A study of cutaneous adverse drug eruptions in dermatologic practice

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Abstract

Cutaneous adverse drug reactions (CADR) are a major problem in drug therapy and is one of the leading causes of morbidity and mortality in health care.

Objectives: 1) To study the diverse clinical spectrum of CADR. 2) To assess the causality and identify the offending drug.

Materials and Methods: Present study was an 18 months prospective, hospital based study conducted, recording a total of 100 patients with various cutaneous ADR. The diagnosis of cutaneous drug reactions was made mainly based on detail history and correlation between the intake of probable offending drug and the onset of rash.

Results: The most common type of CADR patterns recorded among the 100 cases in the present study were Maculopapular rash (30%), Fixed drug eruption & bullous variant (19%), Acute urticaria (18%), Acneiform eruptions (6%), Erythema multiforme & Stevens – Johnson syndrome (SJS) in (5%), Exfoliative dermatitis & Photosenstivity in (4%), Angioedema, Vasculitis & Hyperpigmentation in (2%), Toxic epidermal necrolysis (TEN), Drug hypersensitivity syndrome & Pruritus in (1%) each. The drugs most often implicated were Antimicrobials(40%), NSAIDs (30%), and Anticonvulsants (11%). Antimicrobials were implicated in (43.3%) of Maculopapular rash followed by NSAIDs (33.3%). Antimicrobials (52.6%) and NSAIDs (42.1%) in FDE. Urticarial reaction was caused mainly by NSAIDs (44.3%). Life threatening severe cutaneous adverse drug reactions (SCARs) such as SJS, TEN & Drug hypersensitivity syndrome (DHS) were seen 7% of total cases.

Conclusion: Although it was a monocentric study, this study revealed a high frequency of cutaneous drug reactions with different clinical presentations, induced by frequently used antibiotics, analgesics and anticonvulsants as and when used giving an interesting data with respect to onset, severity and clinical presentation.

Keywords: Cutaneous adverse drug reactions, Antimicrobials, Severe Cutaneous Adverse Reactions.

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Introduction

An adverse drug reaction (ADR) may be defined as an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product[(1)].

Adverse Cutaneous Drug Reactions are responsible for approximately 3% of all disabling injuries during hospitalization[(2,3)]. The incidence of CADRs in developed countries range from 1-3% among in patients, whereas in developing countries such as India it is 2-5% of the in-patients. Maximum number of cases are seen in the 3rd and 4th decade with slight male predominance.

A wide spectrum of cutaneous manifestations ranging from Maculopapular rash to severe Toxic Epidermal Necrolysis (TEN) can be produced by different classes of drugs. Some severe CADRs may result in serious morbidity and even death[(2,3)]. Antimicrobials are implicated in majority of the patients followed by Anticonvulsants and NSAIDs.

It is most challenging and practically difficult to identify the offending drug when the patient is on multiple drugs because of myriad clinical symptoms, poorly understood mechanisms of drug-host interaction, relative paucity of laboratory testing that is available for any definite and confirmatory drug-specific testing. Therefore in practice, diagnosis of CADR is purely based on clinical judgement[4].

Materials and Methods

This prospective study comprises total of 100 subjects from both outpatients as well as in-patients departments recorded during the period of 18 months.

An informed consent, a stepwise approach was followed to evaluate the patients, detailed history and thorough clinical examination was carried out. To establish the etiological agent for a type of reaction, attention was paid to the drug history, temporal correlation with the drug, duration of the rash, approximate incubation period, morphology of the eruption, associated mucosal and systemic involvements and improvements of lesions on

withdrawal of drug were considered. The underlying disease for which drug were taken was also noted.

The diagnosis was based on WHO criteria, Clinical history, Morphology of the reaction pattern, improvement of the condition on discontinuation of the suspected drugs.

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

Results

A total of 100 patients with cutaneous adverse drug reactions were included in the study. 55 (55%) were males, 45 (45%) were females. The male to female ratio in the study was 1.22:1 **[Table 1]**. Maximum number of patients belonged to age group of 20 to 39 years **[Table 2]**.

