

A STUDY OF ADVERSE CUTANEOUS DRUG REACTIONS DUE TO ANTI MICROBIALS AT A RURAL BASED TERTIARY CARE CENTRE, GUJARAT.

Dr.RahulKrishna S Kota, Dr.Rita V Vora*, Dr.Shailee S Gandhi, Dr.Rochit R Singhal

Department of Skin and VD, Pramukh Swami Medical College, Gujarat, India.

Abstract

Keywords: Cutaneous adverse drug reaction, Maculopapular rash, Fixed drug eruption, Fluroquinolones.

Background: Cutaneous reactions are common manifestations of adverse drug reactions. Antibiotics are not only one of the most commonly used drugs but also those which commonly causes adverse cutaneous drug reaction(ACDRs). It is very important to have detailed knowledge regarding ACDRs due to anti microbials.

Objective: To find out various clinical patterns of drug reactions, common ACDR due to antimicrobials, the most common anti microbials responsible for it.

Materials and methods: This was a cross sectional analytical study carried out in Gujarat for five years, which included all the patients with clinical diagnosis of cutaneous adverse drug reaction due to antimicrobials. It is a preformed proforma based study which included detailed clinical history, clinical examination.

Results: Total of 120 patients were having ACDR due to antimicrobials. Males included 64. Most common age group was between 21-30 years in 26.7%patients. Most common group of antibiotic group involved was fluroquinolones in 30.8%patients. Most common drug implicated was ciprofloxacin in 15% patients. Most common pattern of ACDR was maculopapular rash in 34.2% patients.

Conclusion: Antimicrobials are very commonly prescribed drugs and various patterns of cutaneous drug reactions have been observed due anti microbials. It is very important to know regarding common culprit drug and various patterns of ACDR.

Introduction

Antibiotics are one of the most commonly used drugs in daily practice not only by registered medical practitioners but also by quacks. They are also self prescribed by patients due to over the counter availability of many antibiotics in countries like India. Any undesirable change in the structure or function of the skin, its appendages or mucous membranes, caused by a drug encompasses cutaneous adverse drug reaction. Antibiotics are also one of the common agents causing cutaneous adverse drug reactions may be due to their extensive use. Adverse Cutaneous drug reactions (ACDRs) is very commonly reported with the incidence of about 2.2% which is increasing as the number of new drugs are being marketed and prescribed.(1) ACDRs accounted for 0.7% of total admissions and 1.8% of total deaths in a South Indian hospital.(2)Though majority of ACDR are minor and self limiting reactions, there are several life threatening adverse drug reactions like Steven Johnson syndrome and Toxic Epidermal Necrolysis.(3) The present study highlights various pattern of ACDRs due to anti microbials along with the commonest responsible drug with various clinical presentation.

Materials and methods

The study was carried out in the department of dermatology in a teaching institute at a rural based tertiary care centre of Gujarat from april 2010 to march 2015 after getting ethical approval from HREC of the institute. The study included all the patients with symptoms and signs suggestive of adverse cutaneous drug reaction after intake of anti-microbials. All the data was recorded in a predesigned proforma with the consent of patients and analysis

was done. An attention was paid to the drug history, temporal correlation with the drug, duration of the rash, appearance of signs and symptoms, morphology of the eruption, associated mucosal or systemic involvement and improvement of lesions on withdrawal of drug. 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, a diagnosis of ACDR was reached after exclusion of other aetiologies and similar disorders like reactions due to food, infections and environmental factors. 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.

Results

A total of 120 patients enrolled in the study, among which 64 (53.3%) were males and 56 (46.7%) were females. Most common age group was third decade both in males and females (Table 1). Most common presenting complaint was redness in 26 (21.7%) patients followed by itching in 24 (20%) patients. Most common illness for which anti microbials were taken for was fever in 32 (26.7%) patients.(Table 2) Time between taking of the drug and development of lesions was 1-3 days in 25% of patients and it was 1-12 hours in 21.7%, It was more than 1 month in 12 (10%) patients. One hundred thirteen patients (94.2%) developed CADR to the prescribed drugs while rest 7 (5.8%) developed to self administered drugs. Route of administration was oral in 105 (87.5%) patients and parenteral in 15 (12.5%) patients. Past history of cutaneous drug reaction was seen in 29 (24.2%) patients out of which past history of cutaneous drug reaction with same drug was seen in 12 (10%) patients. Family history of cutaneous drug reaction was seen in 6 (5%) patients. Atopy or allergic tendency was seen in 9 (7.5%) patients. Fifty six patients (46.7%) had body surface area involvement less than 25%, 32 (26.7%) patients had involvement between 25-50% while 17 (14.2%) patients had involvement between 51-75%. Only 15 patients (12.5%) had body surface area more than 75%.

