

Medication Desensitization: Characterization of Outcomes and Risk Factors for Reactions

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Abstract

Background: Although its mechanisms are poorly understood, desensitization has been used to induce a temporary state of immune unresponsiveness in patients who have IgE-, non-IgE-, or pharmacologically mediated reactions when a drug has no alternatives. **Objectives:** The purpose of this study was to characterize the outcomes and identify risk factors for reactions during drug desensitization. **Methods:** A retrospective review of electronic medical records of adult patients undergoing drug desensitization from January 1, 2011, to December 31, 2013, was conducted in 2 intensive care units at a tertiary medical center. We used multivariate analysis to determine if specified risk factors were associated with reacting during the desensitization. Reactions were classified according to the pretest probability prior to desensitization, and then, reactions during desensitization were classified based on the occurrence of cutaneous reactions as follows: successful with no reaction, mild reaction, moderate reaction, or failed. Failure could result from any systemic allergic or cutaneous reaction resulting in procedure termination. The desensitizations were also assessed to determine if the patient required de-escalation secondary to a reaction. **Results:** A total of 88 desensitizations were performed in 69 patients. Desensitization was completed with no cutaneous reaction in 85% of patients. No baseline characteristic, medication class ($P = 0.46$), or indication for desensitization ($P = 0.59$) was associated with having a reaction. Reported histories of urticaria ($P < 0.0001$) and labored breathing ($P = 0.003$) during prior exposure were significant in identifying patients who might have a reaction during desensitization. However, neither history of urticaria nor labored breathing was independently associated with having a reaction in multivariate analysis (OR = 0.979, 95% CI = 0.325–2.952, $P = 0.970$, and OR = 1.626, 95% CI = 0.536–4.931, $P = 0.739$, respectively). **Conclusions:** Drug desensitization is safe for patients who have no alternative for therapy. Reported allergy histories of urticaria and labored breathing are both associated with having a reaction during the desensitization process.

Keywords

desensitization, allergy, immunology, anaphylaxis, critical care, basic pharmacology

Background

Drug hypersensitivity reactions are heterogeneous and involve all types of immune responses.¹ Immediate and accelerated reactions that are IgE mediated or related to non-IgE-mediated mast cell activation typically manifest with cutaneous symptoms, including flushing, pruritus, and urticaria but can also include more severe symptoms such as tachycardia, hypotension, airway obstruction, and desaturation. With these types of reactions, re-exposure to the initial antigen, even in low doses, can lead to the release of inflammatory mediators by activation of mast cells or basophils, and in severe cases, anaphylaxis.² Some of the most common causes of these immediate hypersensitivity reactions include β -lactam antibiotics, sulfonamides, radiocontrast media, local anesthetics, aspirin, and nonsteroidal anti-inflammatory drugs.^{3,4}

Point-of-care strategies to confirm or delabel patients of drug allergies, such as skin testing, are logistically difficult and also lack sensitivity for the identification of IgE-mediated reactions in the inpatient and acute care setting.⁵ Drug tolerance is a temporary induction of tolerance to a compound responsible for a hypersensitivity reaction. Desensitization can be accomplished for hypersensitivity reactions that involve IgE, non-IgE, or pharmacological

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mechanisms.^{4,6-9} Inducing a state of tolerance is used for therapeutic purposes and remains effective as long as exposure to the drug continues. Typically, protocols begin with a dose of the medication around 1/10000 to 1/100000th of the final dose. The subsequent doses are given in incremental fashion, typically by doubling the dose, to present the antigen to the patient.^{2,7,10,11}

Case series from several institutions have reported successful drug desensitizations.^{6,8,9,11-14} One 5-year retrospective review evaluated the safety and utility of antibiotic desensitizations in a small population of predominantly young patients suspected of having an Ig-E-mediated reaction, of whom 90% had cystic fibrosis. Of these desensitizations, 75% were deemed safe and successful, defined by completing the desensitization procedure without any reaction and the patients being able to tolerate repeated administration of the full dose.¹⁵ Another larger report of 413 desensitizations to chemotherapeutic agents in 98 patients has also been published. All patients received the full dose of the medications, and 67% of the patients had no reaction. Of the remaining desensitizations, 27% had mild reactions, and 6% had severe hypersensitivity reactions, with one of the severe reactions requiring rescue epinephrine.^{2,14} The high success rate and low number of cases requiring termination prompts evaluation of the outcomes of a more diverse patient population receiving not only an antibiotic or chemotherapy desensitization but other agents as well.¹⁵

