

Desensitization for drug allergy

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Purpose of review

Desensitization for drug allergy is the induction of temporary clinical unresponsiveness to drug antigens. Gradual reintroduction of small doses of drug antigen at fixed time intervals allows for the delivery of full therapeutic doses, protecting patients from anaphylaxis. Rapid desensitizations permit the use of essential antibiotics in severely infected allergic patients or aspirin in aspirin-sensitive cardiac patients undergoing revascularization. We review the indications and outcomes of recent protocols for desensitization to antibiotics and aspirin.

Recent findings

Despite the success of rapid desensitizations, the cellular and molecular inhibitory mechanisms are incompletely understood. In-vitro mast cell and basophil models implicate molecular signaling molecules syk and STAT6. Rapid desensitization protocols treat type I mast cell/IgE dependent reactions, such as anaphylaxis, as seen with sensitization to penicillin, cephalosporins, and other antibiotics. Anaphylactoid reactions induced upon initial drug exposure and with similar clinical presentation as immunoglobulin E-mediated reactions, as seen with aspirin, vancomycin and taxenes, can also be treated with rapid desensitizations.

Summary

Successful rapid desensitization protocols for treating adverse reactions to antibiotics and aspirin allow for treatment of critically infected patients and aspirin-sensitive cardiac patients. Standardized protocols with high success rates should be implemented as the standard of care.

Keywords

antibiotics, aspirin, desensitization, hypersensitivity reactions

Introduction

The development of rapid desensitizations for the treatment of drug hypersensitivities is aimed at providing essential medications while protecting patients from severe reactions induced by anaphylactic and anaphylactoid mechanisms. 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 or 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 [2–5,6*,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 anaphylactoid reactions. These reactions can result from direct release of mediators from mast cells or basophils, such as in vancomycin-induced red man syndrome, intravenous contrast dyes or taxenes.

Rapid desensitization: principles and cellular and molecular targets

Desensitizations for type I hypersensitivity reactions in penicillin allergic patients were first developed 50 years ago [8]. Successful cases of rapid progressive penicillin re-administration led to the concept of temporary clinical tolerization [3]. 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 [4]. 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 [7*,8], and, more recently, chimeric and humanized monoclonal antibodies in chronic inflammatory diseases [7*]. Since rapid desensitizations reintroduce potentially lethal drugs into highly sensitized patients, the molecular mechanisms need to be elucidated in order to improve the efficacy and safety of these

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Abbreviation

NSAID nonsteroidal antiinflammatory drug

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procedures. Recent studies of in-vitro rapid antigen desensitizations implicate mast cells and basophils as cellular targets, as well as syk [9], a signal-transducing molecule, and STAT6 [10], a signal transducer and transcription activator responsible for the transcription of IL-4 and IL-13.

Desensitization to antibiotics

Antibiotics can induce anaphylactic and anaphylactoid reactions amenable to rapid desensitization. The best studied antibiotics would include β -lactams with 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 4–11% of patients due to the related core β -lactam ring structure [11]. Specific cephalosporin IgE antibodies can be directed toward side-chain determinants that are not shared with β -lactam ring-containing drugs [12], 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 has been shown to be tolerated by penicillin and β -lactam allergic patients [13^{*}]. Only immediate type I reactions to penicillin and β -lactams are amenable 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 amenable to rapid desensitizations.

All patients with a history of IgE-mediated hypersensitivity and a positive skin test to either the minor or major penicillin determinant 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 [14]. An intravenous protocol was later developed to treat 15 severely infected patients which included 10-fold incremental doses [15] and induced in 30% of patients non-life-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 [16,17]. 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 were related to non-IgE-mediated symptoms [17]. A typical protocol for desensitization to intravenous penicillin and cephalosporins starts at 1/10 000 to 1/100 the target dose, and doubling doses are delivered every 15–20 min over the course of several hours until reaching the target dose [14,18]. Ceftazidime desensitization was done in seven cystic fibrosis patients to treat IgE-mediated hypersensitivity reactions [19] with no major systemic reactions during desensitization. A recurrent rash occurred in two patients on the seventh and twelfth day following desensitization; one patient was successfully re-desensitized 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 [20]. A series of eight patients with positive skin test to penicillin and cephalosporins (cefepime, ceftriaxone, and cefazolin) were desensitized to β -lactam drugs using a protocol of 2 h and 15 min in which triple doses were administered every 15 min without major side effects [21^{**}]. 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 [22].

We 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 (see Table 1). 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 min to deliver approximately twice the dose of the previous step. This model is based on the chemotherapy standard desensitization protocol, which we have used for 347 desensitizations in 2005 and 2006 for carboplatin, cisplatin, paclitaxel, doxorubicin, rituximab, infliximab and others [7^{*},8,23^{*}]. We have performed 42 successful antibiotic desensitizations in 2005 and 2006 with this protocol (personal communication; see Table 2). Side effects during antibiotic desensitizations were mild and include flushing, warmth, tingling, pruritus, erythema, rash, and hives. No serious events occurred, all patients were treated for their full courses, and no late reactions were observed.

