

Case Report

Anaphylaxis following intravenous paracetamol: the problem is the solution

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Summary

Paracetamol is a ubiquitous analgesic and antipyretic that is widely administered, including by anaesthetists. Immediate hypersensitivity reactions to intravenous paracetamol are particularly rare. We report two cases involving four separate episodes of anaphylaxis to intravenous paracetamol in different perioperative settings without a past history of intolerance to the oral form. The allergological investigations are described, during which it became evident that both patients were allergic to an excipient (mannitol) present in the formulation and that neither was allergic to the principal agent (paracetamol). The importance of referral and investigation of perioperative drug reactions is underscored by these two cases.

Key Words: acetaminophen [paracetamol], anaphylaxis, excipient, mannitol, pharmaceutical solutions

Paracetamol is a common non-opioid analgesic with a favourable safety profile. Anaphylactic reactions to paracetamol are very rare, with only a few cases reported of allergy to oral preparations^{1–7}. From a well-established perioperative allergy investigation service, we report two patients who developed anaphylaxis to the same brand of intravenous paracetamol (Perfalgan®, Bristol-Myers Squibb, Mulgrave, Victoria) administered perioperatively. The underlying cause of these cases of anaphylaxis proved novel and they highlight the necessity of referral for allergic investigation after a perioperative drug reaction^{8,9}, as well as the importance of considering all medications and formulations in the allergologic work-up, including the excipients, which are of significance on rare occasions. Written informed consent was obtained for the medical histories to be used in scientific publications as well as use of the photograph in Case 1.

Case 1

A 39-year-old woman was referred for investigation of three anaphylactic reactions that occurred during and shortly after post-mastectomy breast reconstructive surgery. Relevant allergic history included mild asthma and eczema, as well as occasional intolerance to mushrooms. Uneventful

induction of anaesthesia for reconstructive surgery was performed with midazolam, fentanyl, propofol, rocuronium, parecoxib, and dexamethasone. Approximately an hour later, midway through the procedure, the patient developed sudden cardiovascular instability manifested by severe hypotension and tachycardia, and accompanied by difficulty with ventilation. Intravenous paracetamol (Perfalgan) had just been administered. A surgically related tension pneumothorax was suspected but the clinical picture did not improve following needle thoracotomy. Anaphylaxis was then presumed and managed successfully. Surgery was ceased and the patient was transferred to the ICU. There, a small apical pneumothorax was diagnosed and an intercostal drain inserted before discharge to the ward. Upon arrival in the ward, another episode of anaphylaxis was again diagnosed. This responded well to immediate conventional treatment. Intravenous midazolam, paracetamol (Perfalgan) and local infiltration of lignocaine with adrenaline had been administered just prior to chest tube insertion. The next day, a third episode of anaphylaxis developed and was promptly treated. Detailed examination of the patient records showed that administration of intravenous paracetamol (Perfalgan) was temporally closely associated with the acute clinical destabilisation and she was referred for allergological investigation.

A raised serum tryptase level of 23.8 µg/l (normal <12 µg/l), taken one hour after the first anaphylactic reaction, supported the diagnosis of anaphylaxis. Intradermal skin testing was performed in the presence of positive and negative controls according to a standardised dilution protocol. Midazolam, fentanyl, morphine, propofol, cephalothin, vecuronium, rocuronium, suxamethonium,

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Accepted for publication on June 29, 2015

pancuronium, cisatracurium, dexamethasone, parecoxib, lignocaine, povidone-iodine, chlorhexidine and paracetamol (Perfalgan, 1 g per 100 ml) were tested. The latter has no verified dilutions for intradermal testing and as a precaution testing was commenced at 1:10,000, followed by 1:1000, 1:100 and 1:10. Diagnostic wheal responses were present at 1:1000, 1:100 and 1:10 test dilutions of Perfalgan. All other substances were negative for wheal and flare. ImmunoCAP® (Phadia Laboratory Systems, Thermo Fisher Scientific, Waltham, MA, USA) serum specific IgE to pholcodine, morphine, chlorhexidine and latex were negative.

