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REVIEW

Utility of desensitisation for allergy to antibiotics

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ABSTRACT

Immediate-type allergic reactions to medication are potentially life threatening and can hamper the drug therapy of several medical conditions. If no alternative drug treatment is available, a desensitisation procedure may secure the continuation of necessary therapy by inducing a temporal state of tolerance. Desensitisation is only appropriate in case of a strong suspicion of an IgE-mediated allergic reaction. It should be performed by trained clinicians (allergy specialists) in a hospital setting where treatment of a potential anaphylactic reaction can be done without any delay. In this article, literature describing desensitisation procedures for several antibiotics is reviewed.

KEYWORDS

Antibiotics, drug allergy, diagnosis, provocation, desensitisation

INTRODUCTION AND DEFINITIONS

A drug allergy is an adverse drug reaction that results from a specific immunological response to a medication. Allergic drug reactions account for about 6 to 10% of all adverse drug reactions, but up to 10% of fatal adverse drug reactions in the adult population have an allergic origin.[1]

Adverse drug reactions can be divided into two main groups: the side effects and the hypersensitivity reactions, otherwise known as type A and type B reactions, respectively. Hypersensitivity reactions include all reactions that cannot be explained by the mechanism of the effect of the drug; as such this category contains the allergic reactions, defined as any reaction which involves the immune system but also enzyme-related reactions.

The World Allergy Organisation (WAO) has recommended dividing drug hypersensitivity reactions into immediate reactions (onset within one hour of exposure) and delayed reactions (onset after one hour), based upon the timing of the appearance of symptoms.[2] The signs and symptoms of the immediate reactions are directly attributable to the vasoactive mediators released by mast cells and basophils; the immunological route involved in this type of reaction is IgE. The most common signs and symptoms are urticaria, pruritus, flushing, angio-oedema (sometimes leading to throat tightness with stridor), wheezing, gastrointestinal symptoms, and anaphylactic shock.

The immunological mechanism involved in the delayed-type reaction is the T-cell reaction, also known as the type IV reaction. Nowadays we subdivide the type IV reactions into types IVa, IVb, IVc and IVd (*table 1*).[3]

The drugs most commonly implicated in immediate as well as delayed hypersensitivity reactions in adults are beta-lactam drugs, i.e., penicillins and cephalosporins.

Diagnostic procedures in drug allergy are usually confined to a detailed clinical history and confirmation of the immunological mechanism of the reaction, if present. The ENDA (European Network for Drug Allergy), a task force of the European Academy of Allergy and Clinical Immunology (EAACI), has set up guidelines on how to perform these tests.[4] In drug allergy, skin tests and *in vitro* laboratory tests are cumbersome; apart from penicillin determinants and amoxicillin for the IgE-mediated reactions, test reagents for skin tests are not standardised and the predictive value of the test is variable. The same is true for specific IgE laboratory tests. As for delayed type IV reactions, only skin tests (delayed reading

Table 1. *Revised type IV hypersensitivity reactions*[3]

Type of reaction	T-cell type	Immune reactant	Possible effector mechanism	Clinical symptoms (example)
IVa	Th1	IFN-γ, TNF-α	Monocyte / macrophage activation	Contact dermatitis, bullous exanthema
IVb	Th2	IL-5, IL-4, IL-13, eotaxin	T cells driving eosinophilic inflammation	Maculopapular and bullous exanthema
IVc	Cytotoxic T cells	Perforin, granzyme B	CD4+/CD8+ mediated T cell killing	Contact dermatitis; maculopapular, pustular and bullous exanthema
IVd	T cells	CXCL-8, GM-CSF	T cell leading to recruitment and activation of neutrophils	Pustular exanthema

of intracutaneous tests and patch tests) are available, although promising results are reported for the lymphocyte transformation test to evaluate T-cell mediated reactions. The lymphocyte transformation test (LTT) measures the proliferation of T cells to a drug *in vitro*, from which one concludes a previous *in vivo* reaction due to a sensitisation. This concept of the LTT has been confirmed by the generation of drug-specific T-cell clones and the finding that drugs can directly interact with the T-cell receptor, without previous metabolism or need to bind to proteins. Very few labs, however, are able to perform this LTT and this test is only investigated in a small number of drugs.

