ORIGINAL ARTICLE

Profile of Adverse Drug Reactions with Fixed Drug Combinations: How Big is the Problem?

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Abstract

The current study was undertaken to analyze the profile of adverse drug reaction (ADR) contributed by fixed drug combinations (FDC). A cross-sectional, retrospective study was conducted over a period of 2 years to evaluate the profile of ADR contributed by FDC using suspected ADR data collection form used under Pharmacovigiliance Programme of India (PvPI). A total number of 2242 ADRs were reported during the study period of two years out of which drug combinations responsible for ADRs were 589 (26.27%). Fixed drug combinations (FDC) contributing to ADRs were 88(3.9%). As per latest WHO essential drug list, irrational FDC were responsible for 83 (3.70%) accounting 94.3% of the total FDC. Whereas, only 5(0.2%) of rational FDC contributed to the total pool of ADRs. Most frequent drug combination contributing to ADR was of anticancer drugs leading to vomiting and alopecia, where as most common irrational FDC was aceclofenac plus thiocolchicoside and ofloxacin plus ornidazole leading insomnia & rash respectively. Levodopa plus carbidopa and trimethoprim plus sulphamethoxazole were two common rational FDC contributing to ADRs. The above results underscores that drug combinations and FDC as well as irrational FDC substantially contribute towards the pool of total ADRs.

Key Words

Pharmacovigiliance, ADR, FDC, Rational, Irrational Drug Combinations

Introduction

Fixed drug combinations (FDC) are popular in clinical practice mainly because of improved patient compliance and decrease pill burden. FDC is pharmacologically acceptable only if the combination has a proven therapeutic and safety advantage over single ingredients administered separately. The pharmacological rationality of FDCs is established if drugs act by different mechanisms and have supra-additive effect, have similar pharmacokinetics profile, and drugs do not have supra-additive toxicity. (1, 2)

However, irrational prescribing of FDCs is a major health concern in India as irrational fixed dose combination products can be equally harmful. (3) Many of the FDC available in Indian market lack therapeutic rationale for their use, leading to wasteful expenditure. (4-6)

Irrational drug combination is one of the risk factors for adverse drug reactions (ADRs) beside others like are female gender, advancing age, pediatric age, multiple drug usage, smoking, alcohol, inappropriate drug usage and irrational drug combinations. (7)

ADRs due to FDC are very well reported individually but least studied entity in Indian context where FDC are very popular. Hence, to best of our knowledge the first study to analyze the profile of adverse drug reaction (ADR) contributed by fixed drug combinations (FDC) was undertaken.

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Material and Methods

A retrospective observational cross-sectional analysis was carried out over a period of two years to evaluate the profile of adverse drug events related to FDC/Drug combinations in ADRM Centre, working under 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 & Arsonson, 2000. (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). Where as 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 (8) Naranjo scale. (9) Detail subgroup analysis of ADRs detected and various socio-epidemiological, drug related parameters like combination antibiotics, route of drug administration, rational/irrational combinations /FDC were also analyzed in the current study.

Inclusion: Any ADR occurring with FDC/ Combination from OPD or inpatient of any severity, duration and any type of reaction were included. *Exclusion:* Whereas, any case of poisoning, medication error, over dosage, over/ non-compliance, natural products/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.

Result

A total number of 2242 ADRs were reported during the study period of two years out of which drug combinations responsible for ADRs were 589 (26.27%). Fixed drug combinations (FDC) contributing to ADRs were 88(3.9%). As per latest WHO essential drug list, irrational FDC were responsible for 83 (3.70%) accounting 94.3% of the total ADRs due to FDC's. Whereas, only 5(0.2%) of rational FDC contributed to the total pool of ADRs. Most frequent drug combination contributing to ADR was anticancer drugs leading to vomiting and alopecia, where as most common irrational FDC as WHO essential Drug List 2013 FDC was NSAIDs plus Muscle Relaxants and ofloxacin plus ornidazole leading insomnia & rash respectively. Levodopa plus carbidopa and trimethoprim plus sulphamethoxazole were two common rational FDC contributing to ADRs. The detail profile of ADRs due

combinations and FDC have been presented in table form (*Table-1-4*)

Discussion

Though the number of isolated reports of ADR with FDC / Combination are there but the reports of detailed

Table.1 Profile of Adverse Drug Reactions with FDC

Parameters	N (%)
1.Total No. of ADRs during study period	2242
2.Total No. of ADRs due to Drug combinations	589 (26.27%)
3.Total No. of ADRs due to FDC	88 (3.9%)
4.Total No. of ADRs due to Irrational FDC as per WHO 2013 EDL	83 (3.70%)
5.Total No. of ADRs due to rational FDC as per WHO 2013 EDL	5(0.2%)

