ASSESSMENT OF MEDICATION SAFETY OF FIXED-DOSE COMBINATION DRUGS IN THE INPATIENT DEPARTMENT AT A TERTIARY CARE HOSPITAL, IN INDIA

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Article History: Received: 12.07.2022 **Revised: 01.08.2022** **Accepted: 11.09.2022**

Abstract

Objective: The present study is aimed to evaluate the medication safety of fixed dose combination drugs at a tertiary care hospital.

Methodology: It is a prospective observational study conducted in inpatient setting. The data collected in pre design data collection form, who are assessed for the period of six months. Hospitalized patients who were taking at least one fixed dose combination drugs and had a hospital stay of 48 hours were considered for this study. The collected data included demographics, fixed dose combination drugs usage pattern and safety analysis data. The data was compiled in excel and analyzed using Micromedex.

Result: A total of 200 patients were included in this study. Majority of patients were male (51.5%). Hypertension (14.5%) and diabetes mellitus (10%) were major co-morbidity. Out of 200 prescriptions analyzed, 322 drugs were fixed dose combination. The average number of FDCs prescribed was (1.62±0.78). Equal distribution of adult and geriatric FDCs prescribing was observed. As per category analysis, a higher number of fixed dose combination were related to antibiotics (18.01%) followed by antihypertensive (12.73%). The fixed dose prescribed from WHO EML was 20 (6.21%), from National Essential Medicine Lists were 296 (91.92%) and from hospital formulary of tertiary hospital were 317 (98.44%). Most commonly prescribed FDCs were aspirin/atorvastatin (7.45%) and rabeprazole/domperidone (7.45%) in the 200 prescription analyzed. drugs and fixed dose combinations was obtained from CIMS, IDR and Drug today. Of the 29 FDCs analyzed, 65% were found to be more cost effective than their total cost of individual components. The incidence of FDCs drug interaction was 21%. Among antibiotic 40 FDC were irrational followed by 22 in antihypertensive. Among the analyzed prescription, five banned drugs were observed that combination of paracetamol with tramadol in which paracetamol is 500 mg.

Conclusion: It was observed that hospital physicians prescribed fixed dose combination drugs from essential drug lists. Most of the fixed-dose combination drug was cost-effective. This study concluded that the pharmacists can play a significant role in assessing and controllindrug-relateded problems of FDCs.

Keywords: Drug combinations, fixed-dose combination (FDC), drug interaction, WHO guideline, prescription analyzes.

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Doi: 10.53555/ecb/2022.11.12.259

Introduction

Fixed dose combination (FDC) is a combination of drugs that includes two or more active pharmaceutical ingredients combined in a single dosage form. Such combination of drugs is being used in a wide range of conditions anisre also used in the treatment of HIV/AIDS, tuberculosis, malaria, etc., which are considered to be foremost infectious disease threats in the world [1]. The Food and Drug Administration, the USA defines a combination product as a product composed of any combination of a drug and a device or a biological product and a device or a drug and a biological product or a drug, device, and a biological product [2].

Combination products, also known as fixed dose drug combinations (FDCs), are combinations of two or more active drugs in a single dosage form. The Food and Drug Administration, USA defines a combination product as 'a product composed of any combination of a drug and a device or a biological product and a device or a drug and a biological product or a drug, device, and a biological product' [2]. It is widely accepted that most drugs should be formulated as single compounds. Fixed ratio combination products are acceptable only when the dosage of each ingredient meets the requirement of a defined population group and when the combination has a proven advantage over single compounds administered separately in therapeutic effect, safety or compliance [3]. FDCs are highly popular in the Indian pharmaceutical market and have been particularly flourishing in the last few years. The rationality of FDCs should be based on certain aspects such as: [4]

• the drugs in the combination should act by different mechanisms.

• The pharmacokinetics must not be widely different.

• The combination should not have supra-additive toxicity of the ingredients.

Most FDCs have the following demerits:

• Dosage alteration of one drug is not possible without alteration of the other drug.

• Differing pharmacokinetics of constituent drugs pose the problem of frequency of administration of the formulation.

• By simple logic there are increased chances of adverse drug effects and drug interactions compared with both drugs given individually.

The recent 14th model list of essential drugs prepared by the WHO (March 2005) includes 312 formulations of which 18 are fixed dose drug combinations [10-11]. The World Health Organization's (WHO) Model list of Essential Drugs provides examples of some rational FDCs such as [5]:

• sulfamethoxazole + trimethoprim

• antitubercular FDCs like rifampicin + isoniazid, isoniazid + ethambutol, etc.

