RESEARCH ARTICLE

Clinical Study of Adverse Cutaneous Drug Reactions at a Rural Based Tertiary Care Centre in Gujarat

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Received: 07.01.2013
Accepted: 01.02.2013

DOI: 10.5455/njppp.2013.3.120-127

ABSTRACT

Background: ACDRs (Adverse cutaneous Drug Reactions) is a major problem in drug therapy and is one of the leading causes of morbidity and mortality in health care.

Aims & Objective: To study the clinical pattern, most common offending drugs & relation between absolute eosinophil count & various ACDRs.

Materials and Methods: The prospective observational study was carried out from April 2010 to March 2011 in the Dermatology department at a rural based tertiary care hospital in all patients irrespective of age and sex suspected of having drug reactions seen during the period of one year after taking their written consent.

Results: Out of total 100 cases (51 males and 49 females), most common affected age group was 21-30yrs and most common presenting complaint was itching (37%). The most common ACDRs were maculopapular rash (25%) followed by fixed drug eruptions (23%) and urticaria (22%). Antimicrobials were the most common drug group incriminated in 54% followed by NSAIDs in 23% and anticonvulsants in 11%. Diclofenac, AKT, phenytoin and ciprofloxacin were the commonest incriminated drugs. Using the WHO guidelines for causality assessment, 9 were certain, 70 were probable and 21 were possible cases. Eosinophilia (AEC>500) was seen in 20% (15/74) cases.

Conclusion: Physicians are expected to be well informed with common drug eruptions to diagnose them at the earliest, stop the offending drug and initiate the treatment at the earliest & also the patients should be counseled & educated regarding the importance of carrying the drug list.

KEY WORDS: Absolute Eosinophil Count; Adverse Cutaneous Drug Reactions; Antimicrobials; Fixed Drug Eruption; Maculopapular Rash

INTRODUCTION

An adverse cutaneous drug reaction (ACDR) is an undesirable change in structure and function of the skin, its appendages, or mucous membranes due to drugs.[1] ACDRs are the most common among the various reactions attributed by the drugs.[2]

Drug eruptions vary in their appearance, rapidity of onset, severity and underlying immunopathological mechanisms. They can range from pruritus or rash to severe and life-threatening Stevens Johnson Syndrome or toxic epidermal necrolysis.[3]

The incidence of cutaneous drug eruptions is about 2.2% and is higher amongst inpatients and females. Fatal reactions to drugs occur even though benign reactions are more common. The diagnosis of cutaneous drug eruptions is based on detailed history and correlation between drug intake and the onset of rash.[4] The cutaneous eruptions are visible and hence their reporting is earlier and better as compared to the drug reactions involving internal organs and other systems. Similarly, the response to the treatment for the cutaneous drug reactions is also better perceived.[3]

Drug reactions can be classified into immunologic and nonimmunologic etiologies.[5] The majority (75-80%) of adverse drug reactions are caused by predictable, non-immunologic effects, the remaining 20-25% of adverse drug events are caused by unpredictable effects that may or may not be immune-mediated.[6]

The present study was carried out to know the age, sex incidence and clinical pattern of ACDRs, to recognize the offending drug (self-medication or prescribed), to evaluate mortality and morbidity associated with drugs, to educate the patients, to avoid self-administration of drugs and re-administration of offending drugs.

The history-taking for drug intake is an art which includes direct, indirect, suggestive, evocative and repetitive questioning. It takes time but answers are golden in case of cutaneous drug reactions and drug-induced dermatitis.[4]

Objectives

1. To find out the clinical patterns of drug reactions at a rural based tertiary care centre.
2. To find out the drugs responsible for the drug reactions and the relationship between absolute eosinophil count and the types of ACDRs.

