Acta Derm Venereol (Stockh) 1989; 69: 223–226

Cutaneous Drug Reactions: Clinical Types and Causative Agents

A Five-year Survey of In-patients (1981–1985)

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We collected a 5-year series of drug eruptions. There were 225 cases, 128 of them verified by a positive provocation test. The most common types of clinical reaction were fixed drug eruptions, exanthematous eruptions and urticarias. The drugs most often responsible for the eruptions were antimicrobial agents and antipyretic/anti-inflammatory analgesics. Comparing this series with our three previous series from the same hospital, the total number of drug eruptions proved to have decreased over the last 30 years. The main groups of drugs causing skin reactions have remained the same, but in recent years the proportion of sulphonamides has diminished. ***Key words: Drug provocation test; Side effects; Fixed drug eruption; Exanthematous drug eruption.***

(Accepted August 25, 1988.)

Acta Derm Venereol (Stockh) 1989; 69: 223–226.

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"There are about 1000 drugs in common use, and approximately 500 of these often cause skin eruptions. With the rapid development of new therapeutic agents, each year new causes of drug-induced dermatitis are added to an already formidable list (1). We have previously studied causative agents of drug eruptions at the Department of Dermatology, University Central Hospital, Helsinki in three different series, from 1956–60 (2), 1961–70 (3) and 1971–80 (4). In this study we present a consecutive 5-year series from the same hospital including also the Department of Allergology, which was not included in the previous studies.

PATIENTS AND METHODS

The study comprises 219 hospitalized patients with drug eruptions. They were selected from all cases with a diagnosis of drug eruption in the hospital patient register during 1981–85. When the etiological diagnosis of a drug-induced reaction was considered questionable, the patient was excluded from the study. 171 patients were from the Department of Dermatology and 48 patients from the Department of Allergology at the University Central Hospital, Helsinki. There were 85 men and 134 women. The age range was from 1 year 8 months to 88 years. The majority of the patients were hospitalized because of an acute drug eruption or for a subsequent provocation test. A few had a drug eruption when in hospital because of some other skin disease. Because some patients had a verified reaction to two or three different agents, the number of cases (225) is larger than that of the patients studied (219). Provocation tests were done to 132 patients. There were 128 cases of a positive provocation in 124 different patients. 123 provocation tests were performed perorally with the suspected drug as described by Kauppinen (3). The test doses were chosen using the following criteria: the clinical type and severity of the reaction; the capacity of the suspected drug to give rise to a cutaneous reaction; and the interval from the eruption to the challenge. If the challenge proved negative, it was usually repeated with a greater dose of the same drug or with another suspect drug. In one case there was also a positive scratch-chamber test with tetracycline. In 5 cases of fixed drug eruption the provocation test was performed topically as described by Alanko et al. (5). A positive serum-RAST test to penicillin-V verified the causative agent in 10 cases. In the remaining cases the causative agent was identified by the typical clinical picture and the timing of the reaction or by the reappearance of the rash after several accidental exposures. The fixed drug eruptions with a typical clinical picture were included even when the causative agent was unknown.

RESULTS

The clinical types of the 225 drug eruptions are shown in Table I. Fixed drug eruption and exanthematous eruption were the most common reactions, each accounting for about one-third of all cases. In both these types of eruption a provocation test proved positive in 2/3 of the cases. The third large group was urticaria/angio-edema, accounting for one in five cases. No provocation tests were performed in the 15 cases of

Table I. *Clinical types of 225 drug reactions*

Eruption	*n*	%	Verified by provocation (%)
Fixed drug eruption	77	34.2	51 (66.2)
Exanthematous eruption	71	31.6	47 (66.2)
Urticaria/angio-edema	45	20.0	26 (57.8)
Gold dermatitis	15	6.7	– (0)
Purpuric eruption	5	2.2	– (0)
Erythema multiforme	4	1.8	2 (50.0)
Lyell's syndrome	3	1.3	– (0)
Stevens-Johnson syndrome	2	0.9	1 (50.0)
Exfoliative dermatitis	2	0.9	1 (50.0)
SLE-like eruption	1	0.4	– (0)
Total	225	100.0	128 (56.9)

gold dermatitis. The other clinical reaction types were rare. Among them were 3 cases of Lyell's syndrome and 2 of Stevens-Johnson syndrome.

