

Survey of Drug Allergy Testing, Challenge, and Desensitization Practice

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Abstract

Background: The lack of standardized skin test products to determine a patient's (hyper-) sensitivity to medications has required physicians to empirically develop their own testing procedures. These approaches include puncture and intradermal skin tests, patch tests and medication challenges. Desensitization protocols are also frequently used when the necessity of a particular medication is urgent.

Objective: This study surveyed drug hypersensitivity testing and desensitization practices reported in 3 allergy journals, over a 5-year period 2004-2008.

Methods: This survey collected reports of skin tests, challenges, and desensitization to medications, vaccines, and diagnostic agents in 3 leading allergy journals. Studies were included if they reported sufficient detail that the reader could reasonably be expected to reproduce the technique reported. We did not include reports of in vitro testing because the ability of the individual practitioner to perform these tests may be limited.

Results: Data for 191 drugs were sufficiently detailed to include. Testing with antimicrobial agents was reported most frequently; and several newer classes of medications such as monoclonal antibodies and interferons are also included. Skin testing to detect medication allergy was the most commonly reported technique; however there were numerous drug challenge and drug desensitization schedules used in practice.

Conclusion: Beyond testing for medications such as antibiotics, corticosteroids and local anesthetics skin testing, challenge, and desensitization schedules have been described for numerous other medication classes. The variety of these schedules is likely driven both by the needs of clinical practice and the lack of standardized skin test preparations.

Keywords: Allergy; Antimicrobials; Challenge; Desensitization; Drug hypersensitivity; Patch testing; Skin testing

Abbreviations: MDM: Minor Determinant Mixture; PEN: Penicillin; PPL: Penicilloyl Polylysine; TMP-SMX: Trimethoprim-Sulfamethoxazole

Introduction

Each year, the release of new drugs, as well as the approval of novel uses of older drugs by the US Food and Drug Administration, increases the potential for adverse reactions to medications. From 1992 to 2002, an average of 41 new drugs was marketed per year in the United States [1]. As of January 1, 2002, more than 3,200 prescription drugs were on the US market. This figure does not include the 600+ herbal medications and nutritional supplements that are widely used [1]. In recent years, the release of new molecular entities totals 259 (24 entities in 2001; 17 in 2002; 21 in 2003; 36 in 2004; 20 in 2005; 22 in 2006; 18 in 2007; 24 in 2008; 26 in 2009; 21 in 2010; and 30 in 2011) [2-6]. Moreover, newer classes of medications (e.g., monoclonal antibodies) and newer vaccines (e.g., Zostavax and human papillomavirus recombinant vaccine quadrivalent), each with the potential for adverse reactions, are steadily being introduced into clinical practice. Currently, in the United States, only one commercial product is approved for detecting immediate drug hypersensitivity (Pre-Pen [benzylpenicilloyl polylysine], AllerQuest LLC, West Hartford, Connecticut). This has left a gap in our ability to predict or confirm the potential ability of medications to cause life-threatening reactions.

Adverse reactions have been described, not only to β -lactam and other antibiotics and antivirals [7-9], but also to nearly every class of medication in clinical use. These include [but are not limited to] chemotherapeutic agents and other blood products [10-13], anti-human immunodeficiency virus agents [14,15], nonsteroidal antiinflammatory drugs [16], tyrosine kinase inhibitors [17], anesthetic drugs [18-20], coagulation factors [21,22], allopurinol [23], bisphosphonates [24], thienopyridines [25], monoclonal antibodies [26], glucocorticoids [27],

vaccines and vaccine components [28,29], and desferrioxamine [30], to mention a few.

Some adverse reactions to drugs are mediated by drug-specific CD4⁺ and CD8⁺ T-cells through their $\alpha\beta$ T-cell receptors [31], and a high frequency of drug-specific T cells has been observed after severe systemic reactions [32]. Also, some reactions to medications will neither be predicted nor diagnosed by skin or in vitro hypersensitivity testing [33,34]. However, skin testing for immunoglobulin E-mediated sensitivity, drug challenges, and desensitization procedures are common, practical methods of approaching the patient with a suspected drug allergy. General guidelines have been published for skin testing for drug hypersensitivity, including the best time for testing after clinical symptoms have occurred, test preparations, test vehicles and concentrations, testing of patients at higher risk, and the use of controls [35].