Severity of reaction according to Hardwigs adverse drug reaction (ADR) severity assessment, was mild in 34 (28.3%), moderate in 83 (69.2%), severe in 3 (2.5%) patients. Most common mucosal surface involved was oral mucosa in 20 (16.7%) patients followed by genital mucosa in 19 (15.8%) patients, conjunctival in 7 (5.8%) patients, anal mucosa in 5(4.2%) patients.

Out of 120 patients, 37 (30.8%) due to fluroquinolones, 23 (19.2%)patients developed ACDR due to anti tubercular treatment (ATT), 25 (20.8%) patients due to beta lactum antibiotics. 20 (16.7%) due to nitroimidazole antibiotics.

Most common type of ACDR due to antimicrobials overall and cephalosporins, fluroquinolones was maculopapular rash in 41(34.2%), 27.8% and 40.5% patients respectively. Most common type of ACDR due to ATT was acneform eruptions seen in 12 (52.2%) Patients. Most common type of ACDR due to nitroimidazole antibiotics was fixed drug eruptions and maculopapular rash seen in 40 % each. (Table 3)

Most common antibiotic responsible for ACDR in our study was Ciprofloxacin in 18 (15%) patients followed by metronidazole in 15(12.5%) patients.

Most common type of ACDR due to antibiotics seen in our study was maculopapular rash (MPR) in 41 patients followed by fixed drug reaction or fixed drug eruption (FDR/FDE) seen in 26 patients. Urticaria with or without angiodema was seen in 16 patients, Angiodema alone was seen in 7 patients. Acneform eruptions were seen in 12 patients, all of them were on anti tubercular therapy. Eleven patients had Steven Johnson syndrome (SJS). Toxic Epidermal Necrolysis (TEN) was seen in 3 patients. Exfoliative dermatitis were seen in 2 patients who were on ATT, Cotrimoxazole. Vasculitis and phototoxic reactions were seen in 1 patient each on Amoxicillin and sparfloxacin respectively. (Table 4)

Discussion

An adverse cutaneous reaction caused by a drug is any undesirable change in the structure or function of the skin, its appendages or mucous membranes, and it encompass all adverse events related to drug eruption, regardless of the etiology.(4) Cutaneous adverse drug reactions are the most frequent of all manifestations of drug sensitivity. ADRs are seen frequently in hospitals due to a combination of factors such as, complexity of diseases, drug interactions, polypharmacy and possible negligence. A cutaneous drug reaction needs to be suspected in a patient who develops rash during a course of drug therapy. The reaction may be due to any medicine the patient is taking whether prescribed or self administered over-the-counter medicine, herbal or homoeopathic preparations, vaccines or contrast media. 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. Mortality can occur in severe reactions, but even without this quality of life may be significantly diminished due to hospitalization, prolongation of hospital stay, and increased morbidity.(5) Drug reactions are a common reason for litigation too. Not warning a patient about potential adverse effects, prescribing a medicine to a previously sensitized patient, and prescribing a related medication with cross-reactivity are common medicolegal pitfalls and therefore should not be taken lightly.(6) It is an utmost necessity for a dermatologist to have a comprehensive understanding of the clinical spectra of ACDR, as well as knowledge of the drugs which are frequently incriminated in such adverse reactions. This would help reduce or minimize the extent of iatrogenic morbidity and mortality. (6) It has been estimated, that from one third to as high as one half of ADRs, are believed to be preventable.(7)

Cutaneous drug reactions may be caused by several different mechanisms, but in many cases the exact mechanism is unknown. Many drug eruptions are the result of a hypersensitivity reaction with an underlying immune mechanism. Skin reactions as a result of non-immunological causes are more common and include cumulative toxicity, overdose, photosensitivity, drug interactions, and metabolic alterations. (8)

The frequency of ACDR in a particular population is influenced by the drug utilization habit, the reaction rates of various drugs and pharmacogenetic traits of the population studied. Genetic variations in the metabolism of a drug, HLA association to HLA-B1502 and any other underlying systemic disease play important role.(4) In genetically susceptible patients, it is immunologically mediated. The genetically determined glutathione depleted keratinocytes will have role in the pattern of cutaneous manifestation. Moreover, keratinocytes adducts can trigger MCH dependent clonal proliferation of T cell lymphocytes. (9)

In general, it has been assumed that elderly patients experience skin reactions from drug therapy at higher rates: a finding that may seem to correlate with falling testosterone levels in case of elderly men.(10) In contrast to that, our study showed incidence of drug reactions to be most common in the age group 21-30 years.

