A STUDY OF 218 DRUG ERUPTIONS

M. Z. MANI * AND MARY MATHEW †

Summary

Two hundred and eighteen instances of drug eruptions were observed in 210 patients, during a period of 5½ years. The incidence was 1.2% of all new dermatology cases and the male–female ratio was 1.5 : 1. The mean age of patients in this series was observed to be 33.8 years. Exanthematous eruptions were most frequent (27.5%), followed closely by fixed drug eruptions (26.6%) Urticaria was third in frequency, but the incidence was considerably less (9.6%). The serious eruptions of Stevens-Johnson syndrome and toxic epidermal necrolysis together constituted 7.8%. Eruptions due to antituberculous drugs accounted for 15.6% of the total. The drugs which were responsible for the largest number of eruptions were in order of frequency : thiacetazone, sulphonamides (including cotrimoxazole), ampicillin, chloroquine, metamizole (analgin) and aspirin. Thiacetazone caused several types of eruptions and was responsible for two deaths : one in a patient of toxic epidermal necrolysis, and the other in a case of Stevens-Johnson syndrome. Furazolidone was noticeable in producing a severe urticaria in 3 patients. Four cases of definite fixed drug eruption were encountered in which there was no history at all of any drug ingestion.

KEY WORDS : Drug eruption, Exanthematous, Fixed drug eruption, Thiacetazone, Sulphonamides, Ampicillin, Chloroquine, Regional variation.

Many of the drugs in current use are double-edged weapons. Apart from their known benefits to the patient, they are also well known to cause adverse reactions, which may either be mild or so severe as to be fatal. Thus it is imperative that in each patient the risk of drug administration should be weighed against the expected therapeutic benefit[1]. Various estimates have put the incidence of drug reactions ranging from 1 – 3% and even upto 5 – 10% of hospitalized patients[1,2,3]. Drug eruptions (cutaneous reactions to drugs) constitute the commonest type of drug reaction[1,3]. The incidence of drug eruptions is very difficult to determine and most estimates are inaccurate. The majority of drug eruptions are presumed to be caused by an allergic mechanism, and are produced when the drug comes into contact with the skin or mucosa

* Assistant Professor,
Dermatology Section,
Department of Medicine

† Professor & Head,
Department of Medicine,
Christian Medical College & Brown Memorial Hospital, Ludhiana-141008, Punjab.

Present address of principal author :
Dermatology Department,
Wanless Hospital,
Miraj Medical Centre,
Miraj-416410, Maharashtra.

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by way of the general circulation[3]. By this definition, contact dermatitis is excluded. In the best interests of the patient, it is mandatory to correctly diagnose and classify the type of drug eruption and to avoid using the unqualified, non-specific term "drug rash". Precise evaluation of each patient helps in narrowing down the list of suspected drugs and is a better guide to future therapeutic options.

Exanthematous eruptions present with erythematous macules or maculopapules simulating scarlet fever and measles respectively. Occasionally, there may be papular or psoriasiform lesions. In case the offending drug is continued, the condition may progress to a more serious exfoliative dermatitis[1]. Lichenoid eruptions resemble lichen planus with violaceous, flat-topped, itchy papules. Fixed drug eruptions (FDE) characteristically recur on the same site whenever the offending drug is readministered. They are localized and asymmetrical and heal leaving prominent hyperpigmented macules. They form an exception to the general rule that eruptions are disseminated and bilaterally symmetrical. Acneiform eruption resembles acne vulgaris and as it is usully mild, the causative drug can often be continued with impunity. Exposure to light is an important factor in the development of photosensitive eruptions, the lesions of which are localized to light-exposed areas. Eczematous eruptions resemble contact dermatitis; they are, however, produced by systemic administration of certain drugs. Serious types of eruptions which may be fatal are : exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis (Lyell's Syndrome, which presents with extensive bullous lesions and areas of denudation of skin resembling scalds).

Provocation with the suspected drug is the only definite proof for establishing that a particular drug has caused the eruption[3]. However, in practice it is not always expedient or possible to do so. Hence, a diagnosis has often to be based on time relations and patterns of reaction, which is no more than an assessment of probability[1].

