Rapid Desensitization for Hypersensitivity Reactions to Medications

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KEYWORDS

• Desensitization • Antibiotics • Aspirin • Chemotherapy
• Monoclonal antibodies • Hypersensitivity reactions

The development of rapid desensitizations for the treatment of drug hypersensitivities is aimed at providing essential medications while protecting patients from IgE and non-IgE hypersensitivity reactions. Serious adverse drug reactions occur in 6.7% of hospitalized patients, and adverse drug reactions are the fourth to sixth leading cause of death in such patients.[1] Drug-induced type I hypersensitivity reactions, such as anaphylaxis, result from the release of mediators from IgE-sensitized mast cells and basophils. Drug-associated anaphylaxis can be triggered by β-lactam antibiotics, such as penicillin and cephalosporins, chemotherapy drugs, such as platins, therapeutic monoclonal antibodies, and others.[2–7] Cross-linking of IgE by drug antigens can lead to limited skin reactions (flushing, pruritus, urticaria, angioedema) or multiorgan system involvement (sneezing, sinus and nasal congestion, cough, shortness of breath, wheezing, abdominal pain, nausea, vomiting, diarrhea) with hypotension and cardiovascular collapse during anaphylaxis. Hypersensitivity reactions induced by drug antigens upon initial exposure, without prior sensitization and with symptoms similar to IgE-mediated reactions, are called "non-IgE hypersensitivity reactions," and can result from direct release of mediators from mast cells and basophils, such in vancomycin-induced red man syndrome, intravenous contrast dyes, or taxenes. In these reactions, nontypical symptoms can occur, such as the severe back and muscle pain seen in patients with taxene and monoclonals reactions.[8]

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Immunol Allergy Clin N Am 29 (2009) 585–606
doi:10.1016/j.iac.2009.04.012 immunology.theclinics.com
0889-8561/09/$ – see front matter

PRINCIPLES AND CELLULAR AND MOLECULAR TARGETS OF DRUG DESENSITIZATION

Desensitization for type I hypersensitivity reactions in penicillin-allergic patients were first developed 50 years ago.[9] Successful cases of rapid-progressive penicillin re-administration led to the concept of temporary clinical tolerization.[10,11] The administration of suboptimal doses of drug antigens, followed by the full therapeutic dose was safely achieved in highly allergic patients, permitting the treatment of severe infections. Following the early success with antibiotics, other empiric protocols were developed to treat hypersensitivity reactions to essential drugs that could not be substituted in allergic patients, such as aspirin in the control and prevention of cardiac diseases,[5] insulin in diabetes,[6] chemotherapy drugs during cancer recurrence,[12,13] and, more recently, chimeric and humanized monoclonal antibodies in chronic inflammatory diseases.[14] Because rapid desensitizations reintroduce potentially lethal drugs into highly sensitized patients, the molecular mechanisms need to be elucidated to improve the efficacy and safety of these procedures. Recent studies of in vitro rapid antigen desensitizations implicate mast cells and basophils as cellular targets, as well as syk,[15] a signal transducing molecule, and signal transducer and activator of transcription 6 (STAT6),[16] which is responsible for the transcription of interleukin (IL)-4 and IL-13.

CLINICAL MANIFESTATIONS

Hypersensitivity Reactions Type I, Mast Cell/IgE Dependent

Drug-induced hypersensitivity reactions type I result from the release of mediators from IgE-sensitized mast cells or basophils and can affect all organ systems, leading to anaphylaxis and death. Drug antigens can sensitize patients after multiple courses, and repeated exposures are needed for the development of specific IgE.[17] Sensitizing drugs can act as complete antigens, such as insulin, or haptens, which are coupled to a carrier protein, such as penicillin.[18] Among chemotherapy drugs, platins, such as carboplatin, cisplatin, and oxaliplatin can induce IgE formation[19] by a mechanism similar to that of metal workers exposed to low molecular-weight platinum salts by inhalation and skin contact.[20] Symptoms are induced by a platinum salt's cross-linking of specific IgE bound to high-affinity IgE receptors, FcεRI (on mast cells or basophils), with the release of membrane and granule mediators. These mediators include vasoactive amines, such as histamine, proteases such as tryptase, and proinflammatory and vasoactive prostaglandins and leukotrienes.[21]

Cross-linking of IgE by drug antigens can lead to limited skin reactions (flushing, pruritus, urticaria, angioedema) or multiorgan system involvement (sneezing, sinus and nasal congestion, cough, shortness of breath, wheezing, abdominal pain, nausea, vomiting, diarrhea), with decreased blood pressure and cardiovascular collapse during anaphylaxis. Reactions can occur within minutes of exposure and minimal amounts of the drug can induce severe reactions in highly sensitized individuals, such as laryngeal edema with asphyxiation. Disseminated intravascular coagulation and seizure-like acitivity are rare complications of anaphylaxis.[22] Retrospectively, finding an elevated tryptase in serum[23] and histamine in urine[24] can confirm the diagnosis.

