Fixed-Dose Combinations

21

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Abstract

Fixed-dose combinations or FDCs are combinations of two or more active pharmaceutical ingredients in a single dosage form in a fixed ratio usually for the same indication. FDCs aim to improve the therapeutic efficacy of each component of the medication while reducing the adverse drug reactions. When produced appropriately, they have the advantage of decreasing the total cost of the medication while improving the ease of administration and adherence to the medication. FDCs make it difficult to identify the causal relationship of toxicity when it occurs and to make dose changes to the individual components. Further, many irrational combinations increase patient's drug exposure aiming to improve the profit margins of the pharmaceutical companies. Strong and rigid guidelines need to be implemented to make FDCs rational and safe.

Keywords

Fixed-dose combinations · Medication · Combinations

21.1 Introduction

- Fixed-dose combinations or FDCs are combinations of two or more active pharmaceutical ingredients in a single dosage form in a fixed ratio usually for the same indication.
- FDCs are different from *co-blistered combinations* (*CBCs*). When two or more medications are packaged in the same blister pack, they are called co-blistered combinations or CBCs.

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21.2 Rationale for the Use of FDCs

FDCs are considered to be rational when there is adequate scientific evidence showing one or more of the benefits as given below:

- Increases therapeutic efficacy
- Reduces adverse drug reactions
- Lowers individual drug doses and exposure
- Lowers the total cost
- Decreases the development of resistance or tolerance
- Improves ease and therefore improves patient adherence

21.3 Criteria for FDCs

There are few conditions to be met before drugs can be combined in a fixed-dose combination:

- The drugs must act through different mechanisms of action.
- The pharmacokinetic profile of the drugs must be similar.
- The drugs should not cause additive toxicity.
- Benefits of using FDCs over individual drugs should be present.

21.4 Advantages of FDCs

Apart from the benefits for which FDCs are combined as shown in the rationale, there can be other advantages of using FDCs over the individual drugs:

- Reduce medication errors
- Facilitate patient compliance
- Simplify and improve the security of supply chains
- Help upscale national drug programs, for example, the antiretroviral therapy or the antitubercular therapy

21.5 Disadvantages of FDCs

- Difficulty in managing toxicity of one of the drugs in the combination.
- Changing individual drug doses is not possible.
- When one drug in the combination is contraindicated, the whole FDC cannot be used in the patient.
- Lead-in dosing or dose escalation (titration) of one of the components is not possible.

- Irrational combinations increase the cost.
- Irrational antibiotic combinations increase antibiotic resistance.

21.6 Examples of Rational FDCs Listed in the WHO Essential Medicines List

21.6.1 Sulfamethoxazole + Trimethoprim

This combination causes a sequential enzymatic blockade of the production of folic acid in bacteria resulting in an antibiotic effect. The combination has been found to have a synergistic action that the combination is often bactericidal while the individual components are bacteriostatic. Sulfamethoxazole is chosen because of matching the pharmacokinetic profile.

21.6.2 Amoxicillin + Clavulanic Acid

Amoxicillin is an extended-spectrum penicillin which is susceptible to the action of beta-lactamases. Clavulanic acid inhibits the action of beta-lactamase. Hence the combination improves the spectrum of amoxicillin.

21.6.3 Levodopa + Carbidopa

This combination is used in the treatment of Parkinson's disease. Levodopa is converted to dopamine in the body by the action of DOPA decarboxylase. This reaction happens both in the central nervous system and in the periphery. The peripheral dopamine results in cardiovascular and GI side effects while reducing the bioavailability to the brain. Carbidopa prevents the peripheral decarboxylation, and hence the combination is effective for patients with Parkinson's disease.

21.6.4 Imipenem + Cilastatin

The half-life of imipenem is short when administered alone as it is degraded by renal dehydropeptidase I. This degradation is inhibited by cilastatin, and hence the antibiotic effect of imipenem is enhanced.

