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Original Research Article

Cutaneous Adverse Drug Reactions with Fixed-Dose Combinations: Special Reference to Self-medication and Preventability

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Abstract:

Introduction: A cutaneous adverse drug reaction (CADR) is any unfavourable cutaneous clinical manifestation that happens after taking a certain medicine. ADRs are more likely to occur when fixed dose drug combinations (FDCs) are used than when a drug is taken alone.

Method: In Department of Pharmacology, Nalanda Medical College, Patna, a prospective, spontaneous ADR reporting research was carried out over a period of one year. ADRs that were reported after suspected FDC usage were assessed for severity (modified Hartwig scale), causality (WHO-UMC likelihood scale), and avoid ability.

Result: 60 ADRs were recorded as a result of FDCs, of which 11 (36.33%) were reported for females and 19 (63.34%) for males. The range of cutaneous ADRs included mild to potentially fatal reactions. 4 (6.6%) of the 2 (3.3%) life-threatening ADRs recorded were attributable to irrational and rational FDCs. The majority of ADRs were brought on by antihistaminic with leukotriene receptor blocker FDCs. 19 (31.6%) and 15 (25%) of the 34(56.6%) antihistaminic with leukotriene receptor blocker FDCs suspected of causing ADRs were rational and irrational, respectively.

Conclusion: Cutaneous ADRs are more likely to be brought on by irrational FDCs. Physicians can combat the evil of illogical prescribing by being aware of and routinely reporting such ADRs.

Keyword: Unwanted Medication Effects, Combination Of Drugs, Prescription Errors, Preventability.

Introduction

A cutaneous adverse drug reaction (CADR) is the most typical form of an adverse drug reaction (ADR). Any unfavourable alteration in the structure or function of the skin, its appendages, or its mucous membranes brought on by a medicine is referred to as a drug-associated adverse drug reaction, or CADR.[1,2] The CADR can be minor and temporary or severe, necessitating hospitalisation and occasionally resulting in morbidity and fatality. CADRs are present in 10 to 45% of ADRs, and they account for about 2-3% of hospital admissions. [3,4] Inpatients and outpatients combined had a pooled incidence of 9.22/1,000 according to a systematic review of CADR in the Indian population. [5] About 2% of CADRs are severe in nature, potentially life-threatening, and occasionally fatal. The majority of CADRs are mild, self-limiting, and resolve upon stopping the offending substance. [4]

CADRs are frequent and may be to blame for 3% of all hospital acquired disabilities.[6] The spectrum includes Stevens-Johnson syndrome (SJS), transient maculopapular rash, fixed-drug eruption (FDE), and toxic epidermal necrolysis (TEN).[7] Fixed-dose combinations (FDCs), which combine two or more active medications into a single dosage form, are widely utilised today. According to research by Bangalore et al., FDCs lower the likelihood of drug noncompliance and have to be taken into account in patients with long-term illnesses like diabetes and hypertension.[8] FDCs, however, carry twice the risk of a single medication with other drawbacks.[9]

The risk of adverse drug reactions (ADRs) has increased with the growing use of fixed dose medication combinations (FDCs), which are twice as risky than a single drug[10] and make it challenging for the prescriber to determine which of the FDC's components was the culprit.[11] The illogical FDCs are openly promoted and prescribed in India, despite the fact that WHO has included the rational FDCs in the model list of essential medications.

ADEs are diverse and frequently have an impact on many organ systems. Drug eruptions' clinical symptoms have been well investigated and

categorised. When compared to internal involvement, which is frequently sub-clinical, cutaneous signs frequently occur early and may allow for a more accurate timeframe. Because of the diversity of drug exposures, cutaneous, and systemic symptoms, developing CAMs using ADE databases may not always be accurate. To find all published CDI for CDEs methodologies, compare the approaches to identify their advantages and disadvantages, and come up with hypotheses for future causality assessment research, a scoping review was used.

The diagnosis of CADR is currently only made clinically. The majority of drug eruptions are treatable and self-limiting upon cessation of the offending substance. Early recovery and a complication-free outcome may result from prompt diagnosis, early detection, and withdrawal of the causative medicine together with symptomatic treatment, corticosteroid therapy, and antihistamines. Additionally, it will considerably lessen the financial strain that ADR places on our nation's healthcare system.

The present study, which attempted to analyse the pattern of ADRs due to the use of FDCs in Nalanda Medical College, Patna was motivated by the lack of information available on ADRs connected to the use of FDCs.

Materials and Methods:

A one-year prospective, spontaneous ADR reporting research was carried out at Department of Pharmacology, Nalanda Medical College, Patna for one years. The institutional ethical committee gave its approval to the project. Following the physician/dermatologist's evaluation, the investigator recorded the ADRs suspected to be related to FDC use from various departments using the CDSCO and an internal case record form. The investigator then evaluated the ADRs for causality, severity, and avoidability using the WHO-UMC scale,8 adapted Hartwig severity scale,9, and the Modified Hallas J. et al. scale10, respectively. Patients or their family were questioned in the event that there was any doubt about the ADR's details, and case reports and CDSCO forms were filled up.

Inclusion criteria: All suspected ADRs that may be related to the use of FDCs, both those that are prescribed and those that are available over-the-counter, whether used by patients as inpatients or outpatients.

Exclusion criteria: ADRs resulting from the use of alternative medical systems include purposeful or inadvertent overdoses, cases that are consistent with the diagnosis of viral exanthem, the emergence of rashes prior to the administration of medication, and incidents involving patients who are mentally retarded and drug addicts.

The difference between the qualities was determined using descriptive statistics and either the Chi Square test or Fischer's exact test. A p value of 0.05 or lower was deemed significant.

