

Critical analysis of antimicrobial and respiratory fixed dose combinations available in Indian market

Abstract

Objective: To analyze the rationality of antimicrobial (AM) and respiratory (RP) fixed dose combinations (FDCs) available in Indian market. **Materials and Methods:** Antimicrobial and RP FDCs enlisted in Indian Drug Review 2010 and 2013 respectively were analyzed by a pretested validated 8 point criteria tool. Each FDC was assessed for number of active pharmacological ingredients, approval by regulatory authority, listing in World Health Organization (WHO) essential medicine list (EML) or National List of Essential Medicine. While efficacy, safety, pharmacokinetic and pharmacodynamic interactions and advantages of each FDC were analyzed by evidence based literature search. Each criterion was scored one for positive and minus one for negative or unfavorable observation. The total score for the tool was 12 and score ≥ 7 was considered rational. **Results:** Of 209 FDCs, 108 were AMs and 101 were RPs. The mean rationality score was 5.41 ± 1.63 (95% CI, 2.15-8.67). Majority of FDCs were irrational (174) while 35 were rational, and only 12 of these were listed in WHO EML 2013. Out of 108 AM FDCs, 21 (19%) were rational while 87 (81%) were irrational. Out of 101 RP FDCs, 14 (14%) were rational while 87 (86%) were irrational and 24 (24%) with unfavorable pharmacodynamic interactions. Majority of the rational AM FDCs were antiretroviral (6) agents while RP FDCs were indicated for chronic obstructive pulmonary diseases. While majority of irrational FDCs were AM plus steroids, β_2 agonists plus antihistaminics/expectorants/anticholinergics/mast cell stabilizers/leukotriene receptor antagonists. **Conclusion:** Rationality assessment of AM and RP FDCs reveals that a substantial number of these FDCs in Indian market are irrational. 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 the regulatory framework for drug manufacturing and marketing.

Key words: Antimicrobial, fixed dose combination, rationality, respiratory

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INTRODUCTION

Fixed dose combination (FDC) is defined as “A combination of two or more active ingredients in a single dosage form in a fixed ratio of doses.” FDC products are acceptable when the dosage of each ingredient meets the requirement of a defined population, and the combination has a proven advantage over single compounds administered separately in therapeutic effect, safety and compliance.^[1] World Health Organization (WHO) essential medicine list (EML) 2013 includes 24 FDCs and most of them belong to antiretroviral, antitubercular and antimalarial class.^[2] Earlier, The Drug and Cosmetic Act (1940) stated “no additional or human data is required and approval to market the product was granted for FDC with an acceptable rationale.” This resulted in mushrooming of FDCs in India, accounting for approximately 44% of domestic pharmaceutical market.^[3] However, an Amendment in 2005 clearly stated FDCs as new drugs and must comply the Schedule Y for marketing approval. With this, FDCs have been categorized into two types for regulatory approval. One, any one of the ingredient is new and proposed to be used for the 1st time is considered a new drug. While FDC in which ingredients are individually approved and marketed for certain claims and are proposed to be combined for 1st time in a fixed ratio or if the ratio of the ingredients in an already marketed combination is proposed to be changed for a particular claim is considered as second category. Thus, the marketing approval of FDC requires to submit all necessary

pharmacological, toxicological and clinical data of individual drug along with the rationale of the combination. Central Drug Standard Control Organization in August 2010 had laid down guidelines for approving the FDCs emphasizing the rationale of combining drugs in a specific ratio.^[4] However, there is no available validated tool to assess the rationality. Thus, the present study was aimed to design a tool to assess the rationality of antimicrobial (AM) and respiratory (RP) FDCs available in Indian market.

