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Research Article

Pattern of cutaneous adverse drug reactions due to the use of fixed dose drug combinations

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ABSTRACT

Background: Fixed dose drug combinations (FDCs) possess a higher risk of causing adverse drug reactions (ADRs) compared to a drug used individually. This study analyzes the pattern of ADRs caused due to the use of FDCs in a tertiary care hospital.
Methods: A prospective, spontaneous ADR reporting study was conducted for two years at a tertiary care hospital. ADRs reported due to suspected FDC use were evaluated for causality (WHO-UMC probability scale), severity (adapted Hartwig scale) and avoidability (Modified Hallas J. et al. scale).
Results: Of the 29 (96.67%) cutaneous ADRs reported, 19 (63.34%) ADRs were due to irrational FDCs, of which 16 (53.34%) were 'probable', 13 (43.34%) were 'possibly avoidable' and 13 (43.34%) were 'mild/level 2' on the severity scale.
Conclusion: Irrational FDCs carry a higher risk of causing cutaneous ADRs. Awareness and regular reporting of such ADRs can help physicians fight the evil of irrational prescribing.

Keywords: Adverse drug reaction, Drug combination, Inappropriate prescribing, Preventability

INTRODUCTION

Adverse drug reactions (ADRs) are an inescapable accompaniment of drug use. ADRs form an important cause of diminished quality of life, increased hospital visits, hospitalizations, increased healthcare costs and even death,[1] due to which drug safety is now a public health priority. The ADRs account for 4-5% of hospital admissions in developed countries like UK and England[2,3] where the disease prevalence, access to medicines, drug use patterns and drug management systems differ markedly from those of developing countries[4] where the picture may be even grimmer.

Cutaneous reactions to drugs are the most common ADRs and the incidence is 2-5% in inpatients of developing countries like India.[2] Any skin disorder can be imitated, induced or aggravated by drugs. Although most of the cutaneous ADRs are mild and self limiting, some life threatening reactions like Steven Johnson's syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) can also occur which account for 2- 7% of all ADRs.[5]

With the increasing use of combination products called the fixed dose drug combinations (FDCs) the risk of ADRs has doubled as these FDCs are twice as riskier as a single drug,[6] and also pose a difficulty for the prescriber to identify as to which of the components of the FDC caused the ADR.[7] Though WHO has enlisted the rational FDCs in the model list of essential drugs, the irrational FDCs are being freely marketed and prescribed in India.

Paucity in the information related to ADRs due to FDC use prompted the present study which was aimed at analyzing the pattern of ADRs due to the use of FDCs in a tertiary care hospital.

METHODS

A prospective, spontaneous ADR reporting study was conducted for a period of two years from Jan 2011 to Dec 2012 at a tertiary care hospital of South India. The study was approved by the Institutional Ethical Committee. After the assessment by the physician/dermatologist, the ADRs suspected due to FDC use from various departments were recorded using the CDSCO and an internal case record form by the investigator and were evaluated for causality, severity and avoidability using the WHO-UMC scale,[8] adapted Hartwig severity scale[9] and by the Modified Hallas J. et al. scale[10] respectively. In case of an unclear data regarding the ADR the patients or their relatives were enquired and the case reports as well as the CDSCO forms were completed.

Inclusion criteria: All the suspected ADRs that may be due to the use of FDCs, both prescribed and over the counter, taken by patients either as inpatients or outpatients.

Exclusion criteria: ADRs due to the use of alternative system of medicines, either deliberate or unintentional overdose, cases consistent with diagnosis of viral exanthem, onset of rashes prior to the consumption of medication, occurring in mentally retarded patients and drug addicts.

Descriptive statistics were used and the difference in the attributes calculated by Fischer's exact test or Chi Square test. p value <0.05 was considered significant.

RESULTS

A total of 30 ADRs were reported due to FDCs, of which 19 (63.34%) occurred in males and 11 (36.33%) in females. The mean age of the patients was 35.23 years.

Twenty nine (96.67%) ADRs were cutaneous reactions among which 19 (63.34%) were due to use of irrational FDCs. Antimicrobial FDCs caused the highest number of ADRs. Of the 19 (63.34%) antimicrobial FDCs which were suspected to have caused ADRs, nine (30%) were rational and 10 (33.34%) were irrational FDCs. The next group to cause higher number of ADRs was that of NSAIDs of which all six (20%) were due to irrational FDCs (Table 1).

