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Prescribing Pattern of Fixed Dose Combinations Focus on Cardiovascular Drugs in Out Patient Department of Private Hospitals

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Abstract: This study was carried out to find the drug prescribing pattern and rationality of cardiovascular Fixed Dose Combinations (FDCs) at out patient department of private hospitals in East Godavari District andhrapradesh, India. Prescriptions of 620 patients suffered by cardiovascular diseases were collected over a period of five months and analysed for average number of drugs per prescription. Collected prescriptions were screened for fixed dose combinations and it classified according to patient's age, gender, duration of drug therapy, cost effectiveness was compared with monotherapy, dosage forms, therapeutic category and dose strength was taken into consideration for evaluate prescribing pattern. Average number of drugs per prescription was 3.65±0.08. Out of 620 cardiovascular prescriptions 234 prescriptions found to have FDCs. In 234 (37.7%) prescriptions, 17 different FDCs were prescribed. Among 234 FDC prescriptions, 124 (52.9%) FDC prescriptions were prescribed for the age group 51-60 years. All the cardiovascular FDCs were prescribed in oral solid dosage forms. Majority of FDCs (46.2%) were prescribed for 1-2 months. In 17 different FDCs, 14 (82.4%) were belongs to antihypertensive category. Out of 17 FDCs analysed, 76.4% were found to be more cost effective than their total cost of individual components. For few FDCs like Telmisartan with Hydrochlorothiazide (HCTZ), Enalapril with HCTZ, Bisoprolol with HCTZ, the total cost of combination was found to be less than that of FDCs. Most of the cardiovascular prescriptions contain Fixed Dose Combinations (FDCs) and most of the FDCs were cost effective but out of total FDCs studied none of them was in accordance with WHO essential medical list and National List of Essential Medicine. So, the rationality behind these combinations was questionable. It seems to be further more clinical trials need for these FDCs to substantiate their safety and efficacy.

Key words: Prescribing practice, rationality, cardiovascular prescriptions, cost effectiveness, fixed dose, patient compliance

INTRODUCTION

Fixed dose combinations contain two or more drugs in fixed ratio to each other in a single dosage form (Anand *et al*., 2008). Most patients are on more than one drug. The

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concomitant use of two or more drugs adds to the complexity of individualization of therapy. The dose of each drug should be adjusted to achieve the optimal benefit otherwise patient compliance is difficult to achieve. To obviate the latter problem, many fixed dose combinations are marketed (Kastury *et al*., 1999). Prescribing more than one drug for a particular ailment has become a very common practice among physicians (Chakraborti, 2007). Whether the pharmaceutical manufacturers make the Fixed Dose Combinations (FDCs) because of demand by the physician or physician prescribes multiple drugs because these dosage forms are easily available is a highly debatable issue (Poudel *et al*., 2008).The best option to treat hypertension is to use more than one drug either as multiple individual drugs or a fixed dose combination therapy (Stanton and Ried, 2002). The use of fixed-dose combinations is a widespread clinical practice in the treatment of various cardiovascular disorders. Frequently involving combination therapy is needed to achieve the recommended BP goals of <140/90 mmHg for most patients and <130/80 mmHg for high-risk patients (Neutel, 2008). Some FDCs can impose unnecessary financial burden, increased adverse effects, as well as hospitalization and decreased quality of life (Pradeep and Purohit, 2008).In 2005, cardiovascular diseases caused 17.5 million deaths worldwide, which are 3.3 times more than AIDS, tuberculosis and malaria combined (Gines and Fuster, 2009). Cardiovascular disease is the world's number one killer disease, responsible for one in every three deaths (Panda *et al*., 2006). As per a report of the WHO (2007), an estimated 17 million people die of Cardiovascular Disease (CVD), particularly heart attack and stroke, every year. The CVD is a group of disorders that includes heart disease (i.e., myocardial infarction and angina), stroke, hypertension, Congestive Feart Failure (CHF), hardening of the arteries and other disorders of the circulatory system. The main aim of the present study was to assess the percentage of fixed dose combination prescribed to cardiovascular disease patients and to evaluate whether these FDCs for rationality.

