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RESEARCH ARTICLE

Evaluation of prescription pattern of fixed-dose combinations in a tertiary care hospital in India – A cross-sectional study

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ABSTRACT

Background: Inappropriate and indiscriminate use of fixed-dose drug combinations (FDCs) may lead to increased cost, unnecessary exposure to drugs, and adverse drug reactions. Government of India had issued a ban notification on manufacturing and sale of few FDCs which involved human risk and no therapeutic justification for their use. Despite the stringent steps from the health-care authorities, such FDCs are available in the market and are being prescribed extensively without considering the appropriate alternative in the form of a single drug formulation. **Aims and Objective:** This study was planned to find out the number FDCs prescribed by clinicians and find out the rationality with respect to the indication. **Materials and Methods:** Prescriptions of patients attending hospital pharmacy and indoor papers of patients admitted in the wards were screened for the presence of FDCs for a period of 6 months. A total of 3500 prescriptions were screened, and collected data were analyzed using descriptive statistics. **Results:** Out of 3500 prescriptions screened, 1000 (28.5%) had FDCs prescribed in it. Out of 1000 FDCs, 151 (15.1%) were prescribed by generic names and 849 (84.9%) were prescribed by brand names. A total of 596 (59.6%) FDCs were prescribed for infectious diseases followed by 195 (19.5%) FDCs prescribed for pain and inflammatory disorders and 169 (16.9%) FDCs were prescribed for diseases affecting the respiratory system. Out of 1000 FDCs, 818 (81.8%) were rational and 182 (18.2%) were irrational. **Conclusion:** The study revealed that the majority of prescriptions had rational FDCs prescribed by the treating doctors reflecting rational use of FDCs in our patients.

KEY WORDS: Fixed-dose Combinations; Irrational; Prescription Patterns; Rational Use

INTRODUCTION

The goal of drug therapy is to achieve the desired therapeutic response without producing toxicity, i.e., maximizing efficacy with minimal untoward effects. Low adherence to the prescribed medications for chronic conditions is well documented in literature, the impact of which is more in developing countries considering the dearth of health resources and inequalities in access to health care.[1-3] Concomitant use of two or more drugs (polypharmacy) adds to the complexity of individualization of drug therapy. To obviate these problems, two or more drugs in a fixed-dose combination were formulated with the objectives of providing benefits in terms of better therapeutic efficacy, improvement in pharmacokinetic profile, lowering the frequency of adverse effects, reduction in the pill burden, and attenuation

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in development of resistance, each reason being adequately supported by sound scientific evidence.[4-6]

As per the World Health Organization (WHO), the term fixed-dose drug combination (FDC) refers to "a product that contains two or more active ingredients." Since the product is of defined composition, the two (or more) ingredients are present in a fixed ratio, hence the term "fixed dose" or "fixed ratio" combination.[5] In recent years, prescribing FDCs has been widely accepted over using single drug formulations as it simplifies the drug therapy particularly in patients with comorbid conditions and also when more than one pathway is involved in disease pathogenesis.[7]

Use of FDCs is associated with many advantages such as synergistic action with increased therapeutic efficacy (e.g., cotrimoxazole; levodopa with carbidopa), reduced adverse effects (e.g., levodopa with carbidopa and thiazides with potassium-sparing diuretics), reduced pill burden, reduction in the development of drug resistance, cost of therapy and better patient compliance (e.g., anti-tubercular drug combinations).[8]

In 2012, an Indian Parliamentary Committee reported that some State Drug Authorities had issued manufacturing licenses for a very large number of FDCs without prior clearance from the Central Drugs Standard Control Organization (CDSCO). This was in violation of rules though till May 2002; there was some ambiguity on powers of the State Drug Authorities in this respect. However, the end result was that numerous fixed-dose formulations, most without CDSCO approval, including drugs banned, restricted, or never approved internationally due to adverse effects, entered the Indian drug market. Use of such FDCs may put the life of patients at risk if used without proper justification.[9,10] FDCs without scientific justification can pose potential difficulties as dosage alteration of one drug is not possible without altering that of the other drug, differing pharmacokinetics of two drugs may affect the therapeutic outcome and perhaps may result in an increase in incidence of adverse drug reactions (ADRs) and drug interactions compared to when both the drugs are given individually. The 20th WHO list of essential medicines (433 medicines) includes 20 FDCs whereas National list of essential medicines of India, 2015 (376 medicines) contains 24FDCs.[11,12] These FDCs were included after due deliberations with scientific justifications. Majority of these FDCs in both the lists belong to antimalarial, antitubercular, and antiretroviral drugs, which emphasize the importance of FDC use in treatment adherence and prevention of drug resistance.[4,11,12]