The commonest ADR reported was FDE (Fixed drug eruption) in 11 (36.67%) patients; which occurred significantly more with irrational FDCs [10 (90.90%)] than with the rational FDCs [one (9.10%)] (p = 0.023, Fischer's Exact test).

The pattern of cutaneous ADRs varied from mild to life threatening reactions. Among the seven (23.33%) life threatening ADRs reported, four (13.33%) were due to irrational and three (10%) due to rational FDCs. The fatal ADRs included SJS, TEN, angioedema, disseminated FDE and erythroderma with exfoliative dermatitis (Table 2).

Twelve (40%) patients needed treatment to manage the ADRs and had prolonged hospital stay due to ADRs while others were treated symptomatically and by withdrawal of the suspected FDC.

More than half 16 (53.34%) of ADRs had a 'probable' association with irrational FDCs and nearly two third of ADRs were 'avoidable' [definitely avoidable six (20%) and possibly avoidable ADRs 13 (43.34%)] that occurred with irrational FDCs. Of all the ADRs reported 16 (53.34%) were mild [level 2 of severity scale of which, 13 (43.34 %) were due to irrational and three (10 %) due to rational FDCs (p= 0.029, χ^2= 4.739, df= 1)]. Rational FDCs caused 11 (36.66%) unavoidable ADRs while irrational FDCs produced a 13 (43.34%) possibly avoidable ADRs (Figure 1).

Table 1: Classes of drugs used as FDCs suspected to produce cutaneous ADRs.

Type of drugs in the FDC (n=29)	Rational	%	Irrational	%
Antimicrobials	09	31.04	10	34.48
NSAIDs	00	00	06	20.68
Sympathomimetics	00	00	01	03.45
Oral hypoglycemics	00	00	01	03.45
Hypolipidemics	01	03.45	00	00
Antihistaminic with leukotriene receptor blocker	00	00	01	03.45

Table 2: Pattern of ADRs reported with the use of FDCs.

Pattern of ADR with FDC use (n=30)	ADRs reported due to Rational FDCs		ADRs reported due to Irrational FDCs	
	No.	%	No.	%
Stevens-Johnson Syndrome	01	03.33	02	06.67
Toxic Epidermal Necrolysis	00	00	01	03.33
Exanthem	02	06.67	02	06.67
Fixed Drug Eruption*	04	13.34	07	23.33 #
Urticaria	01	03.33	03	10
Morbilliform rash	01	03.33	00	00
Maculopapular rash	01	03.33	02	06.67
Exfoliative dermatitis	01	03.33	00	00
Angioedema	00	00	01	03.33
Others **	00	00	01	03.33

