Original Article

Clinical Characteristics and Outcomes of Patients Undergoing Drug Provocation Tests (DPTs)

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Abstract

Introduction: Patients who have an adverse drug reaction are frequently labelled drug allergic without undergoing proper evaluation and confirmatory testing. These drug allergy labels may be inaccurate, leading to unnecessary lifelong avoidance. The aim of this study was to review the patients that underwent drug provocation tests (DPTs) in our centre and examine the usefulness of DPTs in confirming or rejecting a diagnosis of drug hypersensitivity. Materials and Methods: The study design was a retrospective chart review of all adult patients who underwent drug provocation in the allergy unit at the National University Hospital, Singapore, for single or multiple suspected drug allergies from the period January 2009 to June 2011. Results: Eighty-seven patients underwent 123 DPTs (median age 41; interquartile range 28 to 50). Twenty-one patients underwent multiple DPTs. The most common culprit drugs reported were antibiotics (43.9%) of which beta-lactams were implicated in 75.9% of the cases. This was followed by non-steroidal anti-inflammatory drugs (NSAIDS) in 15.4%, paracetamol in 7.3% and both NSAIDs and paracetamol in 3.3%. Rash was the most commonly reported symptom (41.5%), followed by angioedema (32.5%), anaphylaxis (9.8%), and other symptoms including respiratory (2.4%), gastrointestinal (0.8%) and others (13.0%). The majority of DPTs were performed to antibiotics (43.9%), NSAIDs (19.5%) and paracetamol (6.5%). DPTs were negative in 93.5% of subjects and positive in 6.5%. Of the 8 positive DPTs, none had a serious reaction, with 5 patients requiring rescue therapy, which comprised solely of oral antihistamines. Conclusion: Suspected drug hypersensitivity is common but true drug allergy is rare. DPTs remain the gold standard and should be included as part of an investigative protocol. DPTs are a safe and valuable diagnostic tool in the hands of the experienced clinician.

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Introduction

Adverse drug reactions (ADR) account for 3% to 6% of all hospital admissions and occur in 10% to 15% of hospitalised patients, resulting in morbidity, prolonged hospitalisation and higher risk of mortality.[1-3] ADR are defined by the World Health Organisation (WHO) as any noxious, unintended, and undesired effect of a drug that occurs at doses normally tolerated by an individual.[4] In clinical practice, patients with an ADR are frequently labelled drug allergic, but having an ADR does not always mean the patient has a drug allergy. Only when the underlying mechanism is immune mediated, either IgE or T cell mediated, is it referred to as a true drug allergy.[5] However, patients may have drug hypersensitivity that is non-immune mediated and this is referred to as drug intolerance.

The established practice for diagnostic workup for drug allergy includes a detailed and accurate history, physical examination and appropriate in vivo and in vitro testing. In cases of an immediate type reaction, in vivo tests include skin prick tests (SPT), intradermal tests (IDT) and drug provocation tests (DPTs). However, SPT and IDT are validated only for a limited number of drugs. As for in vitro assays, the most common of which is serum specific IgE, validity is even less conclusive.[6] Hence, a definitive diagnosis requires a drug provocation test. A negative DPT excludes a false diagnosis of drug hypersensitivity[7] and therefore has crucial consequences to the patient and clinician.

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A diagnostic DPT is a controlled graded administration of a drug in order to diagnose drug allergy and currently remains the "gold standard".[8] The drug provocated is either the culprit drug, a structurally related compound, or an alternative drug. DPT performed to alternative drugs are done to exclude cross-reactivity of related drugs in the presence of proven hypersensitivity, for example, a cephalosporin in a penicillin-allergic subject or an alternative non-steroidal anti-inflammatory drug (NSAID) in an aspirin-sensitive patient.[9] There is an element of controversy associated with DPT as there is a theoretical risk of inducing a severe and life threatening reaction in an otherwise well patient. Thus, any DPT must be preceded by an individual risk-benefit assessment[9] and for safety, a DPT must be performed in a hospital environment.[10]

Thus, the aim of this study is to highlight the importance, usefulness and safety of DPTs in order to prove or exclude drug allergy in patients who have a label of ADR. Data gathered from this study will assist physicians and patients in the decision-making process of the benefit of passing a drug challenge versus the risk.

Materials and Methods

This study was a retrospective chart review conducted at a single allergy centre in Singapore which carries out diagnostic testing for patients with suspected food, drug and aeroallergen hypersensitivity.

