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Short Communication

Rapid desensitization for non-immediate reactions in patients with cystic fibrosis☆

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Abstract

Non-immediate hypersensitivity reactions to antibiotics in patients with CF represent a real-life challenge for clinicians. Desensitization is often performed in patients who have exhausted all therapeutic options. Whilst desensitization is an established procedure for immediate reactions we assessed the outcomes and safety of desensitization for non-immediate reactions.

We retrospectively reviewed 275 desensitization procedures in 42 patients with a range of non-immediate reactions to six commonly used antibiotics. Desensitization was performed using a 7-step rapid intravenous protocol on a normal medical ward.

250 (91%) of overall desensitization procedures were successful; however, this figure incorporates certain individuals having multiple successful procedures. Individual patient success ranged from 55% with tazocin through to 88% with tobramycin. In the 25 patients who failed desensitization the reactions were mild and the majority occurred within 48 h of starting treatment. Prophylactic anti-histamines and steroids did not reduce the risk of reaction.

Whilst the mechanisms remain uncertain we can confirm that rapid desensitization is a safe and effective way of re-introducing an antibiotic to a patient with a non-immediate reaction.

1. Introduction

Hypersensitivity reactions to antimicrobials represent a real-life challenge in the management of patients with cystic fibrosis (CF). Studies report that up to 20% of adult patients have had multiple reactions to beta-lactam antibiotics [1–3]. Reactions are usually non-immediate and consist of uncomplicated rashes, arthralgia, and fevers. In the first instance the advice is to avoid the offending drug. However, whilst alternative regimens can be devised for most patients there are some for whom all options have been exhausted. In this difficult group of patients desensitization represents the safest method of reintroducing the drug to the patient.

Drug desensitization results in a temporary state of immune tolerance to the offending drug by gradual increasing a suboptimal dose prior to the full therapeutic dose. It is an established procedure in patients with CF and immediate antibiotic reactions [4,5]. Most recently Legere et al. reported 52 successful desensitization procedures in 15 patients with immediate reactions [5]. Previously Turvey et al. reported 57 desensitization procedures in 21 patients with CF and reactions suggestive of IgE mediated immediate reactions [4].

Non-immediate reactions by definition occur after more than one hour and are T cell mediated [6]. There is very limited information available in the CF literature to support desensitization in non-immediate reactions [7,8]. Burrows et al. included a small number of patients with non-immediate reactions in their retrospective study. They did not separate their outcomes from the patients with immediate reactions [7]. Desensitization to non-immediate reactions has been successful in other patient groups, such as with trimethoprim/sulfamethoxazole in patients with HIV [9].

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The aim of this study was to evaluate the safety and effectiveness of a rapid desensitization protocol in a cohort of patients with cystic fibrosis and non-immediate reactions to antibiotics.

2. Methods

We reviewed the medical records of all patients who underwent desensitization at the Regional Adult Cystic Fibrosis Unit in St James's Hospital, Leeds, between 2004 and 2010. Patients were included when their original reaction developed more than 24 h after starting the antibiotic and had no features of an IgE mediated process. This time point was chosen to avoid any overlap with immediate reactions.

The desensitization procedure follows a standard protocol that involves a 7-step approach with 10 fold increases in concentration until the therapeutic dose was achieved. Each step is given over 20 min, with the procedure lasting 2 h and 20 min. Desensitization was performed on the CF ward with a nurse present at all times. For the desensitization to be considered successful the patient needed to complete the full course of treatment. Prophylactic medication, consisting of either an oral steroid and anti-histamine or antihistamine alone, was given according to the discretion of the attending physician.

The study was approved by the Leeds East Ethical Committee.

Statistical analysis of outcomes was performed using the chi-square test, a p-value less than 0.05 was considered significant.

