Fixed Dose Combination Of Drugs: Are They Justified?

Farooq M*, Goyal M**

*Post graduate Resident, **Professor, Department of Pharmacology,
Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Ambala- 133207, India.

Abstracts: Background:Fixed Dose Combinations (FDCs) are combinations of two or more active drugs in a single form. Prescribing FDCs has become a routine affair in medical practice. Combination drugs increase the compliance of patient to the treatment, decrease the pill burden, but may also lead to increase in the cost of the treatment and side effects. There has been increase in the irrational FDCs in the recent past. The rationality of a fixed dose combination is the most controversial and debated issue in today's clinical practice. The eighteenth essential medicine list (EML) of WHO includes 25 FDCs while as the 2011 national list of essential medicines (NLEM) of India includes only18 FDCs. Contrary to this Indian market is flooded with FDCs, the scientific rationale for most of these remains unknown. In India, a fixed dose combination of drugs is considered a "NEW DRUG" and has to be approved by Drugs Controller General, India (DCGI). However, the Indian laws governing the approval and marketing of FDCs are not properly defined, the pharmaceutical manufactures take advantage of these loopholes and market combination that have no pharmacological rationale. [Farooq M NJIRM 2015; 6(5):103-107]

Key Words: Fixed Dose Combinations (FDCs), Rational combination, Irrational combination, Drug Controller General of India (DCGI).

Author for correspondence:. Dr. Majid Farooq, Department of pharmacology, Maharishi Markandeshwar Institute of Medical Sciences and Research, Ambala –133207. Email:drmajidfarooqbhat@gmail.com

Introduction: A number of drugs are available in the market and many of them in the form of fixed dose combinations (FDCs). Fixed dose drug combinations are the products containing two or more active ingredients in a fixed ratio of doses in a single formulation.[1,2] The FDCs may be in form of a tablet, capsule, syrup, powder, injection, etc.[2] The Food and Drug Administration, USA defines a combination as a "product composed of any combination of a drug & a device or a biological product & a device or a drug & a biological product or a drug, device & a biological product".[3,4] There are about 80000 drug formulations available in the Indian market.[1,4] 3500 of them being FDCs.[5] The eighteenth April 2013 essential medicine list (EML) of WHO includes 25 FDCs while as the 2011 national list of essential medicines(NLEM) in India has 348 medicines and includes 18 FDCs.[6,7] FDCs are being prescribed routinely which may be attributed to a number of reasons such as; multi-factorial etiology of a disease, co-morbidities in a patient, to decrease pill load, promotion by pharmaceutical companies etc.[1,2,4,5]

Fixed dose combination: Rational or Irrational. The WHO, defines rational use of drug as, "the use of right drug in the right manner (route, dose, frequency, duration) in the right patient at the right time at the lowest cost to them and their community". However, in reality there is irrationality in every aspect of drug use.[8] The Indian market is filled with FDCs which have no reasonable pharmacological rationale and are irrational. These irrational FDCs are exposing the patients and communities to unnecessary adverse effects and also promote emergence of drug resistant microorganisms.[9] An FDC can be labelled as rational only when; [5,8,9,10,11]

The combination has a better therapeutic response as compared to the individual drugs and the drugs in the combination should be acting by different mechanism of action.

- When one drug in the combination decreases the intensity, severity of side effects caused by other drug in the combination i.e. the toxicities of the ingredients should not be super additive.
- Its ingredients have a similar bioequivalence i.e. their pharmacokinetic and pharmacodynamic properties should be similar or almost similar.

