Drug Eruptions : The Value of Oral Rechallenge Test and Patch Test†

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Abstract

All in-and out-patients, who came for drug eruption consultation at the Dermatology Clinic, Ramathibodi Hospital from December 1997 to November 1998 were included in this study. Medical histories and physical examinations were performed by one of the authors. In suspected cases, a skin biopsy was performed to confirm the diagnosis. Patch test and oral challenge test were performed in some patients who had maculopapular, fixed drug eruption and acute generalized exanthematous pustulosis, with informed consent.

Among 80 patients, the most common cutaneous reaction was maculopapular rash. Antimicrobial drugs were the most common causative agents. The patch test was positive in only one patient from 12 cases. The oral provocative test was positive in two patients from 4 cases.

It is concluded that oral provocative test is still necessary to get a definite diagnosis of causative agent. The value of patch test needs further study.

Key word : Drug Eruption, Oral Challenge Test, Patch Test

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Drug eruptions are common problems, accounting for about 1-2 per cent of new patients attending the Dermatological Clinic, Ramathibodi Hospital. The problem of definite diagnosis for the causative agent is still unresolved. At the present time, the oral rechallenge test is the most reliable test for a definite diagnosis of the causative drug(1). The limitation of this test is the safety of the patient, so it can be used only in mild forms of drug eruption. The patch test was proposed as an alternative test for the diagnosis of the causative agent. It was found to be positive in about 31-37 per cent of the patients (2,3). The problem with the patch test is that it can be used in only some types of drug eruptions which are mediated through delayed type hypersensitivity. Other problems with the patch test are that we do not know the definite concentration of drugs to be used and the best vehicle for testing. In addition, most drug allergens are unknown, some drugs may have to bind with tissue proteins to form hapten, or the metabolites of drugs may be responsible for the reaction.

The purpose of this study was 1) to evaluate the types of cutaneous reaction and their causative drugs in a hospital-based population for a period of 1 year, and 2) to find out whether patch test is beneficial in determining the causative drug.

MATERIAL AND METHOD

The study was performed at Ramathibodi Hospital Medical School from December 1997 to November 30, 1998. All in-and out-patients who came for drug eruptions consultation were included in this study. Medical histories and physical examinations were performed by one of the authors. In suspected cases, skin biopsy was performed to confirm the diagnosis. The criteria for diagnosis were set as follows:

Definite

The eruption occurred after rechallenging or patch testing of the suspected drug.

Inclusion criteria for rechallenge or patch test.

1. Benign form of drug eruption such as maculopapular rash, fixed drug eruption, pustular drug eruption, etc.
2. Informed consent of the patients
3. Non-pregnant women
4. No chronic or severe underlying disease

Probable

Only one drug had been administered within the past few weeks before the eruption occurred. Other probable causes of eruption were excluded with certainty.

Possible

More than one drug administered within the past few weeks before the eruption occurred. The previous incidence of drug eruption as reported in the literature was used as a guideline to identify the causative drug(4-7). Other probable causes of eruption were excluded with certainty.

Patch test

Patch test was performed six weeks after the onset of drug eruption. For fixed drug eruption, the patch test was applied on a hyperpigmented lesion and on normal skin. Patch tests were performed on the upper back of the patients using Finn chamber on Scanpor tape. Tablets were ground and diluted to 5 per cent, 10 per cent and 30 per cent in white petrolatum and 70 per cent alcohol. The content of the capsules were also diluted in the same way. Liquid preparations were tested as is and diluted to 30 per cent in white petrolatum and 70 per cent alcohol.

The test sites were read at 48 h, 72 h, and 7 days after application of the suspected drugs. The results of patch testing were reported according to the International Contact Dermatitis Research Group criteria(8). The patients with contact dermatitis from other causes were also tested by the same drugs and acted as control subjects with informed consent.

Oral challenge test

For patients who had negative patch test, the oral challenge test was performed with informed consent. The test dose was one tablet (capsule) of the suspected drug. If no eruption occurred, we waited for 7 days, then started another suspected drug until the eruption appeared.