With more than 3600 medical intensive care unit (MICU) admissions every year, including the patients admitted or transferred for medication desensitizations, Vanderbilt University Medical Center has developed more than 20 desensitization protocols to various antimicrobial agents, chemotherapeutics, and monoclonal antibodies. This study was conducted to determine the safety and efficacy of drug desensitization on multiple different classes of medications in a more diverse patient population and to determine if any specific risk factors predisposed patients to having a reaction during the desensitization process. With these results, the study should help shed light on the feasibility of performing desensitizations in an alternative area outside of the MICU, most ideally in patients who are at a lower risk of having a reaction. It is hypothesized that drug desensitizations are safe and effective to temporarily induce a tolerant state and allow a patient to receive treatment with an agent previously ruled out because of an allergic history.

Methods

Study Design and Participants

A retrospective analysis was conducted in patients who were admitted to the MICU or cardiovascular intensive care unit for the purpose of desensitization from January 1, 2011 to December 31, 2013. Patients were identified through an electronic MICU admission registry or by a desensitization

order in the electronic medical record (EMR). Data were collected from the EMR. The Vanderbilt University Medical Center's Institutional Review Board determined the study to be exempt and granted waiver of informed consent.

Patients 18 years and older who began a desensitization process at any time during the study period were included. Desensitization outcomes were classified as successful with no reaction, mild reaction, moderate reaction, or therapy failed. Patients failed the desensitization if the procedure was terminated as a result of evidence of any systemic allergic reaction before receiving the final dose of the desensitization. Successful outcomes were defined as receiving the full dose of medication with no documented cutaneous reaction. Mild and moderate reactions were defined as mild or moderate cutaneous reactions with successful completion of the protocol. The desensitization outcomes were independent of any required dose de-escalation. If a patient required de-escalation as a result of a reaction other than a cutaneous response, it may still be considered a successful outcome if the final dose of the protocol was received. Patients may have required a de-escalation of therapy to the last tolerated dose of the therapy after either a cutaneous or other systemic reaction; however, they may also have continued on the trial of desensitization with a retreat of the last tolerated dose. Patients requiring de-escalation of therapy may not have required discontinuation unless the patient was unable to tolerate continued escalated doses or the decision was made to stop the desensitization process.

Objectives

The primary objective of this study was to characterize the outcome of the desensitization. A multivariate analysis was performed to identify whether baseline variables, class of medication, indication for desensitization, or allergic symptoms were associated with having a reaction during desensitization.

Statistical Analysis

Categorical data are reported as numbers and percentages and analyzed using χ^2 tests. Continuous data are reported as means $\pm$ SDs and analyzed using Student's *t* tests. All variables that were considered statistically significant ($P < 0.05$) in univariate analysis were further analyzed by multivariate analysis using logistic regression.

Statistical analyses were performed with IBM SPSS Statistics, version 22. Two-sided *P* values ≤ 0.05 were considered significant.

Results

A total of 88 desensitizations were conducted in 69 patients. Characteristics of the patients are shown in Table 1.

Table 1. Baseline Demographics and Incidence of Reaction During Desensitization.

Characteristic	n = 88	No Reaction During Desensitization, n = 71	Reaction During Desensitization, n = 17	P Value
Male	29 (33%)	48 (68%)	11 (65%)	0.82
Age (years) ^a	44.9 ± 15.6	44.9 ± 16.2	42.3 ± 13.1	0.54
History of CF	25 (28%)	22 (31%)	3 (18%)	0.28
Number of reported drug allergies ^a	4.0 ± 2.9	4.4 ± 2.9	3.6 ± 3.3	0.38
History of previous desensitization	20 (22%)	19 (27%)	1.0 (6%)	0.07

Abbreviation: CF, cystic fibrosis.

^aMean (SD).

Aspirin for aspirin-exacerbated respiratory disease (AERD) was the most common agent desensitized. However, given that the mechanism for AERD is not immunological, the most common medication for immunological desensitization was piperacillin/ tazobactam. The most common indication for desensitization was a planned desensitization, meaning the patient was directly admitted to the ICU for the purpose of being desensitized. Six of these desensitizations were in patients where the initial allergic reaction occurred less than 90 days prior.

