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Original Research Article

Assessment of rational use of fixed dose combinations in hypertension in a tertiary care teaching hospital in north India

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ABSTRACT

Background: Fixed-dose combination (FDC) agents could be considered as an effective therapy in chronic illnesses like hypertension, which have multifactorial etiology. At present, many FDCs have come into the market without being assessed for their efficacy, safety and rationality by the drug regulatory authorities. The objective of the present study was to assess the rational use of fixed dose drug combinations in hypertension.
Methods: It was a cross-sectional observational study conducted in the cardiology outpatient department of ASCOMS and H, Sidhra, Jammu, Jammu and Kashmir from February 2016 to July 2016. In the study 92 prescriptions of hypertensive patients who were on anti-hypertensive fixed-dose drug combinations (FDCs) were recruited after thoroughly evaluated for inclusion and exclusion criteria. Data obtained includes the demographic profile of the patients, pattern of the prescribed FDCs in hypertension, evaluation of the rationality of the FDCs based upon the comprehensive seven-point criteria developed by Panda et al.
Results: In the present study, about sixteen different anti-hypertensive FDCs were observed in the prescriptions of 92 patients during six-month period. It was observed that about 93.75% of FDCs were dual drug combinations. Among the dual drug combinations, most commonly used combination was Olmesartan (ARB; Angiotensin receptor blocker) + Amlodipinine (Calcium channel blocker) in 17.4% of patients. It was also observed that among the 16 different anti-hypertensive fixed dose combinations analysed, 12 FDCs (75%) were found to be rational and 4 FDCs (25%) were found to be irrational.
Conclusions: In the present study it was found that 75% of the FDCs prescribed were rational and 25% were irrational. Therefore, before marketing the FDCs proper assessment of their efficacy, safety and rationality should be done.

Keywords: Fixed-dose drug combinations, Hypertension, Irrational, Rational

INTRODUCTION

A fixed dose combination (FDC) comprises of two or more active drugs in a single dosage form.[1] According to Drugs and Cosmetics Act, 1940, a new FDC is considered as "new drug", hence, it should undergo clinical trials before entering the market.[2] For, successful treatment of chronic conditions like hypertension, patients need to be compliant to the treatment regimens. Fixed-dose combinations have been designed to simplify the medication regimen and potentially improve compliance.[3] At the same time, two drugs having complementary mechanism of action in a single formulation in the form of FDC may provide advantages of each type of agent and reduce some of the adverse-effects of high-dose of individual drugs.[4] Thus, fixed-dose combination agents which have complementary mechanism of action could be considered as an effective

therapy in chronic illnesses like hypertension, which have multifactorial etiology.[5]

Combination therapy is most often employed in patients with hypertension in whom adequate BP (Blood pressure) lowering is not achieved with monotherapy. In many previous studies it has been observed that two-drug antihypertensive combination can be successful in controlling the BP in 60% of hypertensive individuals.[6] However, when the BP of the patients can't be controlled on two-drug combinations, triple fixed-dose combinations are employed. Three-in-one fixed dose combination of reserpine, apresoline and hydrochlorthiazide was the first triple fixed dose formulation to be marketed in US. Tribenzor, a triple fixed dose combination consisting of amlodipine, olmesartan medoximil and hydrochlorthiazide was approved by FDA in July 2010, in obese patients except the normal hypertensive patients.[7]

At present times, however, the issue of rationality of FDCs has grown up as more and more of the combination products have been marketed by the pharmaceutical companies without being proper establishment of their safety and efficacy. Thus, many FDCs have come into the market without being prior approval by the drug regulatory authorities.[8-10] Thus, irrational prescribing of FDCs can lead to adverse drug reactions, higher treatment cost, emergence of resistant organisms and sometimes treatment failure.[11] The eighteenth WHO model list of essential medicines contains 374 drugs with only 26 approved FDCs while in NLEM (National essential medicine) list of India, there are about 348 essential medicine and 16 approved FDCs are present.[6,12,13]

In spite of the drawbacks associated with the FDCs, there are certain merits offered by these combinations products which include simpler dosage schedule that improves compliance, convenience in prescribing, blood pressure targets will be attained more quickly and reduced pill burden.[14-17] Thus, in view of this the present study was undertaken to evaluate the prescribing pattern of fixed-dose combinations in hypertension and to assess their rationality at a tertiary care teaching hospital of north India.

