Clinical study of cutaneous drug eruptions in 200 patients

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ABSTRACT

Background: Cutaneous drug reactions are the most common adverse reactions attributed to drugs. Any skin disorder can be imitated, induced or aggravated by drugs. **Aims:** The present study was carried out to determine the age, sex incidence and clinical pattern of drug eruptions, to recognize offending drugs (self medication or prescribed), to evaluate mortality and morbidity associated with drugs, to educate the patients, and to avoid self-administration of drugs and re-administration of the offending drugs. **Methods:** The diagnosis of cutaneous drug reactions is mainly based on detailed history and correlation between drug intake and the onset of rash. Two hundred patients (112 males and 88 females) presenting with cutaneous drug reactions were studied. **Results:** Fixed drug eruption was seen in 61 patients; others being urticaria and angioedema, morbilliform rash in 37, pruritus in 25, Stevens Johnson (SJ) syndrome in six, purpura in six, exfoliative dermatitis in five, photosensitivity in five, Toxic Epidermal Necrolysis in two, acneiform eruption in three, and erythema multiforme in two patients. The most frequently affected age group was 41-50 years, followed by the 21-30 and 31-40 years age groups. The youngest patient was one year old and the oldest was 80 years old. The period of development of lesions after the intake of drug(s) varies from 01-45 days. Cotrimoxazole was the offending drug in 26 cases, followed by Ibuprofen in 20 cases. **Conclusions:** Fixed drug eruption was the most common drug eruption seen. Cotrimoxazole was the most common cause of drug eruptions.

Key words: Adverse drug reaction, cutaneous drug reaction

INTRODUCTION

Cutaneous drug reactions have become very common in recent times. The incidence of cutaneous drug reactions is about 2.2% and is reported to be higher among inpatients and females.[1] Fatal reactions to drugs occur even though benign reactions are more common. The incidence increases in proportion to the number of drugs prescribed.

The best drug history comes not from asking "What do you take?," but from asking "What do you take for fever, cold, sinusitis or headache?"

Cutaneous drug reactions are the most common adverse reactions attributed to drugs. Any skin disorder can be imitated, induced or aggravated by drugs. The present study was carried out to determine the age, sex incidence and clinical pattern of drug eruptions, to recognize offending drugs (self medication or prescribed), to evaluate mortality and morbidity associated with drugs, to educate the patients, and to avoid self-administration of drugs and re-administration of the offending drugs. The diagnosis of cutaneous drug reactions is based on detailed history and correlation between drug intake and the onset of rash. History taking for drug intake is an art that includes direct, indirect, suggestive, evocative and repetitive questioning. While arriving at answers can take time, the information itself can be very helpful in preventing cutaneous drug reactions and drug-induced dermatitis.

METHODS

A prospective study comprising 200 cases suffering from drug eruptions, was carried out from July 1997 to June

How to cite this article: Patel RM, Marfatia YS. Clinical study of cutaneous drug eruptions in 200 patients. Indian J Dermatol Venereol Leprol 2008;74:430.
Received: March, 2007. **Accepted:** July, 2007. **Source of Support:** Nil. **Conflict of Interest:** None Declared.

2006. The diagnosis was based on detailed history and clinical examination.

Precise history of drug ingestion including allopathic, homeopathic, herbal remedies and self-medication was taken from patients with cutaneous drug reactions attending the Skin-V.D. department in the SSG Hospital, Vadodara were studied. Careful history of symptoms, other existing skin and systemic diseases, atopy, past history, family history of drug eruption or any other illness was taken. A thorough clinical examination was carried out. The skin, hair, nail and mucosa (eye, oral and genital) were examined.

The diagnosis of cutaneous drug reactions was based on the history of drug ingestion, clinical findings and exclusion of other similar disorders. Diagnosis was confirmed by observing the disappearance of signs and symptoms after the discontinuation of the suspected offending drugs. Re-challenge was done as and when possible in less severe eruptions.

Complete blood counts and routine and microscopic examination of urine and stool were carried out in all patients. Specific or relevant investigations such as liver function tests (LFT), renal function tests (RFT), VDRL, and ELISA test for HIV infection were carried out in selected patients.

Table 1: Age and sex distribution of our cases

Age group (In years)	Male *n*	Female *n*	Total *n*	Percentage
0–10	12	04	16	08
11–20	10	12	22	11
21–30	20	22	42	21
31–40	26	14	40	20
41–50	22	22	44	22
51–60	08	08	16	08
61–70	06	05	11	5.5
71–80	08	01	09	4.5
Total	112	88	200	100

RESULTS

Two hundred patients (112 males and 88 females) were studied. The majority of the patients belonged to the age group of 41-50 years, followed by 21-30 and 31-40 years' groups [Table 1]. The youngest patient was a year old and the oldest was 80 years old. The period of development of lesions after drug intake varied from 1-45 days.

