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AN EVALUATION OF FIXED DOSE COMBINATIONS (FDCs) USED FOR TREATMENT OF DIABETES IN INDIAN MARKET

Supreet Kamni[1]*, Akram A Naikawadi[2], Anant Khot[3]

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[1]Post graduate,
[2]Professor and Head,
[3]Associate Professor,
Department of Pharmacology,
BLDEU's Shri B.M. Patil Medical College and Research Centre,
Vijayapur, Karnataka, India.

***Corresponding author:**
Dr. Anant Khot,
[2]Associate Professor,
Department of Pharmacology, BLDEU's Shri B.M. Patil Medical College and Research Centre, Vijayapur, Karnataka, India.
Email:supreetkamni@gmail.com

ABSTRACT

Objective: - To analyse the rationality of various FDCs used in the treatment Diabetes Mellitus and to find out the irrational FDCs existing in Indian market. Material and Methods: - Study Design: Analytical study. Data on FDC's available in the Indian market was collected from Current Index of Medical Specialities (CIMS) and Monthly Index of Medical Specialities (MIMS) and their rationality was analysed using a pretested tool based on FDCs listed in WHO essential list of medicines and National List of Essential Medicines (NLEM), others based on their pharmacodynamic activity, Pharmacokinetic parameters and significant drug interactions occurring due to API (Active pharmaceutical ingredients) contained within the product Result: A total of 18 combinations were analysed, among those 11 combinations were irrational. Conclusion: Predominantly irrational FDCs are being circulated in the Indian market hence through analyses by prescribers is needed before prescribing to patients in order to avoid ADR. This calls for a close scrutiny of marketed FDCs and educating prescribers to use them with great care and caution also indicates a serious review of regulatory framework for drug manufacturing and marketing.

KEYWORDS: Fixed Dose Combinations, antidiabetics, irrational.

INTRODUCTION

Diabetes mellitus (DM), commonly referred to as diabetes is a group of metabolic diseases in which there are high blood sugar levels over a prolonged period. Globally, an estimated 422 million adults are living with diabetes mellitus, according to the latest 2016 data from the World Health Organization (WHO) [1].

Fixed dose combinations (FDCs) refer to products containing two or more active drugs used in a single dosage form for a particular indication [2]. Prescribing Fixed Dose Combinations (FDCs) in Diabetes mellitus treatment is a routine practice. Although FDCs are associated with many advantages like synergistic action, reduced adverse effects, reduced pill burden, cost of the treatment and improved patients compliance [3] but certain disadvantages like incompatible pharmacokinetics, inflexible dose ratio and increased toxicity are limiting factors.

FDC is acceptable when the combination has proven advantage over single compound administered separately in terms of therapeutic efficacy or safety [4] Considering better patient compliance more and more physicians favour FDCs. As a result, pharmaceutical companies utilize this golden opportunity and market more and more combinations of which many of them are irrational.

MATERIALS & METHODS

Study Design: observational and Analytical study

Sample: Data on FDC's available in the Indian market was collected from Current Index of Medical Specialities (CIMS) and Monthly Index of Medical Specialities (MIMS).

Methods: Rationality was analysed using a pretested tool based on FDCs listed in WHO essential list of medicines

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Tool to assess the rationality of fixed dose combinations

1. Active pharmacological ingredient along with strength .....
   .....
   .....

2. API

	API		
1	Approved by DCGI	Yes (+1)	No (−1)
2	Ingredient: Banned or Controversial	Yes (−1)	No (+1)

API = Active pharmacological ingredient, DCGI = Drug controller general of India

3. Listing in EML WHO/National/Both/None (+1) (0)
4. Efficacy (text book/reference book/pub med/medline/ other)

1	API	Yes (+1)	No (0)
2	FDC	Yes (+1)	No (0)

API = Active pharmacological ingredient, FDC = Fixed dose combination

5. Safety (text book/reference book/pub med/medline/other)

1	API	Yes (+1)	No (0)
2	FDC	Yes (+1)	No (0)

API = Active pharmacological ingredient, FDC = Fixed dose combination

6. Pharmacokinetic (absorption/distribution/metabolism/ excretion/BA/BE/t ½)
   - Interaction Favourable/Unfavourable/Not affected (+1) (−1) (0)

7. Pharmacodynamic-M/A of each ingredient Similar (0)/Different (+1)
8. Advantage of FDC
   - Reduced Yes (+1) No (0)
   - Less ADR Yes (+1) No (0)
   - Convenient Yes (+1) No(0) (frequency or pill count)

Total score: 12

Score ≥7: Rational FDC Score ≤6: Irrational FDC

& national list of essential medicines (NLEM) - on their pharmacodynamic activity, Pharmacokinetic parameters & significant drug interactions occurring due to API (Active pharmaceutical ingredients) contained within the product [5,6].

