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Research Paper

An Observational Study of Clinical Pattern Ofnsaidsinduced Adverse Cutaneous Drug Reactions.

Medical Science

KEYWORDS : Cutaneous drug reactions, NSAIDs.

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ABSTRACT

Adverse cutaneous drug reactions (ACDRs) are caused by a wide variety of agents. NSAIDs are one of the commonest drug groups to cause ACDRs and clinical pattern of cutaneous ADR changing every year.

Aims: Our objective was to evaluate the clinical pattern of NSAIDs induced ACDRs in the tertiary health care center.

Methods: fifty five patients with adverse cutaneous drug reactions were recruited for this study during 2013-2014.

Results: The Most of ACDRs belonged to the age group of 21-30 years (27.27%) with male predominance. The most common eruptions observed were maculopapular rash (34.28%) followed by Erythema multiforme and SJS/TEN (17.17%) & fixed drug eruption (14.28%).

Conclusion: The pattern of ACDRs And the drugs causing them is remarkably different in our population. Knowledge of these drug eruptions, the causative drugs and the prognostic indicators is essential for the clinician.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are medications used regularly in the treatment of arthritis and intermittently for fever, pain and headache. They are most commonly used systemically, usually as an oral formulation but can also be used as a suppository or administered by intramuscular injection. Topical gels and creams containing NSAIDs may be applied to sports injuries, painful joints. NSAIDs are taken by children and adults. Many skin side effects are seen with many different medications and are not specific or diagnostic for any particular medication or chemical structure. Most are mild but they can rarely be life-threatening. NSAIDs are one of the commonest drug groups to cause skin side effects. The gastrointestinal tract and the skin are the two body systems most likely suffer a side effect with NSAIDs. It is difficult to estimate the frequency of skin side effects with NSAIDs as they are commonly purchased without prescription. Therefore, isolating an NSAID as the causative factor of a drug eruption can be a clinical challenge. Alanko *et al.* (1989) found NSAIDs to be the causative agent in 27% of all adverse drug eruptions. As with most drug-induced skin reactions, withdrawal of the trigger medication results in resolution of the rash, although this may take some months and is not universal.

An **Adverse cutaneous drug reaction (ACDR)** is any undesirable change in the structure or function of the skin, its appendages or mucous membranes and it encompasses all adverse events related to drug eruption, regardless of the etiology.[1] Cutaneous adverse drug reactions (CADR) are the most frequent of all manifestations of drug sensitivity. They manifest with varied and diverse morphological pattern ranging from trivial urticaria to severe form of vasculitis or toxic epidermal necrolysis and cutaneous necrosis or gangrene. Fatal reactions to drugs are uncommon, but reactions such as Stevens–Johnson syndrome and toxic epidermal necrolysis (SJS-TEN) and exfoliative dermatitis may result in death even if the eruption is the only manifestation. Commonly used drugs that are implicated in causing ACDRs are penicillins, sulfonamides, anticonvulsants, aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin converting enzyme (ACE) inhibitors, fluoroquinolones etc.[2]

Adverse cutaneous reactions to drugs are frequent, affecting 2-3% of all hospitalized patients.[3,4,5] Fortunately, only approximately 2% of adverse cutaneous reactions are severe and very few are fatal.[6] The incidence of ACDR in developed countries range from 1 to 3% among in patients[7,8] whereas in developing countries such as India, some studies peg it to 2-5% of the in patients.[9-12]

Most drug eruptions are mild, self-limited and usually resolve after the offending agent has been discontinued. Severe and potentially life-threatening eruptions occur in approximately 1 in 1000 hospital patients. Mortality rates for erythema multiforme (EM) major are significantly higher. Stevens-Johnson syndrome (SJS) has a mortality rate below 5%, whereas the rate for toxic epidermal necrolysis (TEN) approaches 20-30% and most patients die from sepsis. The incidence of adverse cutaneous reactions to drugs is higher in women than in men, and elderly patients have an increased incidence of adverse drug reactions.

The pattern of cutaneous reactions differs among various drugs. Hence, understanding the precise nature of ACDR may help narrow down the search for the offending agent. Knowledge of drugs that can cause ACDR can help physicians in choosing safer drugs and therefore can be helpful to society at-large.

Keeping these observations in the background, this study was undertaken in our hospital to evaluate the clinical pattern and the morphology of various cutaneous adverse drug reactions and their causality, severity and potential risk factors.

MATERIAL AND METHODS

The study was a prospective hospital based observational study. After getting approval from the institutional ethical committee, the study was jointly conducted in the Department of Pharmacology and Department of dermatology, NSCB medical college, Jabalpur over a period of one year (October 2013 to September 2014).

The patients attending dermatology OPD with suspected ACDRs and the in- patients referred from other department with suspected ACDRs were enrolled. The participants had given the informed written consent before they were enrolled in the study. The diagnosis of the ACDRs was based on detail drug history and a thorough clinical examination done by consultant dermatologist. The patient who consume medicines other than allopathic medications(like Ayurvedic/Homeopathic etc) & who are not able to recall the name of suspected medicine consumed(improper drug history) were excluded from the study. Detailed history of the patient including present illness, past or concurrent systemic illness & drug history were taken. The crite-

ria for the diagnosis of ADRs[9] were as follows:

1. The time interval between the introduction of the drug and the onset of a reaction should be within a specific time.
2. Improvement in the condition of the patient after dechallenge/withdrawal of the suspected drug.
3. Drug rechallenge producing similar reaction again.