Other antibiotics

Vancomycin is an antimicrobial agent that is often used as an alternative treatment for serious staphylococcal and

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

Full dose		1000.0 mg				Total to be injected in each bottle (mg)
Solution 1	250 ml of 0.040 mg/ml					10.000
Solution 2	250 ml of 0.400 mg/ml					100.000
Solution 3	250 ml of 3.969 mg/ml					992.130

Step	Solution	Rate (ml/h)	Time (min)	Administered dose (mg)	Cumulative dose (mg)
1	1	2	15	0.0200	0.0200
2	1	5	15	0.0500	0.0700
3	1	10	15	0.1000	0.1700
4	1	20	15	0.2000	0.3700
5	2	5	15	0.5000	0.8700
6	2	10	15	1.0000	1.8700
7	2	20	15	2.0000	3.8700
8	2	40	15	4.0000	7.8700
9	3	10	15	9.9213	17.7913
10	3	20	15	19.8426	37.6339
11	3	40	15	39.6852	77.3191
12	3	75	186	922.6809	1000.0000
Total time = 351 min					

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 5–14% in adults. The risk of an adverse reaction to vancomycin increases with concurrent use of narcotics due to non-IgE direct release of histamine from mast cells [24]. 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 carried out [25]. A series of seven patients with serious staphylococcal infections resistant to β -lactam antibiotics underwent rapid continuous intravenous infusion with multiple small increases in vancomycin concentration with a syringe pump similar to the protocol described in Table 1, without major side effects [24].

Table 2 Antibiotic desensitizations performed at Brigham and Women's Hospital 2005–2006 using the protocol from Table 1

Antibiotic	No. of desensitizations
Ancef	1
Ceftaxidime	7
Ceftriaxone	4
Cefazolin	1
Ciprofloxacin	1
Ertapenem	1
Imipenem	9
Meropenem	1
Nafcillin	3
Penicillin	7
Piperacillin	3
Trimethoprim	1
Zosyn	3
Total	42

There were no deaths or anaphylactic events during desensitization. Only mild side effects were observed (i.e. pruritus, flushing). All patients completed the desensitization protocol, reached the target dose, and were able to receive the prescribed antibiotic course.

IgE-mediated hypersensitivity reactions to quinolones have been reported with cross-reactivity among ciprofloxacin and levofloxacin. A 35-year-old woman with chronic granulomatous disease and *Burkholderia cepacia* infection was desensitized to intravenous ciprofloxacin with no side effects, and the treatment was continued for 4 weeks uneventfully [26].

Desensitization to aspirin and nonsteroidal anti-inflammatory drugs

Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) include ibuprofen, indomethacin, sulindac, naproxen, tolmetin, fenoprofen, meclofenamate, ketorolac, etololac, oxaprozin, diclofenac, ketoprofen, flurbiprofen, piroxicam, nabumatone, and mefenamic acid among others. Up to 20% of patients with asthma develop broad aspirin and NSAID intolerance manifested by upper and lower pulmonary symptoms (asthma, rhinoconjunctivitis). Patients without asthma can present cutaneous symptoms with chronic urticaria and angioedema when exposed to aspirin and NSAIDs, and specific allergic reactions induced by one NSAID or aspirin are also described, including anaphylaxis [27]. Desensitization to aspirin is considered in cardiac patients, patients with asthma with recurrent polyps and females with antiphospholipid syndromes during pregnancy.

Desensitization to aspirin and NSAIDs has been performed to provide cardiac protection or anti-inflammatory treatment in intolerant patients with no alternative medications. Desensitization was initiated in 1927 by Widal *et al.* [28] with the administration of small daily doses of aspirin to intolerant patients with asthma until tolerization was achieved. A refractory period was initially observed after a respiratory reaction induced by indomethacin, and tolerance to aspirin was induced after a

Table 3 Desensitization to aspirin in a patient with asthma

Time (min)	Dose (mg)
0	4
90	40
180	81
240	162
330	325
420	650

Aspirin to be continued at 650 mg orally, twice a day. Adapted from White *et al.* [30^{••}].

positive oral aspirin challenge. Although the mechanism of desensitization is unknown, desensitized patients tolerate aspirin and NSAIDs at pharmacological doses, and prolonged desensitization can be achieved by daily administration of aspirin or NSAIDs [29]. Protocols for aspirin and NSAID desensitization are based on the controlled progressive administration of incremental doses starting at 30 mg of aspirin and progressing to 60, 100, 150, 325, and 650 mg at 3 h intervals (Table 3). Respiratory responses are measured by forced expiratory volume at 1 s (FEV1), and a decline of 20% is considered a positive challenge. The dose is then repeated until no reaction occurs and the patient continues until reaching 325 or 650 mg. Cross desensitization is universal for all

Table 4 Desensitization to aspirin in a patient with aspirin-related urticaria-angioedema

Time (min)	Dose (mg)
0	0.1
20	0.3
40	1
60	3
80	10
100	30
120	40
140	81
160	162

Aspirin to be continued at 162 mg once per day. Adapted from Wong *et al.* [5].

