Journal of Cardiovascular Disease Research

ISSN:0975 -3583,0976-2833 VOL13, ISSUE 05, 2022

Original research article

Clinical profile of cutaneous drug reactions in a tertiary care centre

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Abstract

Aim and Objectives: To assess the various drug reaction cutaneous pattern types. to research the prevalence and distribution of drug eruptions in relation to sex, age, administration method, associated infections, and other diseases.

Methods: This is a retrospective study. The 50 patients were selected for this study at Department of D.V.L, Orthopaedics, Dental Surgery, MGM Hospital, Warangal from October 2020 to and March 2022.

Results: The most common cutaneous adverse drug reaction seen in our patients were maculopapular rashes found to be the commonest with 18 patients (comprising 36% of the total), followed by fixed drug eruption in 13 patients (26%), urticaria in 6 patients (12%), Stevens Johnson syndrome in 4 patients (8%), erythema multiforme in 4 patients (8%) and others (including Toxic epidermal necrolysis, erythromelalgia, glossitis, lichenoid drug reaction and Dapsone syndrome) 5 (10%). The most frequent cause of CADRs in both adults and children is the use of antibiotics, with NSAID-acting medications coming in close second. The most frequent trigger for FDE is NSAIDs, specifically paracetamol. Generalized rashes were found to be more prevalent than localized rashes (52% vs. 48%) in terms of pattern of distribution. The mean period of onset for the various drug eruption were almost similar with other studies. It was 14 days for maculopapular reactions and Stevens Johnson syndrome. 13 days for toxic epidermal necrolysis, 23 days for drug hypersensitivity syndrome, 3 days for urticaria and 1 day for fixed drug eruption.

Conclusion: Cutaneous adverse cutaneous drug reactions occur most commonly in the 21-30 years age group with mean age of 26 years. CADRs were found to be more common in the females than in males.

Keywords: Erythema, antimicrobials, necrolysis, erythromelalgia, NSAIDs

Introduction

Adverse drug reactions have recently increased in frequency due to the proliferation of medications. Skin reactions are one of them and account for a sizable portion of all unfavorable drug reactions. Numerous epidemiological and clinical studies have highlighted the many facets of this disorder. Ongoing updates to the vast amount of information on cutaneous adverse drug reactions.

Despite numerous studies and case reports, the incidence of unfavorable cutaneous adverse drug reactions (CADRs) can only be roughly estimated. The CADRs are typically mild and temporary in ambulatory patients, so neither the patient nor the doctors are aware of them. On the other hand, cutaneous symptoms of illnesses that might seem to have a temporal relationship to drug therapy are frequently incorrectly labeled as cutaneous adverse drug reactions [1, 2, 3]. The situation with CADRs is rapidly evolving due to the introduction of newer medications and the rise in patients who are HIV positive. Age, recurrent infections, genetic predisposition, and many other factors are increasingly being recognized as important CADR-affecting factors [4, 5, 6, 7].

Understanding the connection between drugs and rash is currently gaining newer insights. The need to be aware of the latest developments in cutaneous adverse drug reactions has thus become crucial. There aren't many prospective studies in the Indian population that look at the drugs that cause [8, 9, 10, 11] rashes and their appearance.

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Materials and Methods

This is a retrospective study. The 50 patients were selected for this study at Department of D.V.L, Orthopaedics, Dental Surgery, MGM Hospital, Warangal from October 2020 to and March 2022.

Inclusion criteria

- Patients with cutaneous adverse drug reaction

Exclusion criteria

- Reactions where the drug implicated were not known.
- Cases where there is no temporal correlation between the drug intake and onset of rash.

Methodology

The diagnosis of adverse cutaneous drug reactions will be based on history of drug ingestion, clinical findings, temporal correlation between drug intake and onset of rash and exclusion of other similar disorders. Detailed history will be taken with particular stress to the history of drug intake including herbal or self-medication, unani, Ayurveda and other schools of medicine, duration and evolution the of rash, itching and associated systemic symptoms. Past history and family history of atopy and drug eruptions will be noted. Cutaneous examination including nail and mucosa will be done and the type and extent of the lesions will be recorded.