Examples of some of the irrational FDC available in Indian markets are:

- **Nimesulide + paracetamol** – There is no rationality to this combination as both the drugs have same mechanisms of action and paracetamol has negligible anti-inflammatory action, Nimesulide is more potent antipyretic than paracetamol. Moreover, Nimesulide and paracetamol are pharmacokinetically

incompatible as Nimesulide has longer half-life as compared to paracetamol. Also the chances of hepatotoxicity are increased when this combination is used. Nimesulide has also been banned in developed countries due to its hepatotoxic adverse effect.[2,3,12]

- **Ampicillin + Cloxacillin**– Ampicillin is effective against Gram negative bacilli but Cloxacillin not effective against Gram negative bacilli. So, one of the drugs in the combination would be useless. Apart from increasing the cost of therapy it would lead to adverse side effects and development of bacterial resistance to the drug.[2,9,11]

- **Domperidone + Proton Pump Inhibitors** – Proton Pump Inhibitors (Omeprazole, Pantoprazole and Lansoprazole) reduce gastric acid production, provide symptomatic relief in patients with peptic ulcer and also promote healing of esophageal lesions. Combining these drugs with Domperidone (prokinetic agent) is an irrational drug combination as peptic ulcer is not always associated with vomiting also domperidone is less effective than metoclopramide in cases of Gastroesophageal Reflux Disease (GERD) so combining proton pump inhibitors with domperidone seems to be an irrational choice.[2,9,11]

- **Montelukast + Levocetirizine** – Montelukast, the leukotriene antagonist is used as an alternative to inhaled steroids in the management of mild persistent bronchial asthma. They are less effective as they antagonize only one of the several bronchoconstrictor mediators. It has a half-life of 2.7-5.5 hours while as Levocetirizine, a second generation antihistaminic drug having a half-life of 6 -10 hours has limited role in the control of asthma as it is not only histamine that triggers the asthma attack. There is no justification for the use of this combination in bronchial asthma.[2,9,10]

- **Ranitidine + Dicyclomine**– Ranitidine is a H2-antihistaminic and is used to decrease the gastric acid level and thus relieves pain in conditions like peptic ulcer. Dicyclomine is an antispasmodic drug and has no role in a FDC with H2 blocker.[2,9,11]

- **Enalapril + losartan** – Both the drugs affect the renin angiotensin aldosterone (RAS) pathway and increase the risks of adverse effects without increase in the efficacy of the FDC.[2,7,9,11]

- **Norfloxacin/Ciprofloxacin/Ofloxacin+ Tinidazole / Ornidazole** – Fluoroquinolones are ineffective inamoebic dysentery and nitroimidazoles are of little value in bacterial dysentery. However**,** the combinations of fluoroquinolones and nitroimidazoles are widely used for all types of diarrhea and dysentery though this combination has no rationality as both types of dysentery rarely co-exist. This combination also leads to increase in chances of drug resistant strains of microorganisms.[2,3,9,11,13]

Some other commonly available FDCs available in the Indian market, which may be labeled as irrational are: [2,9,10,14]

1. Propranolol + Alprazolam,
2. Ranitidine + Drotaverine,
3. Diclofenac + Rabeprazole,
4. Dicyclomine + Paracetamol,
5. Aspirin + Disordered-5-mono nitrate,
6. Diclofenac + Preservationist,
7. Glibenclamide + Metformin,
8. Gliclazide + Rosiglitazone,
9. Vitamin B1 + Vitamin B6 + Vitamin B12 + Nicotinamide + Calcium pantothenate,
10. Antipsychotics (chlorpromazine, haloperidol, risperidone) + trihexyphenidyl,
11. Mebendazole + Pyrantelpamoate / Levamisole, etc.

Let's try to dissect and analyze the various merits and demerits of FDCs over single agents;

Merits of FDCs: The production cost of FDCs is less as compared to single agents, thus more affordable to the patient.[1,2,4] FDCs reduce the pill burden of the patient, provide convenience in dose schedule and hence improve patient compliance and outcome of the disease.[1,2,4,13.] FDCs also provide convenience to the patient as he/she has to buy only one product as compared to two or more

products. FDCs have a single expiry date (single products may have different expiry dates).[4] Enhanced effect of the combination (e.g. sulfamethoxazole and trimethoprim individually are bacteriostatic but their combination cotrimoxazole is bactericidal).[2,4] Minimization of side effects (e.g. carbidopa + levodopa).[2,4] Therapeutic effects of one drug can be increased by addition of another drug in a combination (e.g. amoxicillin + clavulanic acid).[2,4] FDCs also help in prevention or slowing of antimicrobial resistance in cases such as HIV-AIDS, Tuberculosis, Malaria falciparum, etc.[2]

