Review Article
AMERICAN JOURNAL OF PHARMACY AND HEALTH RESEARCH
www.ajphr.com
2017, Volume 5, Issue 5
ISSN: 2321–3647(online)

Fixed Dose Combination and Disease Management: A Review

Miji Jose[1]*, K. Krishnakumar[1], L. Panayappan[2]
1.Department of Pharmacy Practice, St James College of Pharmaceutical Sciences, Chalakudy, Kerala
2.St James Hospital Trust Pharmaceutical Research Centre (DSIR Recognized), Chalakudy, Kerala

ABSTRACT

Fixed dose combinations (FDCs) are the combinations of two or more active drugs in a single dose form. It is the current hot topic of deliberations in the pharmaceutical industry, drug regulatory agency, and the pharmaceutical trade. Surprisingly, it is not among the doctors prescribe the medicines or the patients who consume. Basically, from one point of view it increases patient compliance, but from other point of view there are chances of consuming medicines, more than what is required. A relook and rationalization may be required in the use of combination product and this is the basis on which this article has been developed.

Keywords: Fixed dose combinations, Essential drugs.

*Corresponding Author Email: stjamespharmacyproject@gmail.com
Received 03 May 2017, Accepted 19 May 2017

Please cite this article as: Jose M *et al*., Fixed Dose Combination and Disease Management: A Review. American Journal of Pharmacy & Health Research 2017.

INTRODUCTION

Nowadays people are usually suffering from several types of various infectious diseases that may corresponds to cardiovascular, hormonal, gastrointestinal, central nervous system disorder. Subsequently, in order to treat such kind of disorder one has to depend upon either of various medicinal agents which are prescribed either as a single drug or in the form of combination product/fixed dose combinations (FDCs). [1]

Combination products, are also known as fixed dose drug combinations (FDCs) drug, are combinations of two or more active drugs in a single dosage form. The World Health Organization (WHO) lists nearly 325 essential drugs, including only 19 of such drug combinations. They provide the advantages of combination therapy while reducing the number of prescriptions and the attendant administrative cost. Fixed dose combinations are valuable only when they have been developed based on sound pharmacokinetic and pharmacodynamics criteria[2].

Categories of FDC Products

FDCs can be classified into several categories:

- Some of the earliest FDCs have been widely accepted as rational combinations of drugs which are suitable for all of their target group of patients, on the basis of pharmacology or patient acceptability.eg:- many topical preparations, such as eye and ear drops and skin formulations.
- Inappropriate drug combinations, where pharmacological claims for synergy or supported by little clinical evidence, e.g.:-the combination of caffeine with analgesics.
- Mixtures of drugs which are of benefit to only a few patients. Examples combinations of potassium sparing diuretics with thiazides and multi component antacid mixtures.
- Combinations of drugs for chronic conditions in which multiple drug regimens are recommended (E.g. HIV / AIDS). Such redeems place a significant pill burden on patients, particularly those with co-morbidities and FDCs in these patients may improve adherence.
- Formulations (E.g. Asthma inhalers) contain two drugs but only one prescription charge is payable, which benefits who pay for their prescriptions.[3]

Fixed Dose Combination: Rational or Irrational

Rational drug therapy means the use of right medicine in right manner (dose, route, frequency of administration, duration of therapy, etc.) in the right patient at the right cost and at the right time.

