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Original Research Article

Adverse drug reactions due to fixed dose combinations: an observational cross sectional study

Roshi*, Vishal R. Tandon

Department of Pharmacology, Government Medical College, Jammu, India

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***Correspondence to:**
Dr. Roshi,
Email: roshigupta1986@gmail.com

ABSTRACT

Background: In modern world, poor compliance has been the main reason of therapeutic failure. Many factors may be responsible for this. The reasons highlighted may be adverse drug reactions (ADRs), pill burden or economic reasons. Fixed drug combinations (FDC) have helped to solve this problem. The present study was conducted to see the ADR due to fixed dose combinations.
Methods: After approval from institutional ethics committee, an observational study was conducted over a period of six months in December 2018 to May 2019 in adverse drug monitoring centre, GMC Jammu.
Results: A total number of 112 ADRs were reported during the study period. FDCs were responsible for ADRs in 64 patients and single drug was responsible in 48 patients. As per latest WHO essential drug list, irrational FDC were responsible for ADRs in 44 patients and rational FDCs were responsible for ADRs in 20 patients.
Conclusions: The results of present study underscores that drug combinations, FDC rational as well as irrational substantially contribute towards the pool of total ADRs.

Keywords: Compliance, Irrational FDCs, Essential medicine list, ADR

INTRODUCTION

Fixed drug combinations (FDC) have become very popular in clinical practice. The reason may be the better patient compliance and decrease in pill burden. FDC is acceptable pharmacologically only if the combination has an established therapeutic and safety advantage over single ingredients, if administered separately. FDC is pharmacologically rational if the drugs act by different mechanisms and have supra-additive effect, same pharmacokinetic parameters and without additional toxicity.[1,2] Many of the FDCs available in Indian market do not have therapeutic rationale but are used.[3-5] Irrational prescribing of FDCs is a major health concern in India as irrational FDCs can prove to be detrimental to the patient.[6] Besides other risk factors like female gender, advancing age, pediatric age, multiple drug usage, smoking, alcohol, inappropriate drug usage, irrational drug combination is one of the risk factors for adverse drug reactions (ADRs).[7] ADRs due to FDCs are very well reported individually but review of literature could not much of studies in Indian setup. Hence, the study was undertaken to analyze the profile of ADR contributed by FDC.

METHODS

A retrospective observational cross-sectional analysis was carried out over a period of six months from December 2018 to evaluate the profile of adverse drug events related to FDC/drug combinations in ADRM Centre, working under Pharmacovigilance Programme of India (PvPI) in a tertiary care teaching hospital from north India using suspected drug reactions monitoring data collection form used under PvPI. Information about patient, suspected ADR, suspected medication, reporter,

date of reaction, date of recovery and presentation of problem were recorded. Under suspected medication, name of drug combinations, brand of manufacturer, generic name of manufacturer (if known), expiry date, dose used, route, frequency and therapy dates as well as reason for prescribing suspected drug combinations were also assessed. The information about de-challenge and re-challenge, concomitant medical treatment record, the relevant laboratory biochemical abnormality were recorded separately. Other relevant history including pre-existing medical conditions like allergy, pregnancy, smoking and alcohol used and any organ dysfunction was noted. The ADRs were defined and categorized as per the definition of Edwards et al.[8] The severity and seriousness of reaction, mode of onset, nature of ADRs, type of reaction, the outcome of reaction and onset time was recorded for every suspected ADRs due to FDC. Severity of reaction was classified as mild (bothersome but requires no change in therapy); moderate (requires change in therapy, additional treatment, hospitalization); severe (disabling or life-threatening). Serious reactions were defined as any event leading to (death, life threatening, prolonged hospitalization, disability, required intervention to prevent permanent impairment/damage, congenital anomaly). Onset of event was categorized as acute (within 60 minutes); sub-acute (1 to 24 hours) and latent (> 2 days). Whereas nature and type of reaction was classified as Type A (augmented); Type-B (bizarre); Type-C (continues use); Type-D (delayed) and Type-E (end of use). Outcome was described as fatal, recovering recovered, unknown, continuing or other) as per recommended SOP of PvPI. The suspected ADRs were classified in term of causality using WHO-UMC scale and Naranjo scale.[8,9] Detail subgroup analysis of ADRs detected and various socio-epidemiological, drug related parameters like combination antibiotics, route of drug administration, rationalor irrational combinations or FDC were also analyzed in the current study.

Inclusion criteria

Any ADR occurring with FDC/combination from OPD or inpatient of any severity, duration and any type of reaction were included.

Exclusion criteria

Whereas, any case of poisoning, medication error, over dosage, over/non-compliance, natural products or alternate medicines and unidentified drugs were excluded.

Statistical analysis

Analysis was carried out with the help of computer software SPSS Version 15 for windows. The data was expressed in n (%). Chi-square test was applied to prove their statistical significance. P value <0.05 was considered significant.

RESULTS

A total number of 112 ADRs were reported during the study period. FDC were responsible for ADRs in 64 patients and single drug was responsible in 48 patients. As per latest WHO essential drug list, irrational FDC were responsible for ADRs in 44 patients and rational FDCs were responsible for ADRs in 20 patients (Table 1).

Table 1: Pattern of ADRs due to drugs.

Parameters	Number
Total ADRs	112
ADRs due to single drug	48
ADRs due to FDCs	64
ADRs due to rational FDCs	20
ADRs due to irrational FDCs	44

Table 2: General characteristics of ADRs.