Despite the current void of standardized skin test reagents, practicing physicians have continued to report their experiences with skin testing and desensitization [36] to a wide range of drugs. Here, we have compiled the experiences with these procedures reported from 2004 through 2008 in three leading allergy journals.

Materials and Methods

Issues of the Journal of Allergy and Clinical Immunology, Allergy,

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and *Annals of Allergy, Asthma and Immunology* from January 2004 through December 2008 were reviewed for reports of skin testing, challenge, or desensitization to medications. Articles, including meeting abstracts, were included in this survey if they contained sufficiently detailed information pertaining to the procedure described [e.g., drug concentrations for epicutaneous, intradermal or patch skin tests, and the medication challenge, or desensitization schedules used] such that this information could reasonably be used to replicate the indicated procedures. In vitro testing was not included in this survey because of the variability of practicing physicians' ability to perform these tests in an office setting. This study was approved by the Mayo Clinic Institutional Review Board.

Results

During the 5-year period, reports of 191 drugs met the simple criteria described above. Our results show that as a class, antibiotics were most commonly skin tested, challenged and/or desensitized for a history of hypersensitivity. There were 39 different antibiotic drugs listed in 31 separate reports. Addition of the β -lactamase inhibitor clavulanic acid (1 report), the antiviral acyclovir (1 report), anti helminthics (2 drugs, 2 reports), antifungals (1 report), anti-malarials (3 drugs, 2 reports) and the HIV-1 protease inhibitor amprenavir (2 reports) brought the total number of antibiotics and antiviral drugs to 48 and the total number of reports to 39.

Other commonly-reported drugs included antineoplastic medications (10 drugs, 15 reports), corticosteroids (10 drugs, 5 reports), neuromuscular blocking drugs (8 drugs, 6 reports), local anesthetic agents (6 drugs, 7 reports) hypnotics (6 drugs, 5 reports), opioid analgesics (5 drugs, 6 reports) and COX-2 inhibitors (5 drugs, 9 reports).

It was not surprising that commonly used medications were examined for hypersensitivity; however, testing was also performed on newer classes of available medications because of their increasing importance in clinical practice. These medications included monoclonal antibodies (5 monoclonal antibodies, 6 reports), and interferons for treatment of multiple sclerosis (3 drugs, 1 report), and vaccines (10 vaccines, 5 reports).

Drug concentrations for epicutaneous and for intradermal skin tests are listed 258 times and for patch tests 27 times. Drug challenges (41 reports) were also performed along with or in lieu of skin tests. 42 drug desensitization schedules were reported. 19 instances of side effects from skin testing, challenges or desensitization occurred. For individual drugs the drug concentrations used for skin testing varied considerably and the type of testing utilized depended on the general route of administration for the drug itself, for example COX-2 inhibitors were generally tested by oral challenge whereas opioid analgesics were tested by epicutaneous and intradermal skin tests.

An alphabetical list of drugs, listed side effects, and concentrations used for epicutaneous, intradermal and patch skin tests as well as challenge and desensitization schedules are given in the Table 1 [38-165].

Adverse reactions to skin testing were reported 20 times in the current survey (Table 1 included as supplementary data). These reactions were generally cutaneous (itching, flushing, erythema, urticaria and delayed cutaneous reactions). Shortness of breath, wheezing, nausea, abdominal pain, and headache also were reported. There were a total of 4 reports of anaphylaxis associated with intradermal testing with penicillin G, penicillin MDM, clavulanic acid, and with amoxicillin. In

each of these instances epicutaneous testing had not been done. This suggests that skin testing is generally safe at the concentrations listed in the Table 1 included as supplementary data, but that the potential for anaphylaxis exists for penicillin-allergic patients who are solely tested intradermally without prior epicutaneous testing.

Side effects occurred to 6 medications from administered drug challenges and to 4 other medications during desensitization. Generally, these responses were dermatologic reactions including flushing, hives, generalized erythema, and pruritus; however, additional symptoms included headache, trembling, abdominal pain and shortness of breath. 3 of 4 patients challenged with etoricoxib experienced an adverse reaction at doses of 20-60 mg. For 3 medications including albendazole, lidocaine and mebendazole a delayed cutaneous reaction occurred following challenge.

