Original Article

Patient-reported multiple drug reactions: Clinical profile and results of challenge testing

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ABSTRACT

Background: Some patients report hypersensitivity reactions to many drugs making it difficult to prescribe medications when they fall ill. **Aim:** To describe the clinical profile of multiple drug hypersensitivity and the results of challenge testing in a large teaching hospital. **Methods:** We performed a five-year retrospective review of the records of patients who complained of reactions to two or more unrelated drugs and avoided medication because of a fear of developing reactions. Oral challenge testing was carried out in hospital with drugs suspected by the patient to cause reactions and/or commonly prescribed medications. A positive reaction was diagnosed when symptoms and signs resembled previously experienced episodes and there was no such reaction with placebo. **Results:** Twenty three patients (aged 14-65 years; 19 females) underwent challenge testing. Their complaints had been present for 1-30 years, with 2-40 drug reaction episodes reported. Antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs) were most commonly implicated, and urticaria/angioedema were the most often reported manifestations. The patients underwent 3-27 challenges with 1-24 drugs. Three had positive challenge reactions with various NSAIDs, 13 developed symptoms and signs that were judged not to be true reactions, and 7 had no reactions. None of our patients qualified for a diagnosis of true multiple drug hypersensitivity. **Conclusion:** Patients who believe they are allergic to multiple, pharmacologically unrelated drugs are usually mistaken. Challenge testing is a reliable way of demonstrating this and providing patients with a list of safe drugs.

Key words: Adverse drug reactions, drug eruptions, multiple drug reactors

INTRODUCTION

Some patients report that they react adversely to many drugs. This poses problems when they fall ill: they do not know which drugs can be taken safely and their doctors are unwilling to prescribe medications for fear of precipitating a reaction. While these patients are encountered in clinical practice, there is no data on the frequency of the problem in the community. Reports of large series of patients indicate that the condition is not rare.[1,2] Unfortunately, no reliable *in vitro* tests are available to determine which drugs should be avoided and which ones are safe, and elective challenge testing has been recommended in this setting.[2,3]

In our department, we have offered challenge tests to patients with drug reactions for several years.[4-6] We describe the findings in patients who underwent challenge testing for suspected multiple drug reactions.

METHODS

All patients who stated that they reacted to two or more drugs and who were, consequently afraid to take medicines were informed that the only reliable way to determine which drugs caused the reaction and which drugs were safe was to undergo challenge testing. This would involve taking drugs under our direct supervision after admission to the hospital and that the procedure would take about two weeks.

A retrospective review of records of all patients who

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underwent challenge tests at our hospital between June 2001 and April 2006 was performed. The duration of drug sensitivity, nature and frequency of reactions, drugs implicated by the patient, and the correlation between drug intake and the reactions were recorded. The results of psychiatric evaluation carried out in some patients were noted.

Drug challenge testing

Patients were admitted to hospital for this procedure which was carried out after obtaining written, informed consent. Patients who reported severe anaphylactic reactions were not tested with the implicated drugs. Drugs and equipment for emergency resuscitation were available in the ward.

The list of drugs tested consisted of a set of commonly prescribed drugs that the patient was likely to need and/or drugs suspected by the patient to be the cause of reactions.

Oral challenge was performed by administering a single therapeutic dose of the drug per day, in the presence of the ward nurse. If suspicion of a true reaction was strong, a half-dose was given on one day followed by the full dose the next day. Most patients were tested with placebo on the first day and by other drugs on the following days. Challenges were carried out initially with one drug per day, but if daily tests continued to be negative, we accelerated the procedure in five patients, administering 1 drug in every 12 h in order to shorten the hospital stay.

Patients were monitored for reactions and any symptoms reported were recorded. Symptoms and signs were evaluated by a dermatologist to assess if they represented non-specific symptoms or a true drug reaction. A true drug reaction was diagnosed when symptoms and the time course of the reaction resembled previously experienced episodes and were accompanied by signs of inflammation in the skin including erythema, wheals, macules and papules. A patient whose findings were not suggestive of a drug reaction was usually challenged with the same drug again to confirm that the reaction was not a true reaction. In patients who developed symptoms during testing, further challenges were performed after all symptoms subsided.

Following completion of testing, a safe drug list containing drugs that had been tested and found safe was provided to the patient. If a true drug reaction was detected, written instructions to avoid the causative drug(s) were given.

RESULTS

Twenty three patients underwent challenge testing. The age of the patients ranged from 14 to 65 years (mean, 36.4 ± 12.4 years), with a female preponderance (19/23, 82.6%). The complaints had been present for 1-30 years (8.5 ± 7.5 years), and the number of episodes of drug reactions reported ranged from 2 to around 40. Most patients reported that their symptoms occurred only with drug intake and not otherwise, appearing immediately or delayed up to two days after the drug was taken. Four patients reported occasional episodes of the same symptoms without any drugs being taken, while two reported predominantly spontaneous episodes.