Patients

We included in our study all adult patients (n = 87) aged 18 and above who underwent DPT during January 2009 to June 2011. These patients were mainly referred as outpatients for the evaluation of drug hypersensitivity. We excluded patients who defaulted their DPT (21 patients), those whose notes were irretrievable or whose case notes had insufficient data available (4 patients) and those who had perioperative anaphylaxis (2 patients). The last group was excluded as there was no indication to challenge them to all the drugs to which they were exposed to during the operation. Patients who experienced severe, life threatening drug reactions such as severe skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, patients with anaphylaxis with positive skin prick tests and pregnant women were not offered a drug provocation test.[10]

A thorough clinical history was obtained[11,12] and an individualised but structured approach was used. If the history was non-compatible with true drug allergy, if the underlying mechanism was non-IgE mediated (e.g. NSAIDS) or if there was only mild cutaneous eruption, the patient was provocated directly. However if there was a possibility of drug allergy, skin tests were performed for the drugs where well validated tests were available[13] (e.g. for beta-lactams). If skin tests were negative, the patient underwent DPT.

Skin Tests and Drug Provocation Tests

SPT and IDT were performed according to established protocols.[14] Patients were advised not to take antihistamines for 3 to 5 days before undergoing these skin tests and were well on the day of the provocation with no signs of coexisting infection. The SPT and the IDT were read at 20 minutes. No late intradermal readings or patch tests were performed. If skin tests were negative, patients underwent a DPT. The majority of our DPTs were oral and done in an outpatient setting. The drug was administered in incremental doses usually in dilution of 1:100, 1:10 and then the remaining therapeutic dose. The time interval between doses was 20 minutes. The DPT was deemed complete after a single maximum therapeutic dose. The patient was strictly observed for localised and systemic symptoms and signs. During the procedure, medical personnel competent in resuscitation and equipment for resuscitation were on standby. Postprovocation, the patient was observed for a minimum of 2 hours for any reaction. A follow-up phone call was made the next day to track patients who experienced a late adverse reaction, and patients were provided a hotline number should any further symptoms occur after that. A DPT was considered negative if no sign of drug hypersensitivity occurred within 24 hours after the therapeutic dose was administered.

Statistical Analysis

Information collected included demographic data, atopic status, underlying diseases, history of previous drug allergy, indications for use of drug, culprit drug, type of drug reaction, whether drug reaction was immediate (reactions that occur within 1 hour after the drug intake) or delayed (reactions that occur more than 1 hour after the drug intake), route of drug administration, clinical manifestations including anaphylaxis and the outcomes post drug provocation test. Statistical analysis was performed using SPSS version 19.

Results

Eighty-seven patients underwent 123 drug challenges, median 1 DPT per person (interquartile range: 1 to 2). The features of the study population and culprit drugs are reflected in Table 1. Most patients were referred through the intrahospital referral services and were seen within 1 month of the referral date. Most of these underwent DPT less than 3 months from their drug reaction and 60% of DPTs were within 1 year from their initial reaction. The initial drug reaction was immediate in 18 (14.6%) patients,

delayed in 62 (50.4%) patients and unclear in the rest of the 43 (35%) patients.

The most common presentations of reported drug hypersensitivity were rash (41.5%) and angioedema (32.5%). Anaphylactic symptoms were reported in 9.8%, subjective or unclear symptoms in 13.0% (Table 1). Of the culprit drugs, antibiotics (43.9%) were most commonly implicated, particularly beta-lactams. Other commonly reported culpable drugs were NSAIDs (15.4%), paracetamol (7.3%) and both NSAIDs and paracetamol (3.3%).

Drug Provocation Tests

One hundred and twenty-three drug provocation tests were done and 93.5% had a negative result. The characteristics of the DPTs are outlined in Table 2. Ninety-eight provocations were to culprit drugs, especially where the history was non-suggestive of a true drug allergy. Of these, the majority were antibiotics. Alternative drugs were provocated in 25

Table 1. Clinical Characteristics of Patients Who Underwent DPT and Characteristics of Culprit Drugs