MATERIALS AND METHODS

A cross-sectional, observational study was conducted at the Department of Pharmacology, B. J. Medical College, Ahmedabad, Gujarat. The data

1. Active pharmacological ingredient along with strength			
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.....			
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		Favorable/Unfavorable/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 (frequency or pill count)		Yes (+1)/No (0)	
Total score: 12			
Score ≥7: Rational FDC			
Score ≤6: Irrational FDC			

Figure 1: Tool to assess the rationality of fixed dose combinations available in Indian market

were collected from an annual Drug Compendium entitled “Indian Drug Review” (IDR) 2010 and 2013 that enlist most of the medicines commercially available in India during a particular year.

Antimicrobial and RP FDCs enlisted in IDR 2010, and 2013 respectively were assessed for rationality. A tool was designed using WHO guidelines for registration of fixed dose combination medicinal products.^[1] The tool consisted of eight point criteria [Figure 1]. The criteria in the tool included active pharmacological ingredient (API) with strength, its efficacy, safety, approval by regulatory authority, listing in WHO EML or National List of Essential Medicines of (NLEM). The evidence for efficacy and safety of the individual API and their combination was searched using standard textbooks, reference books of pharmacology and medicine. In addition, authentic web sources like PubMed data base, Google scholar and Cochrane data base were also used. Pharmacokinetic and pharmacodynamic interactions were checked using Medscape drug interaction checker. Advantages of FDC over individual API in the form of dose reduction, less adverse drug reactions and reduced frequency of administration were assessed by above mentioned evidence based literature search.

As per subject experts opinion from industry and academia each criterion was scored plus one (+1) for positive and minus one (-1) for negative or unfavorable observation. The total score ranged from 1 to 12 and score ≥7 was considered rational. Further the tool was validated by assessment of FDCs already approved by WHO EML 2013 whereby the minimum score obtained of these was seven. The data was entered in Microsoft excel sheet and analyzed using appropriate statistical tests.

RESULTS

Out of 209 FDCs, 108 belonged to AM group and 101 to RP group. The mean rationality score of AM FDCs was 4.91 ± 1.72 while that of RP FDCs was 5.92 ± 1.55 . Majority of AM FDCs contained two APIs (90) while majority of RP FDCs contained 3 or >3 active ingredients [Table 1 and Figure 2]. The rationality score for 12 AM FDCs listed in WHO EML was ≥7 [Table 2]. In

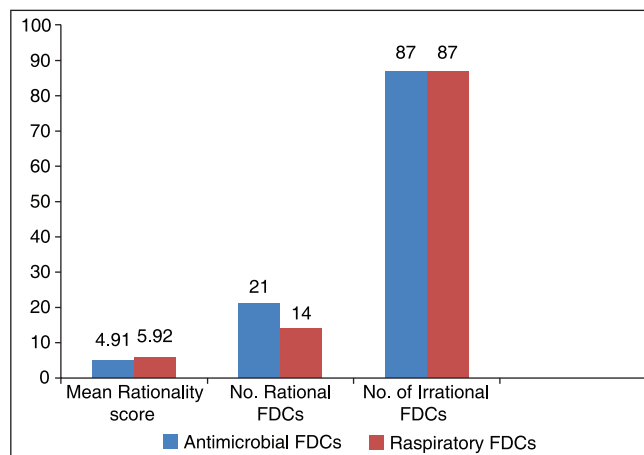


Figure 2: Rationality score and rational and irrational fixed dose combinations in both categories

addition, there were 9 other AM FDCs and 14 RP FDCs scored ≥ 7 as per our tool [Table 3].