3. Results

275 desensitization procedures, involving six antibiotics, were performed in 42 patients. Some patients were desensitized to more than one drug and the original reactions are shown in Fig. 1. The frequency of maculopapular reactions was lower in the tobramycin and colomycin groups when compared to the beta-lactam antibiotics ($p=0.03$). For both tobramycin and colomycin there was a non-significant trend towards a greater frequency of arthralgia and fever.

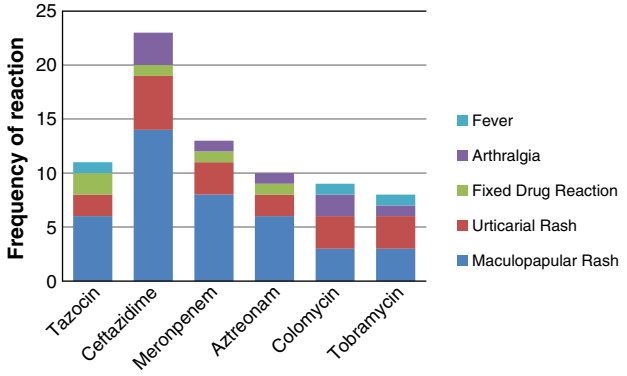

Fig. 1. Comparison of the types and frequency of original reactions encountered for each drug. The majority of all reactions were skin reactions, especially maculopapular and urticarial rashes.

250 (91%) of overall desensitization procedures were successful; however, this figure incorporates many patients who had repeated successful procedures. Individual patient success ranged from 55% with tazocin through to 88% with tobramycin. This data is shown in Table 1.

25 patients failed desensitization and the antibiotic treatment was stopped (Table 2). In keeping with the original reactions any reaction occurring following desensitization was also mild and required no action other than the discontinuation of the drug. All patients who failed desensitization were successfully desensitized to an alternative drug. Only two patients failed more than one desensitization procedure. The first patient failed with tazocin and aztreonam initially but tolerated meropenem desensitization. The second patient failed with meropenem and aztreonam but desensitization was successful with tazocin. No significant correlation was seen regarding higher risk of failure and original reaction type.

Prophylactic treatment with steroids and anti-histamine was given in 108 (39%) of procedures, anti-histamine alone in 54 (20%), and no cover in 113 (41%). There was no significant difference between outcomes and whether prophylactic medication was given, also no difference was seen between clinician decision to start prophylactic medication and the type of original reaction.

Table 1
Overall outcomes of desensitization according to each drug. S = steroid and AH = antihistamine.

Drug	Number of desensitization procedures	Prophylactic medication	Completed full treatment	Success rate per individual
Tazocin	32 in 11 patients	20 with S and AH 4 with AH 8 with no cover	84% (5 failures)	6/11 (55%)
Ceftazidime	83 in 23 patients	28 with S and AH 10 with AH 45 with no cover	90% (8 failures)	15/23 (65%)
Meropenem	42 in 13 patients	18 with S and AH 13 with AH 11 with no cover	90% (4 failures)	9/13 (69%)
Aztreonam	14 in 10 patients	3 with S and AH 3 with AH 8 with no cover	71% (4 failures)	6/10 (60%)
Tobramycin	39 in 8 patients	13 with S and AH 26 with no cover	97% (1 failure)	7/8 (88%)
Colomycin	65 in 9 patients	26 with S and AH 24 with AH 15 with no cover	95% (3 failures)	6/9 (67%)

Table 2
Individual analysis of each of the failed desensitization procedures. S = oral steroid and AH = antihistamine.