The timing of anaphylaxis and positive intradermal tests identified parenteral paracetamol as the most likely cause. However, it was concerning that intradermal test dilutions for Perfalgan had not been independently validated in the literature. Moreover, the patient displayed no allergic symptoms to oral paracetamol, having continued to take it throughout and subsequent to the surgical treatment, and this was perplexing. On all three occasions of anaphylaxis, the Perfalgan brand and formulation of intravenous paracetamol had been administered, leading to a careful examination of the excipients (mannitol, cysteine hydrochloride, sodium phosphate—dibasic dehydrate, sodium hydroxide and hydrochloric acid) for a potential allergen. Cross-reactivity between mushroom and mannitol hypersensitivity has been described and it was decided to investigate this substance further. Due to lack of published data regarding the ideal testing dilutions for mannitol, intradermal testing at 1:10,000, 1:1000, 1:100 and 1:10 dilutions of mannitol 20% were performed. Testing was negative to the 1:10,000 dilution but positive to all other dilutions (Figure 1). Thus, it was concluded that mannitol in the Perfalgan was the allergenic moiety. Surgery was subsequently safely undertaken under general anaesthesia with the omission of Perfalgan and other mannitol-containing preparations. An alert device was prescribed recommending avoidance of all mannitol-containing substances in future.

Case 2

A 73-year-old male awaiting surgery was referred for investigation of a possible anaphylactic reaction to intravenous paracetamol in the past. The medical history included mild asthma and eczema. There was documented hypersensitivity to codeine, dust mites and mushrooms. In 2005, the patient underwent a general anaesthetic and developed anaphylaxis following administration of intravenous paracetamol; he made a full recovery. Two months later, he underwent allergological investigation at another specialist centre. There was a negative skin-prick test to oral paracetamol slurry and a negative oral challenge test to paracetamol. However, allergy testing for the other anaesthetic drugs was not undertaken and he was referred to our centre to complete this process. Intradermal testing was performed of the drugs administered during the anaesthetic

in 2005 (midazolam, propofol, morphine, cephalothin, rocuronium, intravenous paracetamol and chlorhexidine). Examination of the perioperative medical record established Perfalgan as the type of intravenous paracetamol that had been administered during anaesthesia. Positive intradermal responses were demonstrated with Perfalgan at 1:1000 and 1:100 dilutions, as well as to undiluted drug via skin-prick test. All other intradermal as well as serum-specific IgE tests were negative. It was assumed that the patient was allergic to the excipient mannitol in the intravenous paracetamol formulation and future avoidance of mannitol was recommended.