Urticarial wheals (14, 60.7%) and angioedema or localized swelling (14, 60.7%) were the most often reported manifestation of the reactions. Angioedema was associated with respiratory distress in three patients. Other symptoms experienced included giddiness (4), pruritus, either generalized (3) or localized to the palms and soles (2) or a skin rash (5) [Table 1]. Some patients reported multiple symptoms.

Various antibiotics and analgesics/antipyretics were most commonly implicated, along with other drugs including proton pump inhibitors, antitussives, antihistamines, anti-amebics, vitamin supplements, oral corticosteroids, local anesthetics, and ayurvedic or homeopathic preparations.

Patients underwent 3-27 challenges (mean, 15.2 challenges) with 1-24 drugs (mean, 12.1 drugs) [Table 2]. Challenges were not conducted with ayurvedic or homeopathic drugs except in one patient who insisted that we test an ayurvedic anti-arthritic, anti-inflammatory drug that he used to take.

Out of the 23 patients tested, 3 had true drug reactions on challenge, 13 developed symptoms and signs that were judged not to be true reactions and 7 patients had no symptoms/reactions with any of the drugs tested (although this group included 2 not tested with their suspect drugs as their histories strongly suggested true, severe reactions.)

Overall, 47 (13.4%) of the 350 challenges resulted in symptoms in 16 (69.6%) patients. The symptoms reported were mostly non-specific including dizziness, weakness, itching, headache, nausea, vomiting, abdominal pain and tightness of the chest. Six (26%) patients reported symptoms following placebo administration: itch in three, urticaria in one, palmoplantar burning in one and dizziness in one.

Table 1: Symptoms attributed by patients to drug reactions

Symptoms	No. of patients
Cutaneous	
Wheals	14
Angioedema	9
Localized swelling, possibly angioedema	5
Pruritus	
Generalized	3
On palms and soles	2
Rash	5
Gastrointestinal	
Oral ulcers, dysphagia	1
Nausea, vomiting	4
Abdominal pain/ burning	2
Neurologic	
Tremors	1
Giddiness	4
Seizures, neck stiffness, palpitations, sweating	1
Unilateral limb weakness	1
Loss of consciousness	1
Other	
Respiratory distress	3
Redness of eyes, visual blurring	1
Fever	1
Generalized body ache	1

Only 17 (6.8%) challenges in 9 patients were accompanied by clinically detectable signs viz., angioedema, wheals, rhonchi, perioral papules and hypotension. Of these nine patients, three were deemed to have developed true drug-induced angioedema. In the remaining six patients, five did not have any symptoms when challenged with the same drug again and one had similar findings (wheals) when challenged with placebo.

Of the three patients with true reactions, one had angioedema of the eyelids with aspirin, another developed angioedema with respiratory distress with both ibuprofen and diclofenac, but not with paracetamol, nimesulide or valdecoxib, and the last had angioedema of the tongue with dysphagia on receiving nimesulide. The reactions promptly resolved in all three patients with appropriate treatment.

A psychiatric consultation was obtained in eight patients which revealed clinical diagnoses of depression in three patients, generalized anxiety with depression in one patient, possible anxiety disorder in one patient, and an axis III personality with stress in one patient while two patients had no evidence of any psychopathology. The patient with generalized anxiety and depression was noted to have a true drug reaction (angioedema with ibuprofen and diclofenac). No particular factors determined a psychiatric consultation which was undertaken when considered necessary by the referring dermatologist and as per

Table 2: Classes of drugs tested

Drug classes	No. of challenges with each drug class	Specific drugs tested (no. of challenges with each)
Antibiotics	78	Ciprofloxacin (24), roxithromycin (13), amoxicillin (9), cefadroxil (8), erythromycin (7), cephalexin (4), cotrimoxazole (3), azithromycin (2), norfloxacin (2), gatifloxacin (2), amoxicillin/clavulanic acid (1), ampicillin (1), crystalline penicillin (1), ofloxacin (1)
Antiparasitic / antifungal agents	63	Metronidazole (25), chloroquine (20), albendazole (9), fluconazole (9)
Analgesics / antipyretics	117	Nimesulide (28), paracetamol (27), ibuprofen (17), diclofenac (12), rofecoxib (11) etoricoxib (6), valdecoxib (5), aspirin (4), celecoxib (3), ibuprofen/paracetamol combination (2), indomethacin (1), tramadol (1)
Anti-ulcer agents	17	Ranitidine (12), omeprazole (3), pantoprazole (2)
Vitamins / supplements	13	Iron supplements (5), calcium (1), vitamin B complex (5), vitamin C (1), vitamin E (1)
Antidepressants	11	Alprazolam (5), amitriptyline (2), chlordiazepoxide (1), imipramine (1), mirtazapine (1), venlafaxine (1)
Antihistaminics	10	Cetirizine (8), diphenhydramine (1), pheniramine (1)
Others	15	Intradermal lignocaine (4), enalapril (2), prednisolone (2), flumazenil (1), ayurvedic capsule (1), glimipride (1), metformin (1), methotrexate (1), thiocolchicoside (1), tizanidine (1)
Placebo	26	
Total	350	

the convenience and availability of the consultant psychiatrist.