MATERIALS AND METHODS

The study was carried out from April 2010 to March 2011 in the Department of Dermatology of Shree Krishna Hospital and Medical Research Centre, a 550-bedded tertiary care teaching rural hospital attached to Pramukh Swami Medical College, Karamsad, Gujarat after obtaining the approval of the Institutional Ethics Committee. All patients irrespective of age and sex suspected of having drug reactions seen during the period of one year were included in the study after taking their written consent. In every case a detailed history was elicited and a thorough clinical examination was carried out. To establish the etiologic agent for a particular 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 or systemic involvement and improvement of lesions on withdrawal of drug. A diagnosis of ACDR was reached after exclusion of other etiologies and similar disorders like reactions due to food, infections and environmental factors. Essential Investigations were carried out along with absolute eosinophil count and HIV testing after their consent (total 74 patients out of 100 cases underwent AEC and HIV/VCTC testing for the study). If more than one drug was thought to be responsible, the most likely offending agent was noted and the impression was confirmed by subsidence of the rash on withdrawing the drug. The causality assessment was done using WHO guidelines.[7] The severity of the reaction was

graded according to the University of Virginia Health System Adverse Drug Reaction Reporting Program criteria as follows[8]: (a) Mild: A reaction that does not require treatment or prolongation of hospital stay; (b) Moderate: A reaction that requires treatment and/or prolongs hospitalization by at least one day; (c) Severe: A reaction that is potentially life-threatening or contributes to the death of the patient, is permanently disabling, requires intensive medical care (including extended hospitalization), or results in a congenital anomaly, cancer, or unintentional overdose.

All the information was carefully recorded in a specially designed proforma. Analysis was done using frequencies and proportions. All patients were educated regarding ACDRs and given a list of drugs causing reactions for avoiding any mishap in the future.

RESULTS

A total of 29073 patients attended department of dermatology during the study period, of which 100 cases had drug reactions. In the study, 51 were male & 49 were female patients with male-female ratio being 1.04:1. The most common affected age group is 21-30 (27%) [Table 1]. Most common presenting complaint was itching (37%), followed by rash (18%) and swelling (15%). Most of the patients (60%) presented within 3 days of the drug eruption which shows the symptomatic nature of drug reactions. Most common illness for which the patients had taken the culprit drug was Respiratory tract infection (17%) & fever (17%) followed by bodyache (12%), head injury/RTA/stroke/epilepsy (12%) and tuberculosis (10%) (pulmonary/ spine/ abdominal). 89% of patients had history of oral drug administration while 11% cases had parenteral route. It is generally noted that the patients taking parenteral drugs have sudden drug eruptions than those taking oral drugs.

Past history of drug reaction is present in 22 out of 100 cases and out of that 15 cases had history to same drug in past. Only 3 cases had positive family history of drug reactions and 8 cases had history of atopy/ allergy in self. Maximum number of patients (70%) had <50 % body area involvement whereas 18 % cases had >75% body area involvement. 80% cases had mild involvement while 13% had moderate and 7% had severe involvement. The common offending drug groups [Table 2] were antimicrobials (54%) followed by anticonvulsants (11%) and anti-inflammatory drugs (23%). The most common offending drugs were carbamazepine (16.23%) followed by phenytoin (15.15%) and cotrimoxazole (13.53%) however antimicrobials were the most common drug group implicated. The most common morphological types of the ACDRs were maculopapular rash (25%), fixed drug eruptions (23%) and urticarial wheals (22%). The drugs implicated in these reactions with the frequency of occurrence are enlisted in [Table 3].

Most common site involved was upper limb (63%) followed by face (58%), lower limb (55%) and trunk (53%). Oral mucosa was the commonest mucosa involved in 8% cases followed by genital (7%) and conjunctival mucosa (6%). Mucosal involvement was most commonly seen in the EM, SJS and TEN reactions. Eosinophilia (absolute eosinophil count > 500 cells/mm3) was seen in 20% cases (15/74).

Table-1: Age and Sex Distribution in the Study

Age Group	Male	Female	Total
0-10	3	0	3
11-20	2	6	8
21-30	14	13	27
31-40	11	12	23
41-50	10	7	17
51-60	8	5	13
61-70	0	3	3
71-80	3	3	6
Total	**51**	**49**	**100**

Table-2: Commonly Incriminated Drug Groups in Causation of ACDRs

Causative Drug Groups	Number of Cases (%)
Antimicrobials	54 (54%)
NSAIDs	23 (23%)
Anticonvulsants	11 (11%)
Steroids	3 (3%)
Antimalarials	2 (2%)
Antifungals	2 (2%)
Antiretrovirals	1 (1%)
Oral hypoglycemic	1 (1%)
Others	3 (3%)
Total	**100 (100%)**