In view of lack of rationale or evidence and potential safety concern, CDSCO has periodically banned number of FDCs.[4,13] 2 years ago, on March 10, 2016, the Goverment of India imposed ban on 350 FDCs for the safety and efficacy purpose. The government prohibited manufacturing and sale of these medicines because they were found to be "irrational" with regard to lack of any scientific evidence on therapeutic efficacy and indication.[14] The existence of a large number of FDCs with different combinations being manufactured and marketed every year leads to confusion rather than guiding the prescribing doctor. And therefore, the knowledge on the rationality about particular FDCs is absolutely necessary for any clinician for better health-care outcomes.[4] Prescribers need to critically analyze the needs of patients before prescribing FDCs, if required taper off the drugs and substitute appropriate alternatives in the form of single drug formulations with appropriate monitoring. Hence, to find out the preference of the physicians for prescribing FDCs, it was imperative to study the pattern of prescriptions so as to evaluate the frequency and rationality of FDCs being prescribed. Therefore, this study was planned to assess the prescription pattern of FDCs at our tertiary care teaching hospitals and to analyze their rationality as per the WHO guidelines.

Aims and Objectives

The objectives are as follows:
1. To calculate the percentage of FDCs being prescribed to patients
2. To categorize the FDCs into generic and branded FDCs
3. To analyze the FDCs for their rationality as per the WHO guidelines

MATERIALS AND METHODS

Study Design

This was a cross-sectional study conducted by the Department of Pharmacology at the hospital pharmacy and in various wards over a period of 6 months at a tertiary care hospital.

Ethics

Institutional Ethics Committee permission was obtained before the study initiation.

Study Population

Patients attending hospital pharmacy and indoor patients admitted in various wards of our hospital were approached, and their prescriptions were screened for the presence of FDCs in their prescriptions.

Study Procedure

All patients attending the hospital pharmacy were approached and requested to give their written informed consent? to screen their prescriptions for the presence of FDCs in them and then the details of FDCs were noted. Similarly, case papers of indoor patients in various wards of the hospital were also screened

for the presence of any FDC after taking their consent. These prescriptions belonged to different inpatient and outpatient departments of the hospital such as internal medicine, general surgery, obstetrics and gynecology, pediatrics, dermatology, orthopedics, otorhinolaryngology, ophthalmology, and sub-specialties such as pulmonary and chest medicine, and intensive care units. The data were collected over a period of 6 months. The collected data on FDCs was analyzed for rationality using the WHO guidelines.[15]

The FDC was considered as rational if it had

1. Active pharmaceutical ingredients with a complementary mechanism of action
2. Decreased the occurrence of resistance for antimicrobial agents (AMA)
3. Increased the efficacy of the combination
4. Decreased the occurrence of ADRs or toxicity
5. Increased the compliance of the drug therapy with decrease pill burden
6. Decreased the total cost of the therapy and
7. Appropriate dose of each API for defining or for larger groups of population.

Statistical Analysis

Data was entered into MS Excel 2010 and analyzed using descriptive statistics such as numbers and percentages. The statistical analysis was performed using GraphPad Prism version 5.0 for Windows, GraphPad Software, San Diego California USA, www.graphpad.com and SPSS version 20.0.

RESULTS

A total of 3500 prescriptions were screened (n = 3500) and among those 1000 (n = 1000 [28.5%]) prescriptions with FDCs were analyzed as shown in Figure 1. The comparison of the FDCs prescribed as generic names (n = 151 [15.1%]) and brand names (n = 849 [84.9%]) is shown in Figure 2. The pharmacological classes of FDCs prescribed with categorization as per the WHO guidelines as rational or irrational are shown in Table 1. From the total 1000 FDCs analyzed, we found a majority of FDCs 818 (81.8%) were rational while 182 (18.2%) FDCs were irrational, as per the WHO guidelines. Table 1 depicts that major classes of drugs prescribed as FDCs were AMA 596 (59.6%), followed by analgesic and anti-inflammatory drugs 195 (19.5%), antitussives 143 (14.3%), and antiasthma drugs 26 (2.6%).

DISCUSSION

From the results of our study, it is evident that majority of the FDCs prescribed to our patients were rational found to be rational. Almost two thirds of the screened prescriptions had FDCs; however, use of generics was found to be low.

