ISSN 0975-6299 Vol 3/Issue 2/April – June 2012

International Journal of Pharma and Bio Sciences

RESEARCH ARTICLE PHARMACOLOGY

ADVERSE CUTANEOUS DRUG REACTIONS WITH SPECIAL REFERENCE TO NON-STEROIDAL ANTI INFLAMMATORY DRUGS IN A TERTIARY CARE HOSPITAL IN TAMILNADU-SOUTH INDIA

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ABSTRACT

The main objective of the paper is to find out the prevalence, to identify the probable causative agents and contributing factors. Cutaneous drug reactions (CDR) were prospectively among dermatological outpatients from August 2003 to September 2005. The total numbers of patients studied were 37,864. Drug history with clinical examination was done. The type of lesions with duration, age, sex, those patients who brought the offending drugs and reactions due to the particular drug were studied.. CDR was seen in 117 patients (1.1%) more in women, and in areas (face, trunk, extremities). The patterns of reactions were fixed drug eruptions (FDE) (74.36%), Utricaria (11.11%), The drugs incriminated were paracetamol (69.27%), diclofenac sodium (8.51%).. The clinical patterns and drugs causing CDR are similar as other parts of the country except for minor variations. It is obvious that the CDR and drugs causing such reactions are changing every year which may be due to the emergence of newer molecules

KEY WORDS

Cutaneous Drug reactions; Dermatological outpatients; Madurai

INTRODUCTION

Adverse Cutaneous drug reactions can be caused by a wide variety of agents especially among nonsteroidal anti inflammatory drugs. They are responsible for approximately 2-3% of all disabling injuries during hospitalization. Most of the commonly used drugs have reaction rates above 1%.[1] There is a wide spectrum of Adverse Cutaneous Drug Reaction (ACDR) ranging from a transient maculopapular rash to fatal Toxic Epidermal Necrolysis (TEN).[2] The pattern of cutaneous adverse drug (CDR) reactions and the drugs responsible for them keep changing every year. The objective of our study was to ascertain the clinical spectrum among ACDRs among NSAIDs, to elicit the contributing factors and to correlate with the blood group.

MATERIALS AND METHODS

The study was prospective, done over a period of 25 months (August 2003 to September 2005) in the outpatient Department of Dermatology, Government Rajaji Hospital, Madurai. Institutional Ethical Review Board approval was obtained before starting the study. The patients with known history of recent drug intake and development of Cutaneous drug eruptions who were referred to the dermatological outpatient department from other departments and those who came to the outpatient department on their own were considered for the study.

Strict inclusion criteria were followed with persons who brought the drug along with them. Pregnant women and patients taking NSAIDS with other drugs were excluded. The detailed history (including age, sex, and duration of eruption, drugs responsible and complications) and physical examination findings were recorded. Hematological (peripheral smear) and biochemical investigations (blood sugar, liver and renal function tests) were done in all cases. The test like VDRL(Venereal Disease Research Laboratory),TPI(treponema palladium immobilization) test and HIV by (ELISA) were performed in all the patients. Informed consent was obtained from all the patients.

The suspected offending agent was withdrawn or withheld taking care to outweigh the risks over benefit depending on the status of the patient. Appropriate treatment with antihistamines and steroids was given to the patients who were in need of intervention. They were followed up at weekly intervals (for 4 weeks) or until the disappearance of the eruption.

The observations were subjected to simple descriptive analysis and chi square test or student's T test was applied whenever required by using Microsoft excel package.

RESULTS

A total of 117 patients with CDR who attended the outpatient department (37,864) were selected during the study period of 25 months. In 117 patients 40 were males and 77 females. The age group of the study population varied from 2 years – 65 years with a mean age of 36.20 years. The pattern of CDR in relation to gender was shown in Table 1.

Table I
Pattern of Cutaneous Drug Reactions in relation to gender

Pattern	Cases			Percentage %
	Male	Female	Total	
Fixed Drug Reactions	29	58	87	74.36
Urticaria	4	9	13	11.11
Maculopapular rash	4	6	10	8.55S
Exfoliative dermatitis	1	4	5	4.27
SJS/TEN	2	0	2	1.71
Total	40	77	117	100

Table 1 shows that the pattern of CDR observed among the study population were in the order of fixed drug eruptions (74%; 87/117), followed by urticaria (11%; 13/117), maculopapular rash (9%; 10/117), exfoliative dermatitis (4%; 5/117) and SJS/TEN in (2%; 2/117). The mean duration of intake medicine prior to the onset of the drug rash was 14 days. Even though FDE was the commonest one, the occurrences of FDE were independent of gender.