Table-3: Morphological Types of ACDRs and Suspected Drugs with Frequency

Type of ACDR	Drugs Implicated with Frequency of Occurrence	Total (%)
Urticaria	Amoxycillin (2), Aspirin (1), Cefalexin (1), Cefixime (1), Ciprofloxacin (2), Clonazepam (1), Cotrimoxazole (3), Diclofenac (3), Ibuprofen (1), Indomethacin (1), Levofloxacin (1), Metronidazole (2), Phenobarbitone (1), Phenytoin (1), Tamsulosin (1)	22 (22%)
Angiodema	Aceclofenac (1), Diclofenac (1), Gentamycin (1), Metformin (1), Norfloxacin (1), Ofloxacin (1), Ranitidine (1)	7 (7%)
Maculopapular Rash	AKT (1), Amoxycillin (2), Aspirin (1), Carbamazepine (1), Ciprofloxacin (5), Codeine (1), Diclofenac (1), Doxycycline (1), Ibuprofen (1), Leflunamide (1), Metronidazole (1), Nimesulide (1), Norfloxacin (1), Ofloxacin (1), Phenytoin (5), Tinidazole (1)	25 (25%)
FDE	Chloroquine (1), Cotrimoxazole (4), Diclofenac (7), Doxycycline (1), Fluconazole (2), Ibuprofen (2), Metronidazole (2), Norfloxacin (1), Ornidazole (2), Paracetamol (1)	23 (23%)
Acneiform	AKT (7), Prednisolone (3)	10 (10%)
Erythema Multiforme	Diclofenac (1)	1 (1%)
SJS & TEN	Levofloxacin (1), Ofloxacin (3)	4 (4%)
DRESS	Carbamazepine (1), Nevirapin (1)	2 (2%)
Others*	Sparfloxacilin (1), AKT (1), Cotrimoxazole (1), Chloroquine (1), Amoxycillin (1), Phenytoin (1)	6 (6%)

* Phototoxic, Exfoliative Dermatitis, Lichenoid Reaction, Vasculitis

Table-4: Common Offending Drugs in Different Case Series

Study	Common Drugs
Mehta et al[19]	Sulfonamides, aspirin, penicillin etc.
Mani et al[20]	Thiacetazone, sulfonamides, ampicillin, chloroquine.
Bigby et al[21]	Amoxicillin, Cotrimoxazole, ampicillin etc.
Kauppinen et al[22]	Antimicrobial agents, antipyretic, analgesic.
Puavilais et al[23]	Penicillin group, sulfonamides, trimethoprim.
Raviglione et al[26]	Sulfonamides, antipyretic, analgesic, penicillin group, anticonvulsants.
Swanbeck et al[27]	Sulfonamides, trimethoprim, cephalosporin, penicillin group.
Sharma et al[12]	NSAIDS, Cotrimoxazole, phenytoin, carbamazepine, penicillin.
Chatterjee et al[11]	Carbamazepine, phenytoin, Cotrimoxazole, ibuprofen, aspirin
Pudukadan et al[10]	Cotrimoxazole, dapsone, phenytoin sodium, carbamazepine
James et al[21]	Amoxicillin, ampicillin, carbamazepine, phenytoin, ciprofloxacin
Raksha et al[4]	Cotrimoxazole, ibuprofen
Ding et al[22]	Allopurinol, carbamazepine, phenytoin, cotrimoxazole
Hotchandani et al[3]	Cotrimoxazole, NSAIDs (ibuprofen , diclofenac) phenytoin, carbamazepine
Present study	Cotrimoxazole, AKT, phenytoin, ciprofloxacin, ofloxacin, Amoxicillin

According to the WHO guidelines for causality assessment, 9 were certain, 70 were probable and 21 were possible cases.

DISCUSSION

Our study had a comparable number of male and female cases as seen in sushma et al[9] study and Pudukadan et al[10] study while Chatterjee et al[11] study had a very high number of females with M:F of 0.63: 1.

The majority our patients belonged to the 21-40 years age group, the youngest being a 2 years old male child and oldest an 80 year old female. Similar results were reported in Raksha et al[4], Sharma et al[12] and Pudukadan et al[10] study. In Solensky et al[13] study adults aged 20-49 years were at greatest risk of antibiotics-related drug eruptions, probably due to increased exposure to antibiotics. Two other studies noted that the elderly are more commonly affected.[14,15] Adverse reactions to drugs increase with age.[16] This may be due to the increased use of medications by the elderly, increased potential for drug-drug interactions, and altered drug handling by the body. The difference in various studies may be related to the regional variation in the health care seeking behaviour of the population.