Cotrimoxazole was implicated in most (26) of the cases, followed by ibuprofen in 20 cases. The most common pattern of cutaneous drug reactions observed was fixed drug eruption (FDE) (30.5%) followed by urticaria in 18.5%, morbilliform rash in 18% and pruritus in 12.5% of the patients [Tables 2 and 3].

Table 2: Clinical pattern of drug eruptions

Clinical Pattern	Present study (n = 200)		Malhotra *et al*.[2] (n = 54) %	Jhal *et al*.[3] (n = 379) %
	n	%		
FDE	61	30.5	-	-
Urticaria	37	18.5	9.26	21.5
Morbilliform rash	36	18	29.63	50
Pruritus	25	12.5	-	-
S J syndrome	06	03	22.22	13.9
TEN	02	01	-	4.9
Erythema multiforme	02	01	-	-
Purpura	06	03	-	-
Exfoliative dermatitis	05	2.5	-	-
Photosensitivity	05	2.5	-	-
Acneiform eruption	03	1.5	-	-
Oral ulcer	03	1.5	-	-
Dapsone syndrome	01	0.5	-	-
Bullous drug reaction	01	0.5	-	-
Hemorrhagic cystitis	03	1.5	-	-
Angular cheilitis	01	0.5	-	-
Eczematous reaction	01	0.5	-	-
Erythema nodosum	01	0.5	-	-
PR-like DE	01	0.5	-	-

FDE – Fixed drug eruption; SJ syndrome – Stevens Johnson syndrome; TEN – Toxic epidermal necrolysis; PR – Pityriasis Rosea; DE – Drug Eruption

Table 3: Drugs causing fixed drug eruptions

Offending Drug	No. of patients (%) In the present study	Singh *et al*.[4]
Antimicrobials		
Cotrimoxazole	18 (29.5)	08 (50)
Sulfadiazine	02 (3.2)	-
Amoxicillin	02 (3.2)	-
Doxycycline	01 (1.6)	02 (12.50)
Rifampicin	-	01 (6.25)
Griseofulvin	01 (1.6)	01 (6.5)
Antipyretic, Analgesic, Antiinflammatory		
Ibuprofen	05 (8.1)	-
Oxyphenbutazone	-	04 (25)
Diclofenac sodium	03 (4.9)	-
Other NSAIDs	06 (9.8)	-
Paracetamol	02 (3.2)	-
Analgin	02 (3.25)	-
Tramadol	01 (1.6)	-
Antiepileptics		
Carbamazepine	02 (3.2)	-
Phenytoin sodium	01 (1.6)	-
Unknown	14 (22)	-
OTC	01 (1.6)	-
Total	61 (100)	16 (100)

Analgin is a pyrazolone derivative available under the same generic name marketed by IDPL

FDE occurred most commonly due to cotrimoxazole (29.5%) followed by NSAIDs (non steroidal antiinflammatory drugs) in 22.8%, urticaria in 18.5%, morbilliform rash in 18% and pruritus in 12.5%. of the patients. NSAIDs were also the main offenders in causing urticaria, angioedema and morbilliform rash [Tables 4 and 5].

Out of the 25 cases who presented with pruritus, antituberculous therapy (ATT) with isoniazid, rifampicin, pyrazinamide, and ethambutol, and cotrimoxazole were cited to be the reasons for the observed pruritus in two and three patients, respectively. Others were due to drugs like ampicillin, ibuprofen, APC (combination of aspirin, paracetamol and codeine), hydroxyzine hydrochloride, Vitamin A and chloroquine.

There were seven cases of Stevens Johnson (SJ) syndrome, out of which three (42.8%) were due to ibuprofen. Two cases of SJ syndrome were severe; they were managed successfully with intensive care. In addition, there were two cases of toxic epidermal necrolysis (TEN): one due to rifampicin, which was severe but responded well to treatment and one because of an unknown drug, which proved to be fatal.

