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Cutaneous Reactions to Drugs: A Series of In-patients during a Five-year Period

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We have studied drug eruptions at a single clinic since 1956. The last 5-year series comprises in-patients with drug eruptions during the period 1986–1990. The total number of cases in this series was 135, the most common types being fixed eruption, exanthematous eruption and urticaria. The causative agent was confirmed with a provocation test in 102 cases. The most common groups of causative drugs were antimicrobial agents, antipyretic/anti-inflammatory analgesics and drugs acting on the central nervous system. We also present a 35-year series of 1997 cases of drug eruptions, most of them proven with oral provocation. The types of drug eruption and the drug groups causing eruptions seem to be the same throughout the 35-year period. As there are no reliable laboratory methods of examining drug eruptions, oral provocation is the only reliable method in most cases. ***Key words: drug eruptions; exanthematous eruption; fixed drug eruption; drug provocation.***

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Cutaneous side-effects of drugs may depend on toxic reactions, such as overdosage, accumulation, interaction of various drugs, idiosyncrasy or anaphylactoid reaction due to histamine liberation. Drug sensitivity, however, is the most common cause of cutaneous reactions (1). An eruption may be the sole symptom or it may be accompanied by others. Fever is rather common, and in severe cases, different symptoms may be observed in different organs.

In many series reported, the most common clinical types of skin reactions are exanthematous eruption, fixed drug eruption (FDE) and urticaria (2–8), the most common causative drugs being antimicrobial agents, antipyretic/anti-inflammatory analgesics and drugs acting on the central nervous system (3–8).

Sometimes the patient history and clinical picture are so typical that the triggering agent is easily identified. In most cases, however, numerous drugs may be suspected, and even the diagnosis of drug reaction may be uncertain. Laboratory and skin tests are of limited value in examining drug reactions. Prick tests may detect penicillin allergy (9), and topical provocation has been shown to be useful with several drugs causing FDE (10) and also in some cases of exanthematous eruption (11, 12). *In vitro* tests, e.g. RAST, the basophil degranulation test and the lymphoblast transformation test, are unreliable because they can give both false positive and false negative results (13). The only reliable method of confirming the causative drug is rechallenge, though many authorities maintain that drug provocation is justified only when the trigger cannot be identified by any other means and the suspected drug is needed for treatment of the patient (6, 7, 14, 15).

PATIENTS AND METHODS

The study was carried out at the Departments of Dermatology and Allergology of Helsinki University Central Hospital between January 1986 and December 1990. We compiled information on all hospitalized patients with a suspected drug eruption and selected the reliable ones. There were 60 men and 71 women. The age range was from 2 to 82 years. The mean age of men was 42.8 years and that of women 45.1 years. Four of the patients had had reactions against two different drugs; thus the total number of cases was 135. In the majority of cases, a provocation test was performed with the suspected drug in order to confirm the causative agent. The initial test doses were usually 1/3 of the therapeutic single dose. If the provocation proved negative, a higher test dose of the same drug, or a new test drug, could be given after 24 h (14). In some cases of FDE, the local method (10) was used either alone or in addition to the oral challenge. In some cases of carbamazepine-induced exanthema, a patch test with 3% and 10% carbamazepine in a vehicle of aqua, petrolatum and 70% ethanol was performed with positive results on the intact skin of the back, using the Finn chamber technique (16). In some cases, the patient history and the clinical picture were so typical that no further evidence was needed.

RESULTS

The most common clinical types of drug eruption were FDE, exanthematous eruption and urticaria, with 53, 52 and 24 cases, respectively. In addition, there were solitary cases of gold dermatitis (3), erythema multiforme (2) and erythrodermia (1) (Table I).

The causative drug was discovered or strongly suspected in 133/135 cases. In the 2 remaining cases the clinical picture was typical but the causative agent could not be traced. Antimicrobial agents accounted for the largest number of cases (52). Thirty-three of these were caused by sulphonamides and/or trimethoprim. Phenazone derivatives were by far the main agents causing FDE.

Drug eruptions over 35 years (1956–1990)

Skin reactions to drugs have been studied at the Departments of Dermatology and Allergology of Helsinki University Central Hospital for 35 years. There are five consecutive series, the total number of cases being 1997 (Table II). All the series comprised hospitalized patients, except for the first one (1956–60), which included outpatient cases.

Exanthematous eruption formed the largest group of clinical types, accounting for 39% of the total. Urticaria was the second largest with 27%. In the earliest 5-year series, urticaria was the most common clinical type with 44%. FDE accounts for 16% of the total in the 35-year series. Its percentage has continuously increased from the first period (6.3%) to the last (39%). The group "others", including miscellaneous types of eruption, has remained nearly stable in all series except for the last one with only 4.4%. The drugs causing eruptions are listed in Table III. Antimicrobial agents have caused most eruptions in all but the

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Table I. *Drug eruptions, clinical types and causative agents: positive provocations/total 1986–1990*