• anti-parkinsonism FDCs like levodopa + carbidopa

Today many chronic diseases are still difficult to treat satisfactorily with currently available monotherapy [6]. The search for increased efficacy has raised interest in developing drug–drug combinations directed towards independent targets involved in disease pathology [2]. Systems pharmacology involving holistic systems approaches now allows such targets to be identified3. Enhancement of treatment efficacy by adjusting the drug-release profile in the formulation of FDC tablets represents another reason [2]. Finally, the number of drugs prescribed per patient increases with both age and time. Such polypharmacy can result in poor adherence to the pharmacotherapy leading to over- and under-dosing, inducing both safety problems and reduced treatment effectiveness of the prescribed drugs [7].

Rational drug therapy means the use of the right medicine in the right manner (dose, route, frequency of administration, duration of therapy, etc.) in the right patient at the right cost and at the right time. It is staggering to find that over 80,000 formulations are sold in the Indian market, which includes several FDCs and other single-drug formulations. There has been an alarming increase in irrational FDCs in the recent past and pharmaceutical companies manufacturing these FDCs are luring physicians to prescribe their products even when they are not need by the patient. Irrational drug combination is one of the risk factors for adverse drug reactions (ADRs) beside others like are female gender, advancing age, multiple drug usage, smoking, alcohol, inappropriate drug usage and irrational drug

combinations [8].

ADRs due to FDC are very well reported individually but least studied entity in the Indian context where FDC are very popular. Hence this study is conducted to analyse the profile of ADR associated with fixed-dose combination.

MATERIALS AND METHODS

Study Site:

The study was conducted in cardiology ward at Tertiary Care Hospital, India

Study Design:

It was a prospective observational study conducted in hospital inpatient setting.

Study Criteria:

- Inclusion Criteria:

  - All patients admitted in hospital

  - Patients who were taking one FDCs and had a hospital stay of at least 48 hours

- Exclusion Criteria: Patients admitted to Pediatric ward

Material Used:

- Case Record
- Treatment Chart
- Lab Master
- Physician Notes
- Patient Medication Rack
- Nurses Comment
- Site (Micromedex)

Method of Collection of Data:

The newly admitted case was randomly selected on daily basis and reviewed for the drug related problem of FDCs and followed up for the assessment of irrational prescribing and drug interaction.

Study Procedure:

The patient demographics and all medically relevant information were noted in a predefined data collection form. Alternatively, these case charts were reviewed for potential drug interactions, drugs involved in interactions (dose, route, frequency, therapy duration, indication), laboratory investigations, followed up for assessing drug-related problems of FDCs ,and pharmacist's intervention. Rationality of FDCs was assessed using WHO guideline and comparing it with the list published by NEML. The changes and the daily notes in the case sheets were followed until the patient was discharged or shifted to other wards. The Micromedex, Medscape and references books were used as tools to review the prescription and case charts. The clinical pharmacist's intervention was done by suggesting physician about the drug related problems. Cost effective analysis was carried out by comparing total cost of each individual component with the cost of fixed dose combination. The cost of individual drugs and fixed dose combinations was obtained from CIMS, IDR and Drug today.

Drug-drug interaction check was performed using Micromedex-2. According to this tool, drug interactions were categorized as minor, moderate or major which indicates the possible risks of occurrence of the potential drug interactions which can occur in patients, but not the actual severity of drug interactions. The data obtained was used to categorize interactions based on the mechanism as pharmacokinetic or pharmacodynamics. The pharmacokinetic drug interactions were further categorized into interactions based on absorption, distribution, metabolism and elimination. The severities of the interactions were assessed and categorized as major (can cause permanent damage or life risk), moderate (can cause harm and treatment is required) or minor (can cause small or no clinical effect, with no treatment required). The data were stored confidentially and subjected to further analysis using appropriate software.

RESULT AND DISCUSION

The proposed observational prospective study comprised sample size of 200, out of which majority was Males (51.5%). The study population consisted of (49.5%) Adult patient who were receiving FDC's, (49%) Geriatrics patients and rest were adolescent (1.5%). The population comprised of (5.5%) Renal Impaired patients and (2%) were pregnant female patients. Patient receiving FDC's had comorbid condition Hypertension (14.5%), Diabetes (10%), cardiovascular disease (4.5%). Cerebrovascular accident (2.5%), pulmonary disease (2.5%), Cancer (1.5%), Hyperthyroidism (1.5), CKD (1%), Seizure disorder (1%).