Results:

60 ADRs were recorded as a result of FDCs, of which 11 (36.33%) were reported for females and 19 (63.34%) for males. The patients' average age was 35.23 years old.(Table 1)

Table 1: Demographic profile

Gender	No. of cases	%
Male	39	65%
Female	21	35%

Table 2: ADR reporting patterns while using FDCs

Pattern of ADR with FDC use (n=30)	ADRs reported due to Rational FDCs		ADRs reported due to Irrational FDCs	
	No.	%	No.	%
Angioedema	8	13.3%	10	16.6%
Stevens-Johnson Syndrome	3	5%	5	8.3%
Exfoliative dermatitis	2	3.3%	3	5%
Toxic Epidermal Necrolysis	0	0	2	3.3%
Maculopapular rash	1	1.6%	0	0
Morbilliform rash	5	8.3%	1	1.6%
Exanthem	6	10%	2	3.3%
Urticaria	2	3.3%	0	0
Fixed Drug Eruption*	2	3.3%	4	6.6%
Other	0	0	4	6.6%

The range of cutaneous ADRs included mild to potentially fatal reactions. 4 (6.6%) of the 2 (3.3%) life-threatening ADRs recorded were attributable to irrational and rational FDCs. SJS, TEN, angioedema, disseminated FDE, and erythroderma with exfoliative dermatitis were among the fatal ADRs (Table 2).

Table 3:Classes of drugs used as FDCs suspected to produce cutaneous ADRs

Type of drugs in the FDC (n=29)	Rational	%	Irrational	%
Antihistaminic with leukotriene receptor blocker	19	31.6%	15	25%
Antimicrobials	0	0	1	1.6%
Hypolipidemics	0	0	0	0
NSAIDs	8	13.3%	12	12%
Oral hypoglycemics	0	0	3	5%
Sympathomimetics	2	3.3%	0	0

60 of the 31 ADRs involving cutaneous responses were attributable to the use of irrational FDCs. The majority of ADRs were brought on by antihistaminic with leukotriene receptor blocker FDCs. 19 (31.6%) and 15 (25%) of the 34(56.6%) antihistaminic with leukotriene receptor blocker FDCs suspected of causing ADRs were rational and irrational, respectively. The NSAIDs were the next class to generate a higher number of ADRs, and all 8 (13.3%) and 12 (12%) of them were brought on by rational and irrational FDCs (Table 3).

Discussion

ADRs are a constant side effect of drug use, made worse by the irrational drug combinations found in FDCs. Only 22 drug combinations are included in the 17th WHO Essential Drug List [12], and only 17 are listed in the National List of Essential Medicines of India (NLEM) 2011 [13]. Nevertheless, it is astounding to learn that thousands of these FDCs are currently being routinely marketed and prescribed in India. Irrational prescription practises can endanger the patient's health and result in fatal adverse drug reactions (ADRs), which are frequently unreported. at order to analyse the pattern of ADRs produced by the use of FDCs at a tertiary care hospital, a one-year prospective research was initiated.

A total of 30 ADR were recorded, 29 of which (96.67%) were cutaneous. The difficulty of underreporting ADRs [14] has been believed to require that it be overcome by educating the prescribing community and requiring ADR reporting. [15] The illogical FDCs resulted in 19 (63.34%) cutaneous ADRs. Similar reports from a research done in Nepal have been seen. [16] Antimicrobial FDCs were the most frequent offending group for producing the ADRs, followed by NSAIDs with six (20.68%), of which nine (30%) were rational and ten (33.34%) were irrational FDCs. Numerous investigations conducted in India and worldwide support this conclusion. [17,15,16-18]

The most common ADR recorded was FDE, which was considerably more prevalent with illogical FDCs (p=0.023). The majority of life-threatening ADRs, including SJS, TEN, and disseminated FDE, were also caused by irrational FDCs, but they were not significantly more common than rational ones (p=0.097). About 13.33% of all ADRs were contributed by SJS and TEN combined. Other Indian tertiary healthcare facilities have also found a comparable greater prevalence. [19] According to this results, using illogical FDCs carries a higher risk of adverse drug reactions (ADRs), but both types of FDCs may carry a similar risk of ADRs that could be fatal.

One of the disadvantages of this study is that no rechallenge with the suspected FDC was administered to the patients, therefore no 'certain' ADRs could be reported. The majority of ADRs were mild, level 2 on the Adapted Harwig severity scale, and were substantially more common in patients with irrational FDCs (p=0.029) than those with reasonable ones. According to the Hallas J et al. Avoidability scale, more over 40% of ADRs had unreasonable FDCs and were of the "possibly avoidable" category.

However, with the logical FDCs, all ADRs were "inevitable." These findings suggest that irrational FDCs, even those that are moderate, can result in a higher frequency of adverse drug reactions (ADRs), which might be prevented if separate medications or rational drug combinations were employed for the therapy. Before prescribing the illogical FDCs, a thorough history taking, review of the FDCs, and accurate evaluation of the case might have prevented these ADRs and subsequently the cost of therapy, hospitalisation, and patient suffering. Due to the fact that these cases were reported freely and through a spontaneous reporting method, the stated number of ADRs with FDCs may only be the tip of the iceberg.

Conclusion

According to the current study, irrational FDCs can result in a higher number of adverse drug reactions (ADRs), some of which can be prevented by using rational FDCs or separate medications for each component. Additionally, if the spontaneous reporting of ADRs is made required at healthcare facilities, it will be possible to quantify the precise number of FDC-induced ADRs and raise awareness of the risks associated with irrational FDC usage.

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