

Anaphylaxis to intravenous paracetamol containing povidone. A case report and narrative review of excipient allergy related to anaesthesia

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Abstract

Investigation of intraoperative anaphylaxis includes the exclusion of potential trigger agents the individual was exposed to within a plausible interval preceding the reaction. Occasionally, none of these agents will test positive. In this situation it is important to consider that excipients may be responsible for anaphylaxis, that the dilutions prepared to test the medication may not contain an appropriate concentration of the excipient to induce a positive skin reaction, or if an alternative formulation of the medication is tested, it may not contain the culprit excipient. This case describes a patient, who previously experienced an anaphylactic reaction to Betadine[®] (Sanofi-Aventis Australia Pty Ltd, North Ryde BC, NSW) experiencing anaphylaxis in the recovery period after general anaesthesia where Betadine was avoided. The recently administered therapeutics were excluded by skin testing, however further investigation determined that a povidone-containing formulation of paracetamol had been administered. Skin testing with povidone-containing paracetamol resulted in a positive reaction in the patient, but not in a volunteer control. Pharmaceutical excipients are added to medications to increase absorption, shelf-life and efficacy. Different brands of the same drug may contain different excipients. When testing for anaphylaxis with such compounds one must be sure the dilution is appropriate for both the parent compound and the excipient to ensure the accuracy of skin-prick and intradermal testing. This case demonstrates the potential for excipients to cause severe allergy and the importance of detailed history pertaining to previous allergic episodes as even the most unlikely of medications can potentially result in anaphylaxis due to excipients.

Keywords

Excipient, additives, paracetamol, povidone, anaphylaxis, allergy, intradermal testing, intravenous

Introduction

Anaphylaxis is a serious and potentially fatal complication of anaesthesia. There is significant geographical variability and the incidence ranges from 1:18,600 to 1:353 anaesthetic procedures.¹ Common culprits include antibiotics, neuromuscular blocking agents, chlorhexidine, sugammadex and patent blue dye. When the usual culprits are found not to be responsible, one important class of potential triggers that must be considered are pharmaceutical excipients.

Pharmaceutical excipients are present in the formulation of the active drug to aid in delivery, stability or absorption. Tablet excipients may be diluents, binders, disintegrants or colouring agents. Solution excipients may be antimicrobial agents, solubilisers or

preservatives. Usually these additives are irrelevant for treating clinicians, their presence in formulations is often not obvious and may be overlooked. Nonetheless, it is well documented that these agents can cause severe allergic reactions.^{2,3}

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This case and review demonstrates the potential for this to occur, the significant differences in preparation between formulations of the same medication (in this case intravenous paracetamol) and the possibility that a previously-attributed allergic reaction may have been incorrectly attributed to an active ingredient rather than the excipient.

Case

A 55-year-old woman underwent general anaesthesia in combination with interscalene regional anaesthesia for elective shoulder surgery (rotator cuff repair). The intraoperative period was unremarkable and upon completion of surgery the patient was extubated and transferred to the post-anaesthesia care unit (PACU), where she was stable and comfortable.

Approximately 20 minutes following arrival in the PACU the patient suffered a sudden deterioration comprising severe hypotension (systolic pressure 55 mmHg), sinus tachycardia (135 per minute) and hypoxia (pulse oximeter saturation reporting 82%). This responded to treatment with inhaled salbutamol and intravenous crystalloid solution. Adrenaline (epinephrine) was not administered. Four minutes prior to this reaction, paracetamol BNM[®] (Boucher & Muir Pty Ltd, North Sydney, NSW) was commenced by intravenous infusion (1g in 100ml of solution over 15 minutes). There were no cutaneous features.

The patient stabilised within 30 minutes and was transferred to the intensive care unit. Serial mast cell tryptase levels taken were raised at 8.4 µg/l compared to baseline 2.9 µg/l ($> 1.2 \times \text{baseline} + 2 \mu\text{g/l}$), confirming the diagnosis of anaphylaxis.⁴

After discharge, this patient was referred to the anaesthesia allergy clinic (Department of Anaesthesia, Sir Charles Gairdner Hospital, Perth, Western Australia), where intradermal testing was conducted with appropriate dilutions of sugammadex, sugammadex:rocuronium mix, paracetamol Kabi[®] (Fresenius Kabi Australia Pty Ltd, Mount Kuring-Gai, NSW), paracetamol BNM and povidone iodine. There were no other potential triggers identified. Paracetamol and povidone dilutions were performed as follows: 10 mg/ml paracetamol diluted 1:100 with normal saline (0.1 mg/ml) and 5% povidone iodine (aqueous solution) diluted 1:100 with normal saline (0.5 mg/ml). Paracetamol BNM contains 1mg/ml povidone and was diluted 1:2 with normal saline to provide a known non-irritant concentration of povidone of 0.5 mg/ml. This dilution of paracetamol BNM did not produce a reaction in a volunteer control. A positive control (0.8% histamine skin-prick test) confirmed normal skin sensitivity for interpreting the skin tests.

