Original Article

AN AUDIT ON PRESCRIPTION FOR RATIONAL USE OF FIXED DOSE DRUG COMBINATIONS DISPENSED IN THE PHARMACY OF A TERTIARY CARE HOSPITAL

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ABSTRACT

Objectives: The objective of this study would be to evaluate rationale use of fixed dose combinations (FDCs) dispensed in the pharmacy of a tertiary care hospital in Pondicherry.

Materials and Methods: This is a retrospective study where 300 prescription copies were collected, out of which 100 prescription copies containing FDCs was scrutinized in the tertiary care hospital P.I.M.S Pondicherry. The total number of FDCs were 114, which were taken for final analysis. FDCs were analyzed for the different pattern of prescribing and rationalism. Rational use of FDCs was analyzed using WHO seven-point criteria. The data regarding clinical evidence of safety and efficacy based on the WHO seven-point criteria were analyzed.

Results: Out of 114 FDCs, the most commonly prescribed FDCs were aceclofenac with paracetomol (19.30%) and amoxicillin with clavulanic acid (14.04%). The females were prescribed 52.63% of the total FDCs. The FDCs were maximum from the department of orthopaedics (22.81%), followed by ENT (14.03%) and medicine (12.28%). Out of 114 FDCs, 79% were rational, and only 21% of the FDCs were irrational.

Conclusions: The results of this study clearly demonstrate that majority of FDCs dispensed in the pharmacy were found to be rational in accordance with WHO seven-point criteria.

Key words: Audit, Fixed Drug Combinations

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Introduction:

Fixed dose combinations (FDCs) is a combination product of two or more active pharmacological ingredients (APIs) in a single dosage form. In FDCs, drugs from different pharmacological groups having complementary mechanism of action should be combined. The FDC is an innovative product, the main advantages being increase in patient’s compliance, decrease in pill burden, reduced complications and the cost 1.

The safety profile of the established drugs changes when they are combined in a single formulation. 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 2. 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.

There is an increase in the number of irrational FDCs in the Indian drug market at an alarming rate. The concept of rational FDCs has not yet penetrated in the minds of physicians; hence evaluation is needed, as large numbers of FDCs are of little importance in terms of effective health care 3. Out of the total 433 medicines listed under the 20th edition of the WHO list of essential medicines issued in August 2017, only 37 are FDCs 4. Similarly, the Indian list of National Essential List of Medicines (NLEM 2015) lists only 24 FDCs out of the total 376 5.

Drug companies continue to rampantly promote brand-based sales of both rational as well as irrational FDCs with aggressive marketing strategies 6. Medical practitioners currently do not have any alternative and credible platforms – from the professional associations or government agencies – to remain updated on the rational drug innovations and combinations but are forced to choose from an unnecessarily large number of brands being made available in the market 6.

As the clinician update-cum-brand promotion activities are primarily driven by the large field force of medical representatives, this in turn, translates into brand-based prescription behaviour of clinicians, creating a difficult scenario for promotion of generics too6. This is the predominant trend for drug sales, where the irrational FDCs comfortably pass through the sales counters 6. Non-prescription-based sales by the pharmacists and opportunity for
replacement of the brands at the retail pharmacy level are other contributing factors for promotion and rampant growth of FDC.

Rational drug use (RDU) is conventionally defined as “patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time and at the lowest cost to them and their community”. In an effort to initiate rational drug therapy, the World Health Organization (WHO) introduced the concept of an essential drugs list in 1977 and it updates the model list every two years. Although various opinions have been expressed regarding the rationality of FDCs, there are only a few studies taken up to find the rationality of FDCs where there were many irrational FDC which easily outnumbered rational FDC. Fixed dose combination [FDC] are highly popular in the Indian pharmaceutical market and are particularly flourishing in the last few years. The pharmaceutical industry has been manufacturing and marketing fixed dose combinations (FDCs), many of them irrational and harmful for the last two decades. Injudicious use of antibiotic FDCs can rapidly give rise to resistant strains of organisms, which is a matter of serious concern to the health care situation in our resource-poor country. To develop a comprehensive criteria which will be useful and unbiased for the evaluation of FDCs, the guidelines of WHO “Draft guidelines for registration of fixed dose combination medicinal product” accessed on 13th March 2005 and the "Note for guidance on fixed-dose combination medicinal products" by the Committee for Proprietary Medicinal Products (CPMP), Europe and several research papers were carefully studied.

These are well-known guidelines, which serve as benchmark towards a rational FDCs. A comprehensive seven-point criteria developed by Panda et al can evaluate the rationality of the FDCs. Hence with respect to ever-growing irrational FDC prescribed in India, this study aims to see the rationality of the different fixed dose drug combinations (FDC) prescribed in a tertiary care hospital by using WHO seven-point criteria for rationale of FDC.

