Acta Derm Venereol (Stockh) 1984; 64: 320–324

Drug Eruptions: Causative Agents and Clinical Types

A Series of In-patients during a 10-Year Period

KIRSTI KAUPPINEN[1] and SAKARI STUBB[1]

[1]*Department of Dermatology, University Central Hospital, Helsinki, Finland*

Kauppinen K, Stubb S. Drug eruptions: Causative agents and clinical types. A series of in-patients during a 10-year period. Acta Derm Venereol (Stockh) 1984; 64: 320–324.

A series of 446 inpatients with drug eruption was studied to determine the causative agent and the clinical type. In over a half of the cases a provocation test confirmed the drug responsible for the reaction. Sulphonamides/trimethoprim and ampicillin/penicillin followed by phenazones were the most frequent agents causing eruptions. Sulphonamides were also the most common drugs inducing Lyell's and Stevens-Johnson syndromes. Phenazones and barbiturates were the main causes of fixed eruptions. The frequency of in-patients having drug eruption was decreased in the 1971–80 series compared with the earlier one from 1961–70. Also the frequency of Lyell's and Stevens-Johnson syndromes was lower in the latter decade than in the earlier one. *Key words: Stevens-Johnson syndrome; Lyell's syndrome; Sulphonamides; Drug provocation test.* (Received August 25, 1983.)

K. Kauppinen, Department of Dermatology, University Central Hospital Helsinki, Snellmaninkatu 14, SF-00170 Helsinki 17, Finland.

"Drug eruptions is an age-old but always timely and fascinating subject and the time has passed, when it was possible to make up a list of the most common causes of drug eruptions, which would remain valid for many years" Baer & Witten stated in their review of drug eruptions in 1961 (1). For that reason a consecutive ten year series of drug eruptions was studied in the same dermatology clinic as the two previous ones from 1956–60 (2) and 1961–70 (3).

PATIENTS AND METHODS

The study comprises 446 hospitalized patients with drug eruption, treated at the Department of Dermatology, University Central Hospital, Helsinki, during the years 1971–1980. All the patients had a severe or moderate drug reaction. There were 134 men and 312 women with an age range of 2–81 years. In the majority of the cases a provocation test described in earlier publication (3) was used to confirm the agent responsible for the eruption. The test doses of the drug were chosen individually taking into the consideration the nature of the drug suspected, the clinical type of the reaction, the severity of the reaction and the interval from the onset of the eruption to the challenge. The reappearance of the eruption was followed 24 hours before another test dose either of the same or different drug was given.

RESULTS AND COMMENTS

Drugs responsible for the eruptions

The causative agent was discovered or strongly suspected in 430 (96%) out of the total of 446 cases. A positive provocation test confirmed the drug responsible for the reaction in 267 (62%) cases.

Antimicrobial agents was the main group of the drugs inducing skin reactions in the present series (Table I). They formed over a half of the total. Antipyretic and anti-inflammatory analgesics followed by central nervous depressants were the next. There

Table I. *The agents responsible for 430 drug eruptions*

Agent	No.	%
Antimicrobial agents	228	53
Antipyretic/anti-inflammatory analgesics	59	14
Central nervous system depressant drugs	52	12
Gold	26	6
Beta-adrenoceptor blocking agents	24	5.5
Others	41	9.5
Total	430	100

Table II. *Sulphonamides and trimethoprim causing 122 skin reactions*

Short-acting sulphonamides	7
Intermediate sulphonamides	22
Long-acting sulphonamides	14
Sulphonamide combinations	23
Sulphonamide+trimethoprim	41
Trimethoprim	15
Total	122

were rather many cases of eruptions caused by gold and by beta-blocking agents, of which practolol was the most common drug. Because of the severe adverse effects of that drug including various types of skin reactions, ocular disturbances and sclerosing peritonitis (4, 5), the usage of it has nowadays been minimized. The group "Others" comprises some cases induced by muscle relaxants, antihistamines, diuretics, opioid analgesics and 12 miscellaneous drugs, one or two of each.

Sulphonamides and trimethoprim were the most common drugs causing eruptions in this series (Table II). Long-acting as well as intermediate and short-acting sulphonamides had given rise to an eruption. Most of the reactions have been induced by a commonly used combination of sulphonamide and trimethoprim. Trimethoprim alone had also given rise to eruptions.

Ampicillin and penicillin were the most frequent drugs in the group of antibiotics, tetracyclines being in the third place (Table III). The frequency of the other antibiotics was few in number. There was also a group of 32 miscellaneous antimicrobial agents, of which 24 eruptions were induced by nitrofurantoin.