The povidone iodine skin test site showed a greater than 3 mm increase from baseline, producing a 6 mm wheal and surrounding flare. The paracetamol BNM (50% dilution) was also positive, with a 9 mm wheal with surrounding flare. Paracetamol Kabi, sugammadex and sugammadex:rocuronium combination all tested negative.

This patient's history of note includes a previous hypotensive response to Betadine[®] (Sanofi-Aventis Australia Pty Ltd, North Ryde BC, NSW), for which postoperative allergy skin testing was conducted yielding a positive result to povidone. In addition, this patient described a history of allergy to dispersible aspirin, some formulations of which contain povidone.

Discussion

The routine investigation of intraoperative anaphylaxis includes the systematic exclusion of therapeutic agents administered within a plausible interval preceding the reaction. Occasionally, none of these agents will test positive. It is important to consider that excipients may be responsible for perioperative anaphylaxis.²

Excipients are ubiquitous in pharmaceuticals, but labelling standards often demote their importance relative to the active drug. Different brands of the same drug may contain different excipients,⁵ such as with paracetamol BNM and paracetamol Kabi in this case. It is very difficult for anaesthetists to have an up-to-date knowledge of all additives and every excipient contained in the vast amount of medication we administer daily. Therefore, detailed questioning and identification of any patterns of hypersensitivity may increase vigilance for potential excipient allergy, thus reducing the risk of potential life-threatening allergy and cross reactivity.

This case report outlines an increasingly common presentation of perioperative anaphylaxis after emergence from anaesthesia,⁶ with what we believe is an under-recognised cause of false negative skin-test investigations. The immediate management of anaphylaxis resulted in a good patient outcome despite the absence of adrenaline (epinephrine) administration which is an essential component of accepted treatment guidelines.

Intradermal allergy testing requires controlled exposure to potential allergens in small concentrations to minimise the risk of serious reaction or false positive (irritant) results. As such, medications are usually diluted based on the active drug concentration, but this may not be appropriate to assess allergy associated with excipients. As such the excipient concentration may be too low, resulting in a falsely negative result. Alternatively, the dilution that may be appropriate for the excipient may not reduce the active drug to a non-irritant concentration, resulting in a false positive

reaction. In this case, an alternative formulation of the excipient with a different parent drug must be sought. Where possible utilising solutions that contain only the excipient mitigates these issues.

Due to the increase in sensitivity and improved negative predictive value of intradermal testing, Australian and New Zealand Anaesthetic Allergy Group guidelines support the use of intradermal testing without prior skin-prick testing for the investigation of hypersensitivity reactions, as was done in this case. Guidelines in other regions of the world advocate initial skin-prick testing followed by escalated intradermal testing to minimise the risk of potential hypersensitivity during testing.⁷ It is appropriate that a risk assessment be done for each patient prior to skin testing.

Povidone (polyvinylpyrrolidone PVP), the culprit compound in this case, is commonly used as an excipient in many medications and is most commonly recognised for its use in iodine-based antiseptic solutions such as Betadine. Its ability to dissolve in acids, chloroform, ethanol, ketones and water allows its use as a polymer vehicle for the suspension and dispersion of medications across a wide range of mediums. It is also used as a binder in wet granulation processes, as coating agents, stabilising agent and viscosity increasing agent.^{5,8}

There are multiple intravenous paracetamol brands readily available in Australia. This includes paracetamol Kabi and paracetamol BNM commonly used in Western Australian hospitals. Paracetamol Kabi contains 3.7 g mannitol, 10 mg cysteine hydrochloride and nitrogen. Paracetamol BNM contains mannitol, povidone, sodium hydroxide (for pH adjustment), dibasic sodium phosphate dihydrate and water for injection⁹. Paracetamol Kabi is predominantly stocked in Western Australian hospitals.

Given the potential severity and consequences of such a reaction and the prevalence of povidone in many of the medications utilised within anaesthesia, we feel it prudent to highlight the relevant medications that contain povidone. For patients with confirmed or suspected allergy to an excipient it is essential to check the ingredients (including inactive), of all medications prior to administration, to ensure these patients are not given a substance that has the potential to result in anaphylaxis.

