient 2 in this series developed hypotension, rash and facial swelling, but this was not associated with an increase in mast cell tryptase. The weakest case for anaphylaxis is patient 3 in Sadleir et al's series, who had an episode of bronchospasm related temporally to administration of sugammadex, but which improved rapidly following a second dose of sugammadex and a bronchodilator. Mast cell tryptase concentrations

were not done, but the lack of deterioration after the second dose of sugammadex makes a mechanical (airway manipulation) or chemical (aspiration of gastric contents around the tracheal tube cuff in a patient with known acid reflux) cause distinct possibilities.

While previously reported cases have used skin-prick tests to neat[5] or diluted[6] sugammadex to investigate the causative agent, the cases of Jeyadoss et al[3] and Sadleir et al[4] are the first to report intradermal testing. The British Society of Allergy and Clinical Immunology guidelines for the investigation of anaesthetic anaphylaxis recommend the use of skin-prick tests prior to intradermal tests[11] but Jeyadoss et al and Sadleir et al reflect current practice in Australia in their choice of intradermal tests as the first line investigation. Based on their case, Jeyadoss et al[3] suggest that a 1:1000 dilution is sufficiently sensitive for intradermal testing with sugammadex but Sadleir et al[4] conclude that 1:100 is required. However, this is based on the assumption that their case[2] was a true case of sugammadex anaphylaxis, and we have already questioned the certainty of this. If Sadleir et al's case[4] was true anaphylaxis, their conclusion that 1:1000 dilution is incompletely sensitive holds, but if was not anaphylaxis then the positive response to 1:100 dilution would indicate that this dilution lacks specificity. Sadleir et al[4] cite their previous work in which none of 11 volunteers demonstrated a response to intradermal testing with a 1:77 dilution of sugammadex[14], but clearly this type of study needs to be extended considerably before precise estimates of specificity can be derived.

Positive skin-prick and/or intradermal tests imply an IgE-mediated mechanism of anaphylaxis; however, none of the reported cases had prior exposure to sugammadex. This may indicate that environmental sensitisation has occurred through exposure to cyclodextrins found widely in the food and pharmaceutical industry[15]. A similar process of environmental sensitisation is thought to have occurred with neuromuscular blocking agents, whose quaternary amine is found in hair dyes and other products.

Another reason to suspect a possible IgE-mediated mechanism is the observation that when sugammadex and rocuronium are pre-incubated (as demonstrated by Sadleir et al[4]), the ability of sugammadex to cause mast cell degranulation during skin testing is attenuated. One hypothesis for this finding is that the binding of rocuronium to sugammadex either 'hides' the responsible epitope on sugammadex or induces conformational change which then prevents cross-linking with mast cells. However, it is possible that mast cell degranulation is a non-specific phenomenon which is reduced when the overall shape of the compound is changed through binding with rocuronium. An alternative hypothesis is that the rocuronium–sugammadex molecule has a unique anergic quality which directly moderates the anaphylaxis cascade.

In parallel with this phenomenon, it has been observed clinically that severe rocuronium-induced anaphylaxis appears to improve following administration of sugammadex. Several authors[16,17] describe a complete and almost immediate diminution of anaphylaxis after efforts to control the signs and symptoms with standard treatment such as adrenaline have failed. However, another report describes a similar, dramatic improvement in anaphylaxis without the administration of sugammadex[18], and this may simply represent a feature of rocuronium-induced anaphylaxis.

If encapsulation of rocuronium by sugammadex can reverse anaphylaxis to rocuronium it raises the possibility of extending the principle to the use of cyclodextrins more widely for the treatment of drug-induced anaphylaxis. It might be possible, for example, to design other cyclodextrins for agents such as penicillin. This is an appealing idea, but much more work is needed to uncover the exact mechanism of action of cyclodextrins and the inherent risk they carry for inducing anaphylaxis themselves.

In countries where sugammadex has been licensed for clinical use, the main obstacle to its more widespread use has been its cost rather than efficacy. An increasing recognition of side-effects, including anaphylaxis as reported in this issue, might appear to justify the decision of the United States Food and Drug Administration to withhold its approval of sugammadex, but such an assessment must be made in the context of the frequency of adverse effects of the currently available drugs, especially suxamethonium, which would be reduced by the availability of sugammadex.

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