Photosensitivity was seen mainly due to ciprofloxacin and

Table 4: Drugs causing morbilliform rash

Offending drugs	No. of patients (%) In the present study
Antimicrobials	
Cotrimoxazole and sulfadiazine	02 (5.5)
Ciprofloxacin	03 (8.3)
Norfloxacin	01 (2.7)
Sparfloxacin	03 (8.3)
Ofloxacin	01 (2.7)
Amoxicillin	02 (5.5)
Metronidazole	01 (2.7)
Albendazole	01 (2.7)
NSAIDs	
Ibuprofen	03 (8.3)
Diclofenac	01 (2.7)
Valdicoxib	01 (2.7)
Other NSAIDS	01 (2.7)
Folic acid (yellow)	01 (2.7)
Vitamin B complex (yellow)	03 (8.3)
Magnesium trisilicate (yellow)	01 (2.7)
Antiepileptics	
Carbamazepine	02 (5.5)
Phenytoin / Phenobarbitone	01 (2.7)
Others	
Oral corticosteroid	01 (2.7)
Chloroquine	01 (2.7)
Nevirapine	01 (2.7)
Hazmola*	01 (2.7)
Unknown	01 (2.7)
Total	37 (100)

*Ayurvedic medicine with multiple ingredients

Table 5: Drugs causing urticaria and angioedema

Offending drugs	No. of patients (%) present study
Antipyretic, Antiinflammatory	
Ibuprofen	05
Aspirin	01
Diclofenac	03
Paracetamol	03
Valdicoxib	01
Unknown NSAIDS	07
Antimicrobials	
Cotrimoxazole	01
Tetracycline	01
Cephalexin	02
Ciprofloxacin	01
Dapsone	01
Others	
Loperamide	01
Omeprazole	01
Vitamin AD (red color)	02
Bisacodyl (yellow color)	01
Total	35 (100%)

sparfloxacin in four cases. Five cases of exfoliative dermatitis (2.5%) occurring due to carbamazepine (two), ibuprofen and NSAIDs and dapsone were seen. There were four cases of purpura—the offending drugs being aspirin, chloroquine, griseofulvin and an unknown drug. One case of angular cheilitis was due to isotretinoin.

Besides cutaneous drug reactions, we had three cases of hemorrhagic cystitis and one case of aplastic anemia due to cyclophosphamide.

Re-challenge was done in 40 cases of mild cutaneous drug reaction, out of which positive results were found in 29 cases.

Patients were given a list of common drugs causing a particular type of eruption and advised to avoid these drugs, chemically related drugs and OTC (Over the Counter) products.

Patients were instructed that even ayurvedic and other alternative medicines could cause adverse drug reactions. Even their family members were advised to avoid particular groups of drugs.

DISCUSSION

The most common drugs found to cause cutaneous reactions were NSAIDs in 42 cases (21%) followed by the sulpha group in 28 cases (14%) in our study. Pudukadan et al. reported cotrimoxazole (22.25%) followed by dapsone (17.7%) as the most common offenders.[2]

The most commonly observed eruption in our study was FDE (30.5%) followed by urticaria (18.5%) and morbilliform rash (18%). Pudukadan *et al*, reported similar results in that the most common pattern in their study was FDE (31.1%) followed by maculopapular rash (12.2%).[2] In contrast to our and Pudukadan's results, Malhotra *et al*, reported morbilliform rash in 29.63%, SJ/TEN in 22.22% and urticaria in 9.26% cases as the common patterns of eruption.[3] Jhaj *et al*. reported 50% cases of morbilliform rash, 21% cases of urticaria, 13.9% cases of SJ syndrome and 4.9% cases of TEN.[4]

Most of the patients had taken the medications for pain, fever and infection. Cotrimoxazole was the most common cause of FDE in our study similar to the findings by Singh *et al*.[5] NSAIDs and cotrimoxazole were also found to be common causes of cutaneous drug reaction in a study by Shrivastav *et al*.[6]

Additive and preservatives are common causes of urticaria. The exact percentage of reactions to additives is not known but these agents are considered to be important in fewer than 10% of patients with chronic urticaria. The most frequently implicated food additives are tartrazine and other azo dyes including amaranth and sunset yellow.[7]

One case of sulfone syndrome (dapsone syndrome—exfoliative dermatitis, fever, generalized lymphadenopathy and raised serum transaminases) was observed in our study, while dapsone (sulfone) syndrome was observed in 10 out of 604 patients (1.6%) over a period of four years in a study by Prasad.[8]

Quinolone was a common cause of morbilliform rash and photosensitivity in our study which indicates the increased use of quinolones.

Ibuprofen was a common cause of EM and SJ in our study, whereas one case of SJ was reported due to paracetamol. Halevi *et al*. reported TEN due to acetaminophen,[9] while carbamazepine was the most common cause of TEN and SJ syndrome in a study by Devik *et al*.[10]

The incidence of acneiform eruptions induced by isoniazid (INH) was 0.53% in a study by Sharma[11] while this was 2% in our series.

All drugs must be regarded as being potentially hazardous and the risk due to drug reactions must be weighed against the expected therapeutic benefit for each patient.

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