Table III. *Antibiotics causing 74 skin reactions*

Ampicillin/Pivampicillin	31
Penicillin	20
Amoxicillin	3
Azidocillin	2
Dicloxacillin	1
Tetracyclines	13
Tetracyclin	11
Doxycyclin	1
Demethylchlortetracyclin	1
Chloramphenicol	2
Erythromycin	1
Streptomycin	1
Total	74

Table IV. *Clinical types of 446 drug reactions*

Type	No.
Exanthematous eruption	189
Fixed eruption	92 (16)
Urticaria/Angioedema	57
Eczematous eruption	47
Erythema multiforme	18
Generalized erythroderma	10
Stevens-Johnson syndrome	8
Lyell's syndrome	8
Photosensitivity reactions	5
Purpuric eruption	4
SLE-like reaction	2
Erythema nodosum	1
Drug fever	5
Total	446

Table V. *The agents responsible for severe bullous mucocutaneous drug reactions from the years 1971–80*

Agent	Lyell's syndrome	Stevens-Johnson syndrome	Generalized bullous fixed eruption	Total
Sulphonamides	7	3	1	11
Phenazones			8	8
Barbiturates			5	5
Penicillin		2		2
Nitrofurantoin	1			1
Hydrochlorthiazide			1	1
Phenytoin		1		1
Unknown		2	1	3
Total	8	8	16	32

Phenazones (phenazone and phen. salicylate) were the most frequent agents in the group of antipyretic and anti-inflammatory analgesics. Acetylsalicylic acid was in second place. Barbiturates followed by carbamazepine and phenytoin were the most common agents in the group of central nervous depressants.

Clinical types of skin reactions

The 446 drug eruptions studied were divided into 13 clinical types (Table IV). Exanthematous eruptions formed the largest group (42%), fixed eruptions taking second place (21%) and urticaria/angioedema third place. There were 32 cases of severe bullous mucocutaneous eruptions, including 8 cases of both Lyell's and Stevens-Johnson syndromes and 16 of generalized bullous type out of 92 fixed eruptions. The causative agent could be traced in 86 cases of fixed eruption and confirmed by a positive provocation test in all but two. Phenazones and barbiturates were the most frequent agents responsible for the fixed eruptions for localized macular as well as for generalized bullous types of reaction.

In the present series of drug eruptions sulphonamides were the most frequent triggers of Lyell's syndromes (Table V). Sulphafurazole combined with sulphamethoxydiazine was the drug incriminated in four cases. In the remaining three the causative agent was some other combination of a short-acting and a long-acting sulphonamide.

Table VI. *Skin reactions to drugs*

A 25-year series from the Department of Dermatology, University Central Hospital, Helsinki

Years	No. of cases	Causative drugs: Antibiotics No.	Antibiotics %	Sulphonamides/trimethoprim No.	Sulphonamides/trimethoprim %	Others No.	Others %	Unknown No.	Unknown %
1956-60	553	104	19	13	2	370	69	66	12
1961-70	620	151	24	124	20	289	47	56	9
1971-80	446	74	17	122	27	234	52	16	4
1956-80	1 619	329		259		893		138	

Table VII. *Sulphonamides responsible for Lyell's and Stevens-Johnson syndromes and generalized bullous fixed eruptions in 1956–1980*

Years	Lyell's syndrome	Stevens-Johnson syndrome	Gener. bullous fixed eruption	Alto-gether
1956–60	2/3	1/1	1/1	4/5
1961–70	28/36	11/16	1/8	40/60
1971–80	7/8	3/8	1/16	11/32
1956–80	37/47	15/25	3/25	55/97

The sulphonamides given rise to Stevens-Johnson syndrome were sulphamethoxydiazine, sulphamethoxazole and salazosulphapyridine. In one case only, a sulphonamide (sulphamethoxydiazine) was the agent responsible for generalized bullous fixed eruption.

COMPARISON WITH THE PREVIOUS REPORTS

Skin reactions to drugs in in-patients have been studied in the Department of Dermatology, University Central Hospital, Helsinki, for 25 years. There were 1 619 cases altogether, observed in one five-year and two ten-year series separately (Table VI). The frequency of patients treated for a drug eruption was lower in the past decade than in the previous ten-year and earlier five-year series.

Antimicrobial agents (antibiotics and sulphonamides/trimethoprim) formed about a half of the total in both series from the last two decades. There was not much difference in the frequencies of eruptions caused by antibiotics, between the three series. The frequency of drug eruptions provoked by sulphonamides was low in 1956–60, but had increased greatly in 1961–70, forming one-fifth of the total and in 1971–80, over one-fourth. The frequency of unknown drugs remained lowest (4%) in the series from 1971–80.

