CURRENT CUTANEOUS DRUG REACTION PATTERNS IN SINGAPORE

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SYNOPSIS

A 2-year study of cutaneous drug eruptions was carried out among inpatients in the Singapore General Hospital. One hundred and seven consecutive patients were studied. Their ages ranged from 12 to 83 years with a mean of 45 years. The male to female ratio was 1.0 to 1.3. The cutaneous drug eruption patterns were as follows: exanthema (39.3%), erythema multiforme/ Stevens-Johnson syndrome (16.8%), urticaria (15.9%), photodermatitis (5.6%), fixed drug eruption (4.7%), eczema (4.7%), toxic epidermal necrolysis (3.7%) and vasculitis (0.4%). The common drugs implicated were: ampicillin (26.2%), aspirin (10.3%), Bactrim (R) (9.3%), allopurinol (8.4%) and tetracycline (7.5%). Antimicrobial agents accounted for 51.4% and analgesic/anti-inflammatory agents for 17.8% of all cases. The mortality rate was 2.7%. One death each was attributed to toxic epidermal necrolysis, Stevens-Johnson syndrome and generalized exfoliative dermatitis.

INTRODUCTION

Adverse drug reactions are common events in hospital practice. Most of these manifest as skin eruptions and have an allergic, that is, immunologic basis. The purpose of this study is to evaluate the pattern of drug eruptions and the drugs responsible for such reactions among inpatients in the Singapore General Hospital. Such information helps to update the spectrum of allergic drug reactions seen in hospital practice. This is important as new drugs are continually introduced into the market.

PATIENTS AND METHODS

This study was carried out over a two-year period from February 1981 to January 1983. One hundred and seven consecutive patients with cutaneous eruptions from ingested or injected drugs seen at the Singapore General Hospital were studied. All patients were seen by one or both the authors. The patient profile was defined. The induction time, defined as the interval period between drug ingestion and reaction, was determined. The pattern of reaction and the probable offending drug was identified in each instance. Features of allergic drug reactions have been defined (1) - Table 1. Rashes unrelated to drug intake or those reactions which were non-immunologic in origin were excluded.

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Table I — Features of Allergic Drug Reactions

1. Prior exposure (usually for treatment) without adverse effects.
2. The reactions usually appear only after several days of treatment after first exposure to the drug.
3. The risk of reaction still exists at doses far below the therapeutic range.
4. Clinical manifestations do not resemble the general pharmacologic effects of the drug and cannot be predicted from animal testing.
5. The reactions occur in a small proportion of the population.
6. The reactions usually are restricted to a limited number of syndromes generally accepted as allergic in nature.
7. In a few instances antibiotics or T lymphocytes have been identified that react specifically with the drug or a metabolite.
8. The same reactions can be reproduced on administering a small amount of the suspected drug or drugs of similar chemical structure.

RESULTS

Altogether 107 patients were studied. The ages ranged from 12 to 83 years with a mean of 45 years. The male to female ratio was 1.0 to 1.3. The ethnic group distribution is shown in Table II.

Table II — Ethnic Group Distribution

Ethnic Group	Number of Patients	Percentage	Ethnic Composition of Hospital Admissions 1981 (Percentage)
Chinese	88	81.2	82.8
Indian	10	9.3	7.8
Malay	6	5.6	4.8
Others	3	3.9	4.6
Total	107	100.0	100.0

The type of reactions were categorised into 9 patterns namely exanthema, erythema multiforme major (Stevens-Johnson syndrome), urticaria, generalized exfoliative dermatitis (G.E.D.), photodermatitis,eczema, fixed drug eruption (Figure 1), toxic epidermal necrolysis (Figure 2) and vasculitfs. The numbers seen and the relative incidence of each is listed in Table III.

The probable causative drugs are given in Table IV. Anti-microbials accounted for 55 cases (of which 28 were due to ampicillin) and analgesics/anti-inflammatory drugs for 19 cases.

The induction time for exanthemas varied from 1 to 15 days with a mean of 5 days. For erythema multiforme/ Stevens-Johnson syndrome, it ranged from 1 to 40 days with a mean for 14 days. For urticaria, symptoms occurred within 30 minutes.

There were 3 deaths in this series. One died of toxic epidermal necrolysis due to phenylbutazone, the second from Stevens-Johnson syndrome due to Bactrim (R) and the third from G.E.D. due to allopurinol.