A total of 85% of the desensitizations were successful, meaning that the patient received the final dose with no cutaneous reaction. The remaining 15% of the desensitizations either had a cutaneous reaction, but still completed the protocol, or failed the desensitization because of a systemic allergic response requiring termination of the protocol (Figure 1).

No differences were seen between medication class ($P = 0.46$) and the indication for desensitization ($P = 0.59$) in patients who did and those who did not react during the desensitization (Table 2).

Three rescue medications were given during 23 of the observed desensitizations. Diphenhydramine and albuterol were each administered during 10 desensitizations, with an average number of 1.5 diphenhydramine doses being given per incident of reaction and albuterol being used 2.4 times per incident of reaction. Epinephrine was administered during 3 of the 88 desensitizations, with an average number of 1.7 doses given per incident of reaction.

An allergic history of urticaria or labored breathing during prior medication exposure were the only symptoms consistent with IgE-mediated reactions that were significant in identifying patients who might have a reaction during the desensitization process ($P < 0.0001$ and $P = 0.003$, respectively; Table 3).

Neither factor remained significant of being predictive of a reaction when a multivariate analysis was conducted using logistic regression (history of urticaria: OR = 0.979, 95% CI = 0.325-2.952, $P = 0.970$; history of increased respiratory effort: OR = 1.626, 95% CI = 0.536-4.931, $P = 0.739$). The average length of stay in the ICU was just >2 days, with the average length of stay in the hospital being 5 days.

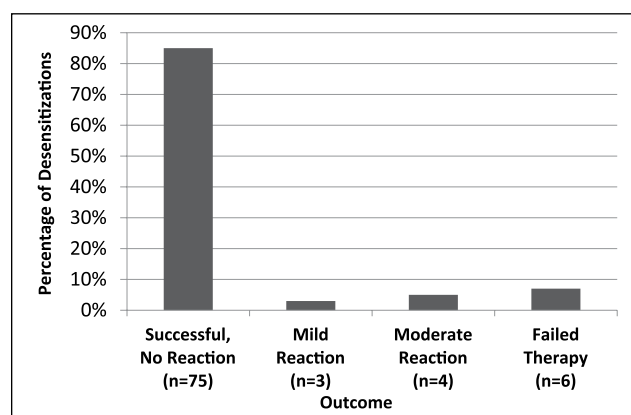


Figure 1. Outcomes of the 88 desensitizations. An outcome classified as successful was seen in 85% of the patients. Mild cutaneous reactions were seen in 3%. A moderate reaction was seen in 5%. The procedure was terminated in 7% of the desensitizations and classified as a failure because of any evidence of a systemic allergic reaction. These patients did not receive the final dose of the desensitization.

Discussion

Desensitization is performed out of need for a drug when typical diagnostic procedures cannot be performed with sufficient timeliness—that is, when a patient has been identified as skin test positive and the treatment of the implicated drug is deemed essential. It is acknowledged that many patients with effective desensitization without adverse effects would have also had negative responses to skin testing or an oral challenge.⁵ We report the outcomes from a diverse series of drug desensitizations as well as risk factors that may be predictive of patients having a reaction during the desensitization process. A total of 85% of all the drug desensitizations over the 3-year time period were successful, with patients receiving the final dose and not having a cutaneous reaction. No baseline characteristics were identified as predicting patients who might have a reaction. There were no medication classes or desensitization indications associated with patients having a reaction. Evaluating the patients' self-reported allergic reactions did not identify any association predictive of a patient having a reaction.

Table 2. Medication Class (Panel A) and Indication (Panel B) Predictability of Reaction ($P = 0.46$ and 0.59).

