

Topical provocation in 31 cases of fixed drug eruption: change of causative drugs in 10 years

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The pathomechanism of fixed drug eruption remains to be clarified, but patch testing has been used to determine the causative drug. 31 patients with fixed drug eruption were investigated to evaluate the diagnostic value of patch testing and to compare the causative drugs over the 10 years between the late 1980s and the late 1990s. 22 of them were given an oral provocation test to confirm the results of patch testing. A reaction showing definite infiltration, which occurred in 13 of 22 patients, reliably indicated the causative drug. In contrast, a patch test reaction without definite infiltration was not always correlated with systemic provocation. All except 1 patient found out their causative drug. The most frequent causative drug was sulfamethoxazole-trimethoprim in the late 1980s, but it had become chlormezanone 10 years later.

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Fixed drug eruption (FDE) has characteristic skin lesions, which make the diagnosis easy. However, a reliable way to detect causative drugs remains to be clarified, although the results of patch tests have been encouraging (1–9). 31 patients with FDE have been patch tested, 17 between 1986 and 1990 and 14 between 1996 and 1997, to examine the correlation between patch test results and oral provocation and any change in causative drugs over 10 years.

Patients and Methods

Patch testing was done in 31 patients; 15 were male and 16 female. The age range was 7 to 62 years. The shortest duration of disease was 1 week and the longest 16 years. The rate of recurrence was usually 2 to 5×, but sometimes too frequent to be remembered. The time difference between the patch test and the last attack was variable, with the shortest being 1 week. There was no prevalent site of the lesion. The size and number showed considerable individual variation. Many patients were medicated intermittently for the relief of upper respiratory tract infections and a few had asthma attacks or motion sickness.

The drugs for patch testing were usually applied at 10% in white petrolatum base (pet.). Patch tests were duplicated on a previous lesion and apparently normal skin (usually back) using Finn Chambers on Scanpor tape. Results were read at day (D) 2 and D 4 as subjective (itching, prickling) and objective (erythema, infiltration).

Systemic provocation was performed after obtaining verbal permission from 22 patients. The drugs with a negative patch test were given first and 1/100 or 1/10 of a single therapeutic dose was initially tried.

Results

A total of 27 patches showed reactions in 22 patients, who had received topical and systemic provocation tests. The number of patches applied was 1 to 13, with the average 4.8. 17 patients reacted only to their causative drug, but 5 reacted to 2 kinds of drugs (Tables 1a, b).

A patch test reaction showing definite infiltration occurred in 14 patients, and reliably predicted the results of oral provocation. However, a reaction showing itching with/without erythema did not always correspond with the results of sys-

Table 1a. Results of patch and oral provocation tests between 1986 and 1990

Patient no	Sex/age (years)	Duration	Recurrence rate	Patch test			Correlation
				no. tested	reacted drug	reaction (prelesional)	
1	M/42	5 years	frequent	2	cotrimoxazole*	itching, erythema, infiltration	+
2	M/53	2 years	frequent	3	cotrimoxazole*	itching, erythema	+
3	F/50	4 years	4-5	3	cotrimoxazole*	itching	+
4	M/35	2 years	3	3	mefenamic acid	itching, erythema, infiltration	+
5	F/35	1 year	2	1	mefenamic acid	itching, erythema, infiltration	
6	F/40	1 month	2	3	mefenamic acid	itching, erythema, infiltration	
7	F/30	10 years	4-5	3	phenobarbital	itching, erythema	+
8	F/20	4 years	4	3	phenobarbital	itching, erythema, infiltration	
9	M/26	1 year	3-4	13	chlormezanone	itching, erythema, infiltration	+
10	F/46	2 years	4-5	6	chlormezanone	itching, erythema, infiltration	
11	M/7	2 years	frequent	6	acetylsalicylic acid	erythema	+
					chlorpheniramine	erythema	-
12	F/31	2 years	frequent	5	antipyrin	itching, erythema	+
					acetaminophen	erythema	-
13	F/34	7 months	2	5	aminophylline	itching, erythema, infiltration	+
14	F/21	4 years	2	10	sulpyrin	itching, erythema	-
					acetylsalicylic acid	itching	-
15	F/43	3 years	2-3	4	sulpyrin	itching, erythema, infiltration	
16	F/46	3 years	frequent	10	promethazine	itching, erythema, infiltration	
17	F/29	2 years	2-3	6	ibuprofen	itching, erythema, infiltration	

* cotrimoxazole: sulfamethoxazole-trimethoprim.