MATERIALS AND METHODS

Operational Modality

A prospective study was carried out over five months (July 2009 to November 2009) in the out patient departments of private clinics and hospitals around East Godavari District Andhrapradesh. Prescriptions were collected from the patients suffered with cardiovascular disorders. The total prescriptions were analyzed for number of drugs per prescriptions and then the prescriptions were screened for FDC for their evaluation. The parameters of audit for evaluation for Fixed Dose Combination (FDCs) were:

- Patient's demographics (age, sex etc.)
- Dose strength and dosage schedule
- Duration of therapy
- Therapeutic category
- Cost of the FDC compared with total cost of individual components

The dose of the individual Active Pharmaceutical Ingredients (APIs) was verified from standard textbooks and references in pharmacology and therapeutics. The cost data of the individual components, as well as the FDCs, was obtained from CIMS (Current Index of Medical Specialties) and IDR medclick software (Version 120.04.05.06 Comprehensive and Reliable drug reference).

Assessment of Rationality

Commonly prescribed cardiovascular combinations are arranged according to the percentage of prescribing pattern and their rationality was assessed by the latest WHO model List of EML (15th List, March 2007) and National List of Essential Medicines (NLEM).

RESULTS

About 620 cardiovascular prescriptions were collected from the patients with cardiovascular disorders. Totally 2,265 drugs were prescribed with a mean of 3.65±0.08 per prescription. As shown in Table 1, 69.7% (432) patients were prescribed up to 4 medicines and the rest 30.3% were prescribed from 5 to 9 medicines. More than 2 drugs per prescriptions may result into polypharmacy (Table 1).

Prescribing Pattern of Cardiovascular Fixed Dose Combinations

Out of 620 cardiovascular prescriptions screened, 234 prescriptions were found to have FDCs, in 234 (37.7%) prescriptions, 17 different FDCs were prescribed, in that 17 FDCs, Amlodipine and Atenolol was most commonly prescribed 30 (12.8%) followed by Aspirin and Clopidogrel 26 (11.1%), Telmisartan and Hydrochlorothiazide 23 (9.8%), Losartan and Hydrochlorothiazide 21 (8.9%), Enalapril and Amlodipine 16 (6.8%), Metoprolol and Hydrochlorothiazide 16 (6.8%), Ramipril and HCTZ 14 (5.9%), Enalapril and Hydrochlorothiazide 13 (5.5%), Amlodipine and Losartan 12 (5.1%), Atorvastatin and Fenofibrate 12 (5.1%), Nebivolol and Amlodipine 10 (4.2%), Propranolol and Hydrochlorothiazide 10 (4.2%), Lisinopril and hydrochlorothiazide 9 (3.8%), Losartan and Ramipril 7 (2.9%), Amlodipine and Lisinopril 6 (2.5%), Bisoprolol and Hydrochlorothiazide 6 (2.5%), finally Atorvastatin and Ezetimibe 3 (1.2%). Prescribing pattern of cardiovascular fixed dose combinations and their active pharmaceutical ingredients strength was represented in Table 2.

Age

Among 234 FDC prescriptions, more number of FDC prescriptions were prescribed for the age group of 51-60 years {124 (52.9%)}, followed by 41-50 years {53 (22.7%)}, 61-70 years {48 (20.5%)}, 71-80 years {7 (0.03%)}, 30-40 years {2 (0.009%)} (Table 3). Age group of 51-60 years old patients were mostly affected by cardiovascular disorders.

Gender

In 234 FDC prescriptions, 147 FDC prescriptions were prescribed for males and 87 FDC prescriptions were prescribed for females with cardiovascular disorders.

Table 1: Number of drugs prescribed

No. of drugs	No. of prescriptions	No.
1	48 (7.74)	432 (69.7)
2	127 (20.50)	
3	132 (21.29)	
4	125 (20.16)	
5	102 (16.45)	188 (30.3)
6	52 (8.38)	
7	28 (4.52)	
8	5 (0.81)	
9	1 (0.16)	
Total	620 (100)	