Reaction time is the time taken for the reaction to appear since the last exposure the suspected drug. This was commonly found to be 1 to 7 days in 64 (64%) patients. It ranged from 1 day to 92 days **[Table 3]**.

Various cutaneous adverse drug reactions that were observed in this study were Maculopapular rash, FDE, Acute Urticaria, Acneiform eruptions, Erythema Multiforme, Stevens-Johnson syndrome(SJS), Exfoliative dermatitis, Photosensitivity, Angioedema, Vasculitis, Hyperpigmentation, Toxic Epidermal Necrolysis (TEN), DHS(Drug Hypersensitivity Syndrome), Pruritus **[Graph 1]**.

Maculopapular rash (30%) was the commonest drug reaction followed by FDE & Bullous variant (19%) and Acute Uricaria (18%). Severe drug reaction which includes SJS, TEN, EMF, Angioedema and Exfoliative dermatitis was seen in 17 (17%) of cases. Among the severe cutaneous adverse reactions SCARs, SJS was the commonest with 5 cases followed by TEN & DRESS(Drug Rash with Eosinophilia & Systemic symptoms) 1 case each.

Among the various sites of distribution, face, neck, trunk, extremities & mucosae are the most commonly involved with the involvement being generalized in TEN, Erythroderma, DHS, Maculopapular rash, Urticaria with angioedema & localized involvement with certain sites of predilection in Acneiform eruptions, FDE, EMF.

Of all the various CADR, presence of mucosal involvement was almost always seen in SJS, TEN & Angioedema. Laboratory abnormalities were found in all cases of vasculitis, TEN, DHS followed by Erythroderma & SJS.

Overall, as a group of drugs, Antibacterials including antitubercular therapy (ATT) (40%), were the commonest offending agent, followed by NSAIDs (35%), Anti-epileptics(11%) Steroids (4%), Antihyperglycemics (3%) **[Table 3]**.

Among the Antimicrobials, the commonest offending drug group was Fluoroquinolones (33.33%) followed by Cephalosporins (26.66%), Penicillins (22.22%), Metronidazole (6.66%), Sulphonamides & ATT (4.44% each) and antiretroviral therapy (ART) (2.22%). Among the NSAIDs the commonest offending agent was Diclofenac (31.25%) followed by Aceclofenac (21.87%), Ibuprofen (18.75%), Nimesulide (15.62%) and Naproxen (12.5%). Among the Antiepileptics, Carbamazepine (50%) was the most common offending agent followed by Phenytoin (41.66%), Sodium Valproate (8.33%).

When individual drugs were considered Diclofenac (10%), followed by Aceclofenac (7%), Amoxicillin & Cefixime (6% each) & Ciproflaxacin, Nimuselide & Phenytoin (5% each) were the commonest offending agent.

The commonest offending agents for Maculopapular rash were Antibacterials including ATT followed by NSAIDs, Anticonvulsants. Common sites involved were trunk and extremities.

FDE was commonly caused by Antibacterials followed by NSAIDs. Common sites involved were oral cavity, face, trunk, genitalia and extremities. Five cases of Bullous form of FDE were seen in our study, were caused by Aceclofenac (2 cases), Ofloxacin, Norfloxacin and Nimesulide (one each).

Urticaria was commonly seen due to NSAIDs & Antibacterials in the sites of trunk & face which was associated with angioedema in 2 cases.

Acneiform eruption was commonly caused by Systemic Steroids followed by anticonvulsants. It is interesting that Sodium valproate used as an anticonvulsant produced acneiform eruption. The drugs found to cause severe cutaneous adverse reactions were antibiotics (Ciprofloxacin & Ofloxacin) followed by Carbamazepine, Nevirapine, Diclofenac and Dapsone.

