WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 6.805
Volume 5, Issue 10, 933-943. Research Article ISSN 2277– 7105

SENSITIZATION OF MEDICAL UNDERGRADUATES TO IRRATIONAL DRUG COMBINATIONS

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Article Received on
12 Aug. 2016,

Revised on 01 Sep. 2016,
Accepted on 22 Sep. 2016

DOI: 10.20959/wjpr201610-7149

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ABSTRACT

Background: A single dosage form having two or more active pharmacological ingredients is called a fixed dose combination (FDC). Justification and rationality is found with very few FDC's. Fixed dose combinations have many advantages and disadvantages. A FDC can be rational or irrational depending on the WHO criteria for rationality. FDC play a crucial role in chronic disease treatment adherence with increased compliance. Rationality of a FDC has always been a debatable issue over the years. FDC need to be prescribed, if possible from WHO essential drug list or National Essential Medicine List of India. Sensitization of health care professionals at beginning of their career is very important to curb this problem from the root itself. **Methods:** It was a prospective observational study. Few random students were selected from 2nd year MBBS and were told to note down various FDC's listed in CIMS, MIMS and Drug Bulletin. FDC were later analyzed for rationality based on WHO rationality criteria. Few of the most common FDC which were found irrational have been mentioned in our study explaining the basis for same. **Results:** Many FDC's were scrutinized for rationality and irrational ones were mentioned explaining the reason for same. This denoted that marketing approval for a FDC is very lax and health care professionals are falling prey to unethical practice by pharmaceutical industries, by bribing doctors in form of various goodies. Assessment and vigilance of adverse drug reactions reported or caused by FDC' needs to be done regularly. **Conclusion:** Most of the FDC's which were found irrational in our study were explained. Pharmaceutical companies need to understand importance of rationality before they come up with such combinations. Rational drug combinations are always of immense help to the health care system and cost effective. Guidelines for manufacturing and sales of FDC need to be followed by the Pharmaceutical companies.

KEYWORDS: rational, irrational, fixed drug combinations.

INTRODUCTION

When two or more active pharmacological ingredients (API's) are combined together in a single dosage formulation like tablet, capsule, syrup, powder or injection is termed as fixed dose combination (FDC). In a FDC, a combination is acceptable if drugs having different mechanism of action are brought together. After combination, the FDC becomes an innovation product.[1]

Irrational FDC prescribing has become a menace worldwide. India has also become a big hub for pharma industries making a good market share from FDC's. FDC is often called golden egg by the pharmaceutical companies which bring them a huge profit share. Most common FDC's are antibiotics, analgesics, cough and cold preparations, tonics, multivitamins, iron preparations and antacids. Indian laws for marketing approval of FDC's are very lax and not properly defined which makes a way for these irrational drug combinations to play a profitable part. Most common FDC's are antibiotics, analgesics, cough and cold preparations, tonics, multivitamins, iron preparations and antacids.

Combination in a single formulation may change the safety, efficacy and pharmacokinetic properties of a drug. Irrational drug combinations has become a pattern among developing countries which hamper quality of life of an individual, impose financial burden, hospitalization cost and increase intensity of adverse drug reactions.[2]

FDC are being prescribed widely all over India by both doctors working in private and government hospitals.[3] FDC is usually classified as rational or irrational. Rational drug usage will help patients to receive drugs appropriate to their clinical needs, dosage meeting their own individual requirements for adequate period and at affordable cost.

Most pharmaceutical companies are doing vigorous promotion of their FDC which gain them huge profits, in spite of their FDC being irrational. Equal half-life, apparent volume of distribution and peak plasma concentration are factors taking into consideration before combining a FDC.[4]

The essential medicine list of WHO 2015 has 336 medicines and 27 FDC's[5] whereas the National list of essential drugs of India has 376 medicines and 22 FDC's.[6] Numerous

irrational FDC's are marketed in India under various brand names. Most of them are not a part of essential medicine list.