Drug	Original reaction	Outcome of desensitization	Pre-medication
Tazocin	Maculopapular rash	Maculopapular rash on day 10	No cover
Tazocin	Drug fever	Drug fever on day 7	No cover
Tazocin	Maculopapular rash	Flu-like symptoms on day 1	No cover
Tazocin	Maculopapular rash	Arthralgia on day 1	S and AH
Tazocin	Fixed drug reaction	Fixed drug reaction and pruritis on day 1	S and AH
Ceftazidime	Maculopapular rash	Maculopapular rash on day 3	S and AH
Ceftazidime	Urticarial rash	Fevers and generally unwell with first full dose	No cover
Ceftazidime	Maculopapular rash	Swollen lips and pruritis on day 3	AH
Ceftazidime	Maculopapular rash	Maculopapular rash on day 1	AH
Ceftazidime	Urticarial rash	Urticarial rash and headache day 1	S and AH
Ceftazidime	Urticarial rash	Urticarial rash on day 1	No cover
Ceftazidime	Urticarial rash	Urticarial rash day 1	No cover
Ceftazidime	Maculopapular rash	Flu-like on day 3	No cover
Meropenem	Maculopapular rash	Drug fever and generally unwell on day 2	S and AH
Meropenem	Urticarial rash	Urticarial rash day 3	S and AH
Meropenem	Maculopapular rash	Drug fevers and arthralgia day 2	S and AH
Meropenem	Maculopapular rash	Generally unwell during desensitization	No cover
Aztreonam	Maculopapular rash	Maculopapular rash on day 3	AH
Aztreonam	Pruritis and arthralgia	Pruritis on day 1	S and AH
Aztreonam	Fixed drug reaction	Fixed drug reaction 4 h post desensitization	S and AH
Aztreonam	Maculopapular rash	Maculopapular rash on day 2	No cover
Tobramycin	Maculopapular rash	Unwell and fever during desensitization	S and AH
Colomycin	Urticarial rash	Urticarial rash day 4	No cover
Colomycin	Urticarial rash	Pruritis day 2	AH
Colomycin	Angioedema	Flu-like symptoms day 1	No cover

4. Discussion

Our clinical experience suggests that desensitization is possible in patients with CF and non-immediate reactions. Patients were classified as hypersensitive on clinical grounds alone; this weakness is in keeping with all previous desensitization series. It is notoriously difficult to confirm non-immediate hypersensitivity as both intradermal and patch testing have very low sensitivities with mild antibiotic reactions [10]. In most cases the only way to prove the reaction would be give the patient a further course of the drug intravenously as a form of challenge test, this is generally considered to be inappropriate when clinical suspicion is high. Thirty out of the 42 patients (71%) did have negative skin prick tests performed to the causative drug as part of another study suggesting a non-IgE mediated process. Twelve patients died before the skin testing could be performed. The high mortality rate in this group is not surprising as desensitization is most often performed in patients with multiple allergies and a high burden of disease.

We did not find any correlation between pre-medication and outcome. Certainly the effectiveness of steroids and anti-histamines in T cell mediated reactions is limited and it would not be expected to alter the course of a reactivated immune system. More aggressive immunosuppression with agents such as cyclosporin may be more effective but are unlikely to seen as appropriate in this situation [11].

The procedures were carried on a routine medical ward with close nursing observation. Resuscitation facilities and medical staff were available on the ward in case of complications. The majority of treatment failures (17/25, 68%) occurred within 48 h of desensitization and it is our practice in Leeds that patients are observed on the ward for 48 h post-desensitization.

Little is known about the mechanisms of desensitization for non-immediate reactions. Both regulatory T cells and anti-drug antibodies have been proposed as mediators to suppress drug specific T cells. Regulatory T cells are believed to moderate allergic diseases through inducing immune tolerance [12–14]. It is possible that during desensitization effector T cell responses are controlled by these regulatory cells.

A second mechanism may involve hypersensitive patients mounting a B-cell response and releasing anti-drug antibodies during desensitization. These have been detected in certain individuals [15,16] and it has been demonstrated that anti-penicillin antibody titers rise rapidly during desensitization and then decline slowly with time [15]. The speed of the response in desensitized patients would be in keeping with a secondary antibody response.

In conclusion, desensitization is a useful and safe approach in the management of patients with multiple non-immediate reactions. It should only be used in mild reactions as reactivation of severe reactions is a theoretical possibility. A prospective study with detailed immune surveillance before, during, and after desensitization is needed to unravel the mechanisms involved.

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