Of 108 AM FDCs, 21 (19%) were rational and 87 (81%) were irrational. Out of 21 rational FDCs, 12 were listed in WHO EML 2013 while out of 87 irrational AM FDCs, none was listed in WHO

Table 1: Assessment of antimicrobial and respiratory FDCs using rationality tool

Parameters	Antimicrobial FDCs (n = 111) (%)	Respiratory FDCs (n = 101) (%)
Mean rationality score	4.91±1.72	5.92±1.55
Minimum score	2	1
Maximum score	12	10
Number of rational FDCs	21 (19)	14 (14)
Number of irrational FDCs	87 (81)	87 (86)
Number of API in each FDC		
2	90	36
3	18	28
≥ 4	0	37
FDCs enlisted in WHO EML	12	Nil

FDC = Fixed dose combination, EML = Essential medicine list, WHO = World health organization, API = Active pharmacological ingredients

Table 2: List of FDCs scored ≥ 7 (rational) as per tool and enlisted in WHO EML 2013 (n = 12)

Antimicrobial FDCs (n = 12)	
Imipenem+cilastin	Artesunate+amodiaquine
Lamivudine+nevirapine+stavudine	Artemether+lumifantrine
Lopinavir+ritonavir	Lamivudine+zidovudine
Amoxicillin+clavulanic acid	Lamivudine+zidovudine+nevirapine
Tenofovir+emtricitabine	Rifampicin+isoniazid+ethambutol
Tenofovir+emtricitabine+efavirenz	Sulfamethoxazole+trimethoprim
Respiratory FDCs (n=0)	
None	

FDC = Fixed dose combination, EML = Essential medicine list, WHO = World health organization

Table 3: List of FDCs scored ≥ 7 (rational) as per tool and not enlisted in WHO EML 2013 (n = 23)

Antimicrobial FDCs (n = 9)	
Stavudine+lamivudine	Loteprednol+tobramycin
Atazanavir+ritonavir	Hyaluronic acid+silver sulfadiazine
Tenofovir+lamivudine+efavirenz	Mometasone+fusidic acid
Clindamycin+isotretinoin	Ketoconazole+zinc
Albendazole+ivermectin	
Respiratory FDCs (n=14)	
Budesonide+formoterol	Salmeterol+beclometasone
Doxophylline+terbutaline	Salbutamol+theophylline
Formoterol+fluticasone	Salmeterol+fluticasone
Formoterol+tiotropium	Terbutaline+theophylline
Ipratropium+salbutamol	Formoterol+tiotropium
Montelukast+levocetirizine	Fexofenadine+pseudoephedrine
Beclometasone+salbutamol	Pseudoephedrine+desloratadine

FDC = Fixed dose combination, EML = Essential medicine list, WHO = World health organization

EML 2013. Majority of the rational AM FDCs were antiretroviral (6) agents. Favorable pharmacokinetic interactions were observed in 4 rational FDCs while only two FDCs had advantages of less adverse drug reactions (ADRs) when combined as compared to individual ingredient. Majority of irrational AM FDCs (87, 81%) were combination of AM plus steroids (21) followed by cephalosporin plus betalactamase inhibitor (20), antibacterial plus antiamoebic plus antifungal agents (10) and combinations of ingredients of same class and antibacterial with lactobacilli or serratiopeptidase. Surprisingly, two FDCs contained controversial ingredients such as piperine and coal tar.

Out of 101 RP FDCs, 14 (14%) were rational and 87 (86%) were irrational. However, none of rational RP FDCs scoring ≥ 7 was listed in WHO EML 2013. The rational FDCs were combinations of β_2 agonists plus corticosteroids/anticholinergics/methylxanthines. Favorable pharmacodynamic interactions were observed in 3 rational FDCs. Moreover, three FDCs also had advantage of having less ADRs in combination than single ingredient. The irrational FDCs were combinations of β_2 agonists plus antihistaminics plus expectorants/anticholinergics/sympathomimetics.

DISCUSSION

The results of this study show that a large number of AM and RP FDCs are available in Indian market. Unfortunately, their rationality assessment showed that majority had a score < 7 indicating towards irrationality.