Central and State Drug Control Authorities need to be stringent before granting approval for marketing a FDC. Rationality of a FDC has always been a debatable and controversial issue in developing countries which needs to seek attention.[7]

Rationality has always played an important part in treatment of an individual. As sensitization and upgrading of current information is important among medical undergraduates, we decided to carry out this observational study. If cumulative toxicities and risk: benefit ratio of a FDC is calculated or evaluated before approval, this would certainly increase rationality promotion of a FDC and reduce hazards of irrational ones.

Advantages of fixed dose combinations[8-10]

1. Reduction in number of pills
2. Low manufacturing, packaging and dispensing cost compared to individual products
3. Reduced side effects in few combinations e.g. levodopa + carbidopa
4. Reduced complexity compared to individual regimens
5. Improved compliance in chronic cases like TB, AIDS and Malaria
6. Improved efficacy in form of synergism e.g. estrogen + progesterone, sulfamethoxazole + trimethoprim.
7. Delay resistance development to antimicrobial regimens

Disadvantages of fixed dose combinations[8-10]

1. Dose titration may not be possible e.g. atorvastatin + amlodipine
2. One drug may be useless e.g. vitamins + iron
3. Increased cost due to unnecessary drug e.g. ibuprofen + paracetamol
4. Chance of adverse effects e.g. nimesulide + paracetamol
5. Inadequate dosage of individual contents e.g. multivitamins
6. Difficult to identify medicine causing adverse effect
7. Unsuitable pharmacodynamic profile can make treatment difficult

METHODS

It was a prospective observational study. Few random students were selected from 2nd year MBBS and were told to note down various FDC's listed in CIMS, MIMS and Drug Bulletin. FDC were later analyzed for rationality based on WHO rationality criteria.

WHO[11] has laid down guidelines for rational consideration of FDC:-

- ✓ Active pharmacological components having different mechanism of action
- ✓ Decrease occurrence of resistance for antimicrobial agents.
- ✓ Increased efficacy of combinations
- ✓ Reduced ADR incidence or toxicity
- ✓ Increased compliance of drug therapy
- ✓ Reduced total cost of therapy
- ✓ Combination must be appropriate fulfilling needs of a larger population group

Few of the most common FDC which were found irrational have been mentioned in our study explaining the basis for same. Such observational studies would definitely help students and readers to understand rationality of medicines before using in clinical practice.

RESULTS

In India many FDC's are available produced by various pharmaceutical companies which need to undergo rationality check. We found irrational FDC's easily outnumber the rational ones. Also many FDC's are not included either in WHO essential list or National Essential Medicine List of India.

Following were the FDC's; we criticized for their rationality and were found to be irrational:

1. Piperacillin + Tazobactum

Piperacillin is antipseudomonal penicillin. Tazobactum is beta lactamase inhibitor but unable to inhibit beta lactamase produced by pseudomonas. So, there is no justification for combination against gram positive pseudomonas infection.

2. Ampicillin + Cloxacillin

Cloxacillin is antistaphylococcal penicillin which is a gram positive cocci and Ampicillin is used against gram negative bacilli. Mixed infections are rare. So in a combination, one drug may be always useless and will add to cost of therapy.

3. Mucolytic + Antibacterial

Mucolytics liquefy thick tenacious secretions but these secretions are not always due to respiratory infections. So combining with an antibiotic may not seem rational always.

4. Antitussive + Expectorant + Mucolytics + Decongestant's

Antitussives mainly suppress dry cough whereas expectorants are used in productive cough. So combinations not rational as both have opposite action.

5. Monteluklast + Levocetrizine

Montelukast is a leukotriene antagonist. Levocetrizine is antihistaminic drug. Monteluklast mainly used in prophylaxis of bronchial asthma. Histamine has limited role in etiopathogenesis of bronchial asthma, so the combination may not be a rational one here.[12]

6. NSAIDS + Serratiopeptidase

Serratiopeptidase are oral proteolytic drugs claiming to have anti-inflammatory effects. Serratiopeptidase is destroyed in GIT, so many a times it cannot reach target site of action and also a costlier drug. So combination again may not help.