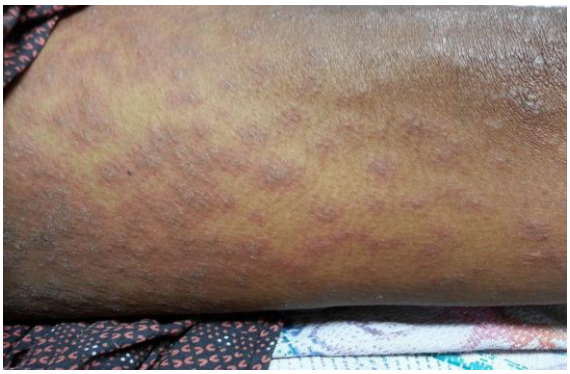


Fig. 1: Maculopapular Rash

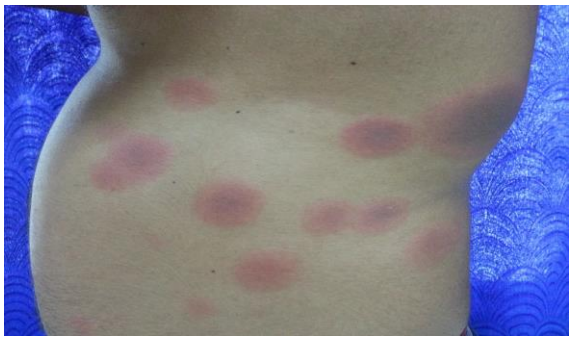


Fig. 2: Fixed drug eruption

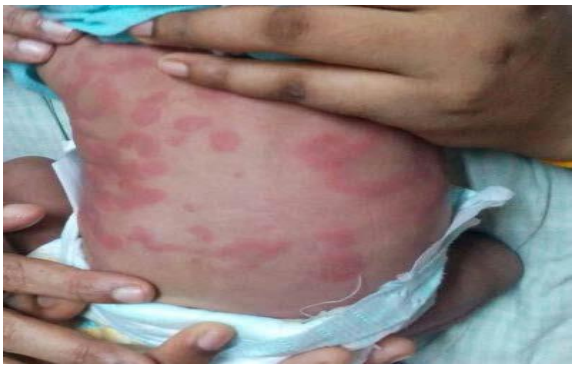


Fig. 3: Acute urticaria to amoxicillin

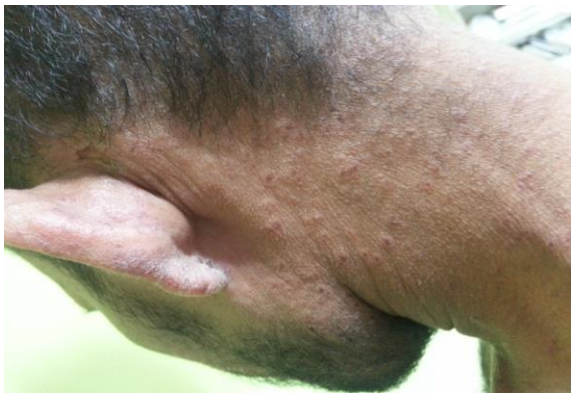


Fig. 4: Erythema multifoerme to diclofenac

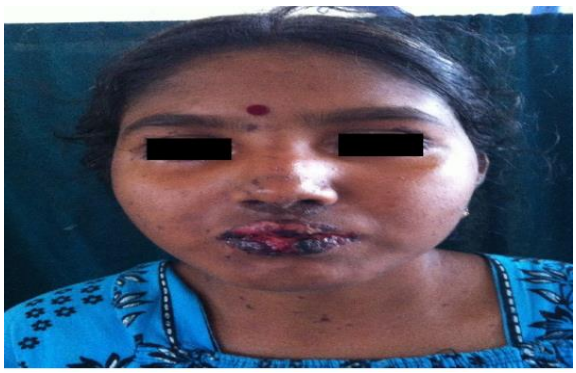


Fig. 4: Stevens Johnson syndrome to cotrimoxazole

Fig. 6: Toxic epidermal necrolysis to ciprofloxacin

Table 1: Sex Distribution

	No. of patients	Percentage
Male	55	55
Female	45	45
Total	100	100

Table 2: Age Distribution

	No. of patients	Percentage
< 19 years	20	20
20 – 39 years	41	41
40 – 59 years	30	30
> 60 years	9	9