Hypertension was most prevalent comorbidity condition in which FDC's drugs were highly used in male and female. FDC drug was highly prescribed in patients with cardiovascular disease which was (37.5%), patients with Diabetes which holds (23%) and patients with Respiratory disorder (13.5%).

FDC'S drugs prescribed most commonly were Antibiotics (18.01%), Antihypertensive (12.73%), Antilipidemic (10.55%), Antidiabetic (9.93%), Antiemetic (8.07%), and Antiplatelet (8.07%). Table1

Table1 Drug Category highly prescribed.

S.No	WARD	PATIENT GENDER				Total	
		MALE		FEMALE			
		N	%	N	%	n	%
1.	5-Alpha reductase inhibitor	16	4.96	2	0.62	18	5.59
2.	Alpha-1-adrenargic blocker	1	0.31	0	0	1	0.31
3.	Analgesic	12	3.72	13	4.03	25	7.76
4.	Anti-inflammatory	0	0	7	2.17	7	2.17
5.	Antipyretic	11	3.41	9	2.79	20	6.21
6.	Antacid	11	3.41	12	3.72	23	7.14
7.	Antiemetic	12	3.72	14	4.34	26	8.07
8.	Antianginal	1	0.31	0	0	1	0.31
9.	Antianemic	2	0.62	4	1.24	6	1.86
10.	Antibiotic	36	11.18	22	6.83	58	18.01
11.	Antifungal	1	0.31	2	0.62	3	0.93
12.	PPI	5	1.55	2	0.62	7	2.17
13.	Anticoagulant	16	4.96	7	2.17	23	7.14
14.	Antilipidemic	23	7.14	11	3.41	34	10.55
15.	Anticonvulsant	3	0.93	6	1.86	9	2.79
16.	Neuropathic pain	5	1.55	5	1.55	10	3.10
17.	Antidiabetic	21	6.52	11	3.41	32	9.93
18.	Antihistaminic	9	2.79	5	1.55	14	4.34
19.	Antihypertensive	10	3.10	31	9.62	41	12.73
20.	Diuretics	11	3.41	7	2.17	18	5.59
21.	Antiplatelet	23	7.14	3	0.93	26	8.07
22.	Antiparkinson	2	0.62	5	1.55	7	2.17
23.	Antitubercular	1	0.31	2	0.62	3	0.93
24.	Calcium supplement	1	0.3105	4	1.2422	5	1.5527
25.	Contraceptive	0	0	2	0.6211	2	0.6211
26.	Hemostatic	0	0	4	1.2422	4	1.2422
27.	Leukotriene inhibitors	8	2.4844	4	1.2422	12	3.7267

Highly prescribed FDC'S drugs were shown in Table 2. According table2, Aspirin + Atorvastatin and Rabeprazole + Domperidone have highly prescribed FDC'S drugs.

Table 2: Top 10 FDC drug highly prescribed.

S.No	Drug	PATIENT GENDER	Total

		MALE		FEMALE			
		N	%	N	%	n	%
1.	Aspirin + Atorvastatin	17	5.27	7	2.17	24	7.45
2.	Rabeprazole + Domperidone	10	3.10	14	4.34	24	7.45
3.	Tramadol + Paracetamol	11	3.41	8	2.48	19	5.90
4.	Amoxicillin+Clavanic acid	11	3.41	6	1.86	17	5.27
5.	Tamsulosin + Dutasteride	15	4.65	2	0.62	17	5.27
6.	Piperacillin + Tazobactam	10	3.10	7	2.17	17	5.27
7.	Montelukast + Levocetirizine	8	2.48	4	1.24	12	3.72
8.	Gabapentin + Methylcobalamin	6	1.86	6	1.86	12	3.72
9.	Telmisartan + Hydrochlorthiazide	3	0.93	8	2.48	11	3.41
10.	Ciprofloxacin + Tinidazole	4	1.24	5	1.55	9	2.79

Out of 200 prescriptions 53% prescriptions contained only 1 FDC drug, 35% contained 2 FDC drugs, 8.5% contained 3 FDC's drugs and 3.5% contained 4 FDC's drugs. Table 3

Table 3 Number of FDC'S per prescription

No of Drug	PATIENT GENDER				Total No of Prescription	
	MALE		FEMALE			
	N	%	N	%	N	%
1	55	27.5	51	25.5	106	53
2	32	16	38	19	70	35
3	12	6	5	2.5	17	8.5
4	5	2.5	2	1	7	3.5
Total	104	52	96	48	200	100