A non-exhaustive list of povidone medications used in anaesthesia include amiodarone, benzathine benzylpenicillin, buprenorphine (patch and sublingual preparation), Buscopan® (Sanofi-Aventis Consumer Healthcare Pty Ltd, Virginia, QLD), celecoxib, clonidine, digoxin, ibuprofen, ranitidine, loratadine, metoprolol, nimodipine, naproxen, penicillin, some oral paracetamol solutions including Panadeine/Panadol® (GlaxoSmithKline Consumer Healthcare Australia

Pty Ltd, Ermington, NSW), promethazine, Targin® (Mundipharma Pty Ltd, Sydney, NSW), tramadol, tranexamic acid and Voltaren® (Novartis Pharmaceuticals Australia Pty Ltd, North Ryde, NSW).⁹

There are numerous case reports detailing contact dermatitis, urticaria and anaphylaxis to topical and oral medications containing povidone,¹⁰⁻¹⁵. Furthermore one case report described anaphylaxis following intra-articular injection of povidone-containing paramethasone acetate¹⁶. To our knowledge however this is the first case report of anaphylaxis to intravenous povidone-containing medication.

Povidone is not the only excipient responsible for causing perioperative anaphylaxis. Many other excipients have caused, or have the potential to cause, anaphylaxis. These include, but are not limited to, benzalkonium chloride (BAC), dextran-20, polyethylene glycol, gelatin and mannitol.

BAC is commonly used as a bactericidal preservative and is another common excipient associated with anaphylaxis.¹⁷ Anaphylaxis was reported following administration of xylometazoline nasal drops containing BAC,¹⁷ following administration of nebulised salbutamol containing BAC¹⁸ and after insertion of a BAC-coated central venous cannula.¹⁹ There has since been a call to remove BAC from all nebulised solutions.²⁰

Dextran-20 is used as an excipient used in haemocoagulase agkistrodon, a medication regularly used in China for patients undergoing abdominal surgery with a history of haemophilia and thrombocytopenia. There have been numerous reports of anaphylaxis to haemocoagulase agkistrodon with speculation this is caused by the dextran-20 due to its high anaphylaxis profile compared to the active drug haemocoagulase agkistrodon.²¹

Polyethylene glycols (PEG) are hydrophilic polymers used commonly in medicine as excipients and plasma volume expanders. There are numerous case reports of anaphylaxis to PEG containing medications including after injection of corticosteroids,^{22,23} erythropoietin and darbepoietin^{24,25} and evacuant solutions.²⁶ Furthermore Wenande et al. discuss an unfortunate case whereby the same patient experienced five episodes of anaphylaxis over a period of 18 months all to PEG used as an excipient in different solutions including chlorhexidine, lidocaine spray, dura sealant material (DuraSeal®, Integra LifeSciences, Princeton, NJ, USA), bisacodyl, clopidogrel and Mepilex® (Molnlycke Health Care, Gothenburg, Sweden) bandages.²⁷

Gelatin, like polyethylene glycol, is also commonly used as an excipient in multiple medications. Its use includes vaccinations, haemostatic agents, plasma

volume expanders and meat products. There are multiple case reports revealing anaphylaxis to gelatin-containing haemostatic agent Floseal®^{28,29} (Baxter International, Deerfield, IL, USA) with one of the case reports revealing the patient also experienced anaphylaxis to vaccinations.³⁰

This is not the first report of anaphylaxis following intravenous paracetamol administration. There have been two reported cases of anaphylaxis to paracetamol (Perfalgan®, Bristol Myers Squibb, Swords, Co. Dublin, Ireland) containing mannitol as an excipient.³¹ Furthermore, mannitol has also been implicated in anaphylaxis following cisapride tablet ingestion.³²

Hydroxypropyl methylcellulose is a constituent in Ocucoat® (Bausch and Lomb, Montpellier, France) and Xylocaine® (Aspen Australia, St Leonards, NSW) gel and has been reported as causing anaphylaxis during cataract surgery.³³ Human serum albumin used as an excipient in fibrinogen concentrate resulted in a near fatal episode of anaphylaxis following mitral valve surgery.³⁴

Conclusion

This case demonstrates the potential for excipients to cause severe allergy and the importance of detailed history pertaining to previous allergic episodes, as even the most unlikely of medications can potentially result in anaphylaxis due to excipients.

Author Contribution(s)

James F Preuss: Investigation; Project administration; Writing-original draft; Writing-review & editing.

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Peter R Platt: Methodology; Writing-original draft; Writing-review & editing.

Paul HM Sadleir: Conceptualization; Investigation; Writing-original draft; Writing-review & editing.

Declaration of conflicting interests

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Ethics

The patient provided consent for the publication of this case report.

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