Panel A			Panel B		
Medication	No Reaction, n = 71	Reaction, n = 17	Indication	No Reaction, n = 71	Reaction, n = 17
Penicillins	23 (32%)	3 (18%)	Planned desensitization	32 (45%)	8 (47%)
Aspirin	16 (23%)	10 (59%)	CF exacerbation	16 (32%)	3 (18%)
Trimethoprim/ Sulfamethoxazole	8 (11%)	1 (6%)	Syphilis	2 (3%)	2 (12%)
Cephalosporins	6 (8%)	1 (6%)	Unspecified bacteremia/ endocarditis	2 (3%)	0 (0%)
Cisplatin	6 (8%)	0 (0%)	Abdominal abscess	2 (3%)	0 (0%)
Carbapenems	2 (3%)	0 (0%)	MSSA bacteremia	2 (3%)	0 (0%)
Infliximab	2 (3%)	0 (0%)	Endocarditis	2 (3%)	0 (0%)
Fluoroquinolones	1 (1%)	1 (6%)	Unspecified infection	2 (3%)	0 (0%)
Vancomycin	1 (1%)	1 (6%)	Osteomyelitis	1 (1%)	1 (6%)
Linezolid	1 (1%)	0 (0%)	Wound infection	1 (1%)	1 (6%)
Aztreonam	1 (1%)	0 (0%)	Bronchiectasis	1 (1%)	0 (0%)
Metronidazole	1 (1%)	0 (0%)	Chest pain	1 (1%)	0 (0%)
Probenecid	1 (1%)	0 (0%)	CMV retinitis/viremia	1 (1%)	0 (0%)
Everolimus	1 (1%)	0 (0%)	Meningitis	1 (1%)	0 (0%)
Immune globulin	1 (1%)	0 (0%)	NSTEMI	1 (1%)	0 (0%)
			Persistent trichomonas	1 (1%)	0 (0%)
			Pneumonia	1 (1%)	0 (0%)
			Coronary artery disease	1 (1%)	0 (0%)
			VRE bacteremia	1 (1%)	0 (0%)
			Cardiomyopathy	0 (0%)	1 (6%)
			STEMI	0 (0%)	1 (6%)

Abbreviations: CF, cystic fibrosis; CMV, cytomegalovirus; MSSA, methicillin-sensitive *Staphylococcus aureus*; NSTEMI, non ST-segment elevation myocardial infarction; STEMI, ST segment elevation myocardial infarction; VRE, vancomycin-resistant Enterococci.

Table 3. History of Allergic Symptoms Consistent With IgE-Mediated Reactions.

Characteristic	No Reaction During Desensitization, n = 71	Reaction During Desensitization, n = 17	P Value
Urticaria	29 (41%)	15 (21%)	<0.0001
Labored breathing	31 (45%)	1 (1%)	0.003
Tongue swelling	15 (21%)	3 (18%)	0.75
Angioedema	10 (14%)	1 (6%)	0.36
Lip swelling	8 (11%)	2 (12%)	0.95
Wheezing	8 (11%)	2 (12%)	0.96
Hypotension	8 (11%)	0 (0%)	0.15
Difficulty swallowing	7 (10%)	4 (24%)	0.13
Other	6 (8%)	0 (0%)	0.21
Vomiting	3 (4%)	2 (1%)	0.23
Abdominal pain	3 (4%)	1 (1%)	0.77
Unknown	2 (3%)	0 (0%)	0.48
Laryngospasm	1 (1%)	0 (0%)	0.62
Stridor	1 (1%)	0 (0%)	0.62

However, focusing only on symptoms that are consistent with IgE-mediated reactions identified patients who had an allergic history of urticaria or of increased work of breathing as having an association predictive of having a reaction.

We sought to identify if any of the patients who had a reaction or required de-escalation had their reported allergy reaction within 90 days of the desensitization because patients are at the highest risk of reaction during desensitization in this time period.¹⁶ Of the non-AERD desensitizations, 6 were

conducted within 90 days of the original allergic reaction. Only 1 of the 6 desensitizations required de-escalation and failed therapy because the protocol was stopped as a result of other systemic reactions. There was no correlation observed regarding the outcome of desensitization and the time since the original allergic reaction.

Prior to the desensitizations, an interprofessional team consisting of members of the Division of Allergy and Immunology, the Division of Infectious Diseases, and the Department of Pharmacy collaborated to design the protocols. Each desensitization was designed using the following general rules when designing desensitization protocols: administration of a 1:10 000 to 1:100 000 of the fraction of the therapeutic dose, gradual increases in concentration over a short time period, 12 to 20 steps, and dose increases usually being double the previous dose and given at 15- to 30-minute intervals.^{7,17} Several other precautions were also taken prior to desensitization. Patient's baseline peak expiratory flow rate was taken to monitor if this was affected during the desensitization. Vital signs and oxygenation were constantly monitored during the entirety of the desensitization as well as signs and symptoms of an allergic reaction for at least 10 minutes following each dose. No patient received premedication prior to desensitization except for the one patient receiving vancomycin. The patient who was desensitized to vancomycin received 1 dose of hydrocortisone and diphenhydramine prior to initiation because of the high likelihood of a reaction.^{4,8,18,19} Other medications, as mentioned previously, were available at the bedside as rescue medications within an anaphylaxis or reaction kit, including albuterol, hydrocortisone, diphenhydramine, and epinephrine.