Table III — Types of Reaction Patterns

Reaction Patterns	Number	Percentage
Exanthema	42	39.3
Erythema multiforme/Stevens-Johnson syndrome	18	16.8
Urticaria	17	15.9
Generalized exfoliative dermatitis	9	8.4
Photodermatitis	6	5.6
Eczema	5	4.7
Fixed drug eruption	5	4.7
Toxic epidermal necrolysis	4	3.7
Vasculitis	1	0.9
Total	107	100.00

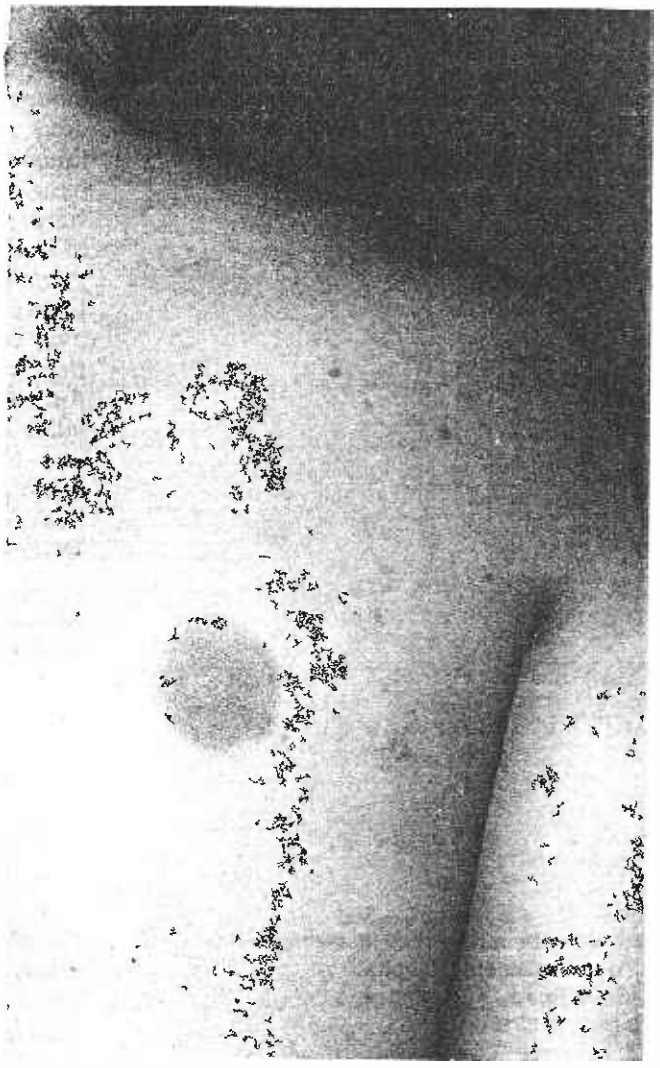

Figure 1.
Fixed drug eruption from tetracycline. A target lesion is shown.

TABLE IV - DRUGS AND REACTION PATTERNS

Drugs	Reaction Patterns									Total
	Exa	EM/SJS	Urt	GED	Pho	Ecz	FDE	TEN	Vas	
Ampicillin	21	3	3	1	–	–	–	–	–	28
Bactrim[R]	7	2	1	–	–	–	–	–	–	10
Tetracycline	1	1	–	–	–	–	5	1	–	8
Griseofulvin	2	–	–	–	1	–	–	–	–	3
Penicillin	1	–	1	–	–	–	–	–	–	2
Sulphonamides	–	–	1	–	–	1	–	–	–	2
Gentamycin	–	–	1	–	–	–	–	–	–	1
5-Fluorocytosine	1	–	–	–	–	–	–	–	–	1
Aspirin	4	–	6	1	–	–	–	–	–	11
Phenylbutazone	–	3	–	–	–	–	–	1	–	4
Paracetamol	–	–	2	–	–	–	–	–	–	2
Mefenamic acid	–	–	1	–	–	–	–	–	–	1
Benoxaprofen	–	–	–	–	–	1	–	–	–	1
Allopurinol	1	2	–	3	1	–	–	1	1	9
Chinese herbs	1	1	–	–	1	1	–	–	–	4
Dilantin	–	1	–	1	–	–	–	–	–	2
Phenobarbitone	–	–	–	–	–	–	–	1	–	1
Carbamazepine	–	1	–	–	–	–	–	–	–	1
Others	3	4	1	3	3	2	–	–	–	16
Total	42	18	17	9	6	5	5	4	1	107

*Sulphamethoxazole-trimethoprim

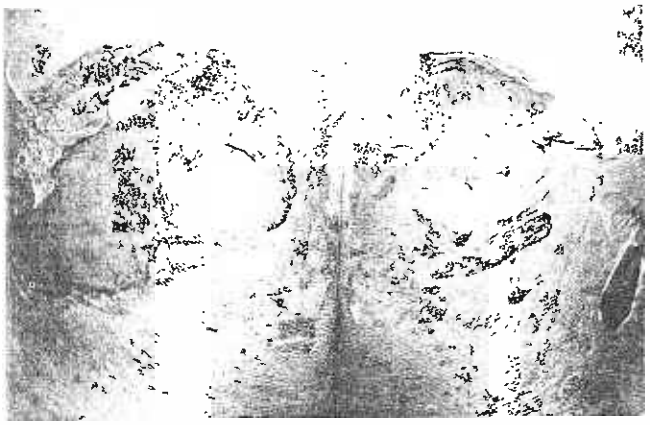

Figure 2.
Toxic epidermal necrolysis from pyrazolone derivative. Note scald-like appearance.