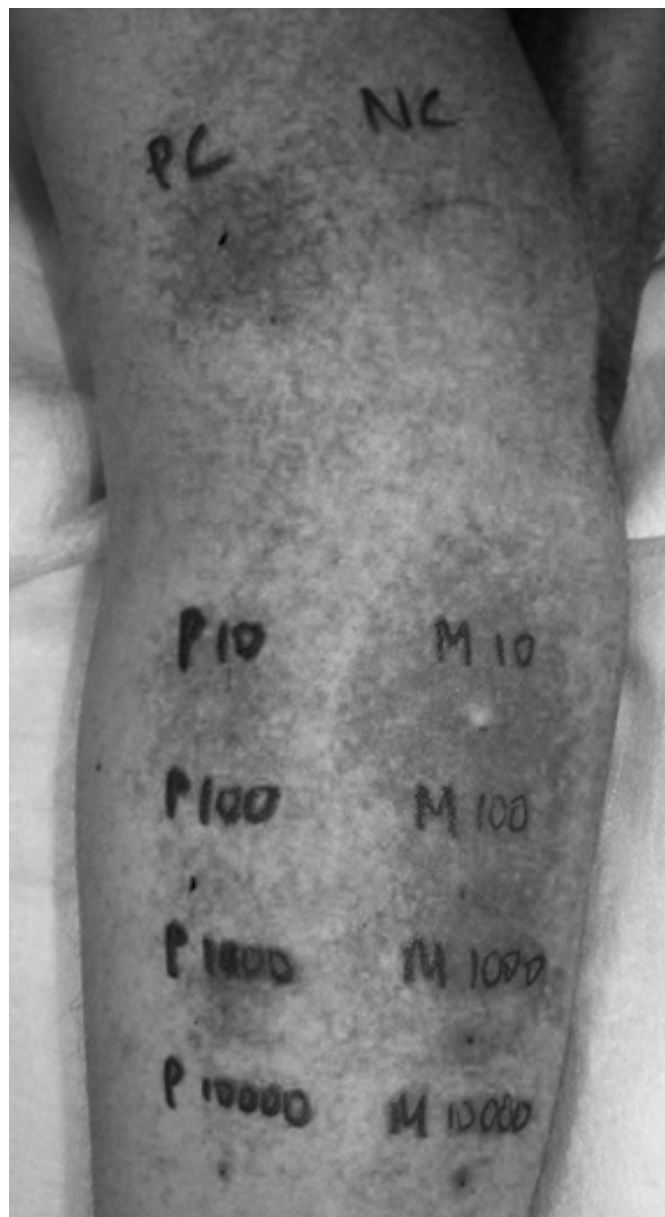


Figure 1: Case 1—diagnostic intradermal reactions to Perfalgan (P) and mannitol (M) at 1:10, 1:100 and 1:1000 dilutions.

Discussion

Medications typically contain one or more principal active ingredients that are responsible for therapeutic effect, as well as other inactive components such as dyes and excipients. Ideally, the latter are inert substances added in order to modify consistency, stability or enhance antimicrobial protection. In the case of Perfalgan, the hydrophilic properties of mannitol render paracetamol more soluble. Anaphylaxis to excipients is rare, but the significance of this case report lies in the fact that both patients appeared to develop anaphylaxis to an excipient (mannitol) in the formulation, rather than to the active ingredient (paracetamol). While it is intuitive and generally more accurate to attribute allergenicity to the active ingredient in intravenous formulations, we would like to stress the importance of additives as possible offending agents, which may be overlooked. This is especially pertinent where the active ingredient is tolerated in another form or pharmacological formulation (e.g. oral), or alternatively, as occurred in both cases presented, when there is a history of possible hypersensitivity to an excipient.

Mannitol is one of the most widely used excipients in pharmacological preparations. Structurally, it is a low molecular-weight, inert hapten. Current guidelines for interpretation of drug allergy testing¹⁰ indicate that positive intradermal and skin-prick tests to mannitol would favour an IgE-mediated mechanism underlying clinical anaphylaxis in both cases. The potential sources of immune sensitisation to mannitol are intriguing; previous mannitol exposure in medications, or other products like mouthwash, chewing gums and processed foods, are possibilities. Interestingly, mannitol occurs naturally in pomegranate and varieties of mushrooms¹¹. Both patients had a history of intolerance to mushrooms and avoidance of mannitol in parenteral solutions may have prevented the intraoperative anaphylaxis. There are published reports documenting hypersensitivity reactions to mannitol infusion^{10,12,13}. After a thorough literature search, we found only one case reporting anaphylaxis to mannitol where it was used as an excipient in a cisapride tablet¹¹. With the assistance of hospital pharmacists, a list of medications containing mannitol was supplied to both patients in order to minimise future risk of repeat reactions.

We considered the possibility of recurrence of initial anaphylaxis rather than discrete anaphylactic episodes in the first patient. Some reports mention risk factors for a biphasic response including a delay in administration of adrenaline, suboptimal dose of adrenaline given to treat the primary reaction and oral administration of the antigen¹². These were absent in this case, which led us to examine the drugs administered in all three events more closely. The reason why paracetamol was administered repeatedly to the patient despite having a severe anaphylactic reaction was because the patient had tolerated oral paracetamol without any adverse reactions in the past on multiple occasions, and had even tolerated paracetamol orally between episodes of anaphylaxis.

Conclusion

Anaphylaxis is unpredictable and usually unexpected, occurring with any drug, including, on occasion, low-risk substances used widely and frequently. Exposure to alternate formulations of an active ingredient may unmask hypersensitivity to an excipient. Seemingly innocuous and ubiquitous off-patent medications may be presented for administration with varying excipients and it is recommended that anaesthetists are aware of this unusual mechanism of drug hypersensitivity. We would also like to stress the significance of clear labelling of all ingredients including excipients in pharmaceutical preparations and reiterate the importance and value of allergological work-up following perioperative anaphylaxis in order to provide planning advice for future anaesthesia providers and to avoid future reactions.

Editor's note

All subsequent trademark symbols (®) have been removed after the first use for ease of reading.

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