COMMENTARY

An Algorithm Based Approach For Evaluation of Rationality of Fixed Dose Combination In India

Kumar Subodh[1], Saikia Dibyajyoti[2]

ABSTRACT

The number of fixed dose combination drugs in India far exceeds other countries like US. Though there are guidelines for development of new FDCs there is no system to check the FDC already available in the market. CDSCO, the Indian drug regulatory body unsuccessfully tried to weed out some of FDCs. This is because there is no system to check rationality of FDCs objectively. Though there are large numbers of literatures available showing prevalence of irrational FDCs in India there is no uniform system to evaluate the rationality. Hence an algorithm based approach is presented to evaluate the rationality of FDCs based upon WHO requirement.

Keywords: Fixed dose combination, CDSCO, Algorithm based approach

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[1]Assistant Professor, Department of Pharmacology, SRMSIMS, Bareilly, Uttar Pradesh, [2]Junior resident, Department of Pharmacology, AIIMS, New Delhi

Corresponding author: Dr. Kumar Subodh Assistant Professor, Department of Pharmacology, SRMSIMS, Bareilly, Uttar Pradesh

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INTRODUCTION

The number of fixed dose combination (FDC) drugs available in India is far more than the other countries.[1] For instance FDC of topical corticosteroids with other agents available in the country, according to MIMS (Monthly Index of Medical Specialties), the commonly used drug information sources in the India, 119 FDCs are available. Surprisingly, out of the available 119 formulations, only 27 features among the Central Drugs Standard Control Organization's (CDSCO) approved list of FDCs since 1961 to July, 2014 in India. These FDCs are not limited to one system and almost all drugs are available as FDC in India. Further there are many brands available to these FDCs.

To deal with this issue CDSCO, the Indian regulatory authority, issued a direction in 2007 to all state licensing authorities to withdraw 294 FDC's which were not licensed by DCG(I). But the manufacture association got a stay from high court and the matter is still sub-judice.[2]

There is a need for a system to evaluate the rationality of the FDC's which are available in market. Therefore, we need an objective assessment method to evaluate these FDC's. Further such a method may also be used for approval of FDC's which contains only generic component as they may not require a fresh trial but the approval can be given if substantial data exist of their advantage over individual drugs.

WHO Drug Information Vol. 17, No. 3, 2003 deals with regulatory challenges associated with fixed dose combination (FDC) products.[3] Apart from giving consideration for drug regulation, it also gives definition, advantage and disadvantages of FDC's. But it is difficult to objectively evaluate the usefulness of FDC's based on these deliberation. Hence we tried to enlist all the points and make an algorithm to make it simple and more objective.

Points which were considered to evaluate usefulness of FDC's:

1. Whether the combination of drugs are having definite advantage over individual drugs or not?
2. What is the probability of disease co-

existence in population?
3. Pharmacokinetics - Whether the pharmacokinetic profile of the individual drugs is matching?
4. Toxicity - whether the toxicity profile of individual drug is same?
5. Whether the dose titration is need for individual components?
6. Chemical compatibility – whether the compounds are chemically compatible when combined together?
7. Cost factor - whether the cost of FDC is more than the individual drugs?
8. Whether the individual components are present in their recommended dose?

The above points were considered to make an algorithm which categorizes the FDC (Fig.1). These categorizations are explained with example in table (Table 1). In the following section the factor which is important for deciding rationality of combining two or more drugs is discussed.

FDCs for single disease

Combination of drugs as a single formulation should have some definite advantage other than just ease of prescription writing. It should confer some benefit which will otherwise not be available by administration of individual components. Drugs may be combined if it increases efficacy, reduces the dose, and helps in reversing or preventing the development of resistance. It may also be needed to increase compliance, but it should be available for those indications where patient compliance is an issue. FDC should not be made just because it can be formulated. The combination should also be such that it should not obscure diagnosis or prognosis evaluation. It may also be done if it helps in mitigating toxicity.

FDCs for co-existing disease

Some FDCs are also available which are not for a single disease. In such cases it should be seen how common or uncommon is the probability of both or more diseases being present at the same time in same patient. For example iron and folic acid supplementation is required during pregnancy whereas a combination of doxylamine and folic acid would be irrational. Doxylamine is indicated for pregnancy induced nausea and vomiting which usually subsides within few weeks while folic is recommended during perico nceptional period. Even in the same disease all components may not be needed at all time. FDC should be prescribed only when all components are required throug- hout the treatment period. For example corticos- teroids and salbutamol is a rational combination because it is general practice to add a corticos- teroid in asthmatic patient. Similarly some FDCs presently available contain components which at certain periods are required together but not indicated throughout in the same patient. Such a combination increases exposures of an unnece- ssary drug to the patient. FDC's of topical steroid with both antibacterial and antifungal are also irrational. It is highly unlikely to have both bacterial and fungal super-infection in the same lesion. Though it is possible majority of patients will not require all three ingredients at same time. FDCs for such uncommon situations are not a necessity but rather may increase the risk of their misuse as physician may tend to use it when he is not sure of diagnosis.