Details of follow-up were available in 3 patients seen 5, 6 and 22 months after challenge testing. All three were taking medications whenever prescribed, but one patient ascribed an episode of urticaria to drug intake, even though her challenge test had been negative.

DISCUSSION

The defining characteristic of this group of patients was their fear of taking medications because of reported reactions to multiple drugs in the past. Apart from this unifying feature, the group was rather heterogeneous in the clinical pattern of reactions, number of drugs implicated and the plausibility of the association of drug intake with the reactions described. As in other studies, women outnumbered men.

Patriarca *et al,*[7] and Schiavino *et al,*[1] reported two series of similar patients who reported drug reactions to more than two chemically, pharmacologically and immunogenically unrelated drugs taken on three different occasions. Skin prick and intradermal tests, patch tests and drug specific Ig E assays with the incriminated drugs were negative in all patients. Challenge tests were not performed with the incriminated drugs but challenge with alternative drugs in the second large study of 480 patients was negative in about 87% of patients.

In our series, though 16 patients developed symptoms during challenge testing only 3 patients had features of a drug reaction. Thirteen patients had symptoms and signs that were judged by the dermatologist not to represent drug hypersensitivity. Many of these reactions did not recur on repeating a challenge with the same drug. These reactions underline the need for supervised testing in a hospital setting where the reactions can be observed by persons with experience in diagnosing drug eruptions. Undertaken at home, the symptoms may have been interpreted as a positive reaction and lead to incorrect conclusions.

Multiple drug hypersensitivity or multiple drug allergy syndrome is defined as the development of drug allergies to two or more structurally or pharmacologically unrelated drugs.[2] This definition excludes patients who react to chemically related drugs e.g., metronidazole and tinidazole or to pharmacologically related drugs e.g., aspirin and ibuprofen. None of our patients qualified for a diagnosis of true multiple drug hypersensitivity.

The discordance between beliefs about hypersensitivity and the results of challenge testing has been studied extensively in the area of food intolerance.[8,9] Large studies have shown that people who think they react to foods are often mistaken. A similar error in perception may lead to the belief of multiple drug hypersensitivity.

What is the genesis of this belief? A chance association of physical symptoms with drug intake, (e.g., the coincidental appearance of urticaria, or development of urticaria associated with an infection for which drugs are taken) may have triggered an impression of drug hypersensitivity in some. Alternatively, a true reaction to a specific drug or drug group e.g., NSAIDs, which are commonly prescribed along with other drugs, may have led to a fear that all drugs would cause a reaction. There is a common belief that allopathic drugs are 'strong' and 'hot' in contrast to traditional remedies; this may have contributed to the perception of hypersensitivity to the entire group of modern medications.

Such a mistaken belief can lead to undesirable consequences: less effective and/or more expensive alternatives may be prescribed in order to avoid allergy due to the incriminated drug. In this context, challenge testing has been recommended to clarify the situation.[1] Asero showed that elective oral challenges were able to identify at least one tolerated antibiotic class in most patients with multiple drug allergy syndrome.[2] The need for testing is even greater where access to medicines is poorly regulated and documented and when patients do not know which drugs they had taken when they developed a "reaction."

Other approaches may also be helpful. Some patients show features of specific phobia, an intense, persistent fear with marked anxiety on exposure to the inciting agent leading to avoidance to an extent that may interfere with normal life. Psychological interventions, alone or combined with challenge testing, may be helpful in these patients.

Our report has some limitations. Only patients willing

to be admitted to hospital for a fairly long period and tested by re-challenge were included and this makes it difficult to generalize our results. Patients who are genuine multiple drug reactors may be less likely to undertake challenge tests. Some patients pointed out that they developed reactions a few days after starting medication. The challenge tests consisted of administering a single dose of a drug on one day and, clearly, cannot detect late reactions. However, most significant drug reactions develop within a few hours after re-exposure[10] and the number of true, late reactions is probably quite small. Other patients told us that their reactions developed when they took drugs in combination, not alone. Some stated that combinations of food and drugs were responsible. Once again, our testing protocol would not pick up these reactions. While it is theoretically plausible that drugs and/or foods interact to produce a substance that triggers a reaction, we were unable to find any documented instances and believe that this is probably quite rare. It is also possible that patients were allergic to one or more drugs that were not included in the list of drugs tested. Another limitation of our study is the lack of information on life after challenge testing in the majority of our patients. Did the extensive testing procedure make any difference to the patient's fear of drugs? Did they take drugs when they needed them? What happened when they did? We obtained answers from three patients all of whom were taking medicines whenever necessary, though one was unable to shake off the belief that her urticaria was induced by drugs. It would be important to have this information for other patients, too.

Patients who believe they have reactions to multiple, pharmacologically unrelated drugs are usually mistaken. Multiple drug hypersensitivity is culturally, and often medically, accepted as a valid diagnosis but true multiple drug reactors appear to be exceedingly rare. Challenge testing is a reliable way of demonstrating this to patients and providing them with a list of safe drugs.

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