METHODS

It was a cross-sectional observational study conducted in the cardiology outpatient department of Acharaya Shri Chander College of Medical Sciences and Hospital (ASCOMS&H), Sidhra, Jammu, Jammu and Kashmir from February 2016 to July 2016. In the study 92 prescriptions of hypertensive patients who were on anti-hypertensive fixed-dose drug combinations (FDCs) were recruited after thoroughly evaluated for inclusion and exclusion criteria.

Inclusion criteria

- All the hypertensive patients of either sex with age ≥18 years attending the cardiology outpatient
- And who were on fixed-dose anti-hypertensive drug treatment.

Exclusion criteria

- The patients with age <18 years with incomplete medical records and who were on monotherapy for hypertension
- And patients who were not willing to participate in the study
- Pregnant and lactating women.

Institutional Ethical Committee approval was obtained before initiating the study. The written informed consent was also obtained from the patients prior to the commencement of the study.

Data obtained by scrutinizing the prescriptions of the outpatients visiting the cardiology department included the demographic profile of the patients, pattern of the prescribed FDCs in hypertension, Evaluation of the rationality of the FDCs based upon the comprehensive seven-point criteria developed by Panda et al, assessment of active pharmacological ingredient present and approval by drug regulatory authorities.[18] In the seven-point criteria developed by Panda et al, max. score is 14 with each criterion carrying a score of 2 and score ≥8 is considered rational.

RESULTS

In the present study, 92 patients who were on anti-hypertensive fixed dose drug combinations were enrolled in the study. Out of 92 patients, 52 (56.5%) were males and 40 (43.4%) were females.

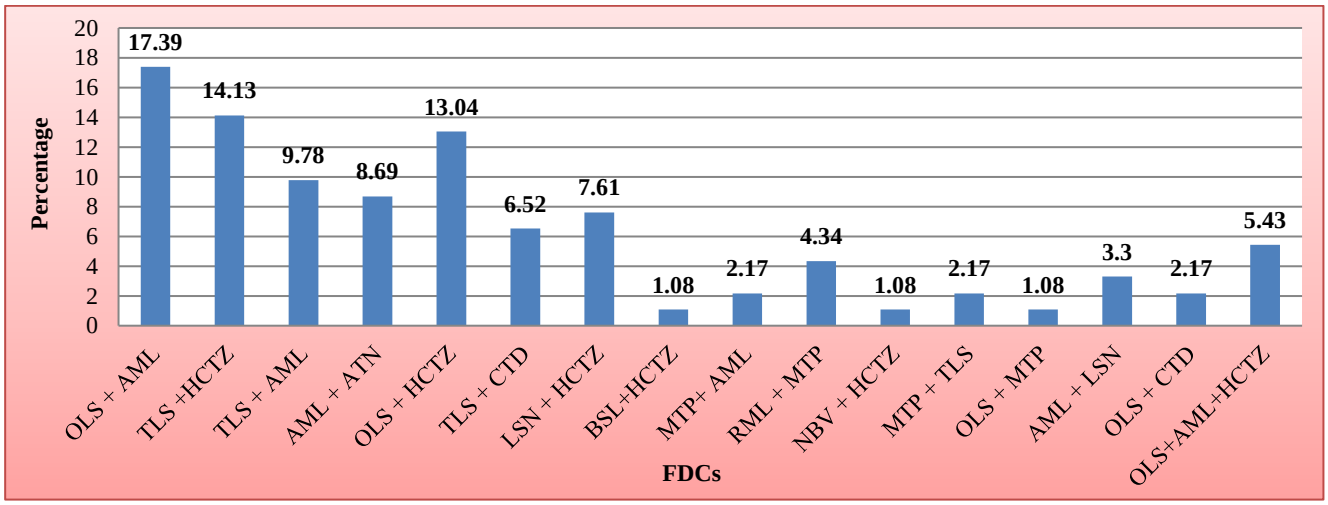
In the present study, about sixteen different anti-hypertensive FDCs were observed in the prescriptions of 92 patients during six-month period. The detail of these FDCs including their brand names, active pharmacological ingredients present with their strengths is mentioned in Table 1. The percentage of fixed-dose combinations prescribed in these 92 hypertensive patients is shown in Figure 1.