For this reason, the drug provocation test, the controlled administration of the suspected drug, is still considered to be the gold standard in order to confirm the diagnosis of drug allergy.[5]

Desensitisation aims at altering the immune response to the drug and results in temporary tolerance, allowing the patient to receive a subsequent course of the medication safely. Although this could be attractive in many patients, this procedure is only undertaken in certain predefined groups and only in type I and certain type IV reactions. Desensitisation should not be attempted in patients with a history of Stevens- Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) because even small doses of the drug may again induce severe progressive reactions. Desensitisation is also not appropriate for patients with type II or type III (IgG-mediated) hypersensitivity drug reactions such as haemolytic anaemia or nephritis. After the culprit drug is stopped, tolerance subsides in hours to days and subsequent administration should again be preceded by a desensitisation procedure.

In this review, we summarise the known literature concerning desensitisation procedures in adult patients with antibiotic hypersensitivity.

GENERAL PRINCIPLES OF DESENSITISATION

In a recent article by the Task Force Drug Desensitisation of the European Academy of Asthma, Allergy and Clinical Immunology, Cernadas *et al.* give an excellent overview of the outlines of the desensitisation procedure.[6] Besides the obvious safety measures such as an intravenous line, trained nurses and doctors and the medication to treat anaphylaxis at hand, the development of a desensitisation scheme is largely dependent of available well-tested protocols in literature and the initial reaction of the patient. Rule of thumb is that the more severe the original reaction was, the lower the starting dose. Therefore, the starting dose can vary between 1:100,000 and 1:100 of the therapeutic dose. Most schedules apply a doubling dose schedule; time between two steps can vary considerably but in the classic penicillin scheme (intravenous) the dose is doubled every 15 minutes until the full therapeutic dose is reached. Both intravenous and oral routes have been described.[7]

Whether premedication with corticosteroids and antihistamines reduces the risk of a desensitisation procedure is not known but one must be aware that by giving the patient antihistamines, the early signs of anaphylaxis during the desensitisation procedure may be masked.

INDICATIONS

Desensitisation to drugs can be considered in patients for whom there are no acceptable alternative drugs. For instance pregnant women with (latent) syphilis who are allergic to penicillin, as this antibiotic is the only treatment for syphilis that sufficiently crosses the placenta. It can also be of use when the alternatives are less effective than the culprit drug, such as cotrimoxazole in HIV patients for *Pneumocystis* prevention. A third reason could be to attempt to improve the underlying disease, i.e. aspirin desensitisation in patients with nasal polyps and severe asthma. Obviously, this last reason is not valid in the case of hypersensitivity to antibiotics.

CONTRAINDICATIONS

As stated above, desensitisation is not appropriate in serious cytotoxic reactions, vasculitis or bullous diseases, such as SJS or TEN. Other contraindications for this procedure are serious comorbidity such as pulmonary disease with an FEV1 less than 70%, uncontrolled cardiac comorbidity or haemodynamically challenged patients. In other situations, the risk must be outweighed by the

benefit such as in patients with renal disease, pregnancy or other diseases in which an anaphylactic reaction could cause severe complications. This is also true for patients who are treated with beta-adrenoreceptor antagonists or other drugs that may complicate the treatment of anaphylaxis. Preferably, these drugs are stopped before a desensitisation procedure is performed.

DESENSITISATION IN ANTIBIOTICS

Desensitisation procedures are reported to be successful in case of an IgE-mediated hypersensitivity reaction such as urticaria, angio-oedema, itch, or anaphylaxis. If reliable skin test procedures are available, such as for beta-lactam antibiotics, these should be performed first. Negative results to intradermal tests with penicilloyl poly-L-lysine and minor determinant mixture reduce the risk of hypersensitivity symptoms upon re-exposure to less than 5%. In these patients, incremental dosing may be chosen; however, studies comparing this strategy with desensitisation with regard to safety and efficacy have not been published. These strategies have been compared in HIV patients with mild to moderate hypersensitivity reactions to trimethoprim-sulfamethoxazole.[8] Success rates were 72% (18/25) for rechallenge and 79.5% (27/34) for desensitisation (not significant).