Most of them (59/117) were in the age group of 20-39 years, followed by 41 patients in 40-59 years, 12 in the 0-19 years and 5 in the age group of more than 60 years. The male to female ratio was nearly 1:2.

The incidence of different types of CDR observed among the study population were in the order of fixed drug eruptions (74 %;), followed by urticaria (11 %;), maculopapular rash (9 %;), exfoliative dermatitis (4 %;) and SJS/TEN in (2 %;).Most of the patients(88/117) developed a rash within 2 weeks while they were taking the incriminated drug.

Of 117 consecutive cases, 33% had previous history of drug allergy to NSAIDS especially for Paracetamol and Ibuprofen. History of premarital/extramarital sex was obtained in 4% (5/117) of patients, 2 were HIV positive and all these patients were VDRL non-reactive.

Family history of drug allergy with NSAIDS was available in 13 of 117 patients (11.11), 5 for paracetamol, 3 for ibuprofen, 3 for diclofenac sodium, and 2 for aspirin .Most of the patients included in the study belonged to low economic status with income below 3000 per month. Of the total cases 50% were illiterate, irrespective of their educational status among women who were conscious of their cutaneous drug reaction.

The common implicated drugs causing the eruption being paracetamol (69.27%; 87/117) followed by diclofenac sodium (8.51%; 10/117), indomethacin (7.69%; 9/117), aspirin (6.84%; 8/117), ibuprofen (6.84%; 8/117) and nimesulide (0.85%; 1/117) are shown in Table 2

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Table II
Distribution of cases in relation to offending agents

Drug Eruption	Numbers	Percentage %
Paracetamol	81	69.27
Nimesulide	1	00.85
Ibuprofen	8	06.84
Diclofenac sodium	10	08.51
Indomethacin	9	07.69
Aspirin	8	06.84

Table 2 shows that the most common drug causing the eruption being paracetamol (69.27%; 87/117) followed by diclofenac sodium (8.51%;10/117), indomethacin (7.69%;9/117), aspirin (6.84%;8/117), ibuprofen (6.84%;8/117) and nimesulide (0.85%; 1/117).

Among the 81patients developed CDR due to paracetamol, only 10 of them were children, the lowest being 2 year old female who had FDE over the left cheek 2 days after receiving paracetamol.

The results of anatomical distribution of CDR are shown in Table 3. Many Patients developed eruptions mainly over the extremities (39%); which is followed by Face, Trunk and Extremities (26%); both Trunk / Extremities (20%), only the Face (8%) and Trunk (7%)

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Table III
Anatomical distribution of CDR

Pattern Vs Sites								
Pattern	**F/T/E**	**T/E**	**F**	**T**	**E**	**F/E**	**F/T**	**Total**
FDE	7	16	9	7	46	1	1	87
Urticaria	10	3	Nil	Nil	Nil	Nil	Nil	13
Maculopapular rash	6	4	Nil	Nil	Nil	Nil	Nil	10
Exfoliative dermatitis	5	Nil	Nil	Nil	Nil	Nil	Nil	5
SJS/TEN	2	Nil	Nil	Nil	Nil	Nil	Nil	2

Table 3 depicts the anatomical distribution of CDR. Most of the patients had eruptions over the extremities (39%); followed by Face / Trunk / Extremities (26%); Trunk / Extremities 20%, the Face 8% and Trunk 7%.

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The results of pattern of reaction to drugs are shown in Table 4. Among the Cutaneous drug eruptions, (64%; 75/117) patients developed fixed drug eruptions due to paracetamol, (5%; 6/117) to ibuprofen

Table IV
Pattern vs Drug

Pattern	Paracetamol	Nimesulide	Ibuprofen	Diclofenac sodium	Indomethacin	Aspirin
FDE	75	1	6	2	3	Nil
Urticaria	2	Nil	Nil	5	2	4
Maculopapular rash	3	Nil	1	2	3	1
Exfoliative dermatitis	1	Nil	Nil	1	1	2
SJS/TEN	Nil	Nil	1	Nil	Nil	1

Table 4 shows that among the cutaneous drug eruptions (64%; 75/117) of patients developed fixed drug eruptions due to paracetamol, (5%; 6/117) developed fixed drug eruptions due to ibuprofen. In 101 of 117 patients the suspected drug was withdrawn and the skin lesions subsided in 90% of them within 30 days.