METHODS:
This is a retrospective study where sample size of 300 prescription copies were collected randomly from the P.I.M.S pharmacy, out of which 100 prescription copies containing FDC’s were included in this study. Sample size was selected based on a similar study by N. KASTURY et al. Study was done in Department of
Pharmacology, the tertiary care hospital P.I.M.S, Pondicherry. The study was conducted from August 2016 to September 2016. This study was approved by P.I.M.S institutional ethics committee. The total number of FDCs were 114, which were taken for final analysis for rationality using WHO guidelines\(^1\) and values were entered in Data collection forms. The details included in each data collection form are provided in Annexure.

Each Yes point of WHO seven-point criteria will carry 2 points and No carries 0 point. Maximum score of 14 is possible.

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<tr>
<th>WHO CRITERIA</th>
<th>Yes</th>
<th>No</th>
<th>Score</th>
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<tr>
<td>1. APIs with complementary mechanism of action.</td>
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<td>6. Decrease the total cost of the therapy and</td>
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<td>7. Dose of each API should be appropriate for defining or larger groups of populations.</td>
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<td>Total Score</td>
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Depending on the score, FDC can be grouped as
- **Rational-** 10 to 14
- **Irrational-** 8 to 10
- **Absurd-** 6 to 8
- **Banned-** 0 to 6

The pharmacological categories of FDCs prescribed as per WHO guidelines for rationality were found out in this study. Total number of FDCs will be taken as “n”. All the results were expressed as percentages and the data calculations were done by Microsoft Excel 2016.

**Results:**
From figure 1, out of 114 FDCs prescribed, 79% were found to be rational and 21% were found to be irrational.
From figure 2, it is clear that females were prescribed 52.63% of total FDCs.

From Figure 3, the FDCs were maximum from the department of orthopaedics (22.81%), followed by ENT (14.03%) and medicine (12.28%).

From Figure 4, the most commonly prescribed FDCs were aceclofenac with paracetomol (19.30%) and amoxicillin with clavulanic acid (14.04%).

From Figure 5, the antibiotics FDCs were predominant with 32% followed by 28% with analgesics.

Discussion:

The study evaluated the prescribing trend of FDCs during a tertiary care hospital. Irrational FDCs is a problem worldwide. At Present, India’s exact data is not known. Hence, this study was done to see the details of prescribing FDCs in a tertiary care hospital. The study showed that majority of prescribed FDC’s were rational FDCs. Approximately; seventy nine percent of the FDCs were rational as they fulfilled...
Brajesh Thankamony. et al., An audit on prescription for Rational use of Fixed dose drug combinations.

The WHO criteria. The most commonly used FDCs were aceclofenac plus paracetomol and amoxicillin plus clavulanic acid. The FDCs were maximum from the department of orthopaedics (22.81%), followed by ENT (14.03%) and medicine (12.28%). The antibiotics FDCs were predominant with 32% followed by 28% with analgesics. Females were prescribed 52.63% of total FDCs.

Twenty one percent FDCs were either pharmacologically incompatible or their pharmacokinetic parameters did not match or their APIs interacted with each other or the combination produced increase in adverse reactions. They didn't fulfil the WHO criteria for rationality. In this study few of the irrational FDCs are as follows.

Nimesulide + Diclofenac combination is having same mechanism of action and is highly irrational. Combining two NSAIDs may increase the side effects of both the NSAIDs. There is little documentary evidence that a preparation containing more than one analgesic is more effective than a single ingredient preparation 13. Enalapril + Losartan - Combining two drugs affecting the same pathway is irrational; it doesn’t add to efficacy 14. Amoxycillin + Cloxacillin- Amoxycillin is inactive against staphylococcus, as most strains produce β-lactamase and cloxacillin is not so active against streptococci. For any given infection, one of the components is useless but adds to cost and adverse effect. Since amount of each drug is halved, efficacy is reduced and chances of selecting resistant strains is increased 15. In Domperidone + Esomeprazole combination, the role of prokinetic agent domperidone isn't clear as peptic ulceration disease isn't always related to nausea and vomiting 15.

According to similar study by Rayasam SP et al, majority of FDC were found to be irrational 3. But in this study, we found the majority of FDC to be rational. In another similar study by Balasubramaniam R et al, majority of FDC were found to be rational 16. In this study also, we found the majority of FDC to be rational. In another study by N. KASTURY et al, majority of FDC were found to be irrational 3. But in this study, we found the majority of FDC to be rational 12.

Health care professionals should keep themselves updated about irrational drugs and banned drugs by the DCGI 17. There's also a requirement for sensitization of the under graduate and post graduate students about the rational FDCs. The pharmacological basis of combining each ingