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Teicoplanin Allergy – An Emerging Problem in the Anaesthetic Allergy Clinic

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Summary

Background: Anaphylaxis to teicoplanin appears to be extremely rare, with only one confirmed case report worldwide. Two anaesthetic allergy clinics in the UK have received a number of suspected cases referred for investigation, and we present here the first case series of teicoplanin allergy.

Methods: We investigated 20 cases of suspected teicoplanin allergy, identified from the two clinics over a period of 2 years. We devised a set of five criteria to categorise the certainty of their diagnosis. These included: (1) reaction within 15 minutes of administration of teicoplanin, (2) ≥2 features of anaphylaxis present, (3) positive skin testing or challenge testing, (4) raised serum mast cell tryptase (MCT), (5) alternative diagnosis excluded. Based on these criteria we defined likelihood of IgE-mediated allergy to teicoplanin as: definite-met all criteria; probable-met criteria 1,2 and 5, plus 3 or 4; uncertain-met criteria 1,2 and 5; excluded- any others

Results: We identified 7 'definite', 7 'probable' and 2 'uncertain' cases of teicoplanin allergy. Four cases were excluded.

Conclusion: IgE-mediated anaphylaxis to teicoplanin appears to be more common than previously thought. This is true even if only definitive cases are considered. Investigation of teicoplanin allergy is hampered by the lack of standardised skin test concentrations. In some cases, there was a severe clinical reaction, but without any skin test evidence of histamine release. The mechanism of reaction in these cases is not known and requires further study.

Keywords

Anaesthetic anaphylaxis; Drug Hypersensitivity; IgE mediated anaphylaxis; Teicoplanin;

Teicoplanin is a glycopeptide antibiotic used frequently in the perioperative setting. In recent years, usage has increased dramatically in line with changes to antibiotic prescribing. Teicoplanin is now first line prophylactic therapy for most orthopaedic work, some cardiac, breast, gastrointestinal, vascular and plastic procedures. It is frequently used as second line therapy in penicillin allergy. In Leeds Teaching Hospitals Trust alone, usage has increased from around 2 million milligrams (mg) administered in 2009-2010, to 7.5 million mg administered in 2014-15.

Teicoplanin is a similar drug to vancomycin, another glycopeptide antibiotic. Vancomycin administration is well known to result in non-immunological histamine release, leading to 'red man syndrome'. This is a rate and dose dependant phenomenon [1]. However teicoplanin has been shown not to cause the same widespread histamine release, even when injected rapidly [2,3] . For this reason, it has long been considered the safe alternative for patients intolerant of vancomycin. A standard adult dose of 400mg made up with 3.2millilitres of sterile water, administered as a slow intravenous bolus, has not been reported in the literature to cause either red man syndrome or other features of histamine release. Although hypersensitivity reactions have been reported [4,5], there is only one case report worldwide of confirmed anaphylaxis to teicoplanin [6]. Since 1990, there have been 107 episodes of possible teicoplanin anaphylaxis reported to the Medicines and Healthcare Products Regulation Agency in the UK [7]. The details of these reactions, how a diagnosis of anaphylaxis was made, and which drugs were co-administered, are not known. We present here the first case series of teicoplanin allergy.

Suspected perioperative anaphylaxis should always be referred for further investigation [8]. Ideally, such investigations are performed in specialist clinics with combined anaesthetic and immunology input, reflecting the often complex clinical scenarios with multiple drug administrations. The first aim of investigation is to determine if the incident was caused by an acute immunological reaction or there was an alternative explanation, such as an exaggerated physiological response to anaesthesia and surgery. A second aim, if anaphylaxis has occurred, is to establish the causative agent and to determine

whether the underlying mechanism was allergic or non-allergic. Allergic mechanisms are IgE mediated, and in such cases safe alternatives to the causal drug must be sought where possible, to ensure patient safety in future anaesthetics.

Experiential evidence from two such anaesthetic allergy clinics in the UK, suggests that perioperative allergy to teicoplanin has become increasingly common. The reactions are often severe and life threatening. However unique problems are encountered when attempting to make a conclusive diagnosis of teicoplanin allergy. The presentation, investigation, and diagnostic dilemmas associated with these cases are examined in detail, and a means of grading the certainty of diagnosis is discussed.

Methods

The Suspected Anaesthetic Allergy clinic of Leeds and the Anaesthetic Reaction Clinic in Central Manchester together cover a population of more than 10 million in the UK, and are run in a similar way. An immunologist and anaesthetist jointly review the patient's notes. When the patient attends the joint clinic, a more detailed history is taken of medical conditions, anaesthetic exposure, drug allergies and other relevant background. Skin testing is performed (informed by the notes review), along with any indicated blood tests. It is generally possible to make a diagnosis at the time of the clinic, without the need for further testing.

A retrospective study was conducted of all cases of suspected perioperative teicoplanin allergy referred to the two clinics. The majority of these had been referred over the previous two years. A total of 20 patients were identified and included in the data analysis. The demographics, co-morbid conditions and planned surgical procedure for each patient are detailed in Table 1. All cases had been investigated within 12 months of the event. We examined the clinical

presentation and follow-up investigations, and devised the following criteria to define the reactions. This is based on guidance for the investigation from the British Society of Allergy and Clinical Immunology [9]. Using these criteria, the certainty with which a diagnosis of allergic anaphylaxis could be made was graded into four categories (see Table 2).

Features of anaphylaxis included: major, unexplained cardiovascular compromise; major, unexplained respiratory compromise; angioedema; urticaria; widespread flushing; itch. The categorisation of cardiovascular or respiratory compromise as 'major and unexplained' was a judgement made by the anaesthetist in the clinic, taking account of any opinion offered by the referring anaesthetist. No predefined absolute or relative changes in cardiovascular or respiratory variables were used; rather, the degree of hypotension or bronchospasm had to be considered to be significant and unexplained for that particular patient, in the context of his/her particular anaesthetic. For example, a hypertensive patient treated with multiple antihypertensive agents, who sustains a fall in blood pressure on induction of anaesthesia, which recovers rapidly with simple treatment, would not meet criteria for 'unexplained hypotension'. Conversely, a normotensive patient who suffers a profound fall in blood pressure on induction, which is resistant to treatment, would meet criteria.

Skin testing comprised skin prick tests (SPT) with or without intradermal tests (IDT). The dilutions of teicoplanin used for these varied substantially between the two units, reflecting the absence of validated skin test dilutions for teicoplanin. The Manchester clinic (patients with prefix M) performed SPT with teicoplanin dilutions of 125 mg/ml and IDT at dilutions of 62.5 mg/ml; the Leeds clinic (patients with prefix L), performed SPT at dilutions of 20 mg/ml and IDT at 2 mg/ml.

The exclusion of alternative causal agents was based on negative SPT unless skin testing and challenge testing for teicoplanin were also negative, in which case

IDTs (with or without challenge testing for antibiotics) were performed. Where doubt remained, specific IgE blood tests were performed, where available.

'Alternative causal agents' included all agents the patient was exposed to during the perioperative period. All patients were routinely skin prick tested with chlorhexidine and latex, as these agents are ubiquitous in UK operating theatres and exposure to both is considered highly likely.

Results

Of the 20 cases in which the reaction was temporally-related to the administration of teicoplanin, seven were categorized 'definite', seven were 'probable', two were 'uncertain', and four were 'excluded' (Table 2 and 3).
It is notable that all cases included cardiovascular or respiratory compromise within the clinical features of anaphylaxis. This may be because anaesthetists are more likely to suspect anaphylaxis when these signs are present, and hence refer for onward investigation; alternatively, it may reflect a tendency for teicoplanin to cause more severe reactions. Also of note, all patients had serial mast cell tryptase levels taken except M7 (Table 2). This is in line with guidelines for the management of suspected anaphylaxis.

Vignettes one to four describe a case from each of these groups in further detail, illustrating the clinical problem and diagnostic pathway.

Vignette 1.

Definite case – L5
A 59 year old woman presented for an elective orthopaedic procedure. She was otherwise fit and well, with no history of atopy and no known drug allergies. She had undergone three previous general anaesthetics, uneventfully. A peripheral nerve block was sited using bupivacaine, prilocaine and lidocaine. She was sedated with fentanyl and propofol. Teicoplanin and gentamicin were administered intravenously (IV), and within a few minutes of this, she developed

nausea, facial swelling, cough and airway compromise, with peripheral oxygen saturation falling to 85%. She was given IV metaraminol and ephedrine, her trachea intubated and lungs mechanically ventilated, and the patient admitted to intensive care. She later made a full recovery. Serial MCT concentrations revealed a peak value of 69 ng/ml (normal range less than 11.5 ng/ml). Skin testing was positive to teicoplanin, but negative for all other agents used. A confident diagnosis of IgE mediated anaphylaxis to teicoplanin was made.

Vignette 2.

Probable case –M6

M6 was male, ASA grade 1, undergoing an elective orthopaedic procedure. He took no regular medicines and had no background of atopy. He had undergone general anaesthesia several times previously, and had received teicoplanin during his most recent anaesthetic two months earlier. Anaesthesia was induced with propofol and remifentanil. Around 30 minutes later he received IV teicoplanin and gentamicin, and immediately developed a widespread rash, hypotension (blood pressure 46/16 mmHg), bronchospasm and cyanosis (peripheral oxygen saturation 78%). He was successfully resuscitated with IV adrenaline, salbutamol, hydrocortisone and chlorphenamine. The operation was abandoned. The peak MCT concentration was raised at 68 ng/ml. Skin prick testing for all agents used was negative. Intradermal testing was also negative for all agents, although there was some localized itch with teicoplanin. A diagnosis of probable teicoplanin allergy was made.

