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IRRATIONAL DRUG COMBINATIONS

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ABSTRACT

Irrational Drug Combinations or Fixed Dose Combinations(FDCs) are combinations of two or more active drugs in a single form. The rationality of a fixed dose combination is the most controversial and debated issue in today's clinical practice. Combination drugs increase the risk of side effects, lead to an ineffective dosage and liability to abuse and may also needlessly increase the cost. Drug combinations make it more difficult to find the causative agent responsible for the adverse reactions. In many cases their stability is doubtful, reducing the efficacy of many preparations. The Fifteenth WHO model list of essential medicines contains only 25 approved fixed dose combinations, whereas in some countries, there are innumerable examples of irrational drug combinations, which are easily available and can be bought even without a prescription. A system of screening the drug combinations that are already licensed and available in the market is implemented in many developed and developing countries.

Keywords: irrational drug, drug combinations, fixed dose combinations (FDCs).

INTRODUCTION

When two or more drugs are combined in a fixed dose formulation like tablet, capsule, syrup, powder or injection, then their plasma half-life should approximately be same. The ratio of dose would depend on the volume of distribution and peak plasma concentration. If the combination of drugs is illogical in terms of plasma half-life and pharmacokinetics of the drug, the combination should be termed as irrational drug combination. Large numbers of such irrational drug combinations are available in the market which unnecessarily increase the cost of medication and add to the side effects of the therapy. Fixed combination useful in case of more etiological reasons of disease. For example, The additive or synergistic effect of combination therapy fully lowers blood pressure in patients who tend to have less than full response to one component only. Antihypertensive monotherapy does not address the

multifactorial nature of hypertension as a disease with many pathways; using more than one drug makes more therapeutic sense, as combined agents cover more than one etiology [1].

Advantages of fixed dose combinations

1. Combination medicines have the advantages of combination therapy as well as advantages related to reducing the number of pills to be taken.
2. Lower costs of manufacturing compared to the costs of producing separate products.
3. The side effects of one medicine can be reduced by combining it with another medicine in FDCs, e.g., levodopa + carbidopa.
4. Reduced administration costs stem from simplified packaging, fewer prescriptions, and lesser dispensing time and cost.
5. Reducing the number of pills diminishes the complexity of the regimen and therefore leads to improved patient adherence.
6. FDCs can improve compliance in the treatment of chronic infectious disease, where in case of drug-resistant

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7. strains, treatment failure, and a threat to public health, e.g., treatment of TB and HIV.
8. The efficacy of one medicine can be synergistically increased by combining it with another, e.g., estrogen + progesterone, sulfamethoxazole + trimethoprim [2-4].

Disadvantages of fixed dose combinations

1. Titration of dose of medicine to suit individual patients is not possible, e.g., atorvastatin 10 mg + amlodipine 5 mg.
2. One of the drugs in the combination may be superfluous or wasteful, e.g., vitamins + iron.
3. FDCs increase the price of the medication if unnecessary drugs are included, e.g., ibuprofen + paracetamol + caffeine.
4. The incidence of adverse effects increases, e.g., nimesulide + paracetamol.
5. In FDCs, there is always a chance that individual medicines may not be present in adequate amounts, e.g., multivitamins.
6. Incompatible pharmacodynamics, e.g., combination of an antihistaminic with an antidiarrheal is dangerous as the antihistaminic action may mask other symptoms and make accurate diagnosis and treatment difficult.
7. It is difficult to identify which medicine in the FDCs has caused an adverse effect [2-4].

Some Of Category wise Irrational Drug Combinations or Fixed Dose Combinations

1. Ampicillin + Cloxacillin

Ampicillin is effective against Gram negative bacilli but Cloxacillin is an Anti-staphylococcal penicillin and not effective against Gram negative bacilli. Mixed Gram negative and Staphylococcal (Gram positive) infection rarely coexists. So, in a patient with a single infection, one of the drugs of the combination would be useless. In addition to the cost of therapy it would add to adverse side effects and resistance of bacteria to the drug. On the other hand the combination would reduce the dose of effective drug to the half and the patient would need longer course of therapy.

2. Antibacterial + Antiamoebic Combinations:

Ciprofloxacin + Metronidazole, Norfloxacin + Tinidazole and Ofloxacin + Ornidazole are such commonly available fixed dose drug combinations. In bacterial diarrhoea only anti-bacterial drug is effective and antiamoebic drug is useless. Similarly, in intestinal amoebiasis only antiamoebic drug is effective while antibacterial drug is useless. Amoebiasis and bacterial diarrhoea rarely coexist. The therapy should be based on the diagnosis to reduce the cost of treatment since in a given case, only one drug of the combination would be effective and the other one would be useless.