Demerits of FDCs: The cost of FDCs may be increased if unnecessary drugs are included in the combination (e.g. paracetamol + ibuprofen + caffeine).[2,4] There are chances that one of the drugs in the FDCs may be wasteful or surplus (e.g. vitamins + iron).[2,4] FDCs may lead to increased incidence of adverse effect (e.g. Nimesulide + paracetamol).[2,4] Combining drugs with incompatible pharmacodynamic properties in a FDC may prove to be detrimental to the health of a patient (for e.g. combination of antihistaminic with antidiarrheal can lead to increased risk of CNS depression).[2] If drugs with different pharmacokinetic properties are combined in a FDC it may lead to unacceptable fluctuation in the plasma concentration of the component drug, also the dose of any component in a FDC cannot be adjusted independently, if desired.[1,2,3,4,9] Adverse effect, if occur, cannot be easily attributed to a particular drug causing it in the combination.[2,4]

There are increased chances of adverse effect and drug-drug interactions by a FDC as compared to a single agent given individually.[3,4,7,9] Moreover if a patient if allergic or has contraindication to one of the components of the FDC, the FDC cannot be prescribed.[1,4,9]

FDCs and the Indian scenario: In the recent years, a huge market for the irrational FDCs has erupted in India; this has been attributed to the promotional activities of the pharmaceutical companies targeted directly to the consumers and/or towards the physicians. In India,according to rule 122E of Drug and Cosmetics Rule, a fixed dose combination of two or more drugs is considered to be a “NEW DRUG” and all new molecules have to be approved by Drugs Controller General, India (DCGI), this is because of the fact that that by combining two or more drugs, the safety, efficacy, and bioavailability of the individual Active Pharmaceutical Ingredient (API) may change.[1,5,9,15,16,17] However, in practice the state drug controllers (SDCs) do provide license for approval and marketing of such combination even though they do not have this legal authority. Once the FDC is approved by a SDC it can be sold in any state of the country, even though it is neither approved by DCGI nor by other SDCs where the product is sold. The Indian laws governing the marketing and approval of FDCs are not properly defined. The pharmaceutical companies take advantage of the loopholes and continue to market absurd, illogical and irrational FDCs and in return reap benefits in terms of high profits.[8,9,11,16,17]

In September 2007 the Drug Controller General of India (DCGI) had circulated a Notification to SDCs declaring 294 FDCs as irrational however, The Confederation of Indian Pharmaceutical Industries (CIPI) moved the Madras High Court and got a stay order on DCGI directive. The CIPI was willing to withdraw the cases if the DCGI agrees to allow licenses to the 150 FDC drugs which were categorized as need further examination.[9,16,17]

DCGI had released several circulars on January 15th, March 21st, July 1stand 5th, August 26th and September 2nd 2013 addressed to all SDCs to ensure all FDC product manufacturers must prove the safety and efficacy of the FDCs which got approved before October 2012 and all those FDCs approved by the SDCs after October without the permission of the DCGI. If not compliant, the said FDCs were supposed to be considered for the ban. The SDCs were incapable to implement these orders rather continue to approve license to pharmaceutical companies for marketing of FDCs.[1,9,17]

In connection to this an expert committee was set up by Central drug standard control organization (CDSCO) which had its first meeting in New Delhi on March 4th, 2013 to formulate a policy on FDCs. This is seen as an important step in development of a guideline for approval of FDCs in India.[9,17] The Drug Controller General India (DCGI) and Drug Technical Advisory Board (DTBA) over the years has

banned many irrational FDCs like analgin + pitofenone, vitamins B1 + B6 + B12, cyproheptadine + lysine, and products containing serratiopeptidase, dextropropoxyphene, etc. but this has not deterred pharmaceutical companies from manufacturing, marketing of new irrational FDCs and luring the practicing doctors to prescribe them to the patients who do not even need them.[3,5,9,14,15,17]