It was observed that about 93.75% of FDCs were dual drug combinations. Only one triple drug FDC was observed in the study in 5.4% of patients. Among the dual drug combinations, most commonly used combination was Olmesartan (ARB; Angiotensin receptor blocker) + Amlodipinine (Calcium channel blocker) in 17.4% of patients followed by Telmisartan (ARB; Angiotensin receptor blocker) + Hydrochlorthiazide (Diuretic) in 13.9% of patients.

Table 1: Types of commonly prescribed FDCs.

Brand names	Antihypertensive FDCs	Strengths
Olmezest AM	Olmesartan + Amilodipine	20mg/5mg
		40mg/5mg
Telmiget H	Telmisartan +Hydrochlorthiazide	40mg/12.5mg
		80mg/12.5mg
Telmiget AM	Telmisartan + Amilodipine	40mg/5mg
		80mg/5mg
Amlopress AT	Amilodipine + Atenolol	5mg/50mg
Olmezest H	Olmesartan + Hydrochlorthiazide	20mg/12.5mg
		40mg/12.5mg
Eritel CH	Telmisartan + Chlorthalidone	40mg/12.5mg
		80mg/12.5mg
Losar H	Losartan + Hydrochlorthiazide	50mg/12.5mg
Concor Plus	Bisoprolol+ Hydrochlorthiazide	5mg/12.5mg
Prolomet AM	Metoprolol+ Amilodipine	25mg/5mg
		50mg/5mg
Cardace Meto	Ramipril + Metoprolol	2.5mg/25mg
		5mg/50mg
Nebicard H	Nevibolol + Hydrochlorthiazide	5mg/12.5mg
Metosartan	Metoprolol + Telmisartan	50mg/40mg
Olmezest Beta	Olmesartan + Metoprolol	20mg/25mg
Amlokind L	Amilodipine + Losartan	5mg/50mg
Olmezest CH	Olmesartan + Chlorthalidone	20mg/12.5mg
		40mg/12.5mg
Triolmezest	Olmesartan+Amilodipine+Hydrochlorthiazide	20mg/5mg/12.5mg

The rationality of the FDCs was assessed using seven point criteria developed by Panda et al which indicated all dimensions of defining a rational FDC. The maximum scoring of seven point criteria is 14 with each criterion carrying a score of 2 and score ≥8 is considered rational. Scoring of the different FDCs prescribed in the study is shown in Table 2. It was also observed that among the 16 different anti-hypertensive fixed dose combinations analyzed, 12 FDCs (75%) were found to be rational and 4 FDCs (25%) were found to be irrational. It was also found that in 87.5% of FDCs, the individual components were present in any one or both the EML of WHO or NLEM of India. However, in 12.5% of FDCs, the individual components were absent in both the lists. The irrational FDCs prescribed in the study are enlisted in Table 3.



Olmesartan: OLS; Telmisartan: TLS; Amlodipine: AML; ATN: Atenolol; LSN: Losartan; RML: Ramipril; HCTZ: Hydrochlorthiazide; Chlorthalidone: CTD; Nebivolol: NBV; Bisoprolol: BSL.

Figure 1: Distribution of prescribed FDCs in hypertensive patients.

Table 2: Scoring of FDCs by seven-point criteria.

Antihypertensive FDCs	Scoring
Olmesartan + Amilodipine	13
Telmisartan +Hydrochlorthiazide	13
Telmisartan + Amilodipine	13
Amilodipine + Atenolol	12
Olmesartan + Hydrochlorthiazide	13
Telmisartan + Chlorthalidone	12
Losartan + Hydrochlorthiazide	14
Bisoprolol+ Hydrochlorthiazide	10
Metoprolol+ Amilodipine	12
Ramipril + Metoprolol	7
Nevibolol + Hydrochlorthiazide	7
Metoprolol + Telmisartan	7
Olmesartan + Metoprolol	7
Amilodipine + Losartan	12
Olmesartan + Chlorthalidone	12
Olmesartan+Amilodipine+Hydrochlorthiazide	13

Table 3: List of irrational FDCs.

