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EVALUATION OF RATIONALITY OF FIXED DOSE COMBINATIONS (FDCs) OF RESPIRATORY DRUGS AVAILABLE IN INDIAN MARKET

Pharmacology

Dr Abhilasha Rashmi Associate Professor, Department of Pharmacology, Second Floor, College Building, Lokmanya Tilak Municipal Medical College & General Hospital, Sion, Mumbai-22, Maharashtra

Dr Smita Mali* Assistant Professor, Department of Pharmacology, Second Floor, College Building, Lokmanya Tilak Municipal Medical College & General Hospital, Sion, Mumbai-22, Maharashtra *Corresponding Author

ABSTRACT

BACKGROUND: This study is done to assess the rationality of FDCs of respiratory drugs (drugs for treatment of asthma, chronic bronchitis, COPD and cough) available in Indian market. Antitubercular drugs are not considered.

METHODS: Data was collected from CIMS (October 2017-January 2018) that enlists most medicines commercially available in India during that period. Each FDC was checked for its presence in recent CDSCO and WHO essential medicines list and their rationality was assessed according to WHO Rationality Scoring Scale.

RESULTS: We found that only 6% FDCs were rational, 28% were irrational and 66% semi-rational. Also, we checked the FDC list approved by DCGI from 1961 till 12th January 2018 and found that only 16.2% of marketed FDCs are actually approved by DCGI.

CONCLUSION: A large number of respiratory semi-rational and irrational FDCs are available in Indian market. We need a close scrutiny of marketed FDCs and prescribers should be educated to use them with caution.

KEYWORDS

Rationality Scoring Scale, Rational, Semi-rational, Irrational

INTRODUCTION

Fixed Dose Combinations (FDCs) are defined by the World Health Organization as combination of two or more active ingredients in a fixed ratio of doses.[1] 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]

FDCs provide the advantage of combination therapy while reducing the number of prescriptions and the attendant administrative costs. Some FDCs can impose unnecessary financial burden, increased adverse effects, as well as hospitalization, and decreased quality of life. Fixed dose combinations are valuable only when they have been developed based on sound pharmacokinetic and pharmacodynamic criteria. The use of FDCs is a widespread clinical practice for various disease conditions. Since there is an increasing trend to develop and market these drugs, more than one third of all the new drug products introduced worldwide during the last decade were FDCs.[3] But the rationality status of many fixed dose combinations marketed in India is not clear.

According to a study done in 2012, the overall prevalence of asthma and chronic bronchitis was 2.05% (adults aged ≥15 years) and 3.49% (adults aged ≥35 years) respectively. An estimated nationwide burden of asthma and chronic bronchitis was 17.23 and 14.84 million respectively.[4] The prevalence of COPD has been calculated to be 3.49% in India by a recently completed nationwide questionnaire-based study. WHO estimates suggest that 90% of COPD-related deaths occur in low and middle income countries. India and China constitute 33% of the total human population and account for 66% of the global COPD mortality.[5] Along with such rise in disease burden, many of the concerned available FDCs are over the counter drugs and some of them also exhibit abuse liability. So, there was a need to study the assessment of rationality of FDCs of respiratory system drugs (mainly drugs for treatment of asthma, chronic bronchitis, COPD and cough) available in Indian market. Antitubercular drugs are not considered as they themselves are a separate large entity of antimicrobial drugs.

MATERIALS & METHODS

This observational study was conducted in the Pharmacology department of a tertiary healthcare institute. The data was collected from CIMS (October 2017 to January 2018) that enlists most of the medicines commercially available in India during that period. Each FDC was checked for its presence in recent updated CDSCO and WHO essential medicines list and their rationality was assessed according to the Rationality Scoring Scale.[6,7]

Rationality Scoring Scale[6,7]

Sr. No	Rationality criteria	Yes	No
1	Active Pharmacological Ingredient (API) from NLEM & WHO EML	All API (+1) At least one API (0.5)	0
2	Dose of API appropriate for intended use	+1	0
3	Proportion of API appropriate for intended use	+1	0
4	API should have different mechanism of action	+1	0
5	Pharmacokinetic and Pharmacodynamic interaction	Favourable (+1) Not favourable (-1)	0
6	FDC facilitates dose reduction of API	+1	0
7	FDC facilitates ADR reduction	+1	0

Maximum score= 9, Minimum score= 0

FDCs are graded as **Irrational (0-<3), Semi-rational (3-<6), Rational (6-9).**

Rationality assessment was done according to standard reference books. Along with other references, all drug interactions were also checked by the "Drug Interaction Checker" provided by www.webmd.com.

RESULTS

The total number of FDCs of respiratory system drugs (mainly drugs for treatment of asthma, chronic bronchitis, COPD and cough) in the study were 342, as found in CIMS. After excluding repetitions of the same drug combinations in different dosage forms, the number of FDCs was 148.

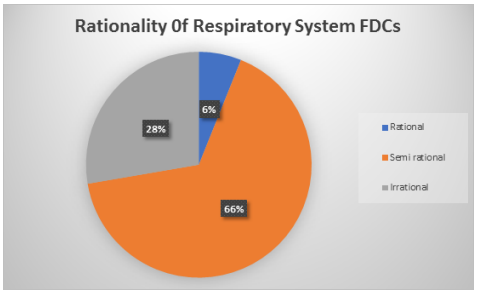
According to the WHO rationality scoring scale, only 9 out of 148 FDCs (6%) were rational, while 41 (28%) were irrational. Maximum of them, i.e. 98 out of 148 (66%) felt into semi rational group (Figure 1).