3. NSAIDs Combinations

Nimesulide, diclofenec, ibuprofen and

Paracetamol are some non-steroidal anti-inflammatory drugs (NSAIDs). There is no justification in combining one NSAID (nimesulide, diclofenec, ibuprofen) with another NSAID (paracetamol) having same pharmacological actions. The increased risk of hepatotoxicity has been reported due to the use of combination of nimesulide with paracetamol. There is increased risk of nephrotoxicity with NSAIDs combinations.

4. H₂ Blocker + Domperidone

Ranitidine and Famotidine are H₂ blockers. H₂ blockers reduce gastric acid production in peptic diseases and give symptomatic relief. The combination of these drugs with antiemetic drug (Domperidone) is an irrational drug combination as peptic ulcer is not always associated with vomiting. Even in gastro-esophageal reflux disease (GERD), the domperidone is less effective as compared to metoclopramide, so combining H₂ blockers with domperidone seems to be an irrational choice.

5. Domperidone + Proton Pump Inhibitors

Omeprazole, Pantoprazole and Lansoprazole are proton pump inhibitors. Proton pump inhibitors reduce gastric acid production in peptic diseases and give symptomatic relief. The combination of these drugs with antiemetic drug (Domperidone) is an irrational drug combination as peptic ulcer is not always associated with vomiting. Even in gastro-esophageal reflux disease (GERD), the domperidone is less effective as compared to metoclopramide, so combining proton pump inhibitors with domperidone seems to be an irrational choice.

6. Ondansetron + Proton Pump Inhibitor or H₂ Blocker

Such combination drugs are prescribed for the acid peptic disease, but the disease is not always associated with vomiting. So, the combination of Ondansetron, an antiemetic drug with antisecretory drug like H₂ blocker (Ranitidine) or proton pump inhibitor (Omeprazole, Pantoprazole or Lansoprazole) seems to be an irrational drug combination.

7. H₂ Blocker (Ranitidine) + Antispasmodic Drug (Dicyclomine)

The pain of peptic ulcer is due to high level of gastric acid but not due to spasm of smooth muscles and will subside only with reduction in gastric acid in stomach by use of H₂ blocker (Ranitidine) or proton pump inhibitor drugs (Omeprazole, Pantoprazole or Lansoprazole). So there is no justification in combining H₂ blocker (Ranitidine) with antispasmodic drug (Dicyclomine).

8. Antacid + Antianxiety Drug

The acid peptic disease is rarely associated with psychosomatic basis. So, there is no justification of combining antianxiety drug like diazepam with antacids.

The simultaneous use of antacids with antianxiety drugs should always be avoided as antacids reduce the absorption of antianxiety drugs.

9. Antacid + Antispasmodic Drug (Dicyclomine)

There is no justification in combining antacids with antispasmodic drug like Dicyclomine, because the pain of peptic ulcer is not due to the spasm of the smooth muscles.

10. Mucolytic Agent + Antibacterial

Ambroxol + Ciprofloxacin or Cefadroxil or Roxithromycin. Ambroxol is a mucolytic agent used to liquefy thick respiratory secretions. There is no justification in combining mucolytic agent with antibacterial, as thick secretions in respiratory tract are always not due to respiratory infections. Also the antibacterial therapy always does not require an associated dose of mucolytic agent.

11. Mebendazole + Pyrantel-pamoate or Levamisole

Dosages' schedule of both the drugs mismatch so the combination of such two anthelmintic drugs is irrational. The Mebendazole is required to be administered twice a day for three days whereas Pyrantel-pamoate or Levamisole should be administered as a single dose.

12. Leukotriene Antagonist (Montelukast) + Bambuterol or Levocetirizine

Montelukast, the leukotriene antagonist is used as alternative to inhaled steroid in the management of mild persistent asthma. Levocetirizine is an antihistaminic drug and has limited role in the control of asthma as it is not only histamine that triggers the asthma attack. Bambuterol is a long acting beta-2 agonist having role in the management of moderate persistent asthma as well as severe persistent asthma. There is no justification in combining of Montelukast with Bambuterol or Levocetirizine.

13. Metformin + Glimepiride + Pioglitazone

Metformin is indicated drug in obese type -2 diabetes mellitus whereas Sulfonylurea (Glimepiride) is indicated drug in non-obese type-2 diabetes mellitus. As per pharmacological principle, other drug should be added only when monotherapy fails. Metformin (biguanide) is to be administered after meal whereas Glimepiride (sulfonylurea) drug is to be administered before meal, therefore even when both the drugs are required, it would be better to administer them separately. Pioglitazone is indicated in suspected cases of insulin resistance. So, the combination of all these drugs in one formulation is an irrational drug combination.