* One of the Fixed Drug Eruption was a disseminated reaction

** Violaceous plaque with central bullae

# $p < 0.023$ Fischer's Exact Test

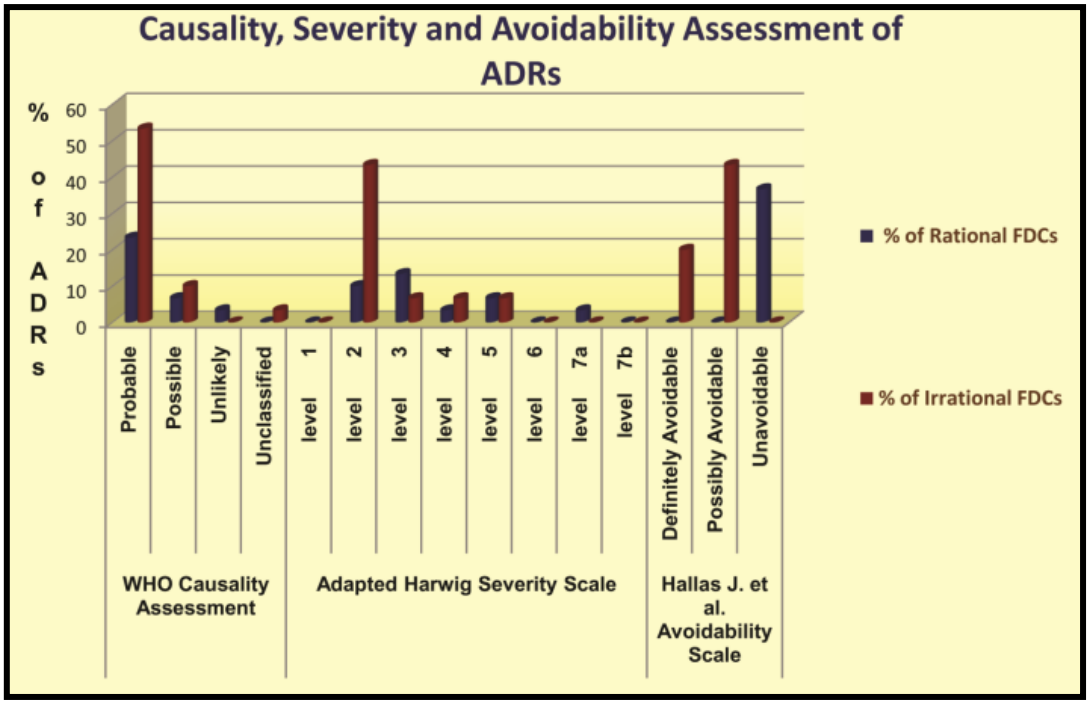

Figure 1: Causality, severity and avoidability assessment of ADRs due to FDC use.

Mild [level 2 of severity scale] 13 (43.34 %) were due to irrational and three (10%) due to rational FDCs (p= 0.029, χ^2= 4.739, df= 1).

DISCUSSION

ADRs always accompany drug use, more so when the drugs are irrationally combined in FDCs. The 17th WHO Essential Drug list consists of only 22 drug combinations[11] and the National list of Essential Medicines of India (NLEM) 2011[12] enlists only 17 of them, but it is astonishing to find thousands of such FDCs being routinely marketed and prescribed in India in the present practice. Irrational prescribing can jeopardize the health of the patient and can lead to fatal ADRs which usually go unreported. This two year prospective study was hence undertaken to analyze the pattern of ADRs caused due to the use of FDCs in a tertiary care hospital. A total of 30 ADR were reported which consisted of 29 (96.67%) cutaneous reactions. It has been a felt need from the past studies that the hurdle of under reporting of the ADRs[13] has to be curbed by sensitizing the prescribing community and mandating ADR reporting.[14]

Nineteen (63.34%) cutaneous ADRs were caused due to the irrational FDCs. Similar reports have been observed with a study conducted in Nepal.[15] Antimicrobial FDCs were the most common {19 [nine (30%) were rational and 10 (33.34%)] were irrational FDCs} offending group for causing the ADRs followed by NSAIDs six (20.68%). Several studies in India and elsewhere corroborate this finding.[3,4,15-17]

The commonest ADR reported was FDE which was significantly higher with irrational FDCs (p=0.023) and also the most of life threatening ADRs like SJS, TEN and disseminated FDE were produced due to irrational FDCs however these were not significantly higher compared to rational ones (p=0.097). SJS and TEN together contributed to about 13.33% of total ADRs. A similarly higher incidence has been reported from other Indian tertiary health care centers as well.[2] These data indicate that the risk of ADRs is more with the use of irrational FDCs but the risk of life threatening ADRs could be similar with both the types of FDCs.

No 'certain' ADRs could be recorded as no rechallenge with the suspected FDC was done in the patients, which accounts for one of the limitations of this study. Maximum number of ADRs were mild, level 2 of severity on the Adapted Harwig severity scale and significantly higher with irrational FDCs (p=0.029) compared to rational ones. More than 40% of ADRs were of 'possibly avoidable' type with irrational FDCs as indicated by the Hallas J et al Avoidability scale. However, all ADRs were 'unavoidable' with the rational FDCs. These results indicate that the irrational FDCs can cause higher number of ADRs even though mild which can be possibly avoided if rational combinations of drugs or the separate drugs were used for the treatment. A careful history taking, review of the FDCs and proper evaluation of the case before prescribing the irrational FDCs could have avoided these ADRs and hence the cost of treatment, hospitalization and suffering of the patient. The reported number of ADRs with FDCs could just be the tip of the iceberg as these cases were reported voluntarily and through spontaneous reporting system.

CONCLUSION

The present study indicates that a higher number of ADRs though mild in severity can be caused due to irrational FDCs which can be possibly avoided if rational FDCs or separate individual component drugs are used. Further if the spontaneous reporting of ADRs is made mandatory at health care centers then the exact number of FDC induced ADRs can be estimated and the awareness be created regarding the dangers accompanying irrational FDC use.

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Ethical approval: The study was approved by the institutional ethical committee

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