Some FDA approved FDC drugs are listed in table 1. However it is staggering to find that over eighty thousand formulations are sold in the Indian market, which includes several FDCs and other single drug formulation. There has been an alarming increase in irrational use of fixed drug combinations in the recent past and pharmaceutical companies manufacturing these FDCs are luring physicians to prescribe their products even when they are not needed by the patients.[4]

Advantages Of FDC Products

- Simpler dosage schedule improves compliance and therefore improves treatment outcomes.
- Costs of manufacturing is lower compared to the costs of producing separate products.
- More convenient for the patient as he has to buy one drug compared to two.
- Reduces inadvertent medication errors.[5]

Disadvantages of FDC Products

- Dosage alteration of one drug is not possible without alteration of the other drug.
- If a patient is allergic or has a side effect to one component, the FDC must be stopped and replaced by separate medications.
- By simple logic there are increased chances of adverse drug effects and drug interactions compared with both the drugs given individually.[5]

Success Factors for FDC products Formulation

- Formulation development challenges.
- Patent feasibility
- Pricing and reimbursement
- Physician consideration[6]

Table 1: Rational FDC drugs.[1,3]

GENERIC COMBINATIONS	CATEGORY	DOSAGE FORM
Amoxicillin + Clavulanic acid	Antibiotic	Tablet
Neomycin + Bacitracin	Antibiotic	Ointment
Cefadroxil + Clavulanic acid	Antibiotic	Tablet, Dispersible tablet
Ceftazidime + Tazobactum (as sodium)	Antibiotic	Injection
Cefixime + Cloxacillin (as sodium) + Lactobacillus (45 million spore)	Antibiotic	Tablet
Sulfamethoxazole + Trimethoprim	Antibacterial	Tablet
Sulfadoxoine + Pyrimethamine	Antibacterial	Tablet
Isoniazid + Ethambutol	Antitubercular	Tablet
Rifampicin + Isoniazid	Antitubercular	Tablet
Rifampicin + Isoniazid + Pyrazinamide	Antitubercular	Tablet
Thiacetazone + Isoniazid	Antitubercular	Tablet
Benzoic acid + Salicylic acid	Antiseptic	Ointment, Cream
Ethinylestradiol + Levonorgestrel	Antifertility	Tablet
E thinylestradiol + Norethisterone	Antifertility	Tablet
Levodopa + Carbidopa	Antiparkinsonism	Tablet
Ferrous salt + Folic acid	Haematinics	Tablet
Lidocaine + Epinephrine	Local Anesthetic-Vasoconstrictor	Injection
Pantoprazole + Domeperidone	GERD	Tablet
Telmisartan + Amlodipine (as besylsate)	Antihypertensive	Tablet

Table 2: Irrational FDC drugs

GENERIC COMBINATIONS	REASON OF IRRATIONALITY
Nimuselide + Paracetamol	Nimesulide is banned in most countries. No documentary evidence of prominent effect of combination
Atorvastatin + Nicotonic acid	Probability of myopathy may increase
Cetrizine + Phenylpropanolamine + Pseudoepherdine	It has potential to cause paracetamol stroke,glaucoma and prostate enlargement
Amoxicillin + Cloxacillin	Amoxicillin is inactive against staphylococcus and cloxacillin is not very active against streptococci. One of the components is useless for any given infection. Increasing the chances of resistance
Enalapril + Losartan	Two drugs affecting the same pathway donot add to efficacy.

FDC PRODUCTS AND DISEASE MANAGEMENT

Anti-infective

Combination therapy is essential for the treatment of HIV/ AIDS. The goals of HIV therapy are to maximally and durably suppress virus to allow recovery of the immune system and reduce the emergence of HIV resistance. At least three active drugs usually from two different classes are required to suppress the virus, allow recovery of the immune system, and reduce the emergence of HIV resistance. The FDCs for the treatment of HIV should have the following criteria

- Contain two or more components of a fully suppressive regimen.
- Require a once or twice daily administration.
- Have clinical efficacy and safety data that support the use of combinations.
- Be commonly used in treatment-naïve patients.
- Have drug interactions and toxicity profiles that allow for concomitant dosing.
- Antiretroviral combination therapy defends against resistance by suppressing HIV replication as much as possible.[7,8]

Antihypertensive

Several drug classes can be utilized in the treatment of hypertension: thiazide diuretics,β-blockers, calcium channel blockers (CCBs),angiotensin converting enzyme(ACE) inhibitors, angiotensin II receptor blockers, α-blockers, and centrally acting agents. These drugs have proved to be safe and efficacious in numerous randomized trials.[9]