Demographic characteristics	
Gender	
Male	30
Female	34
Age	
Paedriatic	7
Adult	20
Geriatric	37
Onset	
Acute	20
Subacute	40
Latent	4
Severity	
Mild	30
Moderate	32
Severe	2
Serious	62
Non serious	2
Recovered	44
Recovering	20
Causality as per WHO-UMC scale	
Probable or possible	14
Certain	50

Majority of ADRs were seen in females, geriatric age group was most commonly involved, maximum of the ADRs were subacute in onset. Most of the ADRs were mild and moderate in nature. Only 2 ADRs were serious. Maximum ADRs had possible correlation as per WHO-UMC causality assessment scale (Table 2). Etodolac and paracetamol combination caused ADRs in maximum number of patients followed by nimesulide and paracetamol among irrational combinations whereas in rational combinations trimethoprim and sulphamethoxazole were responsible for maximum ADRs followed by antitubercular combinations. Naproxen and paracetamol caused ADRs in 4 patients, pseudoephedrine

and bromhexine and azithromycin with cefixime caused ADRs in 3 patients each. Azithromycin and levofloxacin, with combination of terbutaline, bromhexine, etofylline and diclofenac with rabeprazole and other irrational antidiabetic combinations were responsible for ADRs in 2 patients each. Chlorpheniramine with vitamin C, heparin with diclofenac, cefuroxime with linezolid were responsible for ADRs in 1 patient each. Other rational FDCs responsible for ADRs were levodopa and carbidopa in 5 patients, piperacillin with tazobactam in 3 patients, ampicillin with sulbactam in 2 patients and imipenem with cilastatin in 1 patient (Tables 3 and 4).

Table 3: Irrational FDCs causing ADRs.

Irrational FDCs prescribed	No. of patients with ADRs (n=34)
Nimesulide+paracetamol	6
Naproxen+paracetamol	4
Azithromycin+levofloxacin	2
Heparin+diclofenac	1
Cefuroxime+linezolid	1
Terbutaline+bromhexine+etofylline	2
Pseudoephedrine+bromhexine	3
Etodolac+paracetamol	7
Chlorpheniramine+Vitamin C	1
Azithromycin+cefixime	3
Diclofenac+rabeprazole	2
Others	2

Table 4: Rational FDCs causing ADRs.

Rational FDCs prescribed	No. of patients (n=30)
Levodopa +carbidopa	5
Trimethoprim+sulphamethoxazole	10
Piperacillin+tazobactam	3
Imipenem+cilastatin	1
Ampicillin+sulbactam	2
Antitubercular combination	9

Table 5: ADRS due to FDCs.

ADR	No. of patients
Rash	9
Gastritis	8
Vomiting	6
Pain abdomen	10
Insomnia	2
Giddiness	3
Upper GI bleed	1
Diarrhoea	9
Anxiety	5
Deranged LFTs	7
Pruritis	4

Most common ADR was pain abdomen (10 patients) followed by rash and diarrhea in 9 patients. Gastritis was seen in 8 patients, deranged liver function tests in 7 patients, vomiting in 6 patients, pruritis in 4 patients, giddiness in 3 patients, insomnia in 2 patients, and upper gastrointestinal (GI) bleed in 1 patient (Table 5). Upper GI bleed due to diclofenac+rabeprazole and rash due to azithromycin+levofloxacin were serious. Most of the ADRs had recovered.

DISCUSSION

Many studies have been conducted to see the factors responsible for ADRs causation like gender, age, co-morbid conditions, drug interactions but very few studies have been done to see the ADRs due to fixed dose combinations. In present study, many ADRs were seen due to FDCs both rational and irrational. Tandon et al in their study described irrationality among Antihypertensive prescriptions in the form of polypharmacy, generic and fixed dose combinations prescribing.[10] It was proposed in their study that they are likely to affect the final outcome of the therapy by increasing the possible potential of adverse drug event (ADEs). Tandon et al reported isolated case wherein severe GI bleeding was mreported after taking fixed dose combination (FDC) of rabeprazole (20 mg) and diclofenac sodium (100 SR).[11] Although non-steroidal anti-inflammatory drugs (NSAIDs) are known to cause GI bleed but co-administration of proton pump inhibitors has been widely suggested as one of the strategies to prevent these GI complications among NSAIDs users.

Here, this isolated report like the results of current study highlights that FDC can enhance the potential of serious ADEs also. In another isolated recent serious ADR report by Tandon et al of telmisartan plus ramipril fixed dose combination led to angioedema questioning the rationality of angiotensin receptor blocker+angiotensin-converting enzyme inhibitor combination in the treatment of hypertension.[12] Wirtz et al in their study while assessing the safety and rationale of antibacterial fixed-dose combinations in the private sector in latent American countries reported that the majority of antibacterial FDCs lacked therapeutic benefit.[13] Despite the decrease in the consumption of unsafe antibacterials and those lacking sufficient evidence, their use remains high and likely to contribute towards antibacterial resistance and ADRs. Khajuria et al, in their study described that FDCs are responsible for a causing more ADRs that single drugs amongst which irrational combinations were responsible for majority of ADRs as compared to rational combinations (5%).[14]

Limitations

It was a short duration study. There is a need to carry out such studies on large scale.

CONCLUSION

The present study highlights that the fixed dose combinations whether rational or irrational definitely contribute to ADRs. So, these should be prescribed cautiously.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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