The different groups of drugs responsible for skin eruptions are shown in Table II. The two largest groups are antimicrobial agents and antipyretic/anti-inflammatory analgesics. In the latter group the percentage of provocation is highest. Drugs acting on the central nervous system were the third largest group. In the group of reactions by an unknown or not specified drug, 13 of the 18 reactions were fixed eruptions.

Table III summarizes both the clinical types of eruption and the responsible drugs. Eruptions caused by drugs of unknown origin are not included in the table. Certain drugs caused a typical skin reaction (e.g. phenazone salicylate caused fixed drug eruptions, penicillin and acetylsalicylic acid caused urticarias), but most drugs caused several kinds of clinical reaction. The most usual reaction types—exanthematous eruptions, fixed drug eruptions and urticarias—were caused by drugs belonging to different groups. Exanthematous eruptions were mostly due to sulphonamides, ampicillin–amoxicillin and trimethoprim. By far the most important causes of urticarias and angioneurotic edemas were penicillin (phenoxymethyl-penicillin) and acetylsalicylic acid. There were three anaphylactic reactions in this reaction group.

The group 'other reaction types' in Table III includes the more infrequent clinical eruptions. There were 4 erythema multiforme reactions, one of each caused by sulpha-trimethoprim, quinidine sulphate, phenytoin and proquazone. There were also 2 cases of Stevens-Johnson syndrome, one caused by phenazone salicylate verified by challenge, the other by carbamazepine. Of the 3 cases of Lyell's syndrome, one was caused by a combination of sulphafurazole and sulphamethoxydiazine and the other two by oxyphenbutazone. There were 2 cases of exfoliative dermatitis, one caused by allopurinol verified by challenge, the other caused by carbamazepine. The 3 purpuric eruptions were caused one of ech by penicillin-V, nifedipine and sulpha-trimethoprim. The only lupus erythematosus-like (SLE-like) eruption was caused by a combination of hydrochlorothiazide and amiloride. The reaction faded by itself when the diuretic drug was replaced, but reappeared within a week when the original drug was readministered.

DISCUSSION

A 30-year series of skin reactions caused by drugs has been collected at the Department of Dermatology, University Central Hospital, Helsinki. A chronological comparison of the different groups of drugs causing skin reactions is presented in Table IV. The total number of cases has decreased in each consecutive period, taking into account that the Department of Allergology was included in this series with additional 53 drug eruptions in 48 patients. This addition shows not only in the total number of cases but also in the increased number of urticarias. Of the 45 cases of urticarias, 25 came from the Department of Allergology. The main groups of causative drugs have remained the same over the years, the majority of drug

Table II. *Agents responsible for 225 drug reactions*

Drug	*n*	%	Verified by provocation (%)
Antimicrobial agents	95	42.2	52 (54.7)
Antipyretic/anti-inflammatory analgesics	61	27.1	53 (86.9)
Drugs acting on the central nervous system	23	10.2	14 (60.9)
Gold	15	6.7	– (0)
Others	13	5.8	9 (69.2)
Unknown drugs	18	8.0	– (0)
Total	225	100.0	128 (56.9)