Analysis: All the quantitative variables have been expressed as mean and standard deviation and qualitative variables are expressed as percentages and proportions.

RESULTS

Total 18 FDCs were analysed. It was observed that 7 of the FDCs in antidiabetes drugs meet the criteria for rationality but there are 11 combinations found to be irrational.

Glibenclamide + metformin

Gliclazide + metformin

Glimipride +metformin

Glimipride + metformin + pioglitazone

Glipizide + metformin

Glibenclamide + metformin + pioglitazone

Glibenclamide + metformin + volgibose

Glimipride + metformin + Ramipril

Glimipride + metformin + Ramipril + atrovastatin

Glimipride + metformin + atrovastatin

Metformin + fenofibrinate

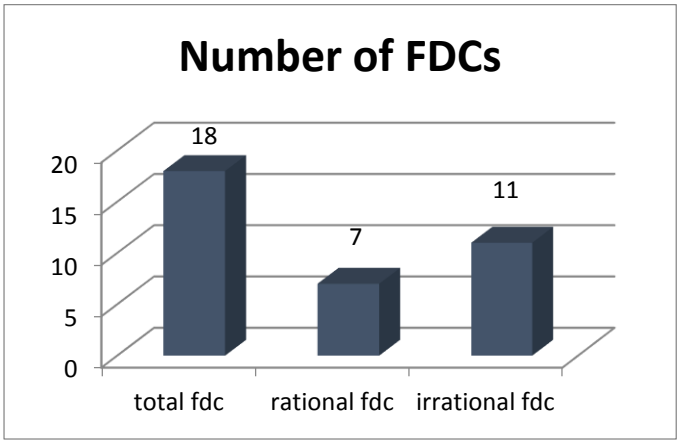

Fig 1. Shows the rational and irrational FDC

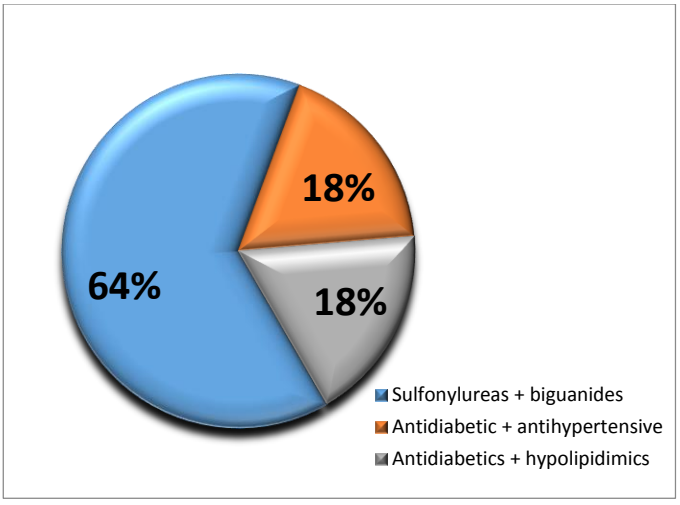

Fig 2. Shows percentages of different FDC's used irrationally

DISCUSSION

Sulfonylureas + Biguanides:

Pharmacokinetics: After oral administration, glimepiride is completely (100%) absorbed from the GI tract. Studies with single oral doses in normal subjects and with multiple oral doses in patients with Type 2 diabetes have shown significant absorption of glimepiride within 1 hour after administration and peak drug levels (Cmax) at 2 to 3 hours. When glimepiride was given with meals, the mean Tmax (time to reach Cmax) was slightly increased (12%) and the mean Cmax and AUC (area under the curve) were slightly decreased (8% and 9%, respectively) [7].

Absorption of sulfoylureas is delayed by food and hyperglycemia

In view of time required to reach an optimal concentration in plasma, sulfonylureas are more effective when given 30min before food [8].

Antidiabetic + Antihypertensive + Hypolipidimics

A study conducted by Nisharan et. Al. showd that FDC when given in combination did not reach peak action of metformin, atrovastatin, and absorption of the metformin was reduced to only 80%, and delayed the absorbtion time which indicated the presence of interaction between these components [9].

They also violate some of the principles of formulation of FDCs like;

a. Increased efficacy in comparison to the individual components given at the same dose,

b. The incidence of adverse reactions in response to treatment with the combination is lower than in that in response to any of the component actives given alone,

c. Improved adherence, simplified therapy,

d. the actives in a combination should have similar pharmacokinetics. [10].

CONCLUSION

To conclude around 62% of the FDCs were found irrational. Indeed, it is very unfortunate and unethical to expose the innocent patients to medicines with unproven efficacy and safety. This calls for a close scrutiny of marketed FDCs and educating prescribers to use them with great care and caution. This also indicates a serious review of regulatory framework for drug manufacturing and marketing.

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Conflicts of Interest: There are no conflicts of interest.

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