Antihypertensive FDCs
Ramipril + Metoprolol
Nevibolol + Hydrochlortiazide
Metoprolol + Telmisartan
Olmesartan + Metoprolol

DISCUSSION

In developing countries like India, the pharmaceutical companies are introducing newer combinations (FDCs) at an alarming rate into the market. Most of these FDCs are being promoted without proper bioavailability studies. Therefore, market has been flooded up with many irrational combination products. The rationality of FDCs should be established at the early phase of their development, as it is very difficult to establish the bioavailability studies of active pharmaceutical ingredients (APIs) in an FDC. Thus, it is very urgent to have some comprehensive criteria to assess the rationality of these FDCs.[6]

In the present study, the results revealed that there were about 16 different types of anti-hypertensive FDCs prescribed to 92 patients. The most common combination was olmesartan + amlodipine in 17.3% of patients followed by telmisartan + hydrochlorthiazide in 13.9% of patients. On assessment of the rationality of these FDCs by seven-point criteria it was found that 75% of FDCs were rational and 25% were irrational. These results are consistent with the previously published studies.[6]

Successful treatment of chronic conditions like hypertension requires lifelong treatment and involves numerous medications to be taken daily. Combining the drugs together decreases the dose of individual drug and reduces the adverse effects.[19,20] The use of fixed-dose combination therapy, in the form of polypill, for cardiovascular prevention was first proposed by Wald et al.[21] A study conducted by Gerbino et al, showed that FDCs are associated with higher adherence rates versus ACE inhibitors and calcium channel blockers taken individually for the treatment of hypertension.[22] A meta-analysis by Bangalore et al, revealed similar results of FDCs reducing risk of medication noncompliance in chronic conditions like hypertension.[3] According to another study, combining several antihypertensive drugs at low doses is likely to be more effective than high dose with a single drug.[23]

It was already documented in the previous studies that active pharmaceutical ingredients present in FDCs should have complementary mechanism of action. This statement also fits good in case of FDCs prescribed in the treatment of hypertension in which APIs should have an additive BP lowering effect by acting on complementary mechanisms involved in the pathogenesis of HT and blocking the counter regulatory pathways triggered by one another. Such rationale of combination can be seen in most of the FDCs in the present study except the combination of RAAS inhibitor (ACEI/ARBs) with a beta blocker.[6]

In the present study, three combinations of (RAAS inhibitor + Beta Blocker) were observed. In this study about 6.52% of hypertensive patients without heart diseases were prescribed with this combination. The use of such a combination for treating hypertension only is questionable as both the drugs in the combination act through same mechanism (RAAS inhibition). ACEI/ARBs + Beta blockers are generally combined together as FDC and given in patients of MI and heart failure but the use of such FDCs for the sole purpose of hypertension is not considered rational as only modest decrease in BP occurs with the use of this combination.[24]

The other FDCs like the Dihydropyridine CCBs and β-blocker is considered to be an acceptable combination for treatment of hypertension. However, non-dihydropyridine CCBs such as verapamil and diltiazem should be avoided in combination with β-blocker because they can increase the chances of A-V block and bradycardia.

Similarly, β-blocker and diuretic FDC is classified as an acceptable combination for treating uncomplicated hypertension, its use is out of favour because of new-onset diabetes. There are also some FDCs like Nebivolol/s-amlodipine which is a favourable combination in terms of excellent glycemic and lipid profile of Nebivolol and chirally pure s-amlodipine but there are no ample studies done on the combination outweighing its benefit to risk.[6] The present study has some limitations being of lesser duration and of less sample size. Therefore, long term studies are needed to be conducted involving a greater number of patients so that more number of FDCs can be analyzed that whether they are rational or not.

CONCLUSION

In the present study it was found that 75% of the FDCs prescribed were rational and 25% were irrational. Thus, although the use of FDCs in chronic illnesses like hypertension increases the compliance with achieving the target BP at lower doses of each individual ingredient; the irrational FDCs are a matter of concern. Therefore, before marketing the FDCs proper assessment of their efficacy, safety and rationality should be done.

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