The starting dose for intravenous procedures is generally 1:1,000,000 to 1:1000 of the full therapeutic dose, but may be higher (1:100) in oral desensitisation.[6] During intravenous desensitisation the doses are infused continuously over intervals of 15 to 30 minutes, followed by intravenous administration of the full therapeutic doses. In the oral procedure, described dose intervals range from 15 minutes to 12 hours. Slow or incomplete absorption from the gastrointestinal tract should be taken into account when choosing this dose interval. An example of an oral and intravenous desensitisation protocol is presented in *tables 2A* and *2B*, respectively.[9,10]

Table 2A. *Oral penicillin desensitisation protocol*[9]

Step	Penicillin (mg/ml)	Amount (ml)	Dose (mg)	Cumulative dose (mg)
1	0.5	0.1	0.05	0.05
2	0.5	0.2	0.1	0.15
3	0.5	0.4	0.2	0.35
4	0.5	0.8	0.4	0.75
5	0.5	1.6	0.8	1.55
6	0.5	3.2	1.6	3.15
7	0.5	6.4	3.2	6.35
8	5.0	1.2	6.0	12.35
9	5.0	2.4	12.0	24.35
10	5.0	5.0	25.0	49.35
11	50.0	1.0	50.0	100.0
12	50.0	2.0	100.0	200.0
13	50.0	4.0	200.0	400.0
14	50.0	8.0	400.0	800.0

The interval between doses is 15 minutes. After the final step observe patient for 30 minutes, then give full therapeutic dose by the desired route.

Table 2B. *Intravenous penicillin desensitisation protocol using a continuous infusion pump*[10]

Step	Penicillin (mg/ml)	Flow rate (ml/h)	Dose (mg)	Cumulative dose (mg)
1	0.01	6	0.015	0.015
2	0.01	12	0.03	0.045
3	0.01	24	0.06	0.105
4	0.01	50	0.125	0.23
5	0.1	10	0.25	0.48
6	0.1	20	0.5	1.0
7	0.1	40	1.0	2.0
8	0.1	80	2.0	4.0
9	0.1	160	4.0	8.0
10	10.0	3	7.5	15.0
11	10.0	6	15.0	30.0
12	10.0	12	30.0	60.0
13	10.0	25	62.5	123.0
14	10.0	50	125.0	250.0
15	10.0	100	250.0	500.0
16	10.0	200	500.0	1000.0

The interval between doses is 15 minutes. After the final step observe patient for 30 minutes, then give full therapeutic dose by the desired route.

Premedication

Premedication can be done with (methyl)prednisolone, antihistamine, and ranitidine with or without montelukast 13, 7, and 1 hours, respectively, before start of the desensitisation procedure. However, early symptoms of anaphylaxis may be masked, while prevention of severe reactions has not been proven.

Symptoms

In almost 50% of the procedures reviewed in the paediatric literature, symptoms occurred during the procedure (reviewed by De Groot and Mulder[11]). For adults mild symptoms are reported in 30 to 80% of penicillin desensitisation procedures.[6] In general, the symptoms can be treated by antihistamines in combination with dose reduction or postponing the dose increase by repeating the symptomatic dose.