Results

Table 1: Distribution of Subjects by Age Group

Age	Number of cases	Percentage
0-10	5	10%
11-20	3	6
21-30	16	36%
31-40	8	16%
41-50	11	22%
51-60	5	10%
60-71	1	2%
71-80	1	2%
Total	50	100%

Table 2: Sex Wise Distribution

Sex	Number of cases	Percentage
Males	17	34%
Females	33	66%

Table 3: Distribution of CADRS in Children and Adults

Catogory	Number of cases	Percentage
Children	7	14%
Adult	43	86%

Table 4: Drugs Implicated in Maculopapular Rash

Drugs	Number of Cases	Percentage
Cefixime	3	6%
Phenytoin	3	6%
Amoxicillin	2	4%
Carbamazepine	2	4%
Ciprofloxacin	1	2%
Metronidazole	1	2%
Nimesulide	1	2%
Pantoprazole	1	2%
Amikacin	1	2%
Cefotaxime	1	2%
Ceftriaxone	1	2%
Diclofenac	1	2%
Total	18	36%

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Table 5: Drugs Implicated in Fixed drug Eruptions

Drugs	Number of Cases	Percentage
Paracetamol	3	6%
Nimesulide	2	4%
Diclofenac	2	4%
Ciprofloxacin	2	4%
Azithromycin	1	2%
Ampicillin	1	2%
Doxycycline	1	2%
Levocetirizine	1	2%
Total	13	26%

Table 6: Sites of Involvement in Fixed Drug Eruptions by Common Drugs

Drug	Number of Cases (N)	Lips	Genitalia	Limbs
Nimesulide	2	2	1	1
Paracetamol	3	2	0	3
Diclofenac	2	1	0	2
Ciprofloxacin	2	0	0	2
Doxycycline	1	1	1	0
Azithromycin	1	0	0	1
Levocetirizine	1	0	0	1
Ampicillin	1	1	0	1

Table 7: Drugs Implicated in Urticaria

Drugs Implicated	Number of Cases	Percentage
Ceftriaxone	2	4%
Amoxicillin	1	2%
Fluconazole	1	2%
Paracetamol	1	2%
Nimesulide	1	2%
Total	6	12%

Table 8: Drugs Implicated in Stevens Johnson Syndrome

Drug	Number of Cases	Percentage
Nimesulide	1	2%
Diclofenac	1	2%
Ibuprofen	1	2%
Sparfloxacin	1	2%
Total	4	8%

Table 9: Drugs Implicated in Erythema Multiforme

Drugs	Number of Cases	Percentage
Ibuprofen	1	2%
Ciprofloxacin	1	2%
Terbinafine	1	2%
Erythromycin	1	2%
Total	4	8%

Table 10: Drugs Implicated in Other Cadrs

Acrds	Drug implicated
Dapsone syndrome	Dapsone
Glossitis	Ofloxacin
Lichenoid drug reaction	Etoricoxib
Toxic epidermal necrosis	Phenytoin
Erythromelalgia	Nefidipine

Table 11: Cadrs Associated with Antimicrobials

Type of reaction	Number of cases	Percentage
Maculopapular	10	20%
Fixed drug eruption	5	6%
Erythema multiforme	4	8%
Urticaria	4	8%
Stevens johnson syndrome	1	2%

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Total	24	48%

Table 12: Cadrs Associated with Drugs Antiepileptics (Phenytoin and Carbamazepine)

Type of reactions	Number of Cases	Percentage
Maculopapular	5	10%
Toxic epidermal necrolysis	1	2%
Total	6	12%

Table 13: Cadrs Associated with Drugs Acting on Nsaids/Analgesics/Antipyretics

Type of reaction	Number of Cases	Percentage
Fixed drug reaction	5	10%
Stevens johnson syndrome	3	6%
Urticaria	2	4%
Maculopapular	2	4%
Erythema multifore	1	2%
Total	13	26%

Table 14: Extent of Involvement in Children and Adults

Pattern	Child	Adult	Total
Localised	4	20	24
Generalised	3	23	26
Total	7	43	50

Table 15: Gender and Extent of Involvement

Pattern	Male	Female	Total
Localised	9	15	24
Generalised	9	17	26
Total	18	32	50

Table 16: Route of Administration among Children and Adults

Route of Administration	Adult	Child	Total
ORAL	35	5	40
IV	5	2	7
ORAL+IV	2	0	2
ORAL+IM	0	0	0
IM	1	0	1
Total	43	7	50

Table 17: Time Interval between Drug Intake and Onset of the Clinical Pattern CADRS

Type of Rash	Number	Mean Time (Days)
Maculopapular	17	14
FDE	13	1
Urticaria	4	1
Stevens Johnson Syndrome	4	14
Toxic Epidermal Necrolysis	1	15
Erythema Muliforme	4	7

Discussion

Both inpatient and outpatient settings experience adverse drug reactions, which are a significant and frequent issue. It is crucial to stay current on the latest developments in drug reaction, including the diagnosis and treatment of these reactions as well as the manifestations of newer drugs and older drugs.