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Rechallenge tests were not done due to ethical reasons.

The results of correlation of blood group are tabulated in Table 5. Among the fixed drug eruptions blood grouping was done in 87 patients, of which 47 patients (40.17%) belonged to O group, 21 patients (17.95%) to B group and 19 patients (16.24%) to A group and none in AB group.

Table V
Blood group vs Drug

Blood Group	Paracetamol	Nimesulide	Ibuprofen	Diclofenac sodium	Indomethacin	Aspirin
O+ve	39	1	1	1	2	Nil
O-ve	3	Nil	Nil	Nil	Nil	Nil
A+ve	14	Nil	3	Nil	Nil	Nil
A-ve	2	Nil	Nil	Nil	Nil	Nil
B+ve	17	Nil	2	1	1	Nil
B-ve	Nil	Nil	Nil	Nil	Nil	Nil
AB				Nil		
Total 87	75	1	6	2	3	Nil

Table 5 depicts that among the fixed drug eruptions blood group was done in 87 patients, of those 47 patients; (40.17%) belonged to O group, 21 patients; (17.95%) to B group and 19 patients; (16.24%) to A group and none in AB group. Chi square value reveals 4.09 and P value is 0.2520 which is not significant.

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The severe type of reactions being Steven Johnson's syndrome, Toxic epidermal necrolysis were found to be associated with ibuprofen and aspirin which constitutes 2% of the cases.

Blood sugar was within normal limits in all the cases included for the study. In the present study eosinophil count varied 17% only. None of them had eosinophiluria.

Renal function test and liver function test does not reveal any abnormalities in all of the study subjects.

DISCUSSION

Cutaneous drug reactions due to NSAIDs were noticed in earlier published reports.[1-3] Female preponderance was noticed in the present study, as like previous studies.[1] The reasons for female preponderance in most of the published series may indicate susceptibility of such individuals or their self awareness on the cosmetic, esthetic aspects of their body.

The study subject may be small due to strict inclusion criteria .

The maximum numbers of cases were in the 3rd and 4th decade which is in conformity with the earlier report.[4]

Adverse cutaneous drug reactions vary in their morphology and distribution. In previous studies [6-10] the most common morphologic type was exanthematous, utricaria, fixed drug eruption, maculopapular rash. Our study has shown fixed drug eruption was the most common followed by utricaria. This variation could probably be due to different ethnic group characteristics and drugs used.

Commonly incriminated drug in our study were paracetamol (69.27%) followed by diclofenac (8.51%), indomethacin (7.69%), aspirin (6.84%), ibuprofen (6.84%) and nimesulide (0.85%).This may be due to frequent use of NSAIDS as over the counter sale.

A simple blood group study among those developed cutaneous drug reaction revealed that cutaneous drug reaction was observed

significantly more among O group persons and none in AB blood group. This was a simple observation and makes one to consider the probable relationship between pharmacogenetics and cutaneous drug reaction.

In the present study neither elevated eosinophil count nor eosinophiluria was noticed as against previous studies.[2]

It may be concluded that the clinical patterns of NSAIDS causing cutaneous drug eruption are remarkably similar to those observed in other parts of the country except for minor variations. Variations help the clinicians and research scientists to work more on pharmacogenetic and bio-informative aspects.

The present study made an impact among different departments of this institution. As a result, institution has introduced educational programme for CRRI's and postgraduates on national policy on ADR.

Interventional measures taken by policy makers for educational aspects for the patients and health care workers were highlighted.

The potential areas of lacunae in cutaneous drug reaction identified during the study period were Pharmacoepidemiology, Pharmacoanatomy, Pharmacogenetics, Pharmacoinformatics.

ACKNOWLEDGEMENT

The authors gratefully acknowledge the support of Dr. N. Meenakshiammal. Director and Head of Institute of Pharmacology, Dr. P.Thirumalai Kolundu Subramaniam, Head of the Department of Medicine, Dr. H. Syed Maroof Sahib, Head of the Department of Dermatology, Government Rajaji Medical College, Madurai, for their encouragement and support for the successful completion of this study.

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