RESULT

From December 1, 1997 to November 30, 1998, 80 patients were diagnosed with drug eruption. These included 37 males and 43 females. The mean age of the patients was 32.2 years (range 4 months to 64 years).

A definite diagnosis of drug eruption was found in 3 patients (3.75%) (Table 1), probable diagnosis in 54 patients (67.50%) (Table 2) and possible diagnosis in 23 patients (28.75%) (Table 3).

The skin lesions appeared 1 to 60 days after drug administration (mean ± SD. 7.84 ± 11.01 days). Anticonvulsant drugs took longer than other medications to cause skin eruption (range 4-120 days, mean ± SD = 30.80 ± 49.99 days).

Rechallenge test

Patch test

Patch test was performed on 12 patients (Table 4). No patient developed immediate positive patch test reactions. One patient with maculopapular drug eruption had positive patch test with 5 per cent phenobarbital in both white petrolatum and 70 per cent alcohol vehicle at 48 hours. The patients with fixed drug eruption had negative patch test results both on the previous site of fixed drug eruption and on normal skin. None of the control cases had a positive reaction.

Oral challenge test

Oral challenge test was performed in 4 patients with 9 drugs. Two patients developed cutaneous eruption from the oral challenge test on 2 days. One had maculopapular eruption from conjugated estrogens, another one had fixed drug eruption from tetracycline.

Table 1. Definite causes of drug eruption (3 patients).

Type of drug eruption	Causative drug	Number of patients with positive test
Maculopapular	Phenobartital	1
	Conjugated estrogens	1
Fixed drug	Tetracycline	1

Table 2. Probable causes of drug eruption (54 patients).

Type of drug eruption	Causative drug	Number of patients	Causative drug	Number of patients
Maculopapular	Penicillin	5	Erythromycin	1
	Ceftriaxone	2	Gentamicin	1
	Co-trimoxazole	2	Mefenamic acid	1
	Phenytoin	2	Metronidazole	1
	Allopurinol	1	Nitrofurantoin	1
	Amoxycillin-clavulanic acid	1	Piroxicam	1
	Ceftazidime	1	Unidentified	1
	Chloral hydrate	1		
Erythema multiforme	Co-trimoxazole	4	Penicillin	1
	Allopurinol	1		
Photoallergic dermatitis	Chlorpropamide	1	Hydrochlorothiazide	1
	Furosemide	1	Piroxicam	1
	Glibenclamide	1		
Stevens-Johnson syndrome	Allopurinol	1	Phenytoin	1
	Co-trimoxazole	1	Sulfacetamide	1
	Ibuprofen	1		
Urticaria	Amitriptyline	1	Spiramycin	1
	Co-trimoxazole	1	Unidentified	1
	Penicillin	1		
Eczema	Chlorpropamide	1	Unidentified	1
	Piroxicam	1		
Acute exanthematous pustular eruption	Ampicillin	1	Unidentified	1
Exfoliative dermatitis	Co-trimoxazole	1	Penicillin	1
Leukocytoclastic vasculitis	Allopurinol	2		
Toxic epidermal necrolysis	Penicillin	1	Phenytoin	1

Table 3. Possible causes of drug eruption (23 patients, some patients received more than one drug).

Type of drug eruption	Causative drug	Number of patients	Causative drug	Number of patients
Maculopapular	Acetaminophen	1	Furosemide	1
	Amikacin	1	Gentamicin	1
	Amitriptyline	1	Imipenem	1
	Amoxycillin	1	Isoniazid	1
	Ceftazidime	2	Penicillin	1
	Clindamycin	1	Rifampicin	1
	Diclofenac	1	Vancomycin	1
	Dicloxacillin	1	Unidentified	1
	Erythromycin	2		
Fixed drug	Amoxycillin	1	Lincomycin	1
	Aspirin	1	Norfloxacin	1
	Chloramphenicol	1	Sulpyrin	1
	Co-trimoxazole	1	Tetracycline	1
	Doxycycline	1	Unidentified	1
	Glibenclamide	1		
Urticaria	Acetaminophen	2	Chlorpheniramine	1
	Amitriptyline	1	Co-trimoxazole	1
	Aspirin	1	Gentamicin	1
	Brompheniramine	1	Norfloxacin	1
Erythema multiforme	Allopurinol	1	Idapamide	1
	Gimfibrosil	1	Perindopril	1
	Hydrochlorothiazide	1		
Exfoliative dermatitis	Isoniazid	1	Rifampicin	1
Photoallergic dermatitis	Isoniazid	1	Rifampicin	1