Values in brackets indicate percentage

Table 2: Prescribing patterns of cardiovascular fixed dose combinations

Cardiovascular FDCs	FDCs prescribed (most common brand name)	Strength (mg)	No. of prescriptions	Prescribed pattern (%)
Amlodipine+Atenolol	Amlong A	5+50	30	12.8
Aspirin+Clopidogrel	Clopitab A	75+75	26	11.1
Telmisartan+Hydrochlorothiazide	Telma H	40+12.5	23	9.8
Losartan+Hydrochlorothiazide	Losar-H	50+12.5	21	8.9
Enalapril+Amlodipine	Amtas-E	5+5	16	6.8
Metoprolol+Hydrochlorothiazide	Betaloc-H	100+12.5	16	6.8
Ramipril+hydrochlorothiazide	Ramace H	2.5+12.5	14	5.9
Enalapril+Hydrochlorothiazide	Enace-D	10+25	13	5.5
Amlodipine+Losartan	Amlopress-Z	5+50	12	5.1
Atorvastatin+Fenofibrate	Atorlip-F	10+67	12	5.1
Nebivolol+Amlodipine	Nebinex AM	5+5	10	4.2
Propranolol+Hydrochlorothiazide	Ciplar-H	40+25	10	4.2
Lisinopril+Hydrochlorothiazide	Lipril-H	5+12.5	9	3.8
Losartan+Ramipril	Loram	50+5	7	2.9
Amlodipine+Lisinopril	Lipril-AM	5+5	6	2.5
Bisoprolol+Hydrochlorothiazide	Lodoz	2.5+5	6	2.5
Atorvastatin+Ezetimibe	Atorlip-EZ	10+10	3	1.2

Table 3: Prescribing of cardiovascular fixed dose combinations according to age group

Age group (in years)	No. of prescriptions	Percentage
30-40	2	0.009
41-50	53	22.700
51-60	124	52.900
61-70	48	20.500
71-80	7	0.030

Dosage Form

All the cardiovascular FDCs were prescribed in oral solid dosage forms.

Duration of Therapy

Out of 234 cardiovascular FDC prescriptions, 44 FDC prescriptions (18.8%) were prescribed up to 7 days, eighty two FDCs (35%) were prescribed for 8-15 days, majority of FDCs (108 drugs, 46.2%) were prescribed for 1-2 months.

Therapeutic Category

Among the 17 cardiovascular fixed dose combinations, majority of FDCs 14 (82.4%) were belongs to antihypertensive category. Two of them belong to antilipidemics, one is Antiplatelet agent. In all the FDCs, individual drugs had different mechanism of action. So the synergistic action of drug was enhanced (Table 4). Therapeutic classification was taken from standard pharmacology and therapeutics books.

Cost Effective Analysis

Cost effective analysis was carried out by comparing total cost of each individual components with the cost of fixed dose combination. The cost of individual drugs and fixed dose combinations was obtained from CIMS, IDR (Indian Drug Review) and Drug today. Of the 17 FDCs analyzed, 76.4% were found to be more cost effective than their total cost of individual components. For few FDCs like Telmisartan with HCTZ, Enalapril with HCTZ, Bisoprolol with HCTZ, the total cost of combination was found to be less than that of FDCs. (Fig. 1).

Determination of Rationality

WHO essential model list (March 2007) and national list of essential medicines were taken into consideration for determination of rationality of cardiovascular fixed dose

Table 4: Therapeutic category of FDC prescribed

Cardiovascular FDCs	Pharmacological classification	Therapeutic category
Amlodipine+Atenolol	Calcium channel blocker+β blocker	Antihypertensive
Aspirin+Clopidogrel	Platelet aggregation inhibitor+Platelet aggregation inhibitor	Antiplatelet
Telmisartan+Hydrochlorothiazide	Angiotensin II antagonist+Thiazide diuretics	Antihypertensive
Losartan+Hydrochlorothiazide	Angiotensin II antagonist+Thiazide diuretics	Antihypertensive
Enalapril+Amlodipine	ACE inhibitors+Calcium channel blocker	Antihypertensive
Metoprolol+Hydrochlorothiazide	β blocker+Thiazide diuretics	Antihypertensive
Ramipril+Hydrochlorothiazide	ACE inhibitors+Thiazide diuretics	Antihypertensive
Enalapril+Hydrochlorothiazide	ACE inhibitors+Thiazide diuretics	Antihypertensive
Amlodipine+Losartan	Calcium channel blocker+Angiotensin II antagonist	Antihypertensive
Atorvastatin+Fenofibrate	HMG CoA reductase inhibitors+Fibric acid derivatives	Antilipidemics
Nebivolol+Amlodipine	β blocker+Calcium channel blocker	Antihypertensive
Propranolol+Hydrochlorothiazide	β blocker+Thiazide diuretics	Antihypertensive
Lisinopril+Hydrochlorothiazide	ACE inhibitors+Thiazide diuretics	Antihypertensive
Losartan+Ramipril	Angiotensin II antagonist+ACE inhibitors	Antihypertensive
Amlodipine+Lisinopril	Calcium channel blocker+ACE inhibitors	Antihypertensive
Bisoprolol+Hydrochlorothiazide	β blocker+Thiazide diuretics	Antihypertensive
Atorvastatin+Ezetimibe	HMG CoA reductase inhibitors+Cholesterol absorption inhibitors	Antilipidemics