The Indian health ministry regularly reviews the marketed FDCs and takes appropriate action against those which are considered as ",irrational," for example, recently in September 2018, a gazette notification was issued to ban 328 FDCs for manufacture, sale, and distribution with immediate effect as there was no therapeutic justification for the concomitant use of the ingredients contained in these FDCs and the potential to cause harm.[4,16] Hence, we decided to undertake this study to assess the pattern of FDC use in patients visiting a tertiary care hospital. In this study, we found 85% of the FDCs were prescribed by the brand names and only 15% were generic names. This finding was similar to the findings in a study by Patel *et al*. (2005)[17] where 90% of FDCs were prescribed by brand names and Rayasam *et al*. (2013)[10] where 95% of FDCs were prescribed by brand names instead of generic names. Few examples of the FDCs which were prescribed as generic names were combinations of amoxicillin and

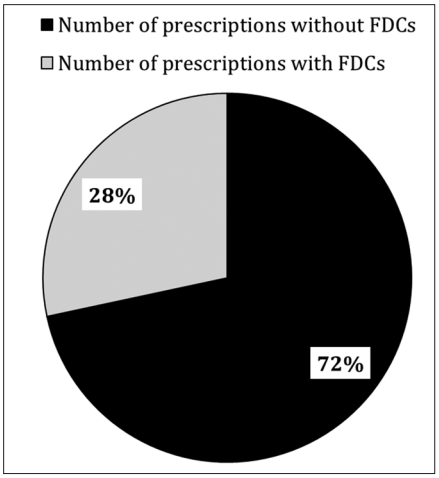

Figure 1: Prescriptions studied for the presence of fixed-dose drug combinations

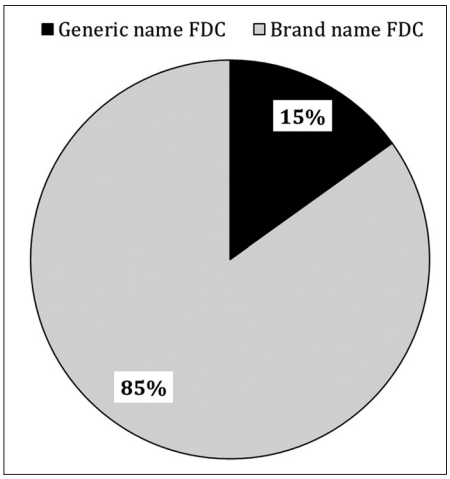

Figure 2: Percentages of fixed-dose drug combinations in the form of generic and brand names

Table 1: Pharmacological classes of FDCs prescribed with categorization as per the WHO guidelines

Class of drugs	Total FDCs (*n*=1000)	Rational FDCs (*n*=818)	Irrational FDCs (*n*=182)
Antimicrobial drugs	596	569	27
Analgesic and anti-inflammatory	195	189	06
Cough remedies	143	08	135
Antiasthma drugs	26	26	00
Antihypertensive drugs	12	12	00
Antidiabetic drugs	08	00	08
Antiplatelet drugs	06	06	00
Antiulcer medicines	06	00	06
Drugs for benign hyperplasia of prostate	04	04	00
Local anesthetic agents	04	04	00

FDCs: Fixed-dose drug combinations

clavulanic acid, cotrimoxazole, paracetamol and diclofenac sodium, glibenclamide, and metformin.

FDC use is justified in conditions such as tuberculosis, malaria, AIDS, leprosy, and other clinically relevant chronic infectious conditions, as they increase the adherence to the therapy and reduce the development of antimicrobial drug resistance.[10] Amoxicillin-clavulanic acid was the most commonly prescribed rational antimicrobial FDC (...) prescribed for infections of ear, sinuses, respiratory system, dermatology, and urinary tract. This particular FDC is considered as rational since the addition of clavulanic acid to amoxicillin re-establishes the activity of amoxicillin against β-lactamase producing microorganisms and thereby widens the antibacterial spectrum of amoxicillin.[18]