DISCUSSION

In the Boston Collaborative Drug Surveillance Programme experience, estimating data obtained on 22,227 consecutively monitored medical impatients, allergic skin reactions occurred in just over 2% (2). Reaction rates of above 50 per thousand recipients were obtained for the sulphamethoxazole-trimethoprim combination and for ampicillin. Features of allergic drug reactions have been alluded to earlier (Table I). The mechanism of sensitization may be related to the molecular structure, or hapten binding. Theoretically the drugs themselves or their intermediates such as quinones, anhydrides, or oxazolones can be the allergens. Coincidental drug therapy may enhance or reduce the allergic effects of the drugs (3). Identification of the specific allergen is thus difficult. Frequently the implication of a particular drug is therefore more judgemental than formal. No good in vitro diagnostic tests are available. Also owing to ethical and safety considerations challenge or provocative tests were done only for those patients with fixed drug eruptions.

In this study we noted no ethnic predisposition. Females were more often affected than males. This female preponderance has also been seen with other studies (2, 4).

The reactions observed fell into 9 recognizable patterns (Table III). The most prevalent pattern was exanthema variously described as erythematous maculopapular or morbilliform or else as a toxic erythema or scarletiniform. This accounted for 39.3% of all cases, exactly half of which is due to ampicillin. Erythema multiforme is the next most common pattern seen (16.8%). Almost all these patients present with the major form of the disease with mucous membrane involvement (Stevens-Johnson syndrome). Urticarial eruptions were also commonly seen (15.9%) and characterized by an acute onset of intensely itchy wheals which are transient. Generalized exfoliative dermatitis and photodermatitis, which accounted for 8.4% and 5.6% of cases respectively, are well known syndromes which may be induced by drugs. Eczematous reactions from endogenous drug intake were relatively uncommon (4.7%). Fixed drug eruptions (Figure 1) are distinctive and recognized in 4.7% of reactions. So are patients with toxic epidermal necrolysis (Figure 2), which resemble scalding and is life-threatening. Four (3.7%) of such cases were seen. The least common pattern was vasculitis (0.9%). This single reaction occurred in a patient taking allopurinol for gout. The diagnosis was proven by a skin biopsy and the condition improved after drug withdrawal.

The drugs implicated in this study are in 2 major categories namely the antimicrobials which were responsible for 51.4% and the anti-inflammatory-analgesic group which was responsible for 17.8% of the reactions.

The pattern of drug reactions is affected by the prescribing habits of our medical practitioners, as is noted by the increasing use of antimicrobial drugs especially ampicillin (5). Ampicillin reactions alone accounted for 26% (28) of the total number of reactions. The great majority of these (21) were in the exanthematic form the so-called "ampicillin rash". Of these, 2 were taking allopurinol for hyperuricemia and gout. There appears to be a higher incidence of ampicillin reactions in patients taking allopurinol (6) but whether this potentiation is by allopurinol or the gouty state is an open question. It has been observed that the ampicillin rash, if this drug were exhibited, in patients with infectious mononucleosis is almost invariable. A higher incidence of this rash is also seen in viral respiratory tract infections, cytomegalic infections and lymphatic leukemias.

Other reactions attributed to ampicillin were erythema multiforme (3), urticaria (3), and generalized exfoliative dermatitis (1). These latter reactions would probably manifest cross-sensitivity to others in the penicillin group, Bactrim (R) used mainly in the sulphamethaxole-trimethoprim combination Bactrim (R) resuilted in 10 adverse skin reactions.

Aspirin, a salicylate, generally causes very few cutaneous reactions. In the Boston experience the reaction rate is less than 3 per 1,000 courses of aspirin. Most of the eruptions suspected to be due to aspirin in this study is urticarial in nature. In these instances aspirin might in fact be acting just as triggers in patients prone to urticaria and the mechanism involved is non-immunologic.

Tetracycline caused all the 5 fixed drug eruptions observed in this study. This is the most common cause for fixed drug eruptions in Singapore today.

Two adverse cutaneous reactions were seen with benoxaprofen [Opren (R)] both eczematous in form (one included in this series). This non-steroidal anti-inflammatory drug has been banned from the market for causing deaths from cholestatic jaundice (7). This event emphasises the fact that we should be on the lookout for potential serious side-effects of new drugs.

Allopurinol, in our experience, is not an uncommon cause of allergic skin reactions particularly in patients with impared renal function. Very serious reactions such as generalized exfoliative dermatitis or toxic epidermal necrolysis can result.

The mortality rate is 2.7%, 3 out of 107 reactions. There was one death each from toxic epdiermal necrolysis, Stevens-Johnson syndrome and generalized exfoliative dermatitis.

In this study we have studied the cutaneous drug reaction patterns in hospital practice. Better notification by all medical practitioners will enable a more accurate picture of the incidence and trends of this problem in the whole of Singapore.

It is important for us to realise that bad reactions from drugs are potentially fatal and it behoves all of us who prescribe drugs to weigh the risk-benefit equation very carefully each time we use a drug.

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