Table.2 Profile of Adverse Drug Reactions with FDC

Age wise classification- Adult, Geriatric & Pediatric-	56(63.63%), 20(22.72%), 12(13.63%)
Sex Distribution- Male vs Female -	61(69.31), 27(30.68%)
Urban vs Rural-	54(61.36%), 34(38.63%)
OPD Vs Inward-	63(71.59%), 25(28.40%)
Route of Drug Administration- Oral/I.V/IM/IA/MDI	70(79.54%)/18(20.45%)/0/0/0
Severity of ADRS - Mild/ Moderate/ Severe-	54(61.36%)/32(36.36%)/2(2.27%)
Mode of onset - Acute/Sub acute/ Latent -	66(75%)/18(20.45%)/ 4(4.54%)
Nature of ADR- Serious Vs Non serious -	8(9.09%)/8090.90%
Type of reactions - A,B, Unclasified -	28(31.81%)/56(63.63%)/ 4(4.54%)
Causality as per WHO - UMC scale -	Probable/Possible 9(10.22%)/ 79(89.77%)
Outcome of the ADRs - Recovered/Recovering-	78(88.63%)/ 10(11.36%)

Table.3 Profile of Adverse Drug Reactions with Drug Combination reported in ADRM Centre During Study Period

S.No	Symptom	Drug Combination
1	Rash	ART (19); Ofloxacin+Ornidazole(17)
2	Vomiting	Anticancer Drugs (118) NSAID's + Muscle Relaxant (12); ART(17)
3	Gastritis	ATT(23)
4	Diarrhoea	NSAID's + Muscle Relaxant (11)
5	Anaemia	ART(29)
6	Epigastric Pain	ATT(26)
7	Jaundice	ATT(33)ART(5)
8	Pain Abdomen	ATT(10)ART(5)
9	Alopecia	Anticancer Drugs(47)
10	Constipation	Carboplatin+Etoposide(2)
11	Loss Of Apetite	Anticancer Drugs(15)ATT(10)ART(8)
12	Urticaria	ART(8)
13	Anxiety	NSAID's + Muscle Relaxant (11)
14	Headache	Anticancer Drugs(6)
15	Insomnia	NSAID's + Muscle Relaxant (25)
16	Nausea	Anticancer Drugs(14)
17	Dizziness	ART(2)
18	Renal Dysfunction	ATT(12)
19	Generalised Weakness	Anticancer Drugs(10);ART(2)
20	Palpitations	ATT(2);ART(2)
21	Dyslipidemia	ART(13)
22	Peripheral Neuropathy	ART(10)
23	Giddiness	Anticancer Drugs(3)
24	Weight Loss	ATT(6)
25	Oral Ulcers	Anticancer Drugs(5)ART(3)
26	Malena	NSAIDs in Combination(5)
27	Lipodystrophy	ART(5)
28	Fatigue	ART(2)
29	Pancreatitis	ATT(1)
30	Sweating	Anticancer Drugs(1)
31	Psychosis	ATT(2)
32	Increased Urine Output	ART(1)
33	Desquamation Of Feet/Hand	Phenytoin+Phenobarbitone(1)
34	Restlessness	ATT(1)
35	Atrial Fibrilation With Embolic Stroke With Hemiplegia	Digoxin+Acitrom+Amlodipine(1)
36	Abnormal Behaviour	Levodopa+Carbidopa(2)
37	Swelling Over Body	ART(1)
38	Burning Sensation Over Body	Etoposide+Carboplatin(1)
39	Bullous Pemphigoid	Cotriomazole+Sulphamethaxazole(1)
40	Hepatic Encephalopathy	ATT(1)
41	Dyspepsia	ATT(1)
42	Loss Of Vision	ART(1)
43	Abnormal Body Movements	ATT(2)
44	Optic Neuritis	ATT(3)
45	Conjunctivitis	ART(1)
46	Leucopenia	Anticancer Drugs(2)
47	Hallucinations	Levodopa+Carbidopa(2)
48	Exacerbation Of Copd	Nimuslide+Paracetamol(1)
49	Periorbital Swelling	Art(1)Cefixime+Clavulanic Acid(1)
50	Bone Marrow Suppression	Anticancer Drugs(2)
51	Throat Pain	ATT(1)
52	K A Nephropathy	Tacrolimus+Mycophenolate(1)
53	Amenorrhoea	5-Flourouracil In Combination(3)