Patient Demographics		**No. of patients, n = 87**
Sex		
Male	40	46.0%
Female	47	54.0%
Age	Years	
25th percentile	28	
75th percentile	50	
Median	41	
Ethnicity		
Chinese	62	71.3%
Malay	11	12.6%
Indian	8	9.2%
Others	6	6.9%
Clinical Manifestations		**No. of DPT, n = 123**
Rash	51	41.5%
Urticarial	25	
Maculopapular	8	
Skin erythema	6	
Pruritis	8	
Non-specific	4	
Angioedema	40	32.5%
Periorbital	32	
Lip swelling	1	
Extremeties	1	
Facial	4	
Anaphylaxis	12	9.8%
Subjective/unclear	16	13.0%
Respiratory symptoms	3	2.4%
Gastrointestinal tract	1	0.8%
Time from Acute Reaction to DPT		
<3 months	54	43.9%
≥3 months, ≤1 year	20	16.3%
>1 year	28	22.8%
Unclear	21	17.1%

Table 1. Clinical Characteristics of Patients Who Underwent DPT and Characteristics of Culprit Drugs (Con't)

Culprit Drugs			
Route of drug			
Oral		102	82.9%
Parenteral		14	11.4%
Topical		7	5.7%
Drug types			
Antibiotics		54	43.90%
Beta-lactams		41	
Penicillin		14	
Amino penicillin		6	
Cloxacillin		2	
Co-amoxiclav		8	
Cephalosporins		12	
	Cefazolin	2	
	Cephalexin	3	
	Cefaclor	1	
	Cefuroxime	3	
	Ceftriaxone	2	
	Multiple	1	
Macrolides		6	
Others		7	
NSAIDs		19	15.4%
Non-selective		15	
Selective Cox-2 inhibitors		4	
Paracetamol		9	7.3%
NSAIDs & Paracetamol		4	3.3%
Antihistamines		7	5.7%
Proton pump inhibitors		7	5.7%
Steroids		1	0.8%
Salbutamol		1	0.8%
Local anaesthetics		3	2.4%
Anti-tussives		2	1.6%
Allopurinol		1	0.8%
Opioids		5	4.1%
Others		10	8.1%

DPT: drug provocation test; NSAIDS: non-steroidal anti-inflammatory drugs

Table 2. Drug Provocation Test Outcomes

	No. of DPT, n = 123
Drugs Provocated	
Antibiotics	54 (43.9%)
NSAIDs	24 (19.5%)
Paracetamol	8 (6.5%)
Proton pump inhibitors	7 (5.7%)
Antihistamine	5 (4.1%)
Opioid	5 (4.1%)
Others	20 (16.2%)
Challenged Drug	
Culprit	98 (79.7%)
Negative	92 (93.9%)
Positive	6 (6.1%)
Alternative	25 (20.3%)
Negative	23 (92%)
Positive	2 (8%)
Challenge Result	
Negative	115 (93.5%)
Positive	8 (6.5%)

DPT: drug provocation test; NSAIDS: non-steroidal anti-inflammatory drugs

patients, of which most were intolerant to analgesics.

Seven patients reacted positively in 8 DPTs, as outlined in Table 3. These reactions were secondary to antibiotics in the majority of cases (62.5%), of which aminopenicillins were most common. Reactions were localised and only required antihistamines as rescue therapy.

Discussion

The major conclusion in our study was that patients with ADR do not necessarily have a drug allergy. Drug allergy was confirmed in only 6.1% of patients with ADR who were challenged to the culprit drug. Furthermore, in those who were challenged to an alternative drug, the majority of patients (92%) passed.

Negative drug allergy workup has immediate implications to doctors in prescribing drugs to patients and in allaying unnecessary anxiety. However, studies have shown patient readiness to accept a label of drug allergy and reluctance to undergo DPT.[10] This was reflected in our study as 21 patients defaulted, despite being scheduled for a DPT. Of these patients, 15 defaulted their first DPT and 6 defaulted their first DPT after having successfully passed an SPT.

Table 3. Clinical Characteristics of Failed Drug Provocation Tests

Patient number	Demographics	Culprit drug	Comorbidities	Clinical manifestation	Challenged drug	DPT indication	Time between reaction & DPT	Failed DPT reaction	Rescue meds
1	53-year-old Chinese Female	Famotidine	Chronic urticaria	Urticarial rash	Famotidine	Exclude hyper-sensitivity	>1 year	Cutaneous	None
1	53-year-old Chinese Female	Erythromycin	Chronic urticaria	Urticarial rash	Erythromycin	Exclude hyper-sensitivity	>1 year	Cutaneous	Antihistamines
2	21-year-old Chinese Female	Amoxicillin	Allergic rhinitis, asthma	Maculopapular rash	Amoxicillin	Exclude hyper-sensitivity	<1 year, >3 months	Cutaneous	None
3	51-year-old Chinese Female	Ketoconazole	Others	Urticarial rash	Ketoconazole	Exclude hyper-sensitivity	<1 year, >3 months	Cutaneous	Antihistamines
4	36-year-old Chinese Male	Amoxicillin	Chronic urticaria	Pruritic rash	Amoxicillin	Exclude hyper-sensitivity	>1 year	Cutaneous	None
5	44-year-old Malay Female	Amoxicillin Clavulanate	None	Erythematous rash	Amoxicillin Clavulanate	Exclude hyper-sensitivity	>1 year	Cutaneous	Antihistamines
6	40-year-old Malay Male	Ketoprofen	Gout	Periorbital angioedema	Etoricoxib	Provide safe alternate drug	<3 months	Angioedema	Antihistamines
7	35-year-old Filipino Female	Etoricoxib	None	Periorbital angioedema	Etoricoxib	Exclude hyper-sensitivity	<3 months	Angioedema	Antihistamines

