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LETTER TO THE EDITOR

Teicoplanin hypersensitivity during anaesthesia and surgery

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We read with interest the paper by Azamgarhi and colleagues who describe a series of patients who had allergic or severe reactions to teicoplanin during anaesthesia and estimate a rate of anaphylaxis of between one episode for every 1655 and 2088 doses delivered [1]. Savic and colleagues have previously described cases with proven and suspected teicoplanin allergy during anaesthesia and the recently published UK Sixth National Audit Project (NAP6) on perioperative anaphylaxis compliments these reports, noting that teicoplanin is the commonest precipitant of severe perioperative allergic-type reactions [2, 3]. NAP6 only included Grade three to five anaphylaxis and omitted milder allergic reactions. We would like to describe our similar experiences.

In Plymouth, the inclusion of teicoplanin in surgical prophylactic antibiotic guidelines for Orthopaedic and Cardiac surgery, and as an alternative in cases of penicillin allergy, has led to a large increase in teicoplanin usage. Pharmacy records for teicoplanin deliveries to the Operating Theatres between 2012 and 2015 were obtained. The typical dose for prophylaxis is 600 mg, giving an estimated 472 doses used per month, estimating 18 000 doses for the 38 months from November 2012 to December 2015. There were no changes in the prophylaxis guidelines during that time.

In November 2012, the Pharmacovigilance Department of the Medicines and Healthcare Products Regulatory Agency was informed of teicoplanin's suspected role in eight perioperative reactions at Plymouth. These demonstrated a variety of presentations, including immune type reactions, with and without a mast cell tryptase (MCT) rise and positive skin tests, and short-lived hypotension with bradycardia. Notably, some of these reactions were severe, requiring periods of resuscitation and admission to Critical Care Units.

As with Azamgarhi and colleagues, local anaesthetists were instructed to dilute teicoplanin and administer it slowly; however, from November 2012 to December 2015, the Plymouth team received 15 further referrals of suspected teicoplanin-induced anaphylaxis during anaesthesia from

three SW Peninsula hospitals. As many of these patients as possible were followed up in an attempt to identify culprit agents through skin testing and challenge testing, formulate safe plans for future anaesthesia and mark medical records with allergy alerts. Our series (see Table 1) is presented using the format borrowed from Savic and colleagues. In addition the anaesthetist's degree of suspicion that teicoplanin was implicated is also noted. Teicoplanin solution concentrations of 20 and 2 mg ml⁻¹ were used for skin prick tests and intra-dermal tests, respectively. We had great difficulty in ascribing the teicoplanin reactions as definite or probable using Savic's criteria, (only two of the 15 cases), due in part due to missing data but in particular to difficulties in definitively excluding the many other perioperative drug exposures as causes of the reaction. These were clearly severe perioperative reactions temporally associated with receipt of teicoplanin all of which the attending anaesthetist held a reasonable suspicion that teicoplanin was implicated.

Many centres co-administer teicoplanin and gentamicin for surgical antibiotic prophylaxis. The allergic risk of gentamicin is generally considered low though between the summers of 2014 and 2017 batches of gentamicin were identified as being contaminated with histamine [4]. There remains the possibility that some of the later allergic events ascribed to teicoplanin may have been due to this contamination. Gentamicin and teicoplanin are pharmaceutically incompatible and will readily precipitate when mixed. In Plymouth, we advise anaesthetists to separate teicoplanin and gentamicin temporaneously and by injection site. Under pressure to inject prophylactic antibiotics prior to surgical incision, anaesthetists may inject these drugs faster and closer together than they realize. Azamgarhi and colleagues note that no incidents of ward-based teicoplanin reactions were recorded. Likewise, we are aware of few ward-based events, and this stark absence of such episodes requires further investigation. The Anaesthetic Anaphylaxis Clinic Anaesthetists, Immunologists and Microbiologists work closely together and