Table 1b. Results of patch and oral provocation tests between 1996 and 1997

Patient no	Sex/age (years)	Duration	Recurrence rate	Patch test			Correlation
				no. tested	reacted drug	reaction (prelesional)	
1	M/45	3 years	6-7	4	chlormezanone	itching, erythema, infiltration	+
2	M/20	4 months	2	5	chlormezanone	itching, erythema, infiltration	+
3	M/34	1 year	4	2	chlormezanone	itching, erythema, infiltration	+
4	M/34	6 years	2	2	chlormezanone	itching, erythema, infiltration	+
5	F/55	3 years	frequent	7	chlormezanone	itching, erythema, infiltration	+
6	F/58	1 year	3-4	3	chlormezanone	itching, erythema, infiltration	
7	F/56	1 week	1	5	chlormezanone	itching, erythema, infiltration	
8	F/47	1 year	2	5	phenobarbital	itching, erythema	+
9	F/62	6-7 years	2	1	phenobarbital	itching, erythema, infiltration	+
10	M/18	1 month	2	4	phenobarbital	itching, erythema, infiltration	+
11	M/45	16 years	3	8	mefenamic acid	itching, erythema, infiltration	+
					cefadroxil	itching, erythema	-
12	F/54	1 year	2	2	mefenamic acid	itching, erythema, infiltration	+
13	M/29	2 months	2	9	ibuprofen	itching	+
					phenobarbital	itching	-
14	M/62	?	2-3	4	doxycycline	itching, erythema, infiltration	+

temic provocation, 6 patches with such reactions not being correlated with the cause. 1 patient never found out her causative drug, although she had reactions to 2 patches (Tables 1a, b).

The lesions were usually provoked less than 1 h to several hours after systemic administration of the causative drug. Mostly 1/100 to 1/10 the amount of a prescribed single dose was enough to provoke the lesion.

The frequent causative drugs which were confirmed by topical and/or oral provocation, were sulfamethoxazole-trimethoprim (3), phenobarbital (3), mefenamic acid (3) and chlormezanone (2) in

the late 1980s. In the late 1990s, they became chlormezanone (7), phenobarbital (3) and mefenamic acid (2). Acetyl salicylic acid, promethazine, aminophylline, sulpyrine, isopropyl antipyrin and ibuprofen were infrequent causes. The drugs showing false-positive reactions on patch testing were phenobarbital, acetaminophen, cefa drug and chlorpheniramine.

Discussion

Although there are reports that causative drugs of FDE have been identified by patch testing on pre-

lesional nonactive skin (1–9), some authors have reported false-negative reactions to topical provocation (3, 8, 9). Epicutaneous open testing, not patch testing, was used in 1 study (9). In our studies, reactions developed in 36 of 147 patches applied. There was some discrepancy between the results of patch testing and those of oral provocation. This discrepancy could arise from several factors, such as lack of a standard for patch test interpretation, the capacity of making a reactive intermediate in the skin (10–12), and hyperpigmentation with/without thickening of the patch test site, which make accurate reading of results difficult. In cases showing infiltrative reactions, the same drug always provoked the eruption on systemic provocation. In contrast, if the patch tests elicited itching with/without erythema reaction, it was not reliable to conclude that they were the causative drugs. Only 1 patient had a quite different result between patch testing and oral provocation. Therefore, patch testing could be a useful diagnostic tool in FDE and should be performed first to screen for the causative drug.

The drug that was most responsible for FDE in the late 1980s was sulfamethoxazole-trimethoprim, but it had changed to chlormezanone by 1996–1997. Sulfamethoxazole-trimethoprim was no longer a cause of FDE in the 1990s in Korea. Mefenamic acid and phenobarbital kept their position. Change of causative drugs seemed to depend on the consumption rates of drugs, although analgesics, certain muscle relaxants, sedatives and anticonvulsants were mainly responsible (9, 13–16).

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