Various studies across India and few international studies showed that antimicrobials are most common group of drugs causing ACDR with incidence ranging from 30% to 56.9%.(11,12,13,14,15,16). In a systematic review of ACDR, antimicrobials were found to be most common culprits of ACDR accounting for 45.46% of total ACDR(17) However the actual incidence is difficult to determine because many milder forms of reactions are not recorded.

Most common antibiotic group responsible for ACDR in our study was Flouroquinolones 37 (14.5%) followed by beta lactum antibiotics in 25 (9.8%), antitubercular drugs in 23 (9%), nitroimidazole antibiotics in 20 (7.8%) patients. A study from east India showed most commonly implicated group was sulfonamides and allied drugs (17%), followed by fluoroquinolones with nitroimidazoles in (11.3%) and beta-lactam antibiotics in (9.4%), fluoroquinolones alone in (7.5%).(6) In a study by Jhaj et al, implicated drugs were penicillins in 19.4%, cephalosporins in 6.9% patients, anti tubercular drugs 6.9% in patients, sulphonamides in 4.9% patients. (15) In Patel et al study, sulfa drugs were the commonest culprits.(17)

Most common antibiotic responsible for ACDR in our study was Ciprofloxacin in 18 (15%) patients followed by metronidazole in 15(12.5%) patients. Cotrimoxazole was reported as commonest culprit by Hiware et al(14) Pudukadan et al(18) and Shrivastav et al.[19] studies.

In patel et al study, cotrimoxazole account for 12.8% of ACDR.(17) In our study, cotrimoxazole constituted for only 6.7% of ACDR.

Antibiotics accounted for 50.62% of total MPR, 44.07% FDE, 41.82% urticaria and angiodema, 58.33% of SJS/TEN. In systematic review by Patel et al, antibiotics accounted for 36.59% MPR, 67.89% FDE, 22.22% urticaria and angiodema, 37.50% of SJS/TEN.(17)

In our study, anti tubercular drugs caused acneform eruptions in 12 out of 23 patients while in another study acneform eruptions were seen in 4 of 18 patients on ATT.(20)

Azithromycin was responsible for only 2 (1.67%) cases of ACDR in our study while in a study from east India, it was responsible for 5.7 % of ACDR patients.(6) Metronidazole was responsible for 12.5% cases while in a study at Nagpur (14), it was 2.4% and in Patel et al (13) study, it was 3.38%. Ciprofloxacin constituted 15% of total ACDR in our study while it was 3.33% in Nagpur study(14), 2.07% in Patel et al(17) systematic review.

The mean absolute eosinophil count was abnormal in many eruptions, with values more than 500 cells/mm³ in 9 patients and counts above 1000 were seen in 1 patients. According to Romagosa et al,a peripheral eosinophil count carries little diagnostic value in the setting of adverse cutaneous drug eruptions. (21) Guidelines of the American

Academy of Dermatology state that eosinophil counts more than 1000 cells/mm³ indicate a serious drug-induced cutaneous eruption. (4)

In our study, 29 patients (24.2%) patients had previous history of drug reaction. These reactions are avoidable if the physician has taken proper drug history. This highlights the importance of educating patients regarding carrying of a drug list that could probably cause reaction to every physician he visits. The risk of ACDR must be weighed against the expected therapeutic benefit by the physician in patients with previous history of drug reaction.

The causality assessment system proposed by the World Health Organization Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (WHO-UMC), and the Naranjo Probability Scale are the generally accepted and most widely used methods for causality assessment in clinical practice as they offer a simple methodology. In the causality assessment using WHO guidelines, there were 11 certain, 72 probable and 37 possible cases. Naranjo score showed 20 probable cases and 12 possible cases while Hartwigs score showed level 2 in 20 cases and level 3 in 68 cases.(Table 5)

Tables:

Table 1: Age distribution of patients of ACDR due to antimicrobials

Age group	Total(%)
0-10	3(2.5)
11-20	12(10)
21-30	32(26.7)
31-40	19(15.8)
41-50	20(16.7)
51-60	19(15.8)
61-70	9(7.5)
71-80	5(4.2)
>80	1(0.8)
Total	120(100)

Table 2: Illness for which drug taken by the patients with ACDR due to antimicrobials

Illness for which drug taken	Number of cases	Percentage
Respiratory illness (URTI, COPD, asthma, etc.)	17	14.2%
Fever	32	26.7%
Diarrhea	19	15.8%
Bacterial infections (pyoderma/abscess)	8	6.7%
Tuberculosis	23	19.2%
Head injury/RTA/ stroke/epilepsy/seizure	5	4.2%
Others	16	13.3%