In our study majority of patients had taken the offending drugs for respiratory infection, fever, pain or Tuberculosis as seen in Raksha et al[4] study.

In present study, time between taking of drug and development of lesions was <24 hrs in most cases (55%) and 69% (55 cases in <24 hrs + 14 cases in 24-72 hrs) cases developed lesions

within 3 days of taking the culprit drug. In Hotchandani et al[3] study, most cases had reaction time between 1 to 7 days. It is usually considered that chances of saving the patients' life in severe cases are more when aggressive treatment is initiated within 72 hrs (3 days). Early withdrawal of the causative drug improves the prognosis, and drugs with a long half-life are associated with an increased risk of death. Increased age, extensive TEN, delay (more than 3–4 days) in referral to a regional centre, early thrombocytopenia and early empirical antibiotic treatment elsewhere are associated with a worse prognosis.[5] A recent study of severe adverse cutaneous drug reaction showed that delay of referral to the burn centre was confirmed as an important prognostic factor at the Cox regression multivariate analysis and had the greatest influence on mortality. If greater than 4 days it increased the risk of death of 416 times.[17]

Common presenting complaint was itching (37%) followed by rash (18%) and swelling (15%) in present study while, in Pudukadan et al[10] study, major presenting complaint was symptomatic rash (56.7%; 51/90 patients), followed by blistering (22%; 20/90).

In present study, 38% cases had <25% body surface area involvement and 18% cases had >75% involvement whereas in Pudukadan et al[10] study, 45.5% had 0-10% body surface area involvement and just 3.3% had > 90% body surface area involvement.

In our study 80 % cases had mild while others 13% had moderate and 7% had severe type of drug reaction which was comparable with Chatterjee et al[11] study in which there were 12 cases (1.62%) of severe ACDR.

Adverse cutaneous drug reactions vary in their patterns of morphology and distribution. Of the various types of ACDRs seen in our study, exanthematous eruption (25%) was the most common drug eruption followed by fixed drug eruption(FDE) (23%) and urticaria (22 %).

In Sharma et al[12] study, the common types of cutaneous ADR patterns were exanthematous rash (34.6%), FDE (30%) and urticaria (14%). Jhaj et al[18] study, reported exanthematous rash in 50% followed by urticarial in 21.5% and SJS/TEN in 18.8%. The commonest pattern in Raksha et al[4] study was FDE (30.5%), followed by urticaria (18.5%) and exanthematous rash (18%). Pudukadan et al[10] study, reported FDE in 31.1%, followed by exanthematous rash in 12.2%. In older Indian studies the common morphologic patterns are exanthematous, urticarial and/or angioedema, fixed drug eruption and erythema multiforme.[19,20] Studies outside India have also noted exanthematous eruption to be most common type of drug eruption.[15,21,22]

Thus FDE & exanthematous rashes were the commonest with the difference in various studies likely to be due to different geographical areas & the type of drugs prescribed.

In the present study, Antimicrobials were the most common drug group incriminated in 54% cases followed by NSAIDs in 23% and anticonvulsants in 11% cases. Hotchandani et al[3] study showed that antimicrobials (61.4%), nonsteroidal anti-inflammatory drugs (NSAIDs) (22.9%), and antiepileptic drugs (10%) were the most prominent group of drug responsible for ACDRs. Sharma et al[12] reported that drugs most often incriminated for the various ACDR were antimicrobials (42.6%), anticonvulsants (22.2%) and NSAIDs (18%). Pudukadan et al[10] study found, antimicrobials as the major group (58.88%), followed by antiepileptic and NSAIDs (15.55% each). Similar findings were seen in Chatterjee et al[11] study where antimicrobials (34.10%), anticonvulsants (32.88%), anti-inflammatory drugs (21.51%) were the culprit group of drugs.[Table 4]

Antimicrobials and NSAIDs are commonly prescribed by the physicians and general practitioners even illegally practicing quacks for trivial illness so there are more chances of developing reactions to these groups.

As per WHO causality guidelines[7], out of 9 cases in the certain group, 6 were due to NSAIDs, 2 due to antibiotics and 1 due to antifungal. Out of 70 cases in the probable group, 36 were due to antibiotics, 16 due to NSAIDs, 9 due to anticonvulsants and 9 due to other medications. The severe ACDR cases did not undergo rechallenge tests as it was not advisable and unsafe. Out of 9 certain cases, two patients had presented 3 times to our OPD with FDE due to diclofenac & fluconazole and hence these were cases of accidental rechallenge. All the AKT induced drug reactions were kept in possible category as a single drug could not be incriminated out of the 4 AKT drugs (isoniazid, rifampicin, pyrazinamide, ethambutol).

In our study eosinophilia (absolute eosinophil count > 500 cells/mm^3) was seen in 20% cases (15/74). Eosinophilia (AEC>500) was present in 42.2% of patients (38/90) in Pudukadan et al[10] study. In our study only 3 out of the 7 severe cases had eosinophilia in contrast to the Pudukadan et al[10] study where higher mean eosinophil counts were seen in almost all the severe types of drug eruptions.

In our study the mean absolute eosinophil count was 361.65 (done in 74 patients) with 54 patients of mild reaction having a mean AEC of 356.83 and the 20 patients of moderate/severe reaction having mean AEC of 374.65. The p value was not significant.

In Pudukadan et al[10] study, the mean absolute eosinophil count was abnormal in most eruptions, with values more than 500 cells/mm3, except in cases of acneiform eruptions, urticaria/angioedema, and eczematoid, lichenoid and fixed drug eruption patients.

Our study shows that the AEC is not significantly associated with severity of drug reactions though American Academy of Dermatology Guidelines, state that eosinophil counts more than 1000 cells/mm3 indicate a serious drug-induced cutaneous eruption.[28]

It is clearly stated in Dermatology in General Medicine,[29] that elevated peripheral eosinophil count is an uncommon finding in cutaneous drug eruptions and therefore, contrary to the popular belief, its presence or absence is of little importance in excluding or confirming the diagnosis. Also Romagosa et al[30] state that a peripheral eosinophil count carries little diagnostic value in the setting of adverse cutaneous drug eruptions. Thus it may be concluded that, further large scale studies are required, to establish a proper relationship between AEC with clinical patterns and severity the drugs causing ADR.

CONCLUSION

It is very important to keep the provisional diagnosis of drug reaction in all suspected cases with similar presenting features as it may present in various patterns and can be caused by a wide number of drugs. Those patients who are on multiple drugs, on newer drugs or who are at risk of developing reactions are to be kept under close observation.

All physicians are expected to be well informed with common drug eruptions to diagnose them at the earliest, stop the offending drug and initiate the treatment at the earliest to prevent any grave consequences. Dermatologists have the most challenging task in hand to recognise and correctly diagnose at the earliest from the myriad symptoms and signs seen in a drug reaction. Only if experienced clinicians recognize and foster a culture for reporting such reactions to regulatory authorities, drug safety measures can be taken. Pharmacovigilance is an emerging concept in clinical medicine which is still evolving in our country and not completely developed yet. Most of the cases are bound to go unnoticed or overlooked in this era of a booming pharmaceutical industry, overzealous doctors ready to prescribe newer drug molecules & multiple drugs for trivial illness, quacks with little medical knowledge in rural areas of developing countries like India where the doctor to patient ratio is not upto the mark & lack of ability of clinicians to diagnose it at the earliest.

Few newer drug reaction types have been identified with certain uncommon class of drugs in our study (like Fluconazole & paracetamol induced FDE, levofloxacin & ofloxacin induced SJS &TEN, codeine induced maculopapular rash & fluroquinolones induced angioedema).

Usual or unusual, all types of drug reactions are to be notified by clinicians to a responsible body, a watchdog which will help in formulating preventive measures and help both the patients and the treating physicians in a long run.

The patients are to be counseled & educated regarding the importance of carrying the drug list, which should be presented to every physician he goes to and every pharmacist he takes the drugs from, which could in the end prove to be the difference between life & death.

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Cite this article as: Anjaneyan G, Gupta R, Vora RV. Clinical study of adverse cutaneous drug reactions at a rural based tertiary care centre in Gujarat. Natl J Physiol Pharm Pharmacol 2013; 3:129-136.
Source of Support: Nil
Conflict of interest: None declared