7. Glimepiride + Metformin + Voglibose

Glimepiride is anti-diabetic drug useful in non-obese patients whereas metformin preferred in obese diabetic patients. Also glimepiride is to be taken before meals and metformin in between or after meals. In this aspect, one drug may not work so better to prescribe each component separately. Voglibose is an alpha glucosidase inhibitor and is taken at bite of first meal.

8. Pantoprazole + Domperidone

Pantoprazole is a Proton Pump Inhibitor (PPI) used often in treatment of gastro esophageal reflex disease (GERD). Vomiting and nausea are not always found in peptic ulcer disease. Prokinetic agent like domperidone in GERD may or may not improve the outcome so usage of combination is still doubtful.[13,14]

9. Cephalosporin's + Clavulinic acid

Cephalosporins are one of most popular antibiotics used in clinical practice. There are inactivated by cephalosporinases produced by bacteria. Clavulinic acid is lactamase inhibitor which may not useful against cephalosporinases. So again the combination is not justified.[15]

10. Antibacterial + Antifungal + Steroids

Such combinations are irrational as patients never have mixed bacterial and fungal infections at same time. Steroids may help predispose infection in few cases.[16]

11. Phenypropanolamine + Levocetrizine

Phenypropanolamine is banned due to increased chance of hemorrhagic stroke.[17] So again combination is irrational.

12. Nimesulide + Paracetamol

Nimesulide is COX-inhibitor and Paracetamol is a COX-3 inhibitor. Nimesulide is banned due to increased hepatotoxicity risk. As both drugs have almost same pathway mechanism and increased risk of hepatotoxicity, combination becomes irrational.[18]

13. Paracetamol FDC (> 500 mg)

FDC with paracetamol must be in dosage of 325 mg, as there are more chances of angioedema and hepatotoxicity. This was the latest recommendation by WHO and CDSCO.[19]

14. B1 + B6 + B12

WHO has recommended taking these B-complex vitamins through diet rather than in combination products.[20]

15. Norfloxacin/Ciprofloxacin/Ofloxacin + Tinidazole/Ornidazole

Nitroimidazoles are used in diarrhea and dysentery cases along with fluoroquinolones in clinical practice. Most general practitioners think that mixed amoebic and bacterial infections are less common. So either of drug in this combination is useless and add to the heavy cost.[21]

16. H2 blockers + Proton Pump Inhibitors

H2 blockers like ranitidine/ famotidine are combined with PPI's like pantoprazole/ Rabeprazole and are being used in peptic ulcer cases which may not be rational as peptic ulcer is not always associated with vomiting.[22]

17. Dicylomine + Paracetamol

Dicylomine is an anticholinergic acting as antispasmodic whereas paracetamol is an analgesic. Paracetamol promotes sweating and dicylomine inhibits it. So such combination with opposite action might lead to dangerous elevation of temperature in body.[23]

18. Losartan + Enalapril/Ramipril

Losartan is angiotensin receptor blocker (ARB) and Enalapril/Ramipril are angiotensin converting enzyme inhibitors (ACEI). Both have mechanism of action through same pathway. Combination will be ineffective and less efficacious.[24]

19. Paracetamol + Codeine

Paracetamol is a NSAID and codeine a narcotic analgesic. Usually such combinations are prescribed for severe pain, but can lead to excessive sedation which itself is life threatening.[24]

FDC will play a safer part in humans if they are of sound pharmacokinetics and pharmacodynamics. This needs support by evidence based data and literature support.

DISCUSSION

The observational study carried out by medical undergraduates after gathering information from various sources as mentioned earlier certainly played a small part in understanding rationality and basis for same. Most common irrational FDC's having dubious role were antibiotics, nsaids, cough and cold preparations. Pharmacokinetic incompatibility of API's or cross reaction between them would certainly increase chances of adverse drug reactions among patients.

