CUTANEOUS DRUG ERUPTIONS

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SUMMARY

Patients attending a referral Skin Clinic were studied to identify the spectrum of drug eruptions and the offending drugs. There were 51 patients with an incidence of five per thousand and equal sex incidence. Though the pattern of eruption was broadly similar to other reports, unusual reactions were observed. In addition to the skin manifestation, fever and lymphadenopathy were present in most patients. Raised erythrocyte sedimentation rate and eosinopoenia were commonly observed. Clinical acumen and the list of drugs ingested are still the best clues to the diagnosis of drug eruption.

INTRODUCTION

Skin eruption is one of the commonest of the adverse drug reactions and the reported incidences vary from 1 to 3 percent. [1,2,3] However the incidence is probably increasing yearly due to mushrooming of the pharmaceutical industry, the persuasive ability of the drug representatives and the practice of polypharmacy by the attending physician. Though not all patients with cutaneous drug reaction seek hospital treatment, a prospective study of patients with such eruption was done for 18 months to identify the spectrum of drug eruptions and the causative or probable offending drugs. Fifty-one patients with an approximate incidence of 5 per thousand new patients in the Skin Clinic, are included in this report.

MATERIALS AND METHODS

All patients with suspected drug reactions were seen personally. Information of the presence of skin disease before the development of drug reaction, previous sensitivity to drugs, and the list of drugs ingested was obtained. Clinical examination included identification of lymphadenopathy and body temperature. Skin manifestation of the basic disease, if any, for which medication was given, was excluded. Total white and eosinophil cell count, erythrocyte sedimentation rate and VDRL was done in most of the patients. Clinical diagnosis of the type of the rash was occasionally confirmed by histology.

When a patient received multiple drugs, the probable offending drug was identified based on all or some of the following criteria: 1) the drug that is most likely to cause an eruption; 2) the time interval of two or more days between the exposure to the drug and the development of the rash except in patients with urticaria and 3) history of previous exposure to the same drug with or without developing a reaction.

RESULTS

Fifty-one patients (25 males and 26 females) were seen with drug eruptions. Their ages ranged from 11 to 70 years. Table I shows the number of patients in each type of drug reaction. Seven types of drug eruptions were observed. Morbilliform eruption and fixed drug eruption (FDE) together had an incidence of 74.5 percent. Exfoliative dermatitis, photosensitivity and urticaria were uncommon. One patient developed toxic epidermal necrolysis following levamisole therapy for systemic lupus erythematosus. Low grade fever was present in 28 patients and as shown in Table I all types of drug eruptions except photosensitivity were associated with fever. However the incidence of fever in the group with fixed drug eruption was much lower.

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TABLE I
NUMBER OF PATIENTS IN EACH TYPE OF DRUG REACTIONS

Type of Drug Reactions	No. of patients
Morbilliform	21 (14)
Fixed drug eruption	17 (5)
Erythema multiforme/S.J.S.	7 (5)
Exfoliative dermatitis	2 (2)
Photosensitivity	2
Urticaria	1 (1)
Toxic epidermal necrolysis	1 (1)

The figures in brackets indicate the number with fever.

Significant hair loss was noticed in two patients, one who developed morbilliform rash due to ampicillin and another who had erythema multiforme due to furosemide. Generalised lymphadenopathy was seen in four patients with morbilliform rash due to hyosine N-butylbromide (buscopan), trimethoprim-sulphamethoxazole (bactrim), ampicillin and tetracycline. Three of these patients had fever. During the subsequent follow-up the lymph nodes were not palpable. Thirty-five patients were taking more than one drug at the time they developed the rash. Previous sensitivity to other drugs was present in 13 patients.

Total white cell count, done in 39 patients, is shown in Fig. I. In the majority of the patients the counts were within normal range. The erythrocyte sedimentation rate was done in 31 patients and in 28 it was raised (Fig. 2). The VDRL test done in 15 patients, was negative in all. Eosinophil cell count was done in 39 patients. Eosinopoenia occurred in 20 patients and increased cell count in 8 patients (Fig. 3). Higher counts were seen mainly with the morbilliform rash.

Seven patients developed rash as a result of self-medication for constipation in three, headache in two, and generalised weakness in two. Phenolphthalein in the laxative, codeine in the analgesic and tartarate in a 'fruit salt' were the probable offenders. Morbilliform rash was caused by allopurinol, ampicillin, penicillin, trimethoprim-sulphamethoxazole (bactrim), phenobarbitone and hyoscine N-butylbromide (buscopan) (Table II). FDE was caused by phenolphthalein, tetracycline hydrochloride and amaranth (FD & C Red No. 2) is coloured acetaminophen (paracetamol). Erythema multiforme/Stevens-Johnson syndrome (S.J.S) was due to hydrochlorothiazide, phenobarbitone,

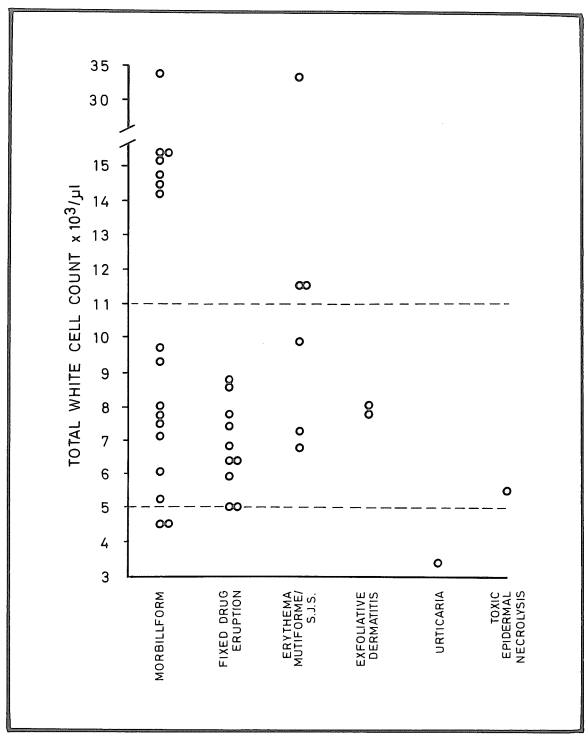

Fig. 1 Distribution of total white cell count in various drug reactions (normal 5-11 x 10^3 /ul)

allopurinol, phenolphthalein and furosemide. Aspirin was responsible for a single case of urticaria. Photosensitivity was due to hydrochlorothiazide. Exfoliative dermatitis was caused by ampicillin and tetracycline.

DISCUSSION

The incidence of cutaneous drug eruption depends, amongst other factors, on the prescription frequency of drugs most likely to produce adverse drug reaction and the severity of the reaction needing attendance at a clinic. An incidence of 5 per thousand is low compared to those in the literature and this may be due to the fact that the study was done in a referral clinic.

Cutaneous drug eruption was reported to be more common in the female [1] but Stewart *et al.* [3] believed that there was no difference in the sex incidence having excluded hirsutism and acneform eruption. As this study, which also did not include the above two adverse reactions, led to a conclusion of equal incidence, the female preponderance is probably not true. The pattern of drug reactions with morbilliform rash as the commonest type is similar to other studies. [4,5] However the incidence

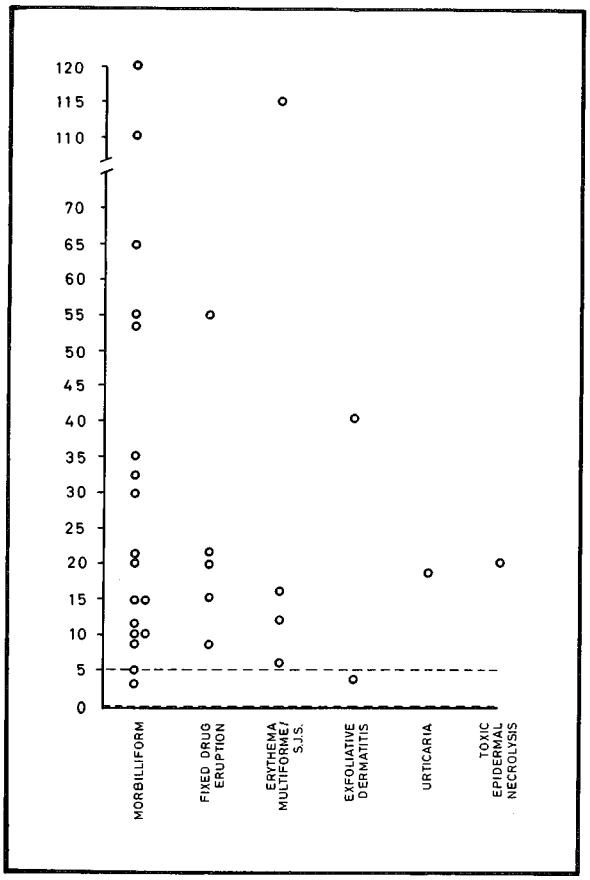

Fig. 2 Distribution of erythrocyte sedimentation rate in various drug reactions (normal rate = 0 to 5 mm/hr)

of FDE is high and this probably varies in different countries [6] depending on the frequency of using the offending drugs. The scarcity of drug-induced photosensitivity in a study from a subtropical country may seem unexpected but deeply pigmented skin, the habit of using umbrellas and other forms of screen when out in the open and the frequently clouded sky filtering off most of the ultra violet light together contribute to a low incidence of photosensitivity. [7] Although urticaria is a common problem in skin clinics, majority of them do not have an identifiable cause. [8] Among patients with urticaria seen in our clinic in only one was there a definite relation to the ingestion of drug (aspirin).

Fever associated with drug reaction was present in 28 patients and the incidence was high in those with morbilliform rash. Table I shows that an acute generalised drug eruption is more likely to be associated with fever than those with subacute onset and limited distribution of rash such as FDE.

TABLE II
DRUGS AND ERUPTIONS

	Morbilliform	Fixed drug eruption	Erythema multiforme/S.J.S.	Exfoliative dermatitis	Photosensitivity
Allopurinol	+		+		
Amaranth (in Paracetamol)	+	+			
Ampicillin	+			+	
Chlorpromazine					+
Codeine		+			
Furosemide			+		
Hydrpchlorothiazide	+				+
Hyosine (in Buscopan)	+				
Penicillin	+				
Phenobarbitone	+	+	+		
Phenolphthalein		+	+		
Tetracycline hydrochloride		+		+	
Trimethoprim/Sulphamethoxazole (in Bactrim)	+				

Lymphadenopathy was seen in four patients with morbilliform rash and three of these had associated fever. The association of morbilliform eruption, lymphadenopathy and fever suggest a constellation of signs forming a syndrome of drug eruption rather than a single feature confined to the skin only.

There was no significant leucocytosis but the sedimentation rate was raised in all types of drug eruptions with an incidence of 90 percent. Stubb [9] reported that leucocytosis occurred during the first six hours of provocation test for drug induced morbilliform rash and FDE but later fell. As most of the patients in this report were seen later than six hours of the onset of the rash, leucocytosis was not observed. Fellner [5] stated that eosinopoenia is characteristic of acute phase of drug reaction and in this study it was observed that eosinopoenia occurred in 20 of the 39 patients in whom the counts were done.

It is believed that there is a high incidence of sensitivity to drugs, particularly to antibiotics in

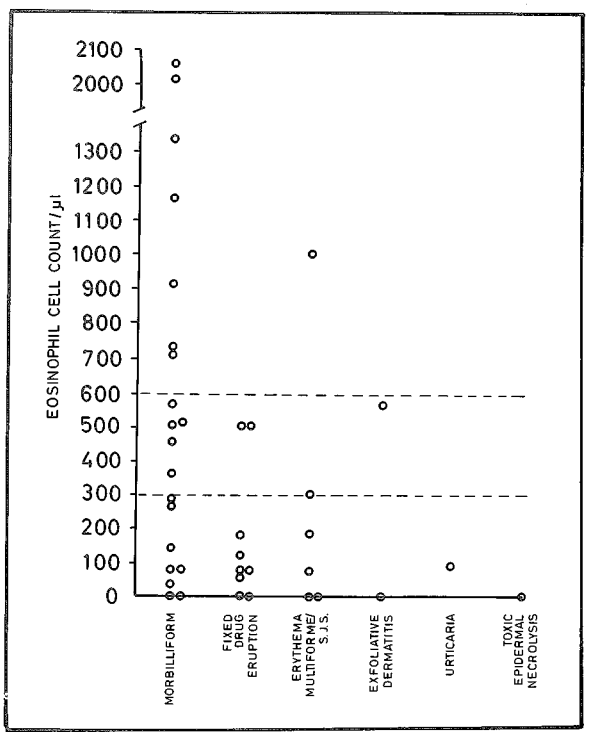

Fig. 3 Distribution of eosinophil count in various drug eruptions (Normal range 300-600 cell/ul)

patients with biological false positive reaction. [10] However none of the patients in whom VDRL test was done, had positive reaction.

Self medication for minor illness was responsible for drug eruption in 7 patients and five of them developed FDE. The pattern of reaction produced by individual drugs as observed here were similar to other reports but unusual reactions like ampicillin causing exfoliative dermatitis and levamisole causing toxic epidermal necrolysis were noted. Colouring agents of the drugs are responsible for some drug reactions. [11]It was found that amaranth (FD & C Red No. 2) found in the acetaminophen (paracetamol) tablets was responsible for FDE in three patients and morbilliform rash in one. It was observed that a given drug produces many types of drug eruptions and many drugs produce identical reaction. This probably makes the identification of the offending drug more difficult especially as yet no reproducible laboratory test confirms the diagnosis of drug reaction.

Methods for detection of drug allergy is still in its infancy and Juhlin [12] stated that anamnesis is still the important method. The two clinical methods frequently used, skin and provocation tests have diagnostic limitation, not to mention the complications and ethical considerations that may arise. Thus, presently, clinical acumen and an accurate list of drugs ingested are the most helpful pointers in the diagnosis of drug eruption and identification of the offending drug.

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