Materials and Methods

This study included 218 instances of drug eruptions seen in 210 patients, who were observed during a period of $5\frac{1}{2}$ years, from 1976 to 1981. Eight patients had 2 episodes of drug eruptions each. The patients were drawn from various sources within the hospital and included dermatology out-patients and in-patients, as well as referred cases from other O. P. Ds. and wards. Whenever possible, a provocation test was attempted starting with the least likely drug first. In other cases a diagnosis was made by a "negative" provocation, by continuing the less likely drugs and withholding the suspected drug. Whenever two or more drugs were withheld, the drug which was considered as more likely to produce the eruption has been included; there being 58 such cases. Cases where either of two drugs belonging to different groups, or any of several drugs given concurrently could have caused the eruption, have been included under appropriate headings (Tables 2 & 3). In cases where there was no clue at all to the identity of the causative drug, a separate group of completely unknown drugs was included (Tables 2 & 3).

Observations

During this period a total of 18,660 patients were seen, which included all new dermatology out-patients and ward patients. The incidence of drug eruptions was thus 1.2%. An analysis of the age of patients revealed that the maximum number of patients belonged to the third decade (31.4%, Table 1). The mean age of patients was 33.8 years and the median was

TABLE 1

Age and Sex distribution of 210 patients of drug eruptions

	M	F	Total	%
0—10	10	1	11	5.2
11—20	15	12	27	12.9
21—30	41	25	66	31.4
31—40	23	21	44	21.0
41—50	10	13	23	11.0
51—60	18	11	29	13.8
61—70	8	1	9	4.3
71—80	—	1	1	0.5
Total	125	85	210	100.0

31 years. There were 3 children below the age of one year and the oldest patient was 75 years old. The male-female ratio was 1.5 : 1, which was comparable to the ratio for all new dermatology O.P.D. patients and ward patients (1.6 : 1).

In this series there were 30 patients who developed 35 eruptions due to antituberculous drugs and among them also, the largest number of patients was seen in the third decade (30%), and the mean age of these patients was 35.4 years. However, in contrast to the whole group, the sex ratio in this group was exactly equal.

Types of eruptions and causative drugs

Exanthematous eruptions were most common (27.5%, Table 3); these being maculopapules in 28 cases, papules in 16 cases, macules in 14 cases and psoriasiform and pityriasis rosea-like eruption in one case each. FDE were almost as frequent as exanthematous eruptions (26.6%). Urticaria was third in frequency but was much less common than the above two eruptions (9.6%). The severe eruptions of Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN) together constituted 7.8% of the total. Uncommon patterns of eruptions included exfoliative dermatitis, eczematous, photosensitive and purpuric eruptions and vasculitis (Table 3).

TABLE 2

Causative drugs in 218 drug eruptions

Drugs		No. of drug eruptions
1. Antibiotic Drugs, 33 (15.1%)		
Penicillin		3
Ampicillin Group		11
Ampicillin	8	
Amoxicillin	3	
Tetracycline Group		7
Tetracycline	4	
Oxytetracycline	1	
Demethylchlortetracycline	1	
Doxycycline	1	
Chloramphenicol		3
Streptomycin		6
Rifampicin		1
Griseofulvin		1
Penicillin or Streptomycin		1
2. Chemotherapeutic Drugs, 63 (28.9%)		
Sulfonamides		6
Short acting	3	
Long acting	2	
Unknown sulfonamide	1	
Cotrimoxazole (Septran)		8
Tuberculostatic Drugs		30
Thiacetazone	19	
Isoniazid	6	
Para-amino salicylic acid	3	
Ethambutol	2	
Anti-Malarial Drugs		13
Chloroquine	10	
Amodiaquine	1	
Unknown anti-malarial drug	2	
Urinary Antiseptic Drug		
Mandelamine		1
Gastro-Intestinal Chemotherapeutic Drugs		
Furazolidone		3
Iodochlorhydroxyquin		1
Tetramisole (Decaris)		1
3. Antipyretic Analgesic Drugs, 47 (21.6%)		
Aspirin		10
Metamizole (Analgin)		10
Phenylbutazone Group		7
Phenylbutazone	3	
Oxyphenbutazone	4	
Phenazone derivatives		2
Ibuprofen (Brufen)		1
Paracetamol		1
Metamizole or Aspirin		2