The clinical pattern of ACDRs was assessed on local examination by consultant dermatologist on the basis of its site, nature, extent, colour & distribution of lesion, and pattern was recorded in form of maculopapular rash, urticaria, angioedema, fixed drug reaction, purpura, photosensitivity etc.

To establish the etiologic agents for ACDRs, attention was paid to the drug history, temporal correlation with the drug, duration of the rash, pattern of lesion, improvement of lesion on withdrawal of drug & recurrence of lesion on rechallenge if possible. Rechallenge was not undertaken in any of our cases because of the possible associated risks.

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 reaction with time or on withdrawing the drug. Finally data was recorded in CDSCO form.[13] and was compiled and analysed.

RESULT & DISCUSSION

A total of 58 cases of adverse drug reactions were identified. Out of these 3 cases had to be excluded from the final because they failed to state the names of the offending drugs or the data was insufficient to make reliable analysis. The remaining 55 cases of ACDRs were analyzed further.

ACDRs were found relatively common in males than in females (ratio 1.75:1) Our study results are similar to the other Indian studies where male preponderance was observed.[14, 15]

Majority of the patients with ACDRs belonged to the age group of 21-30 years followed by 41-50 & > 50 yrs. The ACDRs were more common in adult patients (80%) as compare to the children(20%).

NSAIDs(63.63%) were the most common drugs followed by antimicrobial agents(27.27%) in our study. But many different studies carried out elsewhere in India[12,16,17] have reported antimicrobial agents as the major group of drugs causing ACDRs followed by NSAIDs. Most of the patients had taken the medication for pain, fever and infection. This may be the reason for NSAIDs followed by antimicrobial were the most common agents causing ACDRs in our study population.

Table-1 Clinical Pattern of NSAIDs induced ACDRs (63.63%)

Type of reaction	Frequency	Present study (n=35)
Maculopapular rash	15	34.28%
Erythema multiforme	06	17.17%
Steven Johnson Syndrome/ Toxic Epidermal Necrosis	06	17.17%
Fixed drug eruption	05	14.28%
Urticaria	01	2.85%
Vasculitis	01	2.85%
Photosensitivity	01	2.85%
Total	35	100.00

ACDRs vary in their patterns of morphology and distribution. Of the various types of ACDRs the most common pattern observed was maculopapular rash (34.28%) followed by Erythema multiforme and SJS/TEN (17.17%), fixed drug eruption (14.28%), Other types of ACDRs that were seen in our study included urticaria, Vasculitis and photosensitivity each of 2.85% (Table) In previous studied the most common morphological patterns were exanthematous rash, urticaria, and/or angioedema, fixed drug eruption and erythema multiforme.[18] maculopapular drug eruptions are usually begin within 1-2 weeks of starting a medication and gradually resolve 1-2 weeks following cessation. A study from North India also

Table-2 ***Nonsteroidal Anti-Inflammatory Drugs***

Drug group	Individual drugs	No. of cases	Total no. of cases (%)
NSAIDs	Ibuprofen	8	(35cases) 63.63%
	Diclofenac	5	
	PCM	9	
	Nimesulid	4	
	Indomethacin	1	
	Combiflam (Ibuprofen & PCM)	6	
	Dynapar (Diclofenac & PCM)	2	

found maculopapular rash to be the most common type of ACDR.[17] In a study by Thappa *et al.*[12] most common eruptions observed were fixed drug eruptions (31.1%) and maculopapular rash (12.2%). Thus results in our study are slightly different with study carried out elsewhere in India. This variation could be due to different patterns of drug usage and different ethnic group. Among NSAIDs PCM. Ibuprofen and Combiflam (combination of PCM & ibuprofen) were the frequently reported agents in our study (Table -2).

There is no gold standard investigation for confirmation of a drug-induced reaction. Instead diagnosis and assessment of a drug cause involve analysis of a constellation of features such as timing of drug exposure and reaction time (the reaction was not considered as drug induced if the drug was administered after the onset of reaction), improvement in condition of patient after drug withdrawal or dechallenge, nature of a recurrent eruption on rechallenge, previous history of similar reaction to the same drug.[19]On causality assessment, due to ethical issue rechallenge was not attempted deliberately and hence maximum number of ACDRs were labelled as probable cases

During our study 6 cases of SJS/TEN due to NSAIDs and one case of vasculitis due to ibuprofen were considered severe as they required immediate hospitalization and intensive medical care. Assessing the severity of ACDRs is an essential component in Pharmacovigilance studies as an ACDR may require intervention including the stoppage of the suspected drug(s) and even hospitalization in severe cases.

conclusion

To sum up, the occurrence of ACDRs in the present study was similar in many ways to other studies conducted in India. A wide clinical spectrum of ACDRs ranging from mild maculopapular rash to serious SJS/TEN was observed.

Majority of the patients with ACDRs belonged to the age group of 21-30 years followed by 41-50 & > 50 yrs. Slight male preponderance was observed.

Most frequent ACDRs reported were maculopapular rashes, erythema multiforme, SJS/TEN, fixed drug eruption, exfoliative dermatitis, photosensitivity and vasculitis in decreasing order of frequency.

Considering individual drug, Ibuprofen &PCM followed by Combiflam (Ibuprofen & PCM) Nimesulid were the most common causative agents observed in this study.

On evaluation it is observed that, a proper evaluation and his-

tory taking would have prevented most of the ACDRs cases.

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