21.6.5 Ferrous Salt + Folic Acid

Iron and folic acid are two dietary supplements required during pregnancy. The combination improves compliance in pregnant mothers.

21.7 Examples of Irrational FDCs in the Indian Market

21.7.1 Fluoroquinolone + Nitroimidazole Combination

This combination is commonly prescribed for diarrhea and dysentery. Many cases of diarrhea might not require an antibiotic. Bacterial dysentery is treated with fluoroquinolones, while amoebic dysentery is treated with nitroimidazoles. These two rarely coexist. This FDC increases the patient's exposure to antibiotics causing increased resistance and cost.

21.7.2 Amoxicillin + Cloxacillin

Amoxicillin is an extended-spectrum penicillin commonly prescribed for Gram-negative infections. They are susceptible to the action of beta-lactamases. Cloxacillin is active against Gram-positives only and is resistant to the action of beta-lactamases. Amoxicillin + clavulanic acid is a better combination in this situation.

21.7.3 NSAID Combinations

Combinations like aceclofenac and paracetamol are commonly prescribed as the first-line pain-killers for common conditions. While the pharmaceutical industry claims some benefits, the combination is not required for many and often increases the cost and toxicity. There is no rationale in adding other NSAID combinations as well.

21.7.4 H_2 Receptor Blockers/PPI + Antiemetics

One example of such a combination is rabeprazole and domperidone. The common indication of proton pump inhibitors and H_2 receptor blockers is acid peptic disease. Vomiting is not a common feature, and the use of domperidone is not required in majority of patients.

21.7.5 Ramipril + Telmisartan

The use of two drugs with the same mechanism of action is generally irrational. Multiple ACE inhibitors are generally prescribed for patients with hypertension in view of decreasing the number of drugs that particular patient has to consume. However, most patients do not require simultaneous treatment with two drugs with the same mechanism of action.

21.8 Challenges for FDCs

21.8.1 Pharmaceutical Challenges

- Two or more drug to be made into an FDC must be physically and chemically compatible.
- The particle size of one can affect the uniform distribution of the other in the formulation.
- The dissolution profiles of the drugs combined should match.

21.8.1.1 Market Pressure

- Increased market pressure results in numerous irrational fixed-dose combinations being released to the Indian market

21.9 Examples of Some Banned FDCs in the Indian Market

21.9.1 Irrational Combinations of Aceclofenac (Examples)

- Aceclofenac (SR) + paracetamol
- Aceclofenac + paracetamol + famotidine
- Aceclofenac + paracetamol + rabeprazole

21.9.2 Combinations with Ambroxol and Other Cold Preparations (Examples)

- Ambroxol + levocetirizine + phenylephrine + guaiphenesin + menthol
- Ambroxol + guaifenesin + phenylephrine + chlorpheniramine
- Ambroxol + salbutamol + choline theophylline + menthol
- Caffeine + paracetamol + chlorpheniramine
- Caffeine + paracetamol + phenylephrine + cetirizine
- Dextromethorphan + levocetirizine + phenylephrine + zinc
- Levocetirizine + phenylephrine + ambroxol + guaiphenesin + paracetamol
- Azithromycin + ambroxol

21.9.3 Antibiotic Combinations (Examples)

- Azithromycin + cefixime
- Azithromycin + cefpodoxime
- Azithromycin + levofloxacin
- Azithromycin + ofloxacin

- Clobetasol + neomycin + miconazole + clotrimazole
- Ciprofloxacin + fluticasone + clotrimazole + neomycin
- Doxycycline + serratiopeptidase

21.9.4 Diabetic Combinations (Examples)

- Metformin 500/500 mg + gliclazide SR 30/60 mg + pioglitazone 7.5/7.5 mg
- Metformin 850 mg + pioglitazone 7.5 mg + glimepiride 1 mg
- Pioglitazone 30 mg + metformin 500 mg
- Voglibose and metformin + chromium picolinate

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