Discussion

Despite the large and increasing number of medications used in clinical practice today, available skin test materials for detecting or confirming clinical hypersensitivity are lacking. Such skin test materials are sorely needed because surveys of adverse drug events often do not clearly distinguish allergic reactions from nonallergic events [166]. These latter events can include toxic reactions from an unintentional overdose, adverse drug effects after administration of a normal dose, complement activation, nonspecific histamine release, bradykinin accumulation, activation of leukotriene synthesis, or idiosyncratic intolerance reactions due to genetic susceptibilities [e.g., rapid acetylation profile of some patients increases the risk of hepatotoxic effects with isoniazid] [167]. In the absence of standardized skin tests, physicians are, by necessity, proceeding year by year with empiric trials of skin tests, challenges, and desensitization procedures, as shown by this survey.

Several lines of evidence suggest that improved testing for drug hypersensitivity could improve clinical practice. Adverse drug events affect 10% to 20% of hospitalized patients, with up to one-third of these reactions due to hypersensitivity [168]. When drug provocation tests have been used to confirm a diagnosis of drug hypersensitivity to implicated drugs (β -lactams, aspirin and other nonsteroidal antiinflammatory drugs, paracetamol, macrolides, and quinolones), less than 25% of patients with a suggestive history of drug hypersensitivity had a confirmatory result with reproduction of symptoms [166]. Up to 5% of medical hospital admissions are due to drug reactions [169] and among children treated in emergency departments for allergic drug reactions, more than 60% were caused by antimicrobial agents [170].

A prospective cohort study of adverse cutaneous drug reactions in hospitalized patients showed a prevalence of 0.7%, and the most common dermatoses were morbilliform rash (51.2%), urticaria (12.2%) and erythema multiforme (4.9%) [171]. The most frequently implicated drugs were amoxicillin clavulanate, amphotericin B, and metamizole. In one French report that examined anaphylaxis during 13,000 episodes of general anesthesia from 1999 through 2000, 518 of 789 patients had an immune mechanism verified, with 58.2% of reactions due to muscle relaxants and 15.1% due to antibiotics [172]. In the present survey of non selected patients, both antibiotics and neuromuscular blocking drugs were among the leading medications for skin testing and challenge.

The European Network for Drug Allergy has published guidelines for skin epicutaneous, intradermal, patch, and photopatch tests [37]. These guidelines provide general techniques that can be used to

determine drug sensitivity in at-risk patients, including the best interval between drug hypersensitivity and skin testing, testing of patients who are at higher risk, test preparations, test vehicles and solutions, test concentrations, and interpretation of test results. For patients who have nonimmediate reactions, additional provocation tests are outlined [173].

Clinical experience with antibiotic desensitization in allergic patients has also been reviewed with the aim of establishing standardized protocols. The procedure begins with an antibiotic dose of 2 mcg or 1/1,000,000 of the full therapeutic dose, diluted in normal saline, and delivered by continuous intravenous infusion over 30 minutes. With subsequent 10-fold increases, all are delivered in a similar fashion over 30 minutes. A safe and successful desensitization was achieved in 75% of patients using this procedure [174]. The current series suggests that in addition to these guidelines, alternative testing and challenge and desensitization procedures are common in clinical practice.

The findings given in the present survey illustrate a cross-section of actual current clinical practice of assessing drug hypersensitivity. Year by year the list of drugs that potentially cause untoward reactions will continue to expand. Newer classes of drugs are being released for use in all subspecialty fields. Alternative uses of older medications will also potentially expand the population groups exposed. Based on the results of the current survey, the concentrations listed for epicutaneous skin testing for the listed drugs appear to be safe. Anaphylaxis occurred during intradermal skin tests to 4 antibiotics that were not preceded by an epicutaneous test. Side effects from challenges and desensitization were generally immediate or delayed dermatologic responses, and in no instance did hypotension occur from these procedures. Since most of the reports of this survey comprise one or a limited number of patients it will remain important to stay abreast of current clinical experience with drug testing, challenge, and desensitization procedures.

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