Effectivity

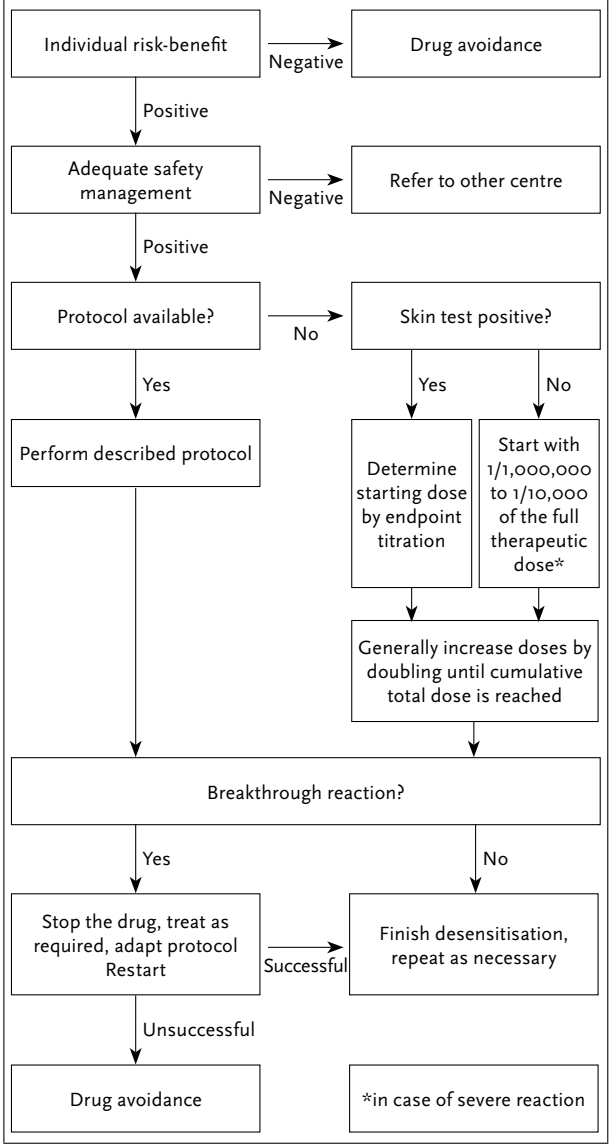
Success rates in case series of cystic fibrosis patients with a type I allergy to beta-lactam antibiotics range from 50 to 100%.[12-14] A case series of adult cystic fibrosis patients with non-immediate reactions to different classes of antibiotics

report a success rate of 55% (tazocin, 32 desensitisation procedures in 11 patients) to 88% (tobramycin, 39 procedures in 8 patients).[15]

Vancomycin can induce either IgE-mediated anaphylaxis or anaphylactoid reactions caused by direct histamine release (red man syndrome). Distinction of these two is difficult, even more so because valid skin tests for IgE-mediated vancomycin hypersensitivity are not available. A review of case reports of patients with vancomycin-induced red man syndrome that could not be managed by pretreatment with antihistamines or slowing down infusion rates showed a success rate of 100% when combining both rapid and slow desensitisation procedures.[16]

With regard to fluorquinolone hypersensitivity, some successful desensitisation procedures to ciprofloxacin in cystic fibrosis patients have been described in patients with urticaria or maculopapular exanthema.[13,17,18].

Figure 1. *General algorithm for drug desensitisation*[6]



Several case series of desensitisation to trimethoprim-sulfamethoxazole in HIV-positive immune compromised patients report success rates varying from 50 to 80%.[8,19-23] Success rates seem to be lower in patients who experienced an urticarial rash compared with those with other rashes. Individual reports of desensitisation to clarithromycin,[24,25] clindamycin,[26] rifampicin,[27] ticarcillin[28] and tobramycin[13,29] have been reported. Most desensitisations reported were successful, but a selection bias towards more successful cases is probable.

Setting

Drug desensitisation should only be performed by clinicians trained in the technique (usually allergy specialists), in a hospital setting (or outpatient setting under close observation), with intravenous access and necessary medications and equipment to treat anaphylaxis. Pharmacy staff may be consulted prior to the procedure to assist with preparation of the required drug dilutions.

Conclusion and practical proposal

An algorithm taking into account all important decisions concerning the antibiotic-allergic patient for whom desensitisation is considered is described in the EAACI position paper on rapid drug desensitisation (*figure 1*).[6] The balance of risks and benefit for each particular individual and the possibility to guarantee patient safety in a particular setting will direct the management of the individual patients. On the other hand, withholding optimal antibiotic therapy because of unfamiliarity with desensitisation protocols and procedures is not in the best interest of patients. Referral to a centre where desensitisation is performed should be aimed at in these particular cases.

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