Drugs		No. of drug eruptions
Unknown antipyretic analgesic drugs		14
4. Central Nervous System Depressant Drugs 14 (6.4%)		
Phenobarbitone		5
Diphenylhydantoin		3
Diazepam		3
Meprobamate		1
Phenobarbitone or Diphenylhydantoin		2
5. Other Groups		
Sulfonylureas		2
Chlorpropamide	1	
Glybenclamide	1	
Antihypertensive drugs and diuretics		4
Ergot derivative	1	
Unknown antihypertensive drug	1	
Hydrochlorthiazide	1	
Frusemide	1	
Steroids		6
Prednisolone	2	
Betamethasone	4	
Drug for indigestion		1
Anti-asthmatic drug		1
Laxatives		2
Doxepram		1
Antihistamines		2
Dimethindene	1	
Chlorpheniramine	1	
Vitamins		3
B-Complex	2	
Multivitamin	1	
6. Either one of two drugs		4
Tolbutamide or Nalidixic acid	1	
Streptomycin or Para-amino-salicylic acid	1	
Streptomycin or ethambutol	1	
Amoxicillin or Aspirin	1	
7. Combination of Several Drugs (Antibiotics, Antipyretic Analgesics, Laxatives and a Diuretic)		7
8. Completely Unknown Drugs		27
9. Not due to Drugs		4
	Total	218*

* See similar footnote in Table 3

Exanthematous eruptions were mainly caused by the following drugs in order of frequency: ampicillin, aspirin, thiacetazone, cotrimoxazole and streptomycin (Table 3). FDE were mainly caused by sulphonamides (including cotrimoxazole), metamizole, phenylbutazone group, antimalarial drugs and tetracyclines. As a group, antipyretic analgesics produced the largest number of FDE (20 cases). In 4 cases of definite FDE there was no history at all of any drug ingestion. In another 2 cases which were exacerbated by antipyretic analgesics, there was a past history of definite aggravation by food items such as garlic and dry fruits. Urticaria was caused mainly by aspirin and furazolidone. The only eruption produced by furazolidone was urticaria, which was characteristically severe and prolonged and needed systemic steroid therapy for control. Lichenoid eruptions were caused by thiacetazone and chloroquine. Exfoliative dermatitis was caused by thiacetazone in 2 cases, ethambutol in one case (Tables 3 and 4) and in another case both by phenobarbitone and diphenylhydantoin. There was one case of cutaneous vasculitis which was caused by a mixed tablet containing an ergot derivative and reserpine (Brinerdin). There was only one case of purpuric eruption which was caused either by tolbutamide or nalidixic acid.

Drugs which produced a wide spectrum of different types of eruptions included in order of frequency: thiacetazone (9 types, Table 4), chloroquine (7 types, Table 3), metamizole (6 types) and unknown antipyretic analgesics (5 types). There were 19 eruptions caused by thiacetazone, of which 16 appeared within 2 months of start of therapy and the remainder took upto 4 months.

TABLE 3

Different Causative Drugs and Clinical Types of Eruptions

Drug	Exanthematous	FDE	Urticaria	Erythema Multiforme	Stevens-Johnson syndrome	TEN	Acneiform	Lichenoid	Vesicular	Exfoliative Dermatitis	Eczematous	Photosensitive	Vasculitis	Purpuric	Pruritus	No. of provocations	Total	%
Penicillin	1		1		1												3	1.4
Ampicillin group	9		1	1													11	5.0
Tetracycline group	2	3	2														7	3.2
Chloramphenicol	1	1							1							(1)	3	1.4
Streptomycin	4				1	1										(3)	6	2.8
Sulfonamides		3			1	2											6	2.8
Cotrimoxazole	4	3		1													8	3.6
Tuberculostatic drugs	6		1	2	3	2	6	4	2	3					1	(10)	30	13.8
Aspirin	6		4														10	4·6
Metamizole		5	1		1	1			1		1					(1)	10	4.6
Phenylbutazone group	1	4	1	1												(1)	7	3.2
Phenazone, Paracetamol and Ibuprofen		3		1													4	1.8
Unknown antipyretic analgesic drugs	3	8	1	1	1												14	6.4
Phenobarbitone		1			1		2			1						(1)	5	2.3
Diphenylhydantoin		1			1					1						(1)	3	1.4
Diazepam & Meprobamate	3								1								4	1.8