Table 1

Teicoplanin-induced reaction, features and investigations

Age and sex	<15 mins	≥2 features anaphylaxis	Clinical features	SPT/IDT Challenge +ve	Details	MCT increase	Alternative excluded	Anaes suspicion high?
42/Male	Yes	Yes	Hypotension, tachycardia, flushing, desaturation, bronchospasm	Yes	SPT negative IDT positive	Yes	Yes	High
74/Male	Yes	Yes	Hypotension, flushing, tachycardia, desaturation, facial swelling	Yes	SPT negative IDT positive	No	Yes	Moderate
32/Male	Yes	Yes	Hypotension, tachycardia	Did not attend for testing		Yes	DNA	Moderate
77/Male	Yes	Yes	Hypotension, tachycardia	No	SPT negative IDT negative	Yes	No	Moderate
49/Female	Yes	Yes	Hypotension, tachycardia	Yes	SPT negative IDT positive	Yes	No	High
46/Female	Yes	Yes	Hypotension, severe bronchospasm	No	SPT negative IDT negative	Not done	Yes	High
64/Male	Yes	Yes	Hypotension, flushing, bronchospasm	Yes	SPT negative IDT positive	Not done	No	High
62/Female	Yes	Yes	Hypotension, bronchospasm, desaturation	Yes	SPT negative IDT positive	Yes	No	High
67/Female	Yes	Yes	Hypotension, tachycardia, flushing, urticaria	Yes	SPT negative IDT positive	Yes	No	Moderate
22/Female	Yes	Yes	Tachycardia, flushing, bronchospasm, desaturation	No	SPT negative IDT negative	No	Yes	Moderate
40/Female	Yes	Yes	Hypotension, bradycardia, flushing	Deceased prior to testing		Yes	No	High
66/Male	Yes	Yes	Hypotension, urticaria	No	SPT negative IDT negative	No	No	Moderate
65/Male	Yes	Yes	Hypotension, tachycardia, desaturation	No	SPT negative IDT negative	Yes	No	Moderate
46/Female	Yes	No	Hypotension, bradycardia	No	SPT negative IDT negative	No	No	Moderate
63/Male	Yes	Yes	Hypotension, flushing	No	SPT negative IDT negative	Yes	No	Moderate

The features of teicoplanin associated reactions, based on that of Savic and colleagues

Anaes suspicion high-attending anaesthetist confident teicoplanin cause of the severe reaction; IDT, intradermal test; MCT, mast cell tryptase; SPT, skin prick test

would have been aware if a series of ward-based teicoplanin reactions was occurring. We agree with Azamgarhi and colleagues that teicoplanin reactions may be related to speed of infusion. We hypothesize that under time pressure on the wards, nursing staff may be more likely to deliver teicoplanin as a slow walk-away infusion. Time pressures in the anaesthetic room may lead to the temptation to deliver teicoplanin by a more rapid bolus, regardless of institutional instructions, to ensure antibiotic administration prior to the surgical start. We have seen patients with short-lived cardiovascular collapse, possibly related to rapid teicoplanin injection.

When assessing the causes of perioperative anaphylaxis, it is often difficult to identify the culprit agent with certainty as anaphylaxis can occur at times of multiple allergen exposure. As described herein, patients can exhibit negative skin prick and intradermal testing and not demonstrate an increase in MCT following suspected teicoplanin reactions as

is well described in the red man syndrome associated with the related antibiotic vancomycin [5]. False negative skin tests may be due to the reaction being non-IgE mediated, and teicoplanin's ability to be associated with severe allergic phenomena without skin changes is a concern. NAP6 notes that some patients demonstrated positive skin testing to more than one agent and in the context of a severe reaction, challenge testing to identify the culprit may not be justifiable.

We applaud the work of Azamgarhi, Savic and NAP6 to highlight the issues associated with teicoplanin; however, we suggest that the incidence of teicoplanin anaphylaxis remains uncertain and there may be more, as of yet unexplained, practical and immunological causes to this phenomenon.

Competing Interests

There are no competing interests to declare.

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