NSAIDs once desensitization has been achieved at therapeutic levels [31]. Patients who have severe gastrointestinal intolerance to aspirin and NSAIDs have been challenged with lysil-aspirin either nasally or bronchially [32,33]. Desensitization has been less successful for intolerant patients with cutaneous reactions [34^{••}]; 22 patients with urticarial reactions induced by aspirin and NSAIDs were desensitized to aspirin and tolerated other NSAIDs after aspirin desensitization was maintained with daily doses of 325 mg. A study of 11 cardiac patients with a history of specific acute urticaria/angioedema after aspirin

Figure 1 Indications, drugs, and diseases treated with rapid desensitisation

Indications	Drug most frequently used	Disease
Anaphylactic IgE-mediated reactions Flushing, pruritus, urticaria, angioedema, laryngeal edema, rhinorrhea, conjunctivitis, shortness of breath, wheezing, bronchospasm, nausea, vomiting, diarrhea, hypotension	Antibiotics Beta-lactams Penicillins, cephalosporins, amino-penicillins Fluroquinolones Ciprofloxacin, levofloxacin	Sepsis Meningitis Pneumonia Pyelonephritis
	Chemotherapy drugs Platins Carboplatin, cisplatin, oxaliplatin	Primary and recurrent metastatic cancers (breast, ovarian, colon)
	Monoclonal antibodies Rituximab, trastuzumab	Chronic inflammatory diseases, cancers (leukemias, breast, ovarian)
Anaphylactoid Direct mast cell/basophil, complement, and leukotriene metabolism reactions Flushing, pruritus, urticaria, angioedema, throat tightness, shortness of breath, nausea, vomiting, diarrhea, hypotension, hypertension, back and/or abdominal pain	Aspirin/NSAIDs	Cardiac protection, asthma w/ nasal polyposis, chronic inflammatory diseases (RA, Crohn's)
	Vancomycin	MRSA
	Chemotherapy drugs Taxenes Paclitaxel, docetaxel	Primary and recurrent metastatic cancers (breast, ovarian, colon)

IgE, immunoglobulin E; MRSA, methicillin resistant *Staphylococcus aureus*; NSAID; nonsteroidal anti-inflammatory drug.

and NSAIDs indicated that nine were able to be desensitized with a fast protocol using incremental aspirin doses at 15–30 min intervals [7*] (Table 4). Similar protocols have been used to desensitize cardiac patients undergoing stent placements [35**].

Long-term aspirin desensitization

Sixty-five aspirin-sensitive patients with asthma were desensitized from 1988 to 1994 [29]. Increasing oral doses of aspirin up to 650 mg were administered and daily doses ranging from 350 to 1950 mg, with a mean of 1214 mg, were used for 1–6 years. Clinical outcomes were measured by the number of sinus infections, surgical procedures, hospital admissions, emergency room visits, recovery of sense of smell, and usage of topical and systemic corticosteroids. There was a significant reduction in the number of sinus infections and asthma hospitalizations, an improvement in the sense of smell, and a decrease in prednisone treatments. A significant reduction in the number of sinus and polyp operations and the use of nasal corticosteroids was also found. Desensitization and maintenance of daily aspirin is recommended in patients who have failed medical treatment and have undergone multiple surgeries for polyps or sinusitis [36*]. The association with leukotriene inhibitors during desensitization helps to shift the response to the upper respiratory tract without blunting the response [30**,34**]. Four pregnant women with antiphospholipid syndrome were desensitized orally to aspirin with few side effects and were maintained for several months on aspirin [37**].

Conclusion

Rapid desensitization protocols are available to patients who present type I mast cell/IgE-dependent hypersensitivity, reactions to antibiotics and to patients with anaphylactoid reactions to aspirin and NSAIDs, in which IgE/mast cell mechanisms cannot be demonstrated, as summarized in Fig. 1. During rapid desensitization, drug antigens are reintroduced in an incremental fashion, allowing for full therapeutic doses to be delivered with minor or no side effects. Temporary tolerization is achieved in hours and can be maintained if drug antigens are administered at regular intervals, depending on pharmacokinetic parameters. Rapid desensitizations should only be done in settings with one-on-one nurse–patient care and where resuscitation personnel and resources are readily available. After a successful desensitization, repeated desensitizations can be done in outpatient or inpatient settings with similar conditions. This would allow cystic fibrosis patients with recurrent infections, and aspirin-sensitive patients, who have discontinued aspirin for diagnostic and surgical procedures, to be safely re-desensitized. Failed desensitizations in which patients cannot achieve the target therapeutic dose are rare and require modified protocols.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 505).

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