This study was done in a tertiary care referral hospital with large outpatient and inpatient numbers. A total of 50 suspected cutaneous adverse drug reactions were documented, over a period of one and a half year.

In this study, there were 1:1.94 male to female CADR patients. Despite the fact that females had a higher frequency of CADRs, compared to other studies, the difference was not statistically significant. As in our study, the majority of studies mentioned in the literature show a higher proportion of females. These differences have been linked to gender-specific differences in pharmacokinetic, immunological, and hormonal factors as well as differences in how men and women use medications, despite the fact that these connections are not entirely clear [12].

The age group of 21 to 30 years had the most cases [16], followed by the age group of 41 to 50 years with 11 cases. As has been seen previously 11, in this study also the number of cases became lesser with extremes of age, with 5 cases in 0-10 yrs and 2 cases in age group >60yrs age.

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Previous studies have also shown that children tend to have a lesser number of drug reactions as compared to adults; also these rashes tend to be minor. Children's immune systems are not as well developed and they are exposed to fewer drugs, which may help to explain this.

A review of the available literature shows that there are only a few studies of cutaneous adverse drug reactions in children and even fewer studies comparing CADRs in adults and children.

7 cases, or 14% of all cases in this study, were in the pediatric age range (0 to 17 years). With regard to the various cutaneous adverse drug reactions in all age groups, maculopapular rashes were discovered to be the most prevalent, occurring in 18 patients (36% of the total), followed by fixed drug eruption in 13 patients (26%), urticaria (acute urticarial) in 6 patients (12%), Stevens Johnson syndrome in 4 patients (8%), erythema multiforme in 4 patients (8%) and others (including toxic epidermal necrolysis, erythromelalg the most prevalent CADR types described in the literature also match those found in our study [13].

In this study, the various CADR types in the adult and pediatric age groups were comparable. The most frequent drug reactions were maculopapular (34% and 42% in adult and pediatric age groups, respectively). Both in the adult and pediatric age groups, fixed drug eruptions were also prevalent.

Among the paediatric patients (0-18yrs), the incidence of maculopapular rash in this study was similar to that of Sharma *et al*. (34% and 20% respectively) [14]. Fixed drug eruption (FDE) was of similar frequency as maculopapular rash in our study which was the next most common CADR in above study [14].

Urticaria/angioedema was found to be the most frequent reaction (45%), followed by maculopapular rash (32%) and fixed drug eruption (12% of patients) in a retrospective study conducted in Singapore by Khoo *et al*. on 111 cases of CADRs in children (age under 12 years).

Antimicrobial medications (20%), CNS-acting medications (phenytoin and carbamazepine) (10%), and NSAIDS (4%), were the most frequent causes of maculopapular rash in this study. This was comparable to a number of other studies [4, 8, 13]. In both children and adults, antibiotics were the most frequent cause. According to studies of CADRs in children conducted by Sharma *et al*. in India [14] and Khoo *et al*. in Singapore [15], antimicrobial drugs were the most frequent cause of maculopapular rash, closely followed by drugs acting on the central nervous system.

In this study, 13 patients (or 26%) experienced fixed drug eruptions. They included 11 adults (84%) and 2 children (16%). In concordance with other studies [11, 13, 16, 17]. NSAIDS/analgesics/antipyretics constituted the major causative drugs (54%) followed by antimicrobials (36%) in adults. However, in children one was with paracetamol and other with doxycycline.

The number of female patients with FDE was more than the male patients. This pattern was seen in some studies in Mahboob A *et al*. [16], while others reported a male preponderance [18].

With regards to site specificity of certain drugs described previously, no specific site involvement with reference to a particular drug was seen in this study.

This study found about 6 cases of urticaria (12%) in connection with medications, which is comparable to what Sharma *et al*. [19] found. Antimicrobial medications, followed by analgesics and antipyretics, were the most frequent causes of urticaria. This matched the other studies [13, 14]. The most frequent cause, followed by NSAIDs/antipyretics, was antibiotic use. This study was comparable to one by Sharma *et al*. [14]. Stevens Johnson syndrome constituted 8% of all cases (that is 4 cases), while 1 case of toxic epidermal necrolysis constituted 2% of all cases. Stevens Johnson syndrome was most commonly caused by NSAIDs/antipyretics, unlike toxic epidermal necrolysis which was due to phenytoin.