The diagnosis of type I hypersensitivity reactions to drugs relies on the demonstration of in vivo or in vitro drug-specific IgE. Skin testing to drug antigens, such as penicillin, has a very high negative-predictive value. Only 1.8% to 3% of patients with a negative skin test present mild skin-limited reactions upon drug re-exposure.[25] Using different reagents, recent European data indicate a lower predictive value (see article by authors elsewhere in this issue). In a population of 126 patients who

received over six courses of carboplatin for recurrent ovarian cancer and were skin tested before each course, only 10 patients with negative skin test presented a hypersensitivity reaction, indicating that the rate of false-negative skin test is as low as 1.5%.[13] In the same population, 7 out of 41 patients with positive skin test were given carboplatin and all presented anaphylaxis. Eighty percent to 90% of patients reactive to present carboplatin have a positive skin test, indicating that the likelihood of a severe hypersensitivity reaction is very high in skin test-positive patients, and that rechallenging those patients is not indicated.

Hypersensitibity Reactions—Non-IgE Mediated

Hypersensitivity reactions induced by drug antigens upon initial exposure, without prior sensitization and with a similar clinical presentation and symptoms as IgE-mediated reactions are mostly considered non-IgE hypersensitivity reactions. Rarely, sensitization to a cross-reactive compound may occur (see article by authors elsewhere in this issue). They can result from the release of mediators from mast cells or basophils, without known IgE mechanism, and with a negative skin test.[26,27] Vancomycin-induced red man syndrome is caused by the direct release of histamine from mast cells and basophils.[28] Among chemotherapy drugs, taxenes can induce severe hypersensitivity symptoms, with cardiovascular collapse within few minutes of first exposure in patients who present a negative skin test. Mechanisms implicated in those reactions include the activation of complement by the diluent Cremophor[29] or the direct release of mediators. Reactions to aspirin and nonsteroidal anti-inflammatory medications include the inhibition of cyclooxygenase-1, decrease in bronchodilator prostaglandins E, and increased generation of inflammatory leukotrienes, as well as the release of tryptase from mast cell upon aspirin exposure in sensitive patients.[30–32]

CELLULAR AND MOLECULAR TARGETS

Although all clinical desensitization protocols are empiric and based on error and trial clinical experiences, in vitro desensitization of mast cells and basophils has provided some understanding of the mechanisms underlying successful in vivo desensitizations. Suboptimal doses of antigen, as low as one-tenth the optimal dose administered before an optimal dose, render mast cells and basophils unresponsive to antigens but not to other activating stimuli.[33] Suboptimal doses can induce unresponsiveness through excessive monomeric antigens, incapable of cross-linking surface FceRI receptors or through the rapid internalization of antigen cross-linked receptors depleting the cell surface.[34] Basophils can be desensitized in vitro to penicillin, but basophils isolated from a patient desensitized to penicillin were activated in vitro by penicillin antigens,[35] indicating that the presence of antigens at all times is critical to maintaining the desensitization state. In vitro rapid desensitization of human mast cells induces the decreased levels of signal-transducing molecules, such as syk, because of ubiquitinilation and degradation.[36,37] Naturally occurring syk-deficient basophils are unresponsive to drug antigens, indicating that syk is critical for activation and for desensitization.[15] In recent studies STAT6, which is responsible for the transcription of IL-4 and IL-13, has been involved in rapid desensitizations. STAT-6-deficient mast cells are capable of releasing mediators during the early phase of IgE cell activation but cannot release late cytokines, such as tumor necrosis factor (TNF)-α and IL-6, and cannot be desensitized to antigens.[16,38]

DESENSITIZATION TO ANTIBIOTICS

All antibiotics can induce IgE and non-IgE hypersensitivity reactions amendable to rapid desensitization, and the most common are β-lactams, including cephalosporins, vancomycin, and quinolones.

Penicillin and Cephalosporins

Patients allergic to penicillin are at risk when exposed to cephalosporins. Cross-reactivity between cephalosporins and penicillins is found in 4% to 11% of patients because of the related core β-lactam ring structure, mostly with first and second generation.[39] Specific cephalosporin IgE antibodies can be directed toward side-chain determinants that are not shared with β-lactam rings containing drugs,[40] posing less of a risk for penicillin-allergic patients. Other antibiotics containing β-lactam rings, such as monobactams (aztreonam), have no significant cross-reactivity with penicillins, and recently imipenem was shown to be tolerated by penicillin- and β-lactam-allergic patients.[41] Only immediate type I reactions to penicillin and β-lactams are amendable to rapid desensitization. Other reactions, such as maculopapular rashes, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous erythema, erythroderma, serum sickness, hemolytic anemia, neutropenia, thrombocytopenia, and acute interstitial nephropathy are not amendable to rapid desensitizations because outcomes are not available after drug re-exposure in these patients.