The reasons for availability and use of the irrational FDCs in India are:

1. FDCs are 'NEW DRUGS' and the approval for their manufacturing and marketing is under DCGI. Once the drug approval date completes 4 years or is included in Indian pharmacopoeia any company having manufacturing license can market the drug without approval of DCGI. Hence massive numbers of brands are available in the Indian market unlike other countries like US and Europe. Many pharmaceutical companies take advantage of SDCs to push through their irrational combinations without proper scrutiny, as most SDCs do not have the facilities and expertise to assess the benefits and harms of the combinations.[1,4,9]
2. Poor and inadequate training of medical graduates regarding Problem-based pharmacotherapy is not a part of undergraduate training. Although, a debate has now started, to include the concepts of Rational Drug Use (RDU), Essential Medicine List (EML), Personal drug (P-Drug) in the curriculum of the medical graduates.[2,10,18,19]
3. Lack of information regarding indication and safety of drugs in medical professionals- Moreover, physicians mostly rely on drug information provided by medical representatives (MRs), literature and booklets from the pharmaceutical companies which tend to leave the information relevant to the safety and efficacy of these irrational FDCs to be divulged. Continuing medical education (CME) if conducted, it is mostly sponsored by drug houses having their own market interests.[2,10,18,19]
4. Lack of diagnostic facilities and uncertainty of diagnosis- many physician try to cover up their uncertainty of diagnosis by prescribing FDCs that are irrational and absurd.[2]
5. Demand of the patient fuelled by direct to consumer pharmaceutical advertisements.[2] In the current Indian scenario it is not only the need but also the right of the patients, prescribers to raise the concerns regarding this murky business of the pharmaceutical companies. A campaign against these meaningless FDCs by all the stakeholders of the society including the pharmaceutical companies, healthcare professionals, drug regulatory authorities must be launched to control this menace.[4,9,14,16]

Proposal and suggestions by the authors:

1. Proper guidelines regarding the approval, manufacturing and marketing, of FDCs should be formulated by drug regulatory authorities and adhered upon by the pharmaceutical industry. Some degree of irresponsibility on the part of the pharmaceutical industry and lack of vigilance of government agencies underlies the increased popularity of irrational drug combinations.[1,2,9,19]
2. Strict implementation of the rules regarding promotion and prescribing of FDCs by pharmaceutical industry and prescribers. Most advertisements in many of the medical journals published from India fail to mention important details pertaining to correct usage of drug combinations. Clinical pharmacists can play an important role in guiding and imparting knowledge to the public.[1,2,19,20]
3. Training of medical graduates for rational drug prescribing, evaluation of rationality of FDCs and continuing medical education (CME) for in-service doctors (both private practitioners and physicians working in government (hospitals) on topics related to newer drug combination, new drug molecules introduced in the market. Earning fixed number of CME credit hours per year should be made mandatory for renewal of registration with medical councils (already MCI and some state councils, such as the Punjab Medical Council, has made it a pre-requisite for license renewal).[2,18,19]
4. Hospitals should constitute drugs and therapeutics review committees to rationalize prescribing and formation of well-developed formulary based on local requirement, mainly of essential drugs and prescribers should be encouraged to prescribe from the same.

5. The physicians and healthcare providers who are/ become aware of the irrationality of a FDC have a moral and social responsibility to dissipate this information to the general public and patients, who bear the financial & physical consequences of the irrational combinations.

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Conflict of interest: None
Funding: None
Cite this Article : Farooq M, Goyal M, Fixed Dose Combination Of Drugs: Are They Justified?Natl J Integr Res Med 2015; 6(5): 103-107