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Chloroquine group & unknown antimalarials	2	4		1			1	3	1		1						13	6.0
Furazolidone			3														3	1.4
Corticosteroids							6										6	2.8
Miscellaneous Drugs*	5	4	3	2			2	1			1	2	1				21	9.6
Either of 2 drugs	3	2			1						1	1		1			9	4.1
Combination of several drugs	3	3							1								7	3 2
Completely unknown drugs	8	9	3	1	1				2	1		1	1				27	12.4
Not due to drugs		4															4	1.8
Total No. of eruptions	60*	58	21	11	12	5†	17	8	9	5‡	4	4	2	1	1	(18)	218	100.0
Percentage	27.5	26.6	9.6	5.0	5 5	3.3	7.8	3.7	4.6	2.3	1.8	1.8	0.9	0.5	0 5			

* All the drugs which are not separately included in this table have been placed in the category of Miscellaneous drugs.

† The total number is 221 instead of 218 This is because 3 drug eruptions were caused by 2 drugs simultaneously.
They were : 1 case of TEN caused by Streptomycin + Para-amino-salicyclic acid.
1 case of exanthematous eruption caused by Streptomycin + Ethambutol.
1 case of expoliative dermatitis caused by phenobarbitone + diphenylhydantoin.

‡ The total number for exanthematous eruptions, TEN and exfoliative dermatitis is 61, 6 and 6 respectively. This is due to the same reason as mentioned in the footnote above.

TABLE 4

Causative Antituberculous Drugs and Clinical Types of Eruptions

Drugs	Exanthematous	Urticaria	Erythema Multiforme	Stevens-Johnson syndrome	TEN	Acneiform	Lichenoid	Vesicular	Exfoliative Dermatitis	Eczematous	Photosensitive	Pruritus	No. of Provocations	Total
Streptomycin	2												(1)	2
Isoniazid						6								6
Thiacetazone	5	1	2	3	1		3	1	2			1	(7)	19
Para-aminosalicylic acid							1	1					(1)	2
Ethambutol									1					1
Rifampicin			1											1
Streptomycin and para-aminosalicylic acid*					1								(2)	1
Streptomycin and Ethambutol*	1												(2)	1
Streptomycin or Ethambutol*											1			1
Streptomycin or Para-aminosalicylic acid										1				1
Total	8	1	3	3	2	6	4	2	3	1	1	1	(13)	35

* Both drugs caused the same cruption.

As a group, chemotherapeutic drugs produced the largest number of eruptions (28.9%), followed by antipyretic analgesics (21.6%) and antibiotics (15.1%, Table 2). Central nervous system depressant drugs accounted for only 6.4% of cases.

Eruptions due to miscellaneous group of drugs (Table 3).

There were 3 eruptions probably due to vitamins, which included one case each of erythema multiforme, exanthematous eruption and urticaria. Antihistamines produced one case of FDE and another case of eczematous eruption. Glybenclamide caused FDE whereas chlorpropamide produced a photosensitive eruption. Frusemide was responsible for one case of exanthematous eruption whereas hydrochlorthiazide produced an acneiform eruption. Other drugs were : rifampicin, iodochlorhydroxyquin and doxepram, which were responsible for one case each of erythema mutiforme, FDE and exanthematous eruption respectively.

Route of administration of the drugs

In 9 cases the drug eruption was produced by administration of the drug by injection; in all other cases the drug was administered orally.

Deaths

There were 3 deaths attributed to the drug eruption itself; of which thiacetazone was responsible for the death of 2 adult females, one of whom developed TEN and the other Steven-Johnson syndrome. The third death occurred in an adult male who developed cutaneous and systemic vasculitis, presumably due to an unknown drug.