All patients with a history of IgE-mediated hypersensitivity and a positive skin test to either the minor or major penicillin determinants should avoid all β-lactam ring-containing medications, including penicillin, amoxicillin, ampicillin, and cephalosporins. Aztreonam and imipenem can be used as indicated by the infectious agents. If penicillin or cephalosporin treatment is mandated by the severity and nature of the infection, rapid desensitization is indicated.

Rapid Desensitization to β-Lactam antibiotics Including Penicillin and Cephalosporins

The first series of rapid penicillin desensitizations included escalating oral doses to treat 15 pregnant syphilis-infected women.[10] An intravenous protocol was later developed to treat 15 severely infected patients, which included 10-fold incremental doses[11] and induced 30% of nonlife-threatening side effects, including serum sickness. Since then, multiple case reports have been published with no series available to validate the efficacy and safety of the different protocols.

Up to 30% of cystic fibrosis patients develop hypersensitivity reactions after multiple exposures to β-lactams, which require rapid desensitizations.[42,43] A recent study indicated that 57 antibiotic desensitizations were done safely in 21 patients, 90% with cystic fibrosis. Most of the antibiotics were β-lactams and the success rate was 75%. Desensitization failures related to non-IgE mediated symptoms.[43]

A typical protocol for desensitization to intravenous penicillin and cephalosporins starts at one-ten-thousands to one-one-hundredth the target dose, and doubling doses are delivered every 15 to 20 minutes over the course of several hours until reaching the target dose.[44] Ceftazidime desensitization was done in seven cystic fibrosis patients to treat IgE-mediated hypersensitivity reactions,[45] with no major systemic reactions during desensitization. A recurrent rash occurred in two patients on the seventh and twelfth day after desensitization, one patient was successfully redesensitized, and one patient discontinued treatment. Cefotaxime desensitization was done in a 51-year-old man with bacterial spondylitis, and the treatment was continued for 4 weeks with no adverse events.[46] A series of eight patients with a positive skin test to penicillin and

cephalosporins (cefepime, ceftriaxone, and cefazolin) were desensitized to β-lactam drugs using a 2-hour and 15-minute protocol in which tripling doses were administered every 15 minutes, without major side effects.[47] An imipenem- and penicillin-allergic patient was desensitized to intravenous imipenem for multiresistant *Acinobacter pneumoniae* and the treatment was continued for 21 days without adverse events.[48]

The author and colleagues have used a standardized protocol at the Brigham and Women's Hospital in Boston, which includes a three solution, 12-step infusion allowing the patients to receive full therapeutic doses after 5.8 h (**Tables 1** and **2**). The solutions were made by 10-fold dilutions of the full target concentration (solution 3). Each solution was administered in four different steps. The rate of each step was increased every 15 minutes to deliver approximately twice the dose of the previous step. This model is based on the chemotherapy standard-desensitization protocol.[49] The author and colleagues performed 42 antibiotic successful desensitizations in 2005 and 2006 with this protocol (**Table 3**).[50] Side effects during antibiotic desensitizations were mild and included flushing, warmth, tingling, pruritus, erythema, rash, and hives. No serious events occurred, all subjects were treated for their full courses, and no late reactions were observed. Subjects were maintained on their antibiotics during the course of their treatments without need for repeated desensitizations.

Other Antibiotics

Vancomycin is an antimicrobial agent that is often used as an alternative treatment for serious staphylococcal and streptococcal infections in patients with hypersensitivity reactions to β-lactam antibiotics or whose infection failed to respond to β-lactam antibiotics. The incidence of adverse reactions has been reported to be in the range of 5% to 14% in adults, with the most common manifestation as the red man syndrome associated to nonspecific histamine release.[51] The risk of an adverse reaction to vancomycin increases with concurrent use of narcotics because of non-IgE-mediated, direct release of histamine from mast cells.[52] Although red man syndrome can be treated with slow infusions, IgE-mediated hypersensitivity reactions resistant to slow infusions have been described in which desensitization has been done.[51] A series of seven patients with serious staphylococal infections resistant to β-lactams antibiotics underwent rapid continuous intravenous infusion with multiple small increases in vancomycin concentration with a syringe pump similar to the protocol described in **Tables 1** and **2**, without major side effects.[52]

IgE-mediated hypersensitivity reactions to quinolones have been reported with cross-reactivity among ciprofloxacin and levaquin. A 35-year-old woman with chronic granulomatous disease and *Burholderia cepacia* infection was desensitized to intravenous ciprofloxacin with no side effects, and the treatment was continued for 4 weeks uneventfully.[53]

Table 1
Rapid intravenous desensitization to 1 g of ceftazidime in a cystic fibrosis patient

Full Dose	1000.0 mg	mg/ml	Total mg to be Injected in Each Bottle
Solution 1	250 cc	0.040	10.000
Solution 2	250 cc	0.400	100.000
Solution 3	250 cc	3.969	992.130

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