Other factors considered for FDC

There are number of FDCs containing vitamins and minerals available in market without any specific indication. Multiple deficiencies of vitamins and minerals in a single person are uncommon. Mineral and vitamin supplementation is also stated to boost immune system in older people, but it has not been found cost effective.[4] Many preparations contain more than 30 components which includes vitamins, minerals and probiotics.[5] Moreover, recommended daily allowance (RDA) required varies widely in different population groups and it would be impossible to maintain the required RDA of all the components by titrating the amount of intake.[6] In maintaining RDA of one component, other components will be either under dosed or overdosed. They are promoted as nutritional supplements and as such difficult to regulate. FDC of metformin and glimepiride with or without pioglitazone is available and one of top selling antibiotic drug. This is despite the fact that metformin needs to be taken after or with meal

Table:1- Categories of FDCs and their general meaning

Category	Context
Unsafe:	1. Contains banned substance 2. Contains toxic substance 3. Increases toxicity - Statins and Fibrates, Didanosine and Stavudine
Definite advantage	The combination of individual drugs results in 1. Overcoming resistance eg. Antimalarial and Antitubercular drugs 2. Increase in efficacy eg. Amoxicillin and Clavulanic cid 3. Dose reduction eg. Ritonavir and Lopinavir 4. Toxicity mitigation eg. INH and Pyridoxine
Definite disadvantage: Unjustifiable	1. Decreases efficacy of component drugs 2. Requires dose enhancement of other drug eg. Cyp inducers 3. Chances of increase resistance 4. One component inhibits activation of prodrug eg. Omeprazole & Clopidogrel
Inconclusive: Single disease Absurd Multiple disease Absurd	No definitive advantage or disadvantage Regular eg. Iron and Folic acid, Prokinetic and PPI, Salbutamol and Corticosteroids Irregular: Doxylamine and folic acid, Antipyretics and Antibiotics Common: eg. HTN and Dyslipidemia (EG) Uncommon: eg. Biotin and Folic acid, Ofloxacin and Ornidazole, Steroid and Antifungal/Antibacterial, Multivitamins
Pharmacokinetic profile Incompatible	Timing/frequency of administration, Interaction with food Not matched
Recommended dose Ineffective	Yes No
Cost Uneconomical	Cheap Costly

Table-2: Common examples of irrational FDCs

FDC category	Example
Unsafe	Any FDC containing banned substances like Phenylpropanolamine, Rosiglitazone, Cisapride, Gatifloxacin, Phenfluramine, Tegaserod, Rimonabant etc. Statins and Fibrates, Didanosine and Stavudine
Unjustifiable	Amoxicillin and Tetracycline
Single disease - Absurd	Doxylamine and Folic acid, Ondansetron and Pantoprazole, Mosapride and Pantoprazole, Mebendazole and Levamisole, NSAID with PPI/ H2 receptor antagonist, Ibuprofen and Colchicines
Multiple disease - Absurd	Ofloaxacin+ Ornidazole, Biotin and folic acid, Steroid with Antifungal & Antibacterial, Ranitidine and Dicyclomine, Dicyclomine and Serratiopeptidase, Dicyclomine with Paracetamol and Cholrdiazepoxide, Aceclofenac with Paracetamol and Tizanidine, Ibuprofen and Carisoprodol
Incompatible	Glibenclamide and Metformin, Glibenclamide, Metformin and Voglibose, Diclofenac and Famotidine , Mebendazole and Pyrantel palmoate, Atenolol with plain Nifedipine
Ineffective	Low dose multivitamins
Dose titration	Antidiabetic, Antihypertensive and Anti epileptic combinations

and glibenclamide is taken before meal making this FDC incompatible. A recent report in lancet suggest that 41 metformin based FDCs are approved in India and more than 500 different brands are available of these formulations. The marketing authorization has been given without any justification and they does not fulfill the criteria laid down by WHO for approval of FDC.[7]

It should also be kept in mind that some drugs require different dosage in different patient or dosage may require titration in same patients. In such cases where interpatient or intrapatient variability is high, FDCs being inflexible, can lead to overdosing or under dosing. For such indications FDCs should not be available. The cost of the drug is important factor in this market

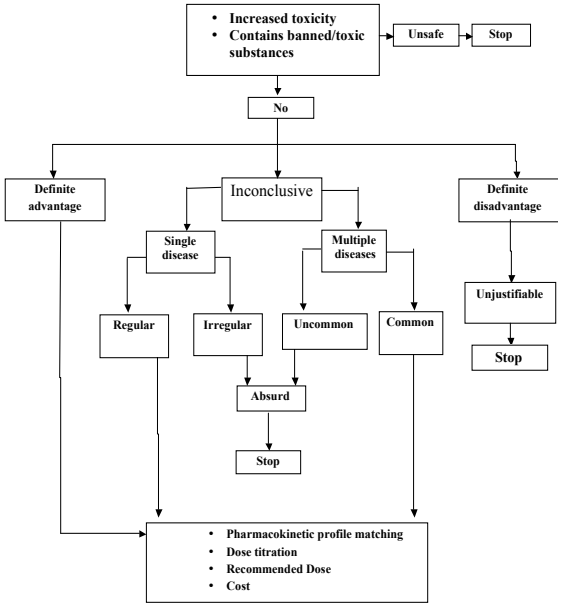

Figure-1: Schematic diagram of algorithm for stepwise evaluation of rationality for fixed dose combination

driven pharmaceutical industry. Economic sense dictates that cost of the FDC should not be more than the individual drugs.

CONCLUSION

Fixed dose combination therapy are essential in certain situations as for stopping emergence of resistance and in cases where it affects the action of other drugs and thus increasing efficacy or reducing toxicity. So, ideally fixed dose combination therapy should be encouraged only where there is strong biological rationale and there is compelling reason of superiority over individual drugs. But such a strategy will lead to most of the FDCs available in Indian market as irrational/ unnecessary. So, we need a balanced approach to either categorize the available FDCs or assigning a score. Decision to weed out the irrational FDCs can then be taken in stepwise manner. Though the categorization all the FDCs in India is huge task, and a simple model may not
be sufficient to do so, this paper is an attempt to realize this objective.

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