Although the number of each medication desensitized was low, with the majority of classes being antimicrobial agents, the variety of medication classes, including antibiotics, chemotherapeutics, monoclonal antibodies, and aspirin, is unique to our study. We had fewer patients with a history of cystic fibrosis than previously reported in Turvey et al²⁰ and a broader inclusion of medications than previously demonstrated in Castells et al.¹⁴ This makes our results more generalizable and not specific to a subset of patients or medication class.^{2,11,14,15} A third strength is standardization of the desensitization process. Our desensitization process requires an allergy consult. This ensures uniform dosage and monitoring. The requirement of a consultation from the allergy and immunology inpatient consultation service means the specialist will collect a pertinent allergy history to determine if a desensitization is necessary as well as to ensure compliance with and completion of the protocol.

This study has some limitations characteristic to it being conducted retrospectively in a single center. However, the large number of protocols, various medication classes, and differing indications may minimize these limitations. Only 69 patients were desensitized during this time period, which

represents a small number in size, but this is still the most diverse published series in terms of medication classes.

A second limitation to the study was that the time of admission was not collected. Instead, calendar days were considered to be entire days. This is why the unexpected, but easily explainable finding of an average length of ICU stay of more than 2 days was found. The majority of the desensitizations were planned, meaning the patient was admitted for the purpose of completing the protocol. The patients who were admitted for a planned desensitization arrived to the hospital in the late morning or early afternoon, and the desensitization typically lasted through the night. The timing of the desensitization process resulted in patients being admitted for 2 calendar days. The timing of the desensitization allows for an appropriate amount of preparation time by the pharmacy and time to acquire 1:1 nursing care needs. This can be further explained by the mean and median number of doses in each desensitization being 16; the mean duration of the desensitization protocols included being 4.7 hours, with typically 15 minutes between each escalating dose; and most patients being directly observed between 0.5 to 1 hours following the last dose. Patients are most always observed in the ICU until after morning rounds in which they are immediately discharged. Some, but not all, patients receive a 1-time full dose prior to discharge.

The largest limitation to this study was the accuracy of the patient's allergic history; however, an attempt was made to overcome this by requiring an allergy service consultation. There are many efforts among nurses, physicians, and pharmacists to reconcile an accurate allergy history on inpatient admission. Some of the patients had recently witnessed reactions; however, the majority of the patients reported histories from many years prior, making them at much lower risk for reactions during desensitization. This surfaces the question about whether or not these reactions were IgE or non-IgE mediated or an allergic reaction at all. Skin testing was only used for 2 cases prior to administration during this study, which is reflective of real-life clinical practice, with skin testing often not being performed. The patients may have been better treated with a graded challenge or low-dose oral challenge to identify the true risk of an IgE-mediated reaction and then to proceed to rapid desensitization if necessary; however, patients who received a graded challenge were not included in this evaluation.

The paucity of severe reactions suggests that the majority of desensitizations could safely be conducted outside the ICU setting and potentially in an outpatient setting, where appropriate monitoring is available. AERD represents a different category of patients who do require careful monitoring, with each escalation of the dose based on FEV1 measurement.²¹ Future research should study the safety and cost-effectiveness of different strategies and settings for the reintroduction of a necessary drug therapy. Our study of desensitization in the ICU has supported this to be a safe and effective

procedure across multiple classes of drugs. However, costs may be contained further by risk stratification and performance of other procedures where possible, such as oral challenge in lower-intensity settings. Because desensitization is only a temporary procedure, all patients who undergo desensitization should ideally be seen by an outpatient drug allergy service to perform skin testing and/or oral challenge as definitive procedures to either delabel patients of the allergy to the drug in question or provide additional information as to avoidance of the drug and/or drug class in question.

In conclusion, this study demonstrates that the majority of patients who undergo drug desensitization have successful outcomes. The most common desensitization was for aspirin for AERD. No baseline characteristic, previous desensitization, specific medication class, or indication for desensitization was definitively predictive for patients having a reaction during desensitization. A previous allergic history of urticaria and/or of labored breathing was associated with cutaneous reactions during desensitization.

Abstract Publication/ Presentation

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Declaration of Conflicting Interests

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