The rational AM FDCs were antiretroviral, antitubercular and antimalarial class of drugs with proven efficacy, safety, pharmacokinetic and pharmacodynamic advantages.^[5,6] While 81% of AM FDCs were irrational, with no justification of combining the ingredients. Our results are in conformity with the observation made by Rayasam *et al.* in 2013 to study prescribing pattern of FDCs among practitioners in central India.^[7] The most pressing concern with irrational FDCs was illogical combination of antibacterial with corticosteroid which decreases the immunity and increases the susceptibility to infections. Moreover, combination of cephalosporin with beta lactamase inhibitor is also not justified as beta lactamase inhibitors prevent destruction of beta lactam ring in penicillin group of antibiotics and thus widens the antibacterial spectrum of latter. However, these are not effective against the extended spectrum cephalosporins such as ceftazidime, ceftriaxone, cefotaxime.^[8] A large number of AM FDCs were fashionable combination of antibacterial with antiamoebic and/or antifungal agents. Amoebic and bacterial infection rarely coexist and such combination not only encourage resistance, but also expose patients to unnecessary risk of adverse drug reactions.^[9] Such FDCs have not been recommended in any standard books, but continue to be available in Indian market. Availability of such products reduces the attempt for a precise diagnosis and only adds to the cost of therapy. It is a well-known fact that lactobacilli as a single agent is used for diarrhea. However, none of the combination of antibacterial plus lactobacilli

had adequate dose (5-10 billion) required to decrease antibacterial induced diarrhea. In addition, many FDCs were combined with serratiopeptidase, an enzyme claimed to promote rapid resolution of inflammation. To our surprise, we could not find any evidence in published literature such as standard books or peer reviewed scientific journals supporting this claim.

On the other hand, no RP FDC has been listed in WHO EML. Majority of RP FDCs (86%) in our study were irrational, many of them targeting cough and the common cold, a self-limiting condition that does not require medicine to cure or prevent it.^[10] Similar observations have been reported by Roy *et al.*^[11] and Desai *et al.*^[10]

Interestingly, our tool found 14 RP FDCs rational with respect to efficacy, safety, and compliance. For example, the combination of long acting β_2 agonist with corticosteroid is rational because corticosteroids increase the expression of β_2 receptors by increasing gene transcription and reduces the adverse effects of β_2 agonist, whereas β_2 -agonists potentiates the local anti-inflammatory actions of corticosteroids by increasing nuclear localization of glucocorticoid receptors and additive suppression of inflammatory mediator release.^[12] Further, combination of methylxanthines plus β_2 -agonists potentiates the therapeutic effect with fewer side effects as compared to β_2 -agonists alone.^[13,14] Literature states that combination therapy with β_2 -agonists and anticholinergics is also effective with improvement of dynamic lung function and good safety profile in patients of chronic obstructive pulmonary diseases.^[15] FDCs of montelukast with antihistaminics were also found to be rational due to its enhanced and complementary pharmacological and clinical effects leading to a reduction in the day and night time symptoms effectively in patients of allergic rhinitis.^[16]

A great discrepancy was observed in the total number of AM and RP FDCs available in Indian market as compared to WHO EML and NLEM. The WHO EML 2013 includes a total of 18 AM FDCs out of total 120 AMs with nil from RP system. Thus, it is almost 11 times the numbers of FDCs to treat infectious and RP diseases in India.

Although there has been no defined rule for the permissible maximum number of constituents in the FDCs, any FDC containing >3 ingredients should be looked at watchfully. Majority of AM FDCs had two ingredients, albeit, majority of RM FDCs had 3 or >3 ingredients. USFDA states that there is no rationale of combining >3 ingredients.^[17]

A commercial and commonly used annual drug compendium among the prescribers was used for data collection and source of information for formulations available in Indian market. A possibility of lack of complete information cannot be ruled out. Nevertheless, the compendium still reflects the actual scenario of marketed drug product of the country.

Thus, it can be concluded that a large number of AM and RP irrational FDCs to treat clinical conditions are available in Indian

market. It is indeed 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 the regulatory framework for drug manufacturing and marketing.

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