Antihyperlipidemic

Out of various available FDC drugs as Antihyperlipidemic, the comparative efficacy of the most popular marketed drugs is being discussed here. These are Vytorin and Advicor. Vytorin is a combination of another statin, simvastatin, and a never drug ezetimibe, while Advicor is a combination of HMG-CoA reductase inhibitor (statin)-lovastatin with an extended release formulation of niacin. For Vytorin, the difference in LDLc lowering compared to its component statin, simvastatin, was a mean of 14% across all doses. For Advicor, the difference in LDLc lowering compared to lovastatin monotherapy ranges from 10-24%.[10,11]

Antidiabetic

An observational study of a database of pharmacy prescription refills for 6502 patients taking metformin & glibenclamide over six months showed no significant difference in concordance among newly treated patients receiving monotherapy, a combination of the two drugs or a FDC[12].

CONCLUSION

The FDCs is becoming popular rapidly; particularly when more than one disease is found in a patient. Patients have already seen the benefits of combination products in areas such as oncology, cardiology, neurological, metabolic disorders, respiratory, HIV, as well as several other areas. On the other side, irrational FDCs may cause unnecessary financial burden on consumers. Drug regulatory bodies should take urgent action to stop the free flow of irrational FDCs

REFERENCES

1. WHO Model List (revised march 2005); Available form: http://whqlibdoc.who.int/hq/2005/a87017_eng.pdf. (Accessed on 10.02.17).
2. Jayanti P, Tiwari P, Uppal R. Evaluation of rationality of FDC: Focus on antihypertensive drugs. Indian Journal of pharm sci. 2006; 68(5):649-652.
3. WHO, Geneva; WHO technical report series No. 867. 37: 1997.
4. Connor J, Rafter N, Rodgers A. Do fixed combination pills or unit of use packaging improve adherence? A systematic review. Bull World Health Organization 2004; 82(12):935-939.
5. Panda J, Tiwari P, Uppal R. Evaluation of rationality of some FDC: Focus on antihypertensive drugs. Indian Journal of Pharm. Sci. 2006; 649-652.
6. Albert I, Wertheimer, Morrison A, Combination drugs: Innovation in pharmacotherapy. Pharmacol and Ther, 2002; 27(1): 44-49.
7. US food and drug administration, fixed dose combination and Co-Packaged drug Products for treatment of HIV, 2004. Available from: http://www.fda.gov/RegulatoryInformation/Guidances/ucm125278.htm. (Accessed on 14.02.17).
8. Ramsay LE, Williams B, Johnston GD, MacGregor GA. Guidelines for management of hypertension: Report of the third working party of the British Hypertension Society. J Hum Hypertens, 1999; 13: 569-592
9. National Cholesterol Education Program Expert Panel on Detection EaToHBCiA. Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adults Treatment Panel III) final report. Circulation, 2002; 106(25):3143-3421.
10. Ballantyne CM, Abate N, Yuan Z, King TR, Palmisano J. Dose-comparison study of the combination of Ezetimibe and Simvastatin (Vytorin versus Atorvastatin in patients with hypercholesterolemia: the Vytorin Versus Atorvastatin (VYVA) study. American Heart Journal, 2005: 149(3):464-473
11. Bays HE, Dujovne CA, McGovern ME. Comparison of once-daily, niacin extended-release Lovastatin with standard doses of Atorvastatin and Simvastatin (the Advicor Versus Other Cholesterol Modulating Agents Trial Evaluation). American Journal of Cardiology, 2003; 91(6):667-672

12. Melikan C, White TJ, Vanderplas A, Dezii CM, Chang E. Adherence to oral antidiabetic therapy in a managed care organization: a comparison of monotherapy, combination therapy, and a fixed combination therapy, Clin Therapeutics, 2002; 24: 460-467.