Nine cases (18%) each of Stevens Johnson syndrome, erythema multiforme, and toxic epidermal necrolysis were observed. This was lower than Sharma *et al*.'s study's [7] findings, which stated that these reactions made up 42% of all cases. According to this study, antimicrobials (cephalosporins and penicillin) accounted for 50% of the causes of these reactions, and antiepileptic drugs accounted for 25%, which was consistent with previous research [19].

43 adults had a total of 23 drug infractions, and 7 cases of CADR in children had 7 drug infractions. Antimicrobials were the most frequently implicated drugs [20, 21, 22], followed by drugs acting on the CNS, NSAIDS/analgesics and antipyretics. Antimicrobials made up 4 out of the 7 drugs implicated in children (57%), compared to 30% of the drugs in adults. The second most popular group included non-narcotic analgesics, antipyretics and narcotic analgesics, accounting for 28% and 11% of drugs in children and adults, respectively.

Many other published studies have revealed the high prevalence of CADRs to antimicrobials in children [22]. This may be explained by the fact that infections (such as upper respiratory tract infections, fever, or gastroenteritis) are the most frequent reason for prescribing medication to children. Antimicrobials would therefore most likely be the most frequently prescribed class of medications in this age group and as a result, be the main cause of CADRs.

Phenytoin was found to cause mainly maculopapular rash and TEN. Carbamazepine was implicated in maculopapular rash. Antibiotics were implicated mainly maculopapular rash, Fixed rug eruption, Erythema multiforme and urticaria. NSAIDS caused mainly fixed drug eruption, SJS, maculopapular reactions and urticaria.

ISSN:0975 -3583,0976-2833 VOL13, ISSUE 05, 2022

Among the various drug rashes, 24 were found to be localized and comprised mainly of fixed drug eruption and erythema multiforme. 26 were generalized and included mainly maculopapular rashes, urticarial and SJS which were more severe.

A case of erythromelalgia was seen in a 47 year old female, who was a know hypertensive since 8 years and was started on nifedipine since last 3 years, since then the patient has been complaining of burning sensation, redness and edema on and off not associated with raynauds phenomenon. Nifedipine was withdrawn and all symptoms subsided rapidly [23].

A case of drug-induced glossitis was observed in a 3-and-a-half-year-old girl who had been taking ofloxacin for URTI four days prior. She had swelling and diffuse erythema of the tongue at that time, which went away when the medication was stopped.

A case of lichenoid drug eruption was seen in a 60 year old female after ingestion of etoricoxib for joint pain, involved sites were hand and dorsal surface of feet with well- defined violaceouss papules with every episode seen after intake of the drug [24].

A case of Dapsone syndrome was encountered in a 30 year old female who was diagnosed of BT Hansens 2 months back and had milder rash after onset of the treatment for which discontinued MB-MDT for 1 month and when she started again she presented to causality with facial edema, intense pruritus and hepatosplenomegaly. Patient recovered over a period of weeks.

Most of the reactions encountered in this study were minor and only a few (6 cases) were major life threatening reactions. With expert care, the mortality and morbidity were drastically reduced. One of the patient suffering from TEN died of developing sepsis and multi organ dysfunction syndrome during the recovery phase.

Conclusion

Cutaneous Adverse cutaneous drug reactions occur most commonly in the 21-30 years age group with mean age of 26 years. CADRs were found to be more common in the females than in males. In females most common type of CADRs was maculopapular rash followed by fixed drug eruption and Erythema multiforme which was similar in Males as well. Maculopapular rash is the most common type of the cutaneous adverse drug reaction in both adults and children. The second most common CADR was FDE in both adult and children. FDE was found occurring more frequently in female than in male patients. Both in adults and children, antimicrobials were the most frequent cause of CADRs, with NSAIDs coming in second. Maculopapular reactions, urticaria, and FDE in adults were most frequently brought on by antibiotics. The most frequent NSAID to cause FDE was paracetamol, which was also the most widely used NSAID. The mean onset of reaction of the various drug eruption were 14 days for maculopapular reactions and Stevens Johnson syndrome, 13 days for toxic epidermal necrolysis, 20 days for drug hypersensitivity syndrome, 1 days for urticaria and 1 day for fixed drug eruption.

Funding Source: None.

Conflict of Interest: None.

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