Table.4 Profile of Adverse Drug Reactions with FDC classified as Rational/ Irrational as per 13th EMD List

S.No	Symptom	Rational	Irrational
1	Rash		Ofloxacin+ornidazole (17) Ofloxacin+nitazoxanide (1) Cefixime+ornidazole (1) Norfloxacine+Ornidazole (1) Azithromycin+Cefixime (1)
2	Vomitting		NSAID's + Muscle Relaxant (12) Ibuprofen+acetaminophen (1) Etodolac + acetaminophen (1) Aceclofenac+Acetaminophen+Tizanidine (1) Aceclofenac+Acetaminophen+seropeptidase (1)
3	Diarrhoea		NSAID's + Muscle Relaxant (11)
4	Anxiety		NSAID's + Muscle Relaxant (11)
5	Insomnia		NSAID's + Muscle Relaxant (25)
6	Malena		NSAIDs in combination(5)
7	Abnormal behaviour	Levodopa+carbidopa (2)	
8	Bullous pemphigoid	Trimethoprim + sulfamethaxazole (1)	
9	Hallucinations	Levodopa+carbidopa (2)	
10	Peri-orbital swelling		Cefixime+clavulanic acid (1)
11	Exacerbation of COPD		Nimuslide+paracetamol (1)
12.	Angioedema		Telmisartan + enalapril (1)
13.	Upper GI Bleed		Diclofenac Sodium + Rabeprazole (1)

evaluation of ADR profile FDC is lacking. There for the present study was conducted to comprehensively evaluate the ADR patterns of spontaneously reported ADRs over a period of two years.

Balat JD *et al* (10) observed in their study that only 5.8%, 9.8% and 10.9% FDCs prescribed were included in WHO (2010), National (2011) and Gujarat State (2011) Essential Medicines Lists (EML), respectively ($P < 0.0001$). 81.5% and 12.3% of the Irrational FDCs that are banned or FDCs containing irrational active ingredients were prescribed respectively. Thereby, indicating that though FDCs are widely prescribed they contain banned or controversial ingredients which carries a high potential to cause ADEs. These findings endorse the findings of the current study that Irrational FDC contribute towards ADEs and affect the health care of patient.

In the study of Tandon VR *et al* (11) reported irrationality among Antihypertensive prescriptions in the form of polypharmacy, generic and fixed dose combinations prescribing. They proposed these are likely to affect the final outcome of the therapy by increasing the possible potential of ADEs. Tandon VR *et al* (12) reported isolated case wherein severe GI bleeding was reported after taking fixed dose combination (FDC) of rabeprazole (20 mg) and diclofenac sodium (100 SR).Although Non-steroidal anti-inflammatory drugs (NSAIDs) are known to cause gastrointestinal (GI) bleed but Co-administration of proton pump inhibitors (PPIs) 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 VR *et al* (13) of telmisartan plus ramipril fixed dose combination led to angioedema questioning the rationality of ARBs plus ACEIs combination in the treatment of hypertension.

Wirtz VJ1 et al (14) 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. 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.

Goswami N *et al* (15) evaluated knowledge, attitude and practices about prescribing fixed dose combinations among resident doctors and pointed out like our study that there is an urgent need to improve knowledge about rationality, EML, usage and banned FDCs in post graduate medical students to promote the rational use of drugs in interest drug safety .

The development of FDCs is important for public health care as it caries advantages being useful particularly in the management of chronic diseases where compliance is a deciding factor for the final therapeutic outcome beside other clinical benefits in the form of increased efficacy, reduced bill burden, potentially lower costs of manufacturing compared to the costs of producing separate products administered concurrently and simpler logistics of distribution. (16)

However, possibility of ADE is likely to be an issue particularly, if a dosing adjustment is warranted in such ADE. In such situation it may be difficult to identify the active ingredient responsible for adverse reaction. In view of existing Appendix VI of Schedule Y (Drugs & Cosmetics Rules 1945, India) for marketing approval of various types of FDCs. The result of the current study highlights the importance of considering the safety data of the ingredients in FDC and calls for serious review by drug regulatory authorities for rationality of FDCs before allowing marketing in the interest of drug safety. (16)

The current study has some of the limitations of being based on spontaneous ADR reporting data and only reflect the ADR pattern of FDCs during the defined period .

Conclusion

The results of present study underscores that drug combinations, FDC rational as well as irrational substantially contribute towards the pool of total ADRs.

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