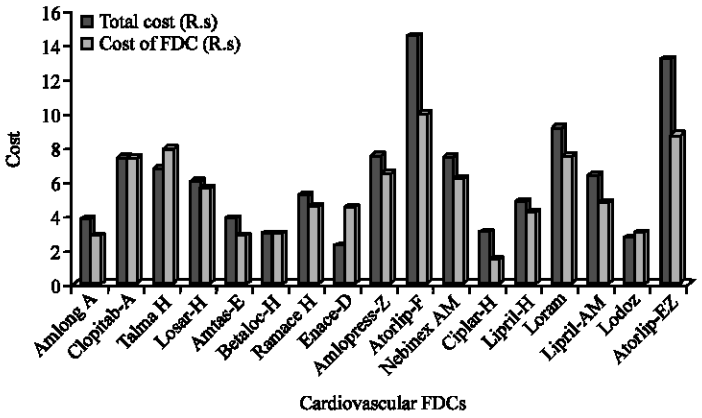

Fig. 1: Cost effective analysis

combinations. The result of the assessment showed that out of 17 commonly prescribed FDCs, none of the FDC was in accordance with both the lists.

DISCUSSION

Correct diagnosis of a disease and its management with drugs, constitute important aspects of patient care which is even more important in case of cardiovascular patients.There are many popular FDCs in the Indian pharmaceutical market, which have flourished in the last few years. The Indian drug control authority has issued notifications banning many FDCs. For this it is very prudent to study the prescribing practice of FDCs in cardiovascular diseases. In the present study, on the average 3.65 drugs were prescribed per patients with cardiovascular disorders which is little lower (0.07) when compare to similar study in Gujarat (Nazima *et al*., 2009).

In our present study, out of 620 cardiovascular prescriptions collected, 234 prescriptions had fixed dose combinations, in which Amlodipine + Atenolol combination was most widely

prescribed, a study of Gogtay and Mathew (1997) revealed that the fixed-dose combination of Amlodipine and Atenolol promises to be an attractive therapeutic option in the management of hypertension.

In our study, out of 234 cardiovascular FDC prescriptions, most of the FDCs belong to the antihypertensive category (82.4%). Present report was found to be similar to that of early findings (Young *et al*., 2000).

Fixed-dose combination decreases patient non-compliance and should be considered in patients with chronic conditions like hypertension for improving medication compliance which can translate into better clinical outcomes (Bangalore *et al*., 2007). In our present study 76.4% were found to be more cost effective than their total cost of individual components so it improves the patient compliance.

Evidence of safety and efficacy is of utmost importance when the two drugs are combined together as a single formulation. In the United States, an FDC is considered as a new drug and it has to be approved by the USFDA before it can be marketed, even though the individual components are available for concurrent use (Panda *et al*., 2006) Drugs and Cosmetics Act, 1940 also takes a similar stand issue.

CONCLUSION

In our study, we found that most of the cardiovascular prescriptions contain Fixed Dose Combinations (FDCs) and most of the FDCs were cost effective. The results of this study clearly demonstrated that the rationality behind these combinations was questionable. Even lot of clinical studies supported to Fixed Dose Combinations for cardiovascular diseases, they were not approved by WHO and NLEM. It seems to be more clinical trials need for these FDCs to substantiate their safety and efficacy. So this could be the subject of study for clinicians and/or pharmaceutical companies for determining the safety and efficacy of these FDCs.

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