We found in our study that most of the times, addition of a second component in a FDC added to the increased cost and adverse drug reaction risk. This might be life threatening requiring hospitalization further increasing financial burden and reduced life quality.[25] FDC's will be a cost effective alternative only when are used for chronic diseases like TB, HIV infections, leprosy and malaria.[26]

Every day new FDC's are being made available to the Indian market. Prescribers are being influenced unethically, censor misleading claims and bribing is done on behalf of pharmaceutical companies for prescribing their FDC's. In terms of essential health care, very few FDC are of importance.[27]

DCGI and state drug controllers need to develop a robust vigilance system for marketing approval of drug combinations entirely based on rationality indicators. No new licenses or renewal for fresh license to be given by state drug controllers if the pharmaceutical companies do not follow the rationality criteria. Strict and urgent action needs to be taken to weed out irrational combinations from market. Scientific data with high impact factor must be taking in to consideration and randomized controlled trials showing superiority over individual drug components would help to generate quality combinations. Practitioners, scientists, regulatory authorities need to question back pharmaceutical companies if they find any signs of irrationality. Such approach would curb down irrational FDC's from market.[28]

Generic FDC having correct dose and if given for appropriate duration would help boost a patient's health status. Basic training programs, circulating drug bulletin, newsletters, standard journals/ textbooks & CME's for medical undergraduates, post graduates, general practitioners and other health professionals must be made available giving information about drugs and patient care. It is also a doctor's duty to keep themselves updated about irrational combinations and banned drugs.

Students need to be taught concepts about P drug, pharmacological basis for combination of each ingredient and ethical laboratory practices.[3]

As Doctors are treated life saver priests next to God, prescribing an irrational FDC not found in standard textbooks by health professionals might land them up in trouble, if a patient knocks the door of a consumer court.[29] Improvement in effectiveness not efficacy is seen with drug combinations. Measurement of drug performance in a clinical trial denotes efficacy. Measurement of drug performance in real practice denotes effectiveness.[30]

Making individual regimens less complex will increase compliance and might turn out to be more effective compared to drug combinations.[31] Therapeutic review committees by hospitals, clinical pharmacists and pharmacovigilance units will play a crucial role in imparting knowledge to health professionals and community.

CONCLUSION

FDC's found irrational were explained in the study. Availability of such irrational combinations in market signifies that pharmaceutical companies are still producing them in huge amounts & health care professionals need to be careful while prescribing such

combinations taking into consideration patient's health and economic status. Pharmaceutical companies need to understand importance of rationality before they come up with such combinations. FDC may not help in eradication of disease but would increase drug resistance, wastage of useful resources, increased treatment failure and mortality risk. Government laws need to be more stringent for action against defaulters. Raising voice against these irrational drug combinations in Indian market will help to reduce the magnitude of problem and a life saver. Rational drug combinations are always of immense help to the health care system and cost effective.

REFERENCES

1. WHO drug information volume 17. Geneva: WHO; 2003. Available at: http:// apps.who.int/medicinedocs/en/d/Js4955e/7.html.
2. Baiardini. I, Guerra. L, Pasquali, M, Bonadonna. P, Pasalaqua. G, Canonica. G.W. Quality of Life in Patients with Adverse Reactions to Drugs: Preliminary Results from A New Questionnaire. J Allergy Clin Immunol, 2004; 113(2): s70.
3. Gautam CS, Aditya S. Irrational drug combinations: need to sensitize undergraduates. Indian journal of pharmacology. 2006; 38: 169-70.
4. Ahmad Najmi, Umme Aiman. A critical appraisal of rational & irrational fixed drug combinations. Asian Journal of Pharmaceutical Science & Technology. 2015; 5(4): Page 335-337.
5. WHO model list of essential medicine 19th list. Available at: http://www.who.int/medicines/publications/essentialmedicines/en/. Cited on 30 August 2016.
6. National list of essential medicines 2015. Available at: http://cdsco.nic.in/Write Read Data/NLEM-2015/Recommendations.pdf.
7. N.K. Jain, A Akarte, P T Deshmukh, P Kanojia, N Gerud, Y Akash. Rationality of FDCs: An Indian Scenario. The pharma research. 2009; (1): 158.
8. Rational use of medicines. Good pharmacy practice - I.P.A. - C.D.S.C.O. - W.H.O. India country office. 15 Vol. 3|Issue 2| 2013 | 52-56.
9. Connor J, Rafter N *et al.,* Do fixed combination pills or unit of use packaging improve adherence. Bull W.H.O. 2004; 82(12): 935-939.
10. Albert I, Wertheimer, Morrison A. Combinations drugs. Innovation in pharmacotherapy. *Pharmacol and Ther*, 2002; 27(1): 44-49.