Drug	Exanthematous eruption	Fixed drug eruption	Urticaria	Other reaction types	Positive provocation /total
Antimicrobial agents	*16/29*	*15/15*	*6/7*	*0/1*	*37/52*
Penicillin	1/1		1/1		2/2
Amoxicillin	1/3		0/1		1/4
Doxycyline	0/1	6/6			6/7
Cephalosporine	0/2				0/2
Erythromycin	2/2				2/2
Clindamycin	1/1				1/1
Sulphonamides	2/2	4/4	4/4		10/10
Trimethoprim	7/8	5/5	1/1		13/14
Sulpha-trimethoprim	1/8			0/1	1/9
Nitrofurantoin	1/1				1/1
Antipyretic/anti-inflammatory analgesics	*3/4*	*27/27*	*16/16*		*46/47*
Phenazone derivatives		25/25	1/1		26/26
Acetylsalicylic acid	1/1		15/15		16/16
Tolphenamic acid	1/1				1/1
Chlormezanone		1/1			1/1
Piroxicam	0/1	1/1			1/2
Ibuprofen	1/1				1/1
Drugs acting on the central nervous system	*9/13*	*6/10*		*0/1*	*15/24*
Barbiturates		1/2			1/2
Carbamazepine	7/10	5/8		0/1	12/19
Phenytoin	1/2				1/2
Maprotiline	1/1				1/1
Others	*2/6*	*0/1*	*1/1*	*1/4*	*4/12*
Hydroxyzine hydrochloride			1/1		1/1
Glibenclamide	0/1				0/1
Hydrochlorothiazide	0/1				0/1
Gold compounds				0/3	0/3
Diltiazem	1/1			1/1	2/2
Allopurinol	1/1				1/1
Chole contrast (iodine derivative)	0/1				0/1
Unknown drug	0/1	0/1			0/2
	30/52	48/53	23/24	1/6	102/135

first series. Antipyretic/anti-inflammatory analgesics are the second most important eruption-inducing group in all series but the first one. The proportion of cases caused by drugs acting on the central nervous system has been similar in all series.

DISCUSSION

The basic trend apparent in our 35-year series of patients with drug eruptions is that the total number of cases has decreased over the years. There are many possible explanations for the decrease. Some earlier drugs known to cause severe reactions, for instance long-acting sulphonamides and barbiturates, have gone almost entirely out of use. Today's drugs, e.g. penicillins, are more highly refined than earlier ones and may therefore cause fewer adverse reactions. Nowadays, new drugs are thoroughly tested for side-effects before they are brought onto the market. Even so, undesired reactions can never be totally avoided.

There are also some practical reasons for the declining number of drug eruptions in the same hospital over the years. The number of hospital beds for dermatological patients has been reduced; thus only severe cases of drug eruptions can be hospi-

Table II. *Clinical types of drug eruptions, a 35-year series*

Type	1956–1960 5 years	1961–1970 10 years	1971–1980 10 years	1981–1985 5 years	1986–1990 5 years	1956–1990 35 years
Exanthematous eruption	186 (34%)	286 (45%)	189 (42%)	71 (32%)	52 (39%)	784 (39%)
Fixed eruption	35 (6.3%)	60 (9.4%)	92 (21%)	77 (34%)	53 (39%)	317 (16%)
Urticaria	241 (44%)	169 (26%)	57 (13%)	45 (20%)	24 (18%)	536 (27%)
Others	91 (16%)	123 (19%)	108 (24%)	32 (14%)	6 (4.4%)	360 (18%)
Total	553 (100%)	638 (100%)	446 (100%)	225 (100%)	135 (100%)	1997 (100%)

Table III. *Drugs causing skin eruptions, a 35-year series*

	1956–1960 5 years	1961–1970 10 years	1971–1980 10 years	1981–1985 5 years	1986–1990 5 years	1956–1990 35 years
Antimicrobial agents	127 (23%)	314 (49%)	228 (51%)	95 (42%)	52 (39%)	816 (41%)
Sulphonamides/Trimethprim	13 (2.4%)	123 (19%)	122 (27%)	26 (12%)	33 (24%)	317 (16%)
Other antimicrobial agents	114 (21%)	191 (30%)	106 (24%)	69 (31%)	19 (14%)	499 (25%)
Antipyretic/anti-inflammatory analgesics	251 (45%)	129 (20%)	59 (13%)	61 (27%)	47 (35%)	547 (27%)
Drugs acting on the central nervous system	78 (14%)	73 (11%)	52 (12%)	23 (10%)	24 (18%)	250 (12%)
Others	31 (5.6%)	66 (10%)	91 (20%)	28 (12%)	10 (7.4%)	226 (11%)
Unknown	66 (12%)	56 (8.8%)	16 (3.6%)	18 (8.0%)	2 (1.5%)	158 (7.9%)
Total	553 (100%)	638 (100%)	446 (100%)	225 (100%)	135 (100%)	1997 (100%)

talized. The most severe cases, such as Stevens-Johnson and Lyell's syndromes, are no longer treated at the Department of Dermatology but rather at the Intensive-care Departments of the University Central Hospital.

Exanthematous eruption is the main clinical type in many series of drug eruptions (2–5, 7), and so it was in our 35-year series (Table II). In the first 5-year series, however, urticaria constituted the largest group. The main triggers of reactions at that time were penicillin and acetylsalicylic acid, both of which are known to give rise to urticaria. In the two most recent series, the number of FDE cases is slightly higher than that of exanthematous eruptions. However, this finding may be attributed to our research team's special interest in examining FDE with both oral and topical provocation (3–7, 10).

The main groups of causative drugs have remained the same over the years (Table III). Antimicrobial agents and anti-inflammatory analgesics were responsible for the majority of the skin reactions. Within the category of antimicrobial agents, sulphonamides and trimethoprim have been the most common causes of eruptions over the years, whereas phenazone derivatives have been the most common cause within the category of anti-inflammatory analgesics.

Many efforts have been made to develop proper laboratory and skin-test methods for detecting causative agents in drug reactions, but without much success. Topical provocation is an alternative to systemic provocation. This method has been proven to verify the causative agent in restricted cases of FDE and maculopapular eruption caused by carbamazepine (10, 11).

Oral provocation is still the only reliable clinical method for identifying the causative agent. The procedure involves only a minimal risk when performed rationally and with caution. We conclude that verifying the drug responsible for the eruption is most important, and oral provocation is the proper method for detecting the causative agent. It is better to induce a mild reaction under controlled circumstances than to allow the patient to suffer repeated severe reactions at home.

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