The prescription analysis for drug interactions revealed that 21% of patients had at least one interaction. Total of 33 drug interaction were found in study population. Among them 52% were pharmacokinetic followed by 34.01% unknown and 15.12% of pharmacodynamic drug interactions. Table 4

Table 4: FDC'S drugs showing type of interaction

Type of interaction	Male		Female		Total No of interaction	
	n	%	n	%	n	%
Absorption	1	3.03	0	0	1	3.03
Antagonism	3	9.09	0	0	3	9.09
Execration	0	0	1	3.03	1	3.03
Metabolism	8	24.24	4	12.12	12	36.36
Synergism	3	9.09	2	6.06	5	15.12
Unknown	8	24.24	3	9.09	11	34.01
Total	**23**	**69.69**	**10**	**30.30**	**33**	**100**

The most common drug interaction was found to be amlodipine and atenolol (30.3%), which can be managed by dose adjustment. The FDCs

having interacting combination is listed in Table 4.

Table 5: FDC's drugs have interacting combination.

S.No	FDC'S	SEVERITY	PATIENT GENDER				Total	
			MALE		FEMALE			
			n	%	n	%	n	%
1.	Amlodipine + Atenolol	Moderate	3	9.09	7	21.2	10	30.3
2.	Aspirin + Clopidogrel	Major	3	9.09	0	0	3	9.1
3.	Isoniazid + Rifampin	Major	1	3.03	2	6.1	3	9.1
4.	Pyrazinamide + Rifampin	Major	1	3.03	2	6.1	3	9.1
5.	Rosuvastatin + Fenofibrate	Major	0	0	2	6.1	2	6.1
6.	Amlodipine + Metoprolol	Moderate	0	0	1	3.1	1	3.1
7.	Atorvastatin + Fenofibrate	Moderate	1	3.03	0	0	1	3.1
	Total interaction		**9**	**27.2**	**14**	**42.2**	**23**	**69.7**

8. From the total prescription analyzed, FDCs of antibiotic followed by antihypertensive and antidiabetic is found to higher. Among antibiotic 40 FDC were irrational followed by 22 in antihypertensive. Among the analyzed prescription, five banned drugs were observed that combination of paracetamol with tramadol in which paracetamol is 500 mg. Combination of paracetamol shouldn't exceed 325mg. The irrational prescribing is given in Table 5.

Most of the FDCs prescribed were antibiotics (18.01%) followed by antihypertensive (12.73%) and antidiabetic (10%). Most commonly prescribed FDCs were aspirin/atorvastatin (7.45%) and rabeprazole/domperidone (7.45%) in the 200-prescription analyzed.

From the total prescription analyzed, FDCs of antibiotic followed by antihypertensive and antidiabetic is found to higher. Among antibiotic 40 FDC were irrational followed by 22 in antihypertensive. Among the analyzed prescription, five banned drugs were observed that combination of paracetamol with tramadol in which paracetamol is 500 mg. Combination of paracetamol shouldn't exceed 325mg. Central drug standard control organization (CDSCO) on 23rd September 2011 issued a circular to all state drug controllers stating not to grant fresh licenses or renewal of licenses of combination products containing paracetamol more than 325 mg per tablet or capsule46. Irrational FDCs is a menace worldwide. Presently, exact data reported from India is not known. Hence, the study was carried out to observe the scenario of prescribing FDCs in the India. The study showed the trend towards prescribing irrational FDCs.

CONCLUSION

This study attempted to evaluate the medication safety of fixed dose combination drug in inpatient hospital setting. The availability of a number of FDCs commercially coupled with a lack of awareness of their rational use; promote the overuse of FDCs in medical stores in India. Of the 200 patients analyzed from in-patient departments, it was observed that hospital physicians prescribed fixed dose combination drugs from essential drug lists. The high rate of irrational prescribing of FDCs in cardiovascular drug therapy is a matter of concern. Awareness and education about irrational FDCs, FDCs containing banned or controversial ingredients will help develop a rational prescribing practice among prescribers. Monitoring of marketed FDCs and a regulation of their use is recommended to minimize the misuse of FDCs.

Most of the FDCs were prescribed for the chronic diseases like hypertension and diabetes mellitus. This practice will improve the medication adherence and overall costs of health care system. The fixed dose combination was found to be cost effective in most of the prescription. This study helped in understanding the mechanism, severity and management of common fixed dose drug interaction in in-patients' prescription. This may help in improving the safe and effective use of drugs in hospital. The use of the drug interaction checker software has greatly aided the study by assessing the findings mentioned above more easily; this would have been harder to achieve if done manually. This study concluded that the pharmacists can play significant role in assessing and controlling drug interaction.

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