The three most common causative drugs were antimicrobial agents (54.29%), antipyretic/anti-inflammatory drugs (11.42%), and drug acting on the central nervous system (6.67%) (Table 5). The most common skin lesion was maculopapular eruption (42.50%), followed by urticaria (11.25%) and erythema multiforme (8.75%) (Table 6).

Treatment of drug eruption consisted mainly of discontinuation of the suspected drug and administration of antihistamine. Some cases also needed topical corticosteroid. The most severe cases, such as exfoliative dermatitis and Stevens-Johnson syndrome, required systemic corticosteroid to control the skin lesions. In most cases the cutaneous eruptions disappeared within 7 days to 1 month after the start of treatment.

DISCUSSION

In this study, maculopapular eruption was the most frequent cutaneous manifestation which accounted for 42.50 per cent of the patients. It is interesting to find out that urticaria was the second most common type of drug eruption instead of fixed drug eruption which was reported in previous studies [5,9]. Antimicrobial agents were still the most common causative drugs. Co-trimoxazole was the most common causative agent followed by penicillin and cephalosporin group, respectively.

Drug eruption may be easily diagnosed from history and clinical features. However, most patients received many drugs at the same time. The problem is which drug caused the cutaneous eruption. The oral challenge test is a gold standard to prove the causative agent but it is hazardous for the patient. Patch test is an alternative method to prove which drug caused the cutaneous reaction. Many reports have mentioned the value of the patch test[2,3,6,10-12].

In the present study, the authors performed a patch test on 12 patients, but only one patient (8.3%) had a positive reaction (Table 4). In this case, the patient did not attend the clinic again, so oral challenge test was not performed. The low percentage of positive patch test in this study might be due to many factors. The drugs being tested might be unable to penetrate into the epidermis, the

Table 4. The results of patch test and oral challenge test in 12 patients.

Patient No.	Type of eruption	Drug	Patch test	Oral challenge test
1	Maculopapular	Conjugated estrogens	-	+
2	Maculopapular	Piroxicam	-	ND
3	Maculopapular	Phenytoin	-	ND
4	Maculopapular	Phenobarbital	+	ND
5	Maculopapular	Gentamicin	-	ND
6	Fixed drug eruption	Tetracycline	-	+
7	Fixed drug eruption	Lincomycin	-	ND
		Sulpyrin	-	ND
8	Fixed drug eruption	Aspirin	-	ND
		Tetracycline	-	ND
9	Fixed drug eruption	Doxycycline	-	-
		Amoxycillin	-	-
10	Fixed drug eruption	Co-trimoxazole	-	ND
11	Fixed drug eruption	Tetracycline	-	-
		Norfloxacin	-	-
		Co-trimoxazole	-	-
		Chloramphenicol	-	-
		Glibenclamide	-	-
12	Acute exanthematous pustular eruption	Ampicillin	-	ND

+ = positive result, - = negative result, ND = not done

Table 5. The definite, probable and possible causative agents of drug eruption.

Causative agents	Per cent
Antimicrobial agents	54.29
Antipyretic/antiinflammatory agents	11.42
Drug acting on the central nervous system	6.67
Others	29.95
Unknown	6.67

Table 6. Clinical types of drug eruption.

Clinical type	Per cent
Maculopapular	42.50
Urticaria	11.25
Erythema multiforme	8.75
Fixed drug eruption	7.50
Stevens-Johnson syndrome	6.25
Photoallergic drug eruption	7.50
Exfoliative dermatitis	5.00
Eczema	3.75
Toxic epidermal necrolysis	2.50
Vasculitis	2.50
Acute exanthematous pustular eruption	2.50

concentration used in patch testing might be too low to elicit a positive reaction. Maculopapular eruption might not be due to cell-mediated immunity in some patients. The drug rash might be attributed to toxic metabolites instead of the drugs used for the patch test. However, further study should be carried out to identify the appropriate concentration of drug used for the patch test as well as appropriate vehicles.