A comparison of frequencies of severe bullous mucocutaneous eruptions and of the reference of the reactions to sulphonamides shows that the frequency was lowest in 1956–60 and highest in 1961–70 (Table VII). During the 25-year study period sulphonamides were the most common agents inducing Lyell's and Stevens-Johnson syndromes but generalized bullous fixed eruptions were infrequently caused by them.

DISCUSSION

The fact that the frequency of in-patients treated for a drug eruption in the Department of Dermatology has decreased during the past decade may be explained by the raised standard of knowledge about side-effects of drugs as well as by a minimized usage of long-acting sulphonamides, which have been the agents most commonly incriminated inducing severe drug reactions such as Lyell's and Stevens-Johnson syndromes. In the present series of drug eruptions the frequency of those reactions, mainly induced by sulphonamides, was highest in 1961–70, which was the period when long-acting preparations were commonly used. Nevertheless the modern intermediate-acting sulphonamides, e.g. sulphamethoxazole, have also given rise to severe bullous reactions (6, 7). There was one case of Lyell's syndrome induced by a combination of sulphamethoxazole and sulphafurazole and one of Stevens-Johnson syndrome by sulphamethoxazole alone in the present series. In the report of fatal reactions to drugs from the Swedish Adverse Drug Reaction

Committee antimicrobial drugs (antibiotics and sulphonamides) were the most common causative agents inducing 21 % of the reactions (8). Sulphonamides and antibiotics were the most frequent drugs also in the present study. In a report from USA by Stewart et al. the drugs most commonly implicated in dermatologic reactions were ampicillin, penicillin G and phenytoin (9). In their investigation exanthematous eruption (rash) was the most common clinical manifestation as also in the present study, but there was not a single case of fixed eruption included, which was the secondly frequent clinical type in our series.

On the drugs causing fixed eruptions there are many individual case reports and some comprehensive lists of the agents most frequently responsible. In the reports from Indien sulphonamides, analgesics and tetracycline were the most common causes of reaction by Sehgal et al. (10) and tetracyclines, metamizole and oxyphenbutazone by Pasricha (11). In the present series as well as in the previous one from Helsinki phenazones and babiturates were the most common agents causing fixed eruptions (3).

The pattern of consumption of drugs is changing continuously in every country at different periods and many new drugs are put on the market every year. Since there are no means to predict the potential capacity of those in regard to provoke adverse reactions, there is a need to identify and register the causative agents to the reactions. A provocation test is the only reliable method for clinical use to identify the drug responsible. Its role should be emphasized, as the clinical history alone is not enough to incriminate a drug.

REFERENCES

1. Baer RL, Witten VH. Drug eruptions. A review. In: Year Book of Dermatology, series 1960–1961, 9–37. Chicago, 1961.
2. Kauppinen K, Rechardt L. Lääkeaineihottumat. Helsingin yliopiston Ihotautien klinikan vuosien 1956–60 aineisto. Duodecim 1963; 79: 269–272.
3. Kauppinen K. Cutaneous reactions to drugs with special reference to severe bullous mucocutaneous eruptions and sulphonamides. Acta Derm Venereol (Stockh) 1972; 52, Suppl. 68.
4. Brown P, Baddeley H, Read AE, Davies JD, McGarry J. Sclerosing peritonitis, an unusual reaction to a beta-adrenergic-blocking drug (practolol). Lancet 1974; 1477–1481.
5. Felix RH, Ive FA, Dahl MGC. Cutaneous and ocular reactions to practolol. Br Med J 1974; iv: 321–324.
6. Aberer W, Stingl G, Wolff K. Stevens-Johnson Syndrome und toxische epidermale Nekrolyse nach Sulphonamideinnahme. Hautarzt 1982; 62: 484–490.
7. Azinge NO, Garrick GA. Stevens-Johnson syndrome (erythema multiforme) following ingestion of trimethoprim-sulfamethoxazole on two separate occasions in the same person. J Allergy Clin Immunol 1978; 62: 125–126.
8. Böttiger LE, Furhoff AK, Holmberg L. Fatal reactions to drugs. A 10-year material from the Swedish Adverse Drug Reaction Committee. Acta Med Scand 1979; 205: 451–456.
9. Stewart RB, May FE, Cullen SI. Dermatologic adverse drug reactions in hospitalized patients. Am J Hosp Pharm 1979; 36: 609–612.
10. Sehgal VN, Rege VL, Kharangate VN. Fixed drug eruptions caused by medications. Int J Dermatol 1978; 17: 78–81.
11. Pasricha JS. Drugs causing fixed eruptions. Br J Dermatol 1979; 100: 183–185.