Table III. *Skin reactions to drugs, causative agents and clinical reactions*

Drug	Exanthematous eruption	Fixed drug eruption	Urticaria angioedema	Other reaction types	Positive provoc./ Total
Antimicrobial agents					
Penicillin	–	–	15	1	0/16
Ampicillin/bacampicillin	8	–	1	–	3/9
Amoxicillin	7	–	–	–	1/7
Tetracyclines	–	5	2	–	4/7
(Doxycycline)	–	(3)	(1)	(–)	(2/4)
Erythromycin	2	–	–	–	2/2
Sulphonamides	17	8	–	1	24/26
(Sulphasalazine)	(5)	–	–	(–)	(5/5)
Trimethoprim	11	3	1	–	14/15
Sulpha-trimethoprim	5	1	2	2	1/10
Others[a]	3	–	–	–	3/3
Antipyretic analgesic drugs					
Phenazone derivatives	1	32	2	1	32/36
Acetylsalicylic acid	–	–	17	–	17/17
Chlormezanone	1	1	–	–	1/2
Oxyphenbutazone	–	–	–	2	0/2
Others[b]	2	–	1	1	3/4
Drugs acting on the central nervous system					
Barbiturates	–	6	1	–	5/7
Carbamazepine	4	3	–	2	6/9
Phenytoin	2	1	–	1	1/4
Others[c]	–	3	–	–	2/3
Gold sodium thiomalate	–	–	–	15	0/15
Other drugs[d]	5	1	3	4	9/13
Positive provocation/Total	47/68	51/64	26/45	4/30	128/207

[a] Metronidazole, nitrofurantoin and methenamine hippurate.
[b] Indomethacin, sulindaque, tolphenamic acid and proquazone.
[c] Chloralhydrate-phenazone, klopoxide and tioridazine.
[d] Allopurinol (2), niphedipine (2), hydroxyzine, kinidine sulphate, methamizole, methoxsalen, tranexamic acid, amiloride-hydrochlorothiazide combination, Disofrol mite R, Toclase exp R and Urografin R.

reactions being caused by antimicrobial agents and antipyretic/anti-inflammatory analgesics. The proportion of sulphonamides was high in the 1960s and 1970s, and has since diminished.

There are many possible explanations for the decrease in drug eruptions. Some drugs of today, e.g. the penicillins, are more purified than earlier and may therefore cause less adverse reactions. The more 'dangerous' drugs are no longer in use, e.g. the long-acting sulphonamides. The diagnoses of drug eruptions are perhaps more accurate today and, for example, exanthematous eruptions of viral origin are better excluded from the later series.

It is obvious that the frequency of cutaneous reactions with a particular drug is correlated to its use. In the report from the Boston Collaborative Drug Surveillance Program (6), drug-specific reaction rates were studied by analysing the data on 15 438 hospital patients. The clinical reactions studied were exanthematous eruption, urticaria and generalized pruritus. Their finding that amoxicillin, trimethoprim-sulfamethoxazole and ampicillin had the highest reaction rates agrees well with our results on the most common drugs causing exanthematous eruptions.

A single drug can cause quite different clinical eruptions. Conversely, a single type of clinical skin reac-

Table IV. *Drugs causing skin reactions, a 30-year series*

	1956–60 5 years	1961–70 10 years	1971–80 10 years	1981–85 5 years	1956–85 30 years
Antimicrobial agents	127 (23%)	314 (49%)	228 (51%)	95 (42%)	764 (41%)
Sulphonamides, trimethoprim	13 (2.4%)	123 (19%)	122 (27%)	26 (12%)	284 (15%)
Other antimicrobial agents	114 (21%)	191 (30%)	106 (24%)	69 (31%)	480 (26%)
Antipyretic/anti-inflammatory analgesics	251 (45%)	129 (20%)	59 (13%)	61 (27%)	500 (27%)
Drugs acting on the central nervous system	78 (14%)	73 (11%)	52 (12%)	23 (10%)	226 (12%)
Others	31 (5.6%)	66 (10%)	91 (20%)	28 (12%)	216 (12%)
Unknown	66 (12%)	56 (8.8%)	16 (3.6%)	18 (8.0%)	156 (8.4%)
Total	553 (100%)	638 (100%)	446 (100%)	225 (100%	1 862 (100%)

tion can be caused by various drugs—or by other factors, e.g. viral infections. Thus, one cannot infer the causative drug from the clinical picture alone, and the only reliable method of confirming a suspected drug reaction is a provocation test with the drug in question.

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