When patch test results are negative, the oral challenge test can be performed which is of diagnostic value. However, the oral challenge test should be performed only when it is necessary to get a definite diagnosis. It can be done only in mild forms of drug eruption such as maculopapular rash, fixed drug eruption, eczematous eruption, acute generalized exanthematous pustulosis, etc. It is contraindicated in severe forms of drug eruption such as Stevens-Johnson syndrome, toxic epidermal necrolysis, vasculitis, urticaria, angioedema. However, even in mild forms of drug eruption, it is not without risk to the patient, so it should be performed with caution. In the present study, only 2 of 4 patients had a positive oral challenge test. The negative result might be due to two factors. First, the drug eruption might not be due to the drugs

tested. Second, the test dose might be too low to elicit a reaction. In patients no. 1 and 6 (Table 4) patch test results were negative, but oral challenge tests were positive. The oral challenge test was more reliable than the patch test. However, further studies are needed to improve the method of the patch test to yield more positive results such as identifying the appropriate concentration of drug used for patch test as well as appropriate vehicles.

In summary, this study showed that maculopapular rash, urticaria and erythema multiform were the three most common types of drug eruption. Antimicrobial agents were the most frequent cause of drug rash, while co-trimoxazole was the most common cause among this group. The oral challenge test was better than the patch test in confirming the causative drug.

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ผื่นแพ้ยา : การทดสอบหายาที่เป็นสาเหตุโดยการให้รับประทานยาซ้ำและการทดสอบโดยแปะยาที่ผิวหนัง

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คณะผู้วิจัยได้ทำการศึกษาผู้ป่วยที่เป็นผื่นแพ้ยาที่มาตรวจที่หน่วยโรคผิวหนังโรงพยาบาลรามาธิบดี ทั้งผู้ป่วยนอกและผู้ป่วยในระหว่างเดือนธันวาคม พ.ศ. 2540 – พฤศจิกายน พ.ศ. 2541 โดยการซักประวัติตรวจร่างกาย และตัดชิ้นเนื้อที่ผิวหนังไปตรวจในรายที่จำเป็นต่อการวินิจฉัย ในผู้ป่วยที่เป็นผื่นแบบ maculopapular rash, fixed drug eruption และ acute generalized exanthematous pustulosis ถ้าผู้ป่วยเซ็นต์ใบอนุญาตยินยอมให้ทดสอบโดยการรับประทานยาซ้ำ และทดสอบโดยการแปะยาที่ผิวหนังก็จะทำการทดสอบเพื่อให้ทราบแน่นอนว่ายาชนิดใดเป็นสาเหตุของผื่น

ได้ทำการศึกษาผู้ป่วยทั้งหมด 80 รายพบว่า ผื่นที่พบบ่อยที่สุดคือผื่นแบบ maculopapular ยาที่เป็นสาเหตุของผื่นแพ้ยาที่พบบ่อยที่สุดคือยาปฏิชีวนะ ได้ทดสอบโดยการแปะยาที่ผิวหนังได้ผลบวก 1 ราย ใน 12 ราย ทดสอบโดยให้รับประทานยาซ้ำให้ผลบวก 2 รายใน 4 ราย

จากการศึกษานี้สรุปได้ว่า การทดสอบโดยให้รับประทานยาซ้ำยังมีความจำเป็นในการที่จะให้การวินิจฉัยที่แน่นอนว่ายาชนิดใดเป็นสาเหตุของผื่นแพ้ยา แต่การทดสอบโดยการแปะยาที่ผิวหนังยังต้องมีการศึกษาเพิ่มเติมต่อไปอีก

คำสำคัญ : ผื่นแพ้ยา, การให้รับประทานยาซ้ำ, การทดสอบโดยแปะยาที่ผิวหนัง

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