DPT: drug provocation test

None had undergone prior DPT. There was no significant variation between the baseline demographics of the patients who defaulted compared to subjects who were included in the study. Despite the reluctance to undergo a DPT, it is interesting to note that in a recent multicentre study, most patients were very satisfied with DPTs for diagnostic purposes. Patients felt more reassured after a DPT, more certain about their diagnosis and had better information about which drugs to take or not to take.[15]

DPTs are a useful diagnostic tool and remain the gold standard to exclude drug hypersensitivity, including both immune (true drug allergy) and non immune-mediated (drug intolerance) mechanisms. They permit testing of a patient with his or her individual metabolism and immunogenetic background.[9] For example in our study, drug labels to beta-lactams were removed in 92.7% of patients. The high negative predictive value (NPV) of beta-lactam DPT has been confirmed in other large studies involving 256 children[16] and 457 adult patients[17] respectively. In these, any reactions post-DPT were non-immediate and not severe.

However there remain controversial issues surrounding DPTs. Also, acceptance among allergists and the availability of DPTs are still limited.[17] Many test procedures are yet to be validated. Protocols for every drug regarding the specific indications, contraindications, substances (active ingredient vs the whole formulation), dose escalation, dosing intervals, grading of the reaction and scoring criteria would be helpful. Furthermore, DPTs to antibiotics raise concerns of ethical issues such as challenging a well patient in the absence of infection and the possibility of developing antibiotic resistance. However, this is weighed against the benefit of removing the erroneous label of a drug allergy and enabling its further use.

In agreement with other studies, false negative provocation results may be caused by the absence of cofactors (comedication, viral infections and physical exercise), brief exposure or observation, tolerance induction[10] or short time interval between the reaction and testing (known as a refractory period). The latter is unlikely in our study as DPTs were scheduled at least 4 to 6 weeks from the date of the alleged reaction. However, nearly 22% were provocated after a year and 17% could not recollect the date of the alleged reaction, which may account for false negatives in our study due to the excessively long interval (natural desensitisation) between the reaction and the testing.[9]

Ideally, DPTs should be performed in a single-blind, placebo-controlled manner to evaluate subjective symptoms that might have contributed to false positive results. However, this practice is time consuming and costly, and in our study, patients who reacted demonstrated objective clinical signs. Other reasons for false positive results could be pre-existing chronic urticaria (present in 42% of challenge positive DPTs) or self-infliction.

DPTs are safe in a controlled setting with specific expertise, as was demonstrated in our study. Even in the event of a positive reaction (often milder than the initial reported reaction), timely dispensation of rescue medication was sufficient to prevent any severe reaction.

The limitations of this study were that it was a retrospective study including only patients who were scheduled for DPT and consequently we were dependent on the treating physicians' notes for the accuracy of the clinical history, examination findings and their decision to provocate or not, which may have led to a possible selection bias. In particular, we do not have the number of patients who had a contraindication to DPT and therefore were excluded by their treating physicians (i.e. those that had an immediate and severe life threatening initial reaction such as anaphylaxis, Stevens-Johnson syndrome and toxic epidermal necrolysis).

It is important to note that the majority of referrals were intrahospital and hence the availability of this service must be highlighted to the family physician or general practitioner who is often the first medical professional to be in contact with the patient.

Conclusion

Despite the controversial issues[20] surrounding drug provocation tests, it is an essential diagnostic tool to accept or refute a diagnosis of drug hypersensitivity. Currently a DPT may be the only reliable means of confirming a diagnosis of drug hypersensitivity where no validated in vitro or in vivo tests exist. The safety of DPT has been reinforced in this study when done under judicious surveillance.

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