FDCs found "Rational" (WHO Rationality Scoring Score 6-9) in our study are-[8,9,10]

1. Formoterol + Budesonide
2. Formoterol + Tiotropium
3. Ipratropium + Levosalbutamol
4. Ipratropium + Salbutamol
5. Beclomethasone + Salbutamol
6. Salbutamol + Budesonide

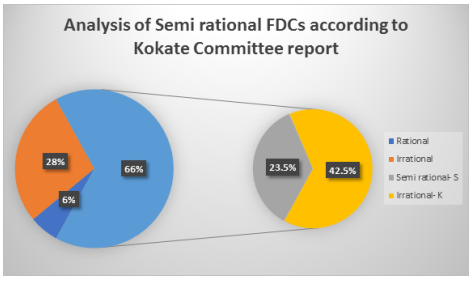
7. Salmeterol + Fluticasone
8. Formeterol + Tiotropium
9. Formeterol + Tiotropium + Ciclesonide

Figure 1- Rationality of Respiratory System FDCs according to WHO criteria (n=148)



We also analyzed our results according to the recommendations of Kokate Committee report February11 and May 201612 regarding FDCs submitted to DCGI. We found that 63 (43%) FDCs which were Semi rational combinations as per our study criteria were irrational as per Kokate Committee report. (Figure 2)

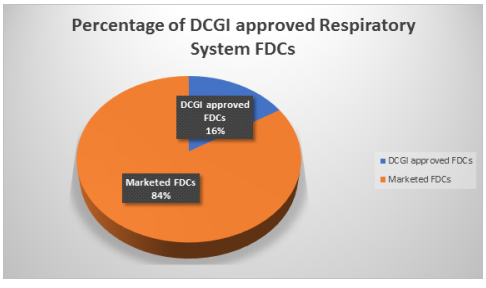
Figure 2- Analysis of Semi rational FDCs according to Kokate Committee report[11,12]



Semirational- S= Semirational according to our study
Irrational- K= Irrational according to Kokate Committee

Also, we checked the FDC list approved by DCGI from 1961 till 12th January 2018 and found that only 24 out of 148 (16.2%) marketed are actually approved by DCGI (Figure 3).[13]

Figure 3- Comparison of DCGI approved FDCs vs actually marked FDCs



DISCUSSION

The results of this study show that a large number of respiratory FDCs are available in Indian market. Unfortunately, their rationality assessment showed that majority had a score <7 indicating their semi rational or irrational status. Only 6% of marketed FDCs are rational according to WHO Scoring scale and only about 16% of them are actually approved by DCGI.

Our study found 9 FDCs rational with respect to efficacy, safety, and compliance. For example, the combination of β2 agonist with corticosteroid is rational because corticosteroids increase the expression of β2 receptors by increasing gene transcription and reduce the adverse effects of β2 agonist, whereas β2 agonists potentiates the local anti-inflammatory actions of corticosteroids by increasing nuclear localization of glucocorticoid receptors and additive suppression of inflammatory mediator release.[14] Also, literature states that combination therapy with β2 agonists and anticholinergics is also effective with improvement of dynamic lung function and good safety profile in patients of chronic obstructive pulmonary disease.[15]

About combinations like Ambroxol/Bromhexine + Salbutamol/ Terbutaline/ Levosalbutamol ± Guaiphenesin ± Menthol ± Theophylline/ Etophylline, it is said that use of a mucolytic along with an anti-asthma drug is liable to be misused as expectorant and exposes the patients unnecessarily to the drugs and their side effects.[11]Though in their next report Kokate Committee has considered this FDC rational as it provides symptomatic relief from bronchospasm in bronchial asthma and chronic bronchitis.[12]

FDCs like Levocetrizine/Cetirizine ± Phenylephrine/ Pseudoephedrine/ Chlorpheniramine ± Paracetamol + Ambroxol/ Guaiphenesin/ Menthol are considered pharmacodynamically irrelevant as mucolytics increase mucus secretion and antihistamines due to their anticholinergic property, dry up all secretions. So, they oppose each other's action. Also, patient may not need all drugs from the FDC for his condition. So, use of such FDC is contributing to misuse of drugs and likely increase in adverse effects.[11]

The combination of Codeine/Dextromethorphan + Chlorpheniramine/ Phenylephrine is also considered irrational as a centrally acting antitussive should not be combined with an antihistaminic drug.[11]

Similarly, in the FDC of Paracetamol + Phenylephrine + Chlorphenira mine, Phenylephrine decreases while Chlorpheniramine increases sedation. So, they are having opposite action to each other.[11]All Paracetamol + Cetirizine combinations show pharmacokinetic incomp atibility because the dosing interval of Paracetamol is TDS/QID while that of Cetirizine is OD/BD.[11] Even though Nimesulide is banned, the FDCs like Nimesulide+ Phenylephrine+ Cetrizine are still marketed.

We compared our results to similar studies and found that our results are in conformity with the observation made by Shah S et al in 2015.[16]

CONCLUSION

Thus, it can be concluded that a large number of respiratory semi rational and irrational FDCs are available in Indian market to treat clinical conditions. It is indeed very unfortunate and unethical to expose the patients to medicines with unproven efficacy and safety. So, we need a close scrutiny of marketed FDCs and educating prescribers to use them with great care and caution. Also, it is desirable that the regulatory authorities carefully review the available evidence before permission is granted for marketing fixed dose combinations.

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