Discussion

In evaluating the results of this study it would be worthwhile to compare the data presented here with two other series: that of Mehta et al from Bombay[4] and Kauppinen's series from Finland[3]. The incidence of drug eruptions was comparable in all 3 series, and ranged from 1-2%. As regards the age and sex incidence and pattern of drug eruptions, our series was similar to the other Indian series of Mehta et al and contrasted with the western series of Kauppinen. In both Indian series there was a predominance of patients in the 3rd decade, whereas, in Kauppinen's series the largest number of patients was seen in the 6th decade; this difference was probably due to the higher longevity in Finland.

There was a preponderance of females in Kauppinen's series, in which the male-female ratio was 1 : 2. However, in the series of Mehta et al males predominated (2.3 : 1). In our series even though males outnumbered females, the difference was less striking (1.5 : 1). Thus, with regard to sex incidence of drug eruptions, there appears to be regional variation, males outnumbering females in India, in contrast to what has been observed in western series[1,3].

With regard to pattern of eruptions, it was observed that FDE was almost as prominent as exanthematous eruptions in both Indian series; urticaria much less common. In Kauppinen's series, however, FDE was only third in order of frequency and were much less common than exanthematous eruptions and urticaria. The drugs causing FDE were broadly similar in all three series; the higher incidence of FDE in India, as compared to Finland, may also be explained on the basis of regional variation.

Comparison of the drugs frequently responsible for eruptions showed important differences between our series and the other 2 series. Whereas, in both other series sulphonamides predominated, in our series they were only second in importance (14 cases, 6.4%, including cotrimoxazole). The low incidence from sulphonamides in our series may be partly attributed to the limited use nowadays of these chemotherapeutic agents, as compared to antibiotics. In this regard, it is of interest that cotrimoxazole was responsible for more eruptions than all other sulphonamides put together (Tables 2 and 3). In our series, the third in order of frequency were ampicillin and chloroquine group (5% each), followed by metamizole and aspirin (4.6% each). The true incidence of metamizole and aspirin would have been even higher, as several of the unknown antipyretic analgesics would probably have belonged to either group. Metamizole, owing to its toxicity, has been almost totally withdrawn from western countries. It is, however, still frequently prescribed in India. Chloroquine occupied a significant position in our series, whereas, it did not account for a single eruption in the series of Mehta et al in 1971. This difference may be attributed to its more frequent use nowadays and reflects the resurgence of malaria in India.

In our series, eruptions due to diuretics, sulphonylureas, antihypertensive drugs and penicillin were insignificant, whereas, thiacetazone had pride of place (19 cases, 8.7%). The higher incidence of thiacetazone, as compared to the series of Mehta et al, may be explained by its more frequent use currently as a standard antituberculous drug. On account of the well known propensity of thiacetazone to cause severe and even fatal reactions in India[5-9], it would be well to reconsider its role as a standard antituberculous drug. In contrast to thiacetazone, however, isoniazid was quite innocuous and only caused acneiform eruption. Eruptions due to antituberculous drugs,

as a group, constituted 15.6% of our series. This high incidence probably reflects the higher prevalence of tuberculosis in this area, as also the fact that our hospital holds a weekly tuberculosis clinic.

It has been stated that FDE is entirely due to drugs[3]. Our data, however, appears to be at variance with this statement; four of our cases appearing to be totally unrelated to drugs. In 2 cases, in addition to drugs, food items also produced exacerbation. The drugs causing FDE in our series were similar to those reported by Pasricha[10], with the notable exception that barbiturates were less frequently encountered as an etiologic agent. In our series, there was no case of FDE produced by any antileprosy drug. The high incidence of FDE due to dapsone in Africa[11] (3%), is in striking contrast to the situation in India, where its incidence is less that 0.1% in South East India[11]. There was not a single case of DDS induced FDE either in Pasricha's series[10] or in ours, both of which were from North India. Thus, the tendency of dapsone to produce FDE appears to show regional variation.

We were able to do provocation tests with suspected drugs in only 18 cases (Tables 3 & 4). It could not be performed more frequently owing to several difficulties such as: unwillingness to prolong the hospital stay in this private hospital, lack of patient compliance, and severity of the eruption. The large proportion of unknown drugs in this series (27 cases, 12.4%) clearly underlines the difficulties in the present system in this country, where drugs are often administered without prescription and without careful recording, either by the physician or the patient. It is thus imperative that there be a continuing education, both for the medical profession and the lay public, regarding the important and vexing problem of drug reactions.

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