Table 3: Reactions time for the various adverse cutaneous drug reactions

Reaction time (days)	No. of patients	Percentage
1 – 7	64	64
8 – 14	15	15
15 – 30	11	11
31 – 60	5	5
> 60	5	5
Total	100	100

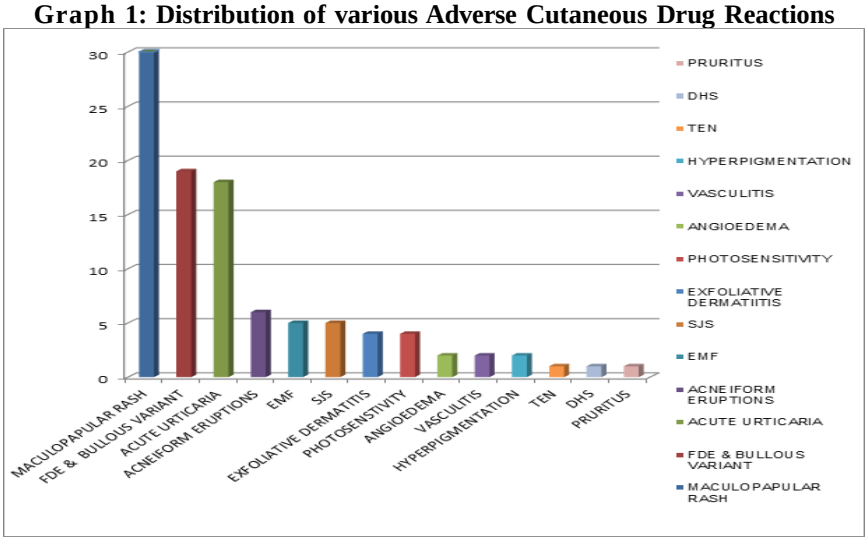
Table 4: Distribution of the various drugs observed in the study

Drug	No. of patients	Percentage(%)
Antibotics & ATT	40	40
NSAID's	35	35
Antiepileptics	11	11
Steroids	4	4
Antihyperglycemics	3	3
Art	1	1
Miscellaneous	6	6
	100	100

Table 5: Comparison of various drugs causing CADRs with other studies

Drugs	Present Study (n=100)	Shinila Sehgal et al[77] (n=80)	R Jhaj et al[81] (n=144)	David P et al[2] (n=90)	Hiware et al[88] (n=872)
Antibacterials including ATT	40 (40%)	32 (40%)	82 (56.9%)	53 (58.88%)	484 (55.5%)
NSAIDs	35 (35%)	28 (35%)	-	14 (15.55%)	162 (18.56%)
Anti-epileptics	11 (11%)	26 (32.5%)	22 (15.27%)	14 (15.55%)	-
Steroids	4 (4%)	5 (6.25%)	-	-	110 (12.61%)
Others	6 (6%)	-	-	-	116 (13.3%)

Graph 1: Distribution of various Adverse Cutaneous Drug Reactions



Discussion

In this study of 100 patients evaluated for CADR, Male preponderance was seen which was similar to a study conducted by V.K. Sharma et al and M. Patel Raksha et al[4,6]. However various other studies showed an equal or a female preponderance [2,3,7,8] indicating that sex does not play much role in the incidence of drug reactions.

The age group of patients with maximum cases occurring within the 20-39 years, similar to studies conducted earlier[2,3,4,7]. However, pediatric and geriatric age showed a decreased incidence which was in concurrence with previous report[7].

Reaction time (RT) ranged from 1 day to 9 2 days, with shortest time for FDE (4-5 hours) and longest for Acneiform eruptions (92 days). In our study it was commonly seen to be within 1-7 days (64%) cases in acceptance with the study done by A.P. Gor et al[9], where they have seen 77.78% of reactions occurring within first 10 days of administration of the implicated drug.