Table 3: Pattern of cutaneous drug eruption due to various groups of antimicrobials

Pattern of drug eruption	AM(%)	ATT(%)	CS(%)	FQ(%)	NI(%)
Urticarial wheals ± Angioedema	16(13.3)	2(8.7)	4(22.2)	3(8.1)	2(10)
Angioedema	7(5.8)	0(0)	3(16.7)	2(5.4)	0(0)
Maculopapular rash	41(34.2)	5(21.7)	5(27.8)	15(40.5)	8(40)
Fixed drug reaction (FDR)	26(21.7)	2(8.7)	4(22.2)	7(18.9)	8(40)

Acneiform	12(10)	12(52.2)	0(0)	0(0)	0(0)
Stevens Johnson's syndrome (SJS)	11(9.2)	1(4.4)	1(5.6)	7(18.9)	2(10)
Toxic epidermal necrolysis (TEN)	3(2.5)	0(0)	1(5.56)	2(5.4)	0(0)
DRESS	0(0)	0(0)	0(0)	0(0)	0(0)
Phototoxic reaction	1(0.8)	0(0)	0(0)	1(2.7)	0(0)
Exfoliative dermatitis	2(1.7)	1(4.4)	0(0)	0(0)	0(0)
Lichenoid reaction	0(0)	0(0)	0(0)	0(0)	0(0)
Vasculitis	1(0.8)	0(0)	0(0)	0(0)	0(0)
Total	120(100)	23(100)	18(100)	37(100)	20(100)

AM:Antimicrobials ATT:Antituberculosis therapy CS:Cephalosporins FQ:Flouroquinolones
NI:Nitroimidazole antibiotics

Table 4 : Various offending drugs and pattern of CADR due to them

Drug	MPR	FDR	Urticaria	Angiodema	Acneiform Eruption	SJS	TEN	EX ds	Vasculitis	Tota
Ciprofloxacin	9	4	2	0	0	3	0	0	0	18
Metronidazole	6	5	2	0	0	2	0	0	0	15
ATT	5	2	2	0	12	1	0	1	0	23
Cefadroxyl	4	1	2	2	0	0	0	0	0	9
Amoxycillin	3	0	2	1	0	0	0	0	1	7
Azithromycin	2	0	0	0	0	0	0	0	0	2
Norfloxacin	2	1	0	1	0	0	0	0	0	4
Ofloxacin	2	0	0	1	0	2	2	0	0	7
Tinidazole	2	1	0	0	0	0	0	0	0	3
Cefixime	1	1	1	0	0	1	0	0	0	4
Clindamycin	1	0	0	0	0	0	0	0	0	1
Doxycycline	1	1	0	0	0	0	0	0	0	2
Leflunamide	1	0	0	0	0	0	0	0	0	1
Levofloxacin	2	2	1	0	0	2	0	0	0	7
Cefuroxime	0	1	0	1	0	0	0	0	0	2
Ornidazole	0	2	0	0	0	0	0	0	0	2
Cotrimazole	0	4	3	0	0	0	0	1	0	8
Ceftriaxone	0	1	0	0	0	0	1	0	0	2
Cefalexin	0	0	1	0	0	0	0	0	0	1
Gentamycin	0	0	0	1	0	0	0	0	0	1
Sparfloxacin	0	0	0	0	0	0	0	0	1	1
Total	41	26	16	7	12	11	3	2	2	120

EX ds: exfoliative dermatitis

Table 5 : Various ACDR assessment scores

WHO-UMC Score	
Causality term	Number of patients (%)
Certain	11 (%)
Probable/Likely	72 (%)
Possible	37 (%)
Unlikely	0 (%)
Conditioned/Unclassified	0
Unclassifiable	0

Naranjo ADR probability scale	
Definite	12 (10%)
Probable	66 (55%)
Possible	42 (35%)
Doubtful	0
Hartwigs severity assessment scale	
Level 1 (Mild)	14 (11.7%)
Level 2 (Mild)	20 (16.7%)
Level 3 (Moderate)	68 (56.7%)
Level 4 (Moderate)	15 (12.5%)
Level 5 (Severe)	3 (2.5%)
Level 6 (Severe)	0
Level 7 (Severe)	0

Conclusion

Antimicrobials are commonly used in medical field against various infections. ACDRs due to anti microbials are serious and avoidable causes of morbidity and mortality which increase the burden of work. Anticipating, recognizing and managing ACDRs is of prime concern so as to minimize its incidence. 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. Their responsibility also extends in suggesting safer group of the drugs and educating patients regarding carrying a list of drugs to be avoided to every physician he visits.

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