14. Domperidone+ Rabeprazole or Domperidone + Esomeprazole. Increased incidence of rhabdomyolysis

15. Prokinetic+Proton Pump Inhibitor

Cisapride+ Omeprazole; Mosapride+ Pantoprazole
In patients with gastro esophageal reflux disease, the use of this combination has shown no benefit due to addition of prokinetic agents.

16. Codeine+NSAID (paracetamol)

This combination is used to treat severe pain or to inhibit pain perception but these combinations can cause excessive sedation which can be dangerous. Needs further examination.

17. Multi vitamin preparations

Multivitamin combination is considered to be irrational. Excessive use may leads to several side effects.

18. Expectorant+central cough suppressants + antihistaminics + bronchodilator+mucolytic agent

Bromhexine Hydrochloride 8 mg + Terbutaline sulphate 2.5 mg + Guaiphenesin 100 mg + Menthol 5 mg, this combination of expectorants is a costlier way of helping a condition which is often self-resolving. Expectorant given in effective doses are often not tolerated and produce adverse drug reaction.

19. Ayurvedic preparations

Himsra + Kakamachi + Kasani + Arjuna + Tharaka, These ayurvedic preparations have no any proven efficacy.

20. Enalapril + Losartan

Combining two drugs affecting the same pathway is irrational; it does not add to efficacy [5-9].

Reasons for irrational use of drugs

1. Lack of information related to indications & safety of drugs.
2. Faulty & inadequate training & education of medical graduates
3. Poor communication between health professional & patient
4. Lack of diagnostic facilities/Uncertainty of diagnosis:
5. Demand from the patient
6. Defective drug supply system & ineffective drug regulation
7. Promotional activities of pharmaceutical industries:

Hazards of Irrational Use of Drugs

Irrational use of drugs may lead to:-

1. Ineffective & unsafe treatment
2. Exacerbation or prolongation of illness.
3. Distress & harm to patient
4. Increase the cost of treatment

What needs to be done?

1. The hit and trial method of combining drugs should be replaced by a rational and logical basis for bringing out a fixed dose drug formulation. Operational, statistical and mathematical models constitute a highly versatile framework for mechanism based modelling (pharmacokinetic/ pharmacodynamic) by taking signal transduction properties of the drug combination into account.
2. There is a need to carefully monitor and censor misleading claims 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. 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.
3. There is a need to strengthen the mechanism for

continuing professional development of practitioners to ensure that they have the necessary knowledge and skills to prescribe rationally. Perhaps the insistence that prescribers, especially those in private practice should undergo a continuing medical education (CME) course once in two years on newer drug combinations, new drug molecules introduced into the market and adverse drug reactions will go a long way in curbing irrational prescribing.

4. ADR reporting should be made mandatory as they are in developed countries. Pharmacovigilance should be more effective.
5. Hospitals should constitute drugs and therapeutics review committees to rationalize prescribing.
6. Finally, medical schools and postgraduate colleges must take the responsibility of training students and young doctors how to assess new drug combinations more logically.

Table :Fixed dose combinations that are approved in National Essential Drug List

S.No	Combination	Therapeutic category
1.	Levodopa + Carbidopa	Anti-parkinsonism
2.	Isoniazid + Rifampicin	Antitubercular
3.	Isoniazid + Ethambutol	Antitubercular
4.	Thiacetazone + Isoniazid	Antitubercular
5.	Benzoic acid+ salicylic acid	Antifungal
6.	Sulfadoxine+ Pyrimethamine	Antimalarial
7.	Ichtammol (10%)+ Glycerine 5%	Antiseptic
8.	Sulfamethoxazole+ Trimethoprim	Antibacterial
9.	Tannic acid+ Glycerine	Antiseptic
10.	Aluminium Hydroxide + Magnesium Hydroxide	Antacid
11	Ferrous salt+ folic acid	Antianaemic

CONCLUSION

Rational combinations can be of immense help to the health care system. These combinations may improve the quality of life for many people. Such combinations (for example, antitubercular and antiretroviral combinations) are used frequently for many diseases. However the irrational fixed dose combination products are considered to be equally harmful. According to the WHO Expert Committee, combination drugs should only be used when there are no alternative of single drugs available for treatment or no alternative single drug is cost-effective for the purpose. Combination drugs increase the risk of side effects and may also needlessly increase the cost.

Combination drugs are irrational also because their stability is doubtful, reducing the efficacy of many preparations.

The analysis of reports received by pharmacovigilance centres show that the common reason for adverse drug reactions is irrational use of medicines. One of the main causes of irrational use of medicines may be availability of irrational fixed dose combinations. Most essential drugs should be formulated as single compounds. Fixed dose ratio combination products are acceptable only when the dosage of each ingredient meets the requirements of a defined population group and when the combination has a proven advantage over single compound administered separately in therapeutic effects, safety or compliance.

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