Maculopapular rash was the commonest followed by FDE, Urticaria and Acneiform eruption as it was so in various other earlier studies[3,4,7,10,11,12,16]. Other reactions seen were EMF, SJS, Exfoliative Dermatitis, Photosensitivity, Angioedema, Vasculitis, Hyperpigmentation, TEN and DHS.

The commonest offending group of drugs as a whole was Antibacterials including ATT followed by NSAIDs and Antiepileptics. Antibacterials were the leading offending group causing cutaneous ADRs to earlier studies[2,4,8,13,16], Antimicrobials comprised of Fluoroquinolones followed by Cephalosporins, Penicillins, Metronidazole, ATT, Sulfonamides & ART.

However, when individual drugs were considered, then Diclofenac was the commonest offending agent similar to a recent study[6,7]. Diclofenac, a caution of note for those who treat & dispense this drug over the counter (OTC) which is almost used by every household can produce a reaction pattern from simple FDE or Morbilliform rash to severe life threatening TEN.

Fluoroquinolones were responsible for 15% of

the cutaneous ADRs. The commonest adverse effects seen were FDE followed by Urticaria, Maculopapular rash, EMF, SJS & TEN. The commonest offending agent amongst this group was Ciprofloxacin followed by Ofloxacin and Norfloxacin. Cephalosporins caused 12% of all the cutaneous reactions, commonly causing Maculopapular rash followed by Urticaria. Penicillins caused 10% of cutaneous reactions. This group was commonly found to cause Maculopapular rash and Urticaria. Sulfonamides which included Co-trimoxazole & Dapsone caused 2% of all the reactions, commonly causing SJS & DHS respectively. Isoniazid was responsible for 2% of all the reactions causing Erythroderma, Vasculitis[5]. Steroids were responsible for 4% of cutaneous ADRs. The commonest CADR seen was Acneiform eruption. The other reactions were purpura.

In the current era of HAART, in our study ART medications (Nevirapine) caused 1% of total CADRs namely SJS. Other drugs causing CADRs includes, Oral hypoglycaemic agents (Glipizide).

Amongst the reactions, Maculopapular rash was the commonest caused by Antibiotics cases followed by NSAIDs and Antiepileptics.

FDE was the second commonest reaction with 19 cases which is in contrast to a recent study by M. Patel Raksha et al[6] whose study showed FDE to be the commonest reaction. In our study, the offending drug for FDE were Antimicrobials followed by NSAIDs. This was in contrast to earlier studies[2,4,6] which showed Sulphonamides to be the commonest offending drug for FDE. This may be due to decreased use of Sulfonamides in these days.

Urticaria was the third commonest reaction with caused by NSAIDs & Antibacterials. Acneiform eruption was seen 6% cases similar to study done by Shinila Sehgal et al showed 6 cases of acneiform eruptions out of 80 CADRs [7]. Common offending agents were Prednisolone followed by Anticonvulsants, Dexamethasone. Interestingly sodium valproate was one drug responsible for acneiform eruption in one case.

Severe cutaneous adverse reactions (SCARs)[14,15] i.e. SJS 5 cases, TEN & DRESS 1 case each comprised of the total cases. The frequency seen in various studies[2,3,6,7,11], ranged from 7-25%. The most common offending group of drugs for such severe reactions were Antibiotics followed by NSAIDs and Antiepileptics. In our study 5 cases of SJS were observed 3 were due to Antibiotics (Co-trimoxazole-1 and Ciprofloxacin-2) and one each to Diclofenac, Nevirapine, which is in contrast to earlier study of Noel MV et al[3] in which Antiepipleptics accounted for majority and in M. Patel Raksha et al[6] it was to NSAIDs mainly. There were 1 cases of TEN to Ofloxacin.

Conclusion

This present study revealed a high frequency of cutaneous drug reactions with different clinical presentations, induced by frequently used over the counter antibiotics, analgesics and anticonvulsants as and when deliberately used giving an interesting data with respect to onset, severity and clinical presentation.

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