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Review Article

Impact of fixed-dose drug combinations regarding the compliance as compared with free-drug regimens

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ABSTRACT

Medication compliance is the act of taking medication on schedule or taking medication as prescribed. It has been observed that over half of all medications prescribed by doctors are never taken, or are discarded during the course of treatment. Complexity of treatment makes the patient to take several medications or doses every day which may lead the things more difficult. People who are very sick sometimes tend to neglect their drug therapy, taking it sporadically or lowering their dose in ways that can be harmful to their health. FDCs have become an important alternative to monotherapy in the treatment of different diseases like hypertension, diabetes, cancer, tuberculosis, asthma and COPD by offering several advantages including patients compliance, simple dosage schedule, superior efficacy and tolerability, reduced risk of adverse events, cheaper shipment and packaging activities. FDC increases the patients compliance but there are chances of consuming medicines, more than what is required. The development of fixed-dose combinations (FDCs) is becoming increasingly important from a public health perspective. Thus, the present study review the advantages and disadvantages of FDC and single therapy and give suitable recommendation towards the drug regimen.

Key words: fixed-dose combinations, drug regimen, patients compliance, treatment

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INTRODUCTION

The development of fixed-dose combinations (FDCs) is becoming increasingly important from a public health perspective. They are being used in the treatment of a wide range of conditions and are particularly useful in the management of complex diseases. The combination of medicines which contains two or more active ingredients at fixed dose in a single tablet is commonly called Fixed Dose Combination (FDC) [1]. FDC mainly presented to simplify complex medical regimens and potentially improve compliance. Therefore, it has also been advocated in several chronic diseases guidelines in hospitals and health authorities. The World Health Organization has published a series of guidelines relating to marketing authorization of finished pharmaceutical products (FPPs).

Currently there are no specific international guidelines for FDCs. Some national authorities have developed their own guidelines, some for specific classes of medicines. The Implications of Fixed Dose Combination (FDC) Compared to Single Pill Combinations (SPC): Based on Patients' View FDCs have advantages when there is an identifiable patient population for whom treatment with a particular combination of actives in a fixed ratio of doses has been shown to be safe and effective, and when all of the actives contribute to the overall therapeutic effect. In addition there can be real clinical benefits in the form of increased efficacy and/or a reduced incidence of adverse effects, but such claims should be supported by evidence [2]. Compliance is the willingness of patients to follow a prescribed course of treatment on time; it is clinically significant as non-compliance can lead to resistance to some drugs [3]. Compliance with medical recommendations, especially with drug therapy, has been recognized to represent a complex challenge since 2400 years ago.

Many studies in the literature have shown the importance of the implementing and producing the FDC over SPC in tertiary hospitals, especially when treating chronic diseases. As a consequence, this will ensure the improvement of patients' compliance [4]. The effect of taking multiple medications, mostly more than five, to manage co-existing health problems is always a challenge to the healthcare providers as well as the patients [5]. It is observed from different literatures that the use of a higher number of therapies has been independently associated with increased costs, risk for adverse events and drug-drug interactions. Regarding different complex diseases [6]. It is also been observed that some FDC are not rational. In the above context it may be recommended that the FDCs those are found to be rational considering safety and efficacy as the most important criteria that drugs should be available in the market for benefit of the people and it is also recommended that the drugs those are irrational urgent action may taken to stop the free flow of FDCs.

BACKGROUND

Combining two or more drugs in a single formulation causes changes in its efficacy, safety, and bioavailability profile; hence, FDCs are treated as new drugs. More than one-third of all the new drug products introduced worldwide during the last decade were FDC preparations. There are unfortunately no worldwide acceptable criteria to define irrational FDCs and no uniform principles or international standards for their development and regulatory assessment [7].

Rational use of drugs requires that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements for an adequate period and at the lowest cost to them and their community [8]. There is a growing concern about the increasing number of irrational FDCs in the developing countries, which impose unnecessary financial burden; increase the occurrence of adverse drug reactions, including allergy, hospitalization; and ultimately reducing the quality of life.

FDCs and to evaluate the rationality of FDCs prescribed in psychiatric patients [9]. The possible benefits of FDCs and/or CBCs are that they can:

- Increase patient adherence to treatment (especially FDCs)
- Delay the development of resistance (especially FDCs)
- Lower the total cost, including production, storage, transport, dispensing and other health system costs
- Reduce the risk of medication errors by prescribers, dispensers or patients themselves
- Simplify and increase security of supply systems (especially FDCs)
- Facilitate patient counselling and education, reduce waiting time
- Help in scaling up access to ARVs, as their use has been associated with a significant increase in enrolment in some pilot ARV programmes.

Problems associated with Fixed Dose Combinations during formulations are [10]-

- Formulating of FDC without any Justifications.
- Exploiting the liberal licensing system, many times, bizarre FDCs find place.

- The existence of unlimited brands of FDCs with different permutations and combinations leads to confusion rather than guiding the prescribing doctor.
- Due to the difficulties in developing new chemical entities, the pharmaceutical industry finds it easier to develop FDCs.

Based on the Pharmacological action and compliance the problems of Fixed Dose Combinations are-:

- Pharmacodynamic mismatch between the two components, one drug having additive/antagonistic.
- effect leading to reduced efficacy or enhanced toxicity.
- Pharmacokinetic mismatch and having peak efficacy at different time.
- Chemical non compatibility leading to decreased shelf life.
- Drug interactions because of the common metabolizing pathway.
- Limitations of finer dosing titration of individual ingredients.

CLASSIFICATIONS Of FDC

FDC can be classified into several categories. Based on the disease management certain disease those need a treatment for long time like HIV, Diabetic, Hypertension, Hyperlipidemia, Tuberculosis [9]. Based on the physician's consideration the FDC may categorized as relative dosing of combination on an individual patient and source of side effect. Based on the formulation i.e. formulation development challenges, patent feasibility and pricing of the product [11].

CRITICAL ISSUES DURING EVALUATIONS OF FDC

The safety is an important sign with regards to the administered of the drug, the efficacy is an important sign with regards to the therapeutic advantage of the FDC compared to monotherapy. The demonstration of bioequivalence between the FDCs and the mono drugs can be very difficult and sometimes, especially insoluble molecules in mono-drugs can complicate the biopharmaceutical and pharmacokinetic behaviours [12]. In stability different pharmaceutically active ingredients may start interactions or incompatibilities that may lead to destabilization; in order to overcome this problem, some modifications should be done during development in order to assure that the product will remain stable during the period defined in the regulations [13].

CONCLUSION

Medicines are an integral part of healthcare. More than one drug is frequently used for treatment of either single ailment or multiple comorbid conditions. Sometimes, two or more drugs are combined in a fixed ratio into a single dosage form, which is termed as fixed dose combinations (FDCs). The use of FDC therapy has been widely accepted in recent years due to its convenience and advantage they provide for treatments. Instead of taking two or more drugs, the use of a single medication has eased the patient's life as well as physicians in prescribing drugs. Since they are the combination of pre-approved drugs, they can be easily administered to patients. The synergistic effect induced by two drugs and with different mechanisms, many problems such as the development of resistance to the drug, stability and side effects can be prevailed. The FDCs are justified when they demonstrate clear benefits in terms of adverse effect compliance and the cost. It is important that the above claims are adequately supported by scientific evidence. A revision, relook and rationalization may be necessary by the Government and Pharmaceutical Company in future regarding the use of combination products.

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