Out of 1000 FDCs prescribed, we found 182 FDCs did not fulfill the WHO criteria for rationality. The reasons for categorizing a few of the irrational FDCs with the appropriate justification are mentioned herewith. Among the analgesic and anti-inflammatory group of drugs, the FDC of diclofenac and paracetamol was prescribed for backache. Both the drugs belong to the same class sharing common mechanism, each component having analgesic activity and diclofenac exerting additional potent anti-inflammatory activity. Furthermore, the pharmacokinetics of these two drugs does not match and paracetamol is added unnecessarily, exposing the patient to medicine actually not needed at all. Hence, instead of administering them as FDCs, both the drugs would provide the requisite benefit if administered separately. Other examples are FDCs of fluoroquinolones with anti-amoebic drugs; this combination also is usually not recommended as most of the times; the infection is either bacterial or amoebic and never mixed.[10] We found that 2.3% of patients were prescribed ofloxacin-ornidazole which is an irrational FDC as quoted in the standard textbooks of pharmacology. This FDC is commonly prescribed for control of diarrhea and/or dysentery as it is highly efficacious with excellent tolerability. The probable reasons for it being used extensively in the gastrointestinal infections by both public and private practitioners are perhaps to cover up the diagnostic imprecision and/or to provide immediate relief from the troublesome symptoms without waiting for reports of the investigations. Such injudicious use of FDCs of AMA only increases the chances of the development of resistant strains that further pose problems in treating the infectious diseases.[19]

Another irrational FDC that we encountered in our study was that of anti-diabetic drugs, FDC of glimepiride and metformin being prescribed to 0.8% of patients. This combination includes drugs which need to be administered at a different time with respect to the meal, as glimepiride to be taken before meals whereas metformin is recommended after meals. Hence, the FDC of glimepiride and metformin is scientifically not a rational as it may affect the therapeutic efficacy of both these drugs.

In another example of an irrational FDC, we found which contained pantoprazole and domperidone prescribed to 0.7% of patients. In the treatment of peptic ulcer disease, this combination may help in initial 1 or 2 days, as burning epigastric pain of peptic ulcer is often associated with nausea and vomiting and for the control of which domperidone is required but once the acid secretion is controlled with pantoprazole, nausea, and vomiting stops and domperidone is not needed at all. As the two drugs produce just the additive effect, the symptoms can effectively be treated by administering both the drugs separately, avoiding the extra, and the unnecessary intake of domperidone by the patient.[10]

In our study, it was found that 14.3% of patients were prescribed cough remedies which contained expectorants, cough suppressants, antihistamines, sympathomimetics, alcohol, and other CNS depressants with no rational basis. All ingredients together may sometimes prove detrimental if the patient exclusively presents with either productive or dry cough. For example, dextromethorphan and guaifenesin combination counteract each other's action, as

dextromethorphan is a cough suppressant and guaifenesin is an expectorant.

Majority of the FDCs that were identified in various prescriptions in our hospital were rational. The most common examples of FDCs prescribed were amoxicillin plus clavulanic acid and artemether plus lumefantrine. 20th list of the WHO essential medicine list (EML) of 2017 contains only 20 FDCs.[11] In this study, we found only 18.2% FDCs which were outside the list of FDCs in the WHO EML and were not according to the WHO criteria toward rational FDCs. Irrational FDC use leads to ineffective and unsafe or overtreatment, exacerbation or prolongation of illness, distress, and harm to the patient, increase the cost of treatment.[20] Prescribing more than one drug leads to drug interactions and ADRs. This practice sometimes may be dangerous and life-threatening as it may need hospitalization and intervention, thereby increasing financial burden.[21] The prescribing doctors, therefore, need to be well trained in rational prescribing so that they are able to make an accurate and sound decisions while selecting and prescribing FDCs based on the pharmacokinetic and pharmacodynamic concepts thereby increasing the efficacy and improving the health outcome. The pharmacological basis of combining each ingredient in the FDC formulations should be taught to undergraduate as well as postgraduate students during their training in medical colleges.[22] Selection of personal drugs, rational drug use, use of rational drug combinations, and ethical laboratory practices should be included in the student's curriculum during their training period. This will not only help in developing the practice of critically analyzing the drug combinations and selecting a rational drug for treating the patients but also inculcate in them the habit of evidence-based rational prescribing.

Strength of the Study

The study involved scrutiny of prescriptions from almost all the departments of the institution. The FDCs were analyzed for their rationality using the WHO guidelines.

Limitations of the Study

The total number of prescriptions screened was less in number considering ours is a tertiary care hospital.

CONCLUSION

This study revealed that the majority of FDCs prescribed were rational. The use of generic FDCs was low. To increase the prescription of rational generic FDCs, they should be made available in the hospital pharmacy. Physicians should periodically review the NLEM for the presence of FDCs in it and restrict themselves to prescribe only those FDCs featuring in it.

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