Vignette 3

Uncertain case – L4

A 59 year old woman presented for an elective orthopaedic operation. She was known to be hypertensive, for which she was treated with an angiotensin converting enzyme inhibitor (taken on the day of surgery). She was otherwise fit and well with no history of atopy and no known drug allergies. In the anaesthetic

room, she was given IV teicoplanin. Within a few minutes she became unwell, with a profound bradycardia, facial swelling and nausea. She was treated with IV atropine, and the operation cancelled. She made a full recovery. Serial MCT measurements were not performed. Skin prick and intradermal testing to teicoplanin was negative. We were unable to confirm anaphylaxis, or to demonstrate an IgE mediated reaction to teicoplanin, in the context of a severe reaction where teicoplanin was the only drug administered. She was therefore given an 'uncertain' diagnosis of teicoplanin allergy and advised to avoid this drug in the future.

Vignette 4

Excluded case – M1

M1 is a man who attended for an elective orthopaedic procedure. He was known to be hypertensive, for which he took bendroflumethiazide and an angiotensin converting enzyme inhibitor. He was otherwise fit and well, but gave a history of allergy to clarithromycin, erythromycin and amoxicillin. He had previously undergone a general anaesthetic without problems. A spinal anaesthetic was sited using bupivacaine and diamorphine, with intravenous midazolam administered for sedation. A urinary catheter was inserted using a lubricant containing lidocaine and chlorhexidine, and teicoplanin given IV. Within 10-15 minutes, the patient developed dyspnoea, became hypotensive (blood pressure 53/39mmHg) and lost consciousness. He was successfully resuscitated and the procedure was abandoned. Serial mast cell tryptase levels were not performed. Skin testing was performed to all agents used, except diamorphine, which is known to have a high rate of false positive skin testing. None of the remaining agents tested positive, including chlorhexidine and latex. The patient was later offered an additional intradermal test for chlorhexidine, not routinely offered at the time of the original clinic. He was also offered challenge testing for diamorphine. He did not attend for either of these. Although there was a severe

clinical reaction, the presence of widespread mast cell degranulation could not be confirmed, and skin testing failed to demonstrate an IgE mediated reaction to teicoplanin. Alternative agents could not conclusively be excluded as having caused the reaction. The patient was therefore excluded from the case series.

Discussion

We present a group of patients who have experienced serious reactions associated with the use of teicoplanin. Between the two sites, the rate of diagnosis for each group was comparable; there were three 'probable' cases at one site and four at the other, but otherwise identical numbers for each of the other groups. Testing was performed according to the protocols current at the time for each site, and were therefore not standardised.

Seven cases appear to have had experienced allergic anaphylaxis, which is an IgE mediated type 1 hypersensitivity reaction. These cases alone would suggest that teicoplanin allergy is more common than previously reported in the literature, although the finding may simply reflect increased use of the drug. One definite case (L6) was not a true perioperative anaphylaxis, but was treated in the emergency department following a dog bite. He had an immediate, severe reaction after administration of teicoplanin (no other drugs administered), with positive skin testing. No MCT levels were taken but all other criteria were met and he was therefore included in our series.

In five of the cases we classified as probable anaphylaxis to teicoplanin, there was a good clinical history for anaphylaxis, a rise in MCT, and exclusion of other causal agents; however skin testing was negative. This might indicate non-specific mast cell activation during the anaphylactic episode, although this has not been demonstrated previously with teicoplanin. Alternatively, the negative skin tests may reflect sub-optimal concentrations of teicoplanin in the dilutions used for testing; in the majority of "probable" cases where skin testing was

negative, the weaker dilutions had been used. Even at dilutions of 62.5 mg/ml, there was one case with several features of anaphylaxis, a MCT rise, and exclusion of all alternative causal agents but with negative skin testing. There are no agreed dilutions of teicoplanin for skin tests, and an irritant concentration threshold in healthy controls has not yet been established.

In the "uncertain" group, there were two patients with a convincing clinical picture for anaphylaxis to teicoplanin, but with no rise in MCT and with negative skin testing. The absence of a MCT rise does not exclude anaphylaxis [10,11] however these results may also indicate that teicoplanin can cause a severe adverse reaction, which mimics anaphylaxis, through an as yet unknown mechanism.

In the four "excluded" cases, there was a severe clinical reaction temporally-related to the administration of teicoplanin, however we were unable to confirm an IgE mediated process or exclude other potential causal agents.

This case series highlights several problems with the investigation of suspected teicoplanin allergy. Although several of our cases appear to be the result of an IgE mediated anaphylaxis, the underlying mechanism cannot be established in a other patients. Further work is needed to establish an appropriate testing regimen for potential teicoplanin allergy, in particular the concentration required for skin testing, which yields high sensitivity but does not cause non-specific irritant effects. There may also be a role for basophil activation testing [12], as an alternative *in vitro* test for specific IgE but more work is needed to establish the validity of such tests. There has been some work in this area, although in the paper cited, there was only *in vitro* evidence of an IgE mediated reaction to teicoplanin, without clinical evidence to support this.

The often severe reactions associated with teicoplanin, and the difficulty confirming a diagnosis, are an increasing problem for anaesthetists. Raised awareness, and improved reporting of suspected teicoplanin allergy is crucial to a more complete understanding of this clinical problem.

Author contributions:

All authors contributed to the initiation and design of the study. NH, TG, SS and LS contributed to data collection. LS wrote the article, with significant contribution from all remaining authors.

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