11. WHO Technical Report Series. WHO expert committee on specifications for pharmaceutical preparations, 39th report, Geneva, WHO, 2005.
12. Boushey HA. Drugs used in asthma, Basic and clinical pharmacology, by Bertram and Katzung 11th edition, 2009; 339-356.
13. Dhaneria SP. Rational and Irrational Drug Combinations. Drug Bulletin, 2010; 35(2): 1-15.
14. Tripathi KD. Drugs for peptic ulcer & GERD, chapter 46, 7th edition, 2016; Page-660.
15. Chambers HF, Deck DH. Beta lactam and other cell wall active antibiotics, basic and clinical pharmacology by Bertram & katzung, 13th edition, 2009; 773-793.
16. Robertson D, Maibach H. Dermatologic pharmacology, Basic and clinical pharmacology by Bertram and katzung 13th edition, New Delhi, 2009; 1047-1065.
17. Tripathi KD. Adrenergic system and drugs, chapter 9, 7th edition, 2012; 137.
18. CDSCO. Website-wide gazette notification GSR 82(E) dated 10.03.2011.
19. CDSCO. Limitations of acetaminophen (paracetamol) in prescription combination products and giving box warning about its liver toxicity [internet]. New Delhi: CDSCO; 2011 September 23. Available at: http://www.cipi.in/DCGI%20CIR23092011.pdf.
20. Deshmukh P, Purohit S. Rationality of Fixed Dose Combinations: Necessity to Weed out the Irrational Combinations Mushrooming in Pharmaceutical Industry. Pharmaceutical Reviews, 2008; 6(1).
21. Chakraborti A. Prescription of FDC drugs for diarrhea. Indian Journal of medical Ethics. 2007; 4: 165-7.
22. Soll AH. Medical treatment of peptic ulcer disease: practical guidelines. JAMA. 1996; 275: 622.
23. Amitav. S: Indian markets fixation with FDCs (editorial) rational drug bulletin. 2002; 12: 1.
24. Kasarla Raju, Elumalai A, Eddla Sridhar. Irrational drug combinations. International Journal of Experimental pharmacology. Vol. 3/Issue 2/2013/52-56.
25. Chandler SC, Lekha S. Fixed dose drug combinations (FDCs): rational or irrational: a view point. Br J Clin Pharmacol. 2008 May; 65(5): 795–796.
26. WHO. Proposal of listing FDCs for infectous diseases [internet] WHO. Available at: http://archives.who.int/eml/expcom/children/Applications/ Monday_2_FDC.pdf.
27. Chakraborti A. Fixed dose combinations in therapy [internet]: pharma voice; 2007 August. Available from http://www.expresspharmaonline .com/20070815/research02.shtml.

28. Hindoliya M, Sharma PK, Dhaneria SP. Prescribing Trends of Fixed Dose Combinations in Teaching and Non-Teaching Hospitals of Ujjain District. Journal of Pharmacy Research, 2012; 5(7): 3503-3505.
29. C.S Gautam, L. Saha. FDCs- rational or irrational: a view point. British Journal of Clinical Pharmacology. 2008 May; 65(s): 795-6.
30. Glasgow RE, Lichtenstein E, Mercus AC. Why don't we see more translation of health promotion research to practice? Rethinking the efficacy to effectiveness transition. American Journal of Public Health. 2003; 93(8): 1261-7.
31. Podolsky SH, Greene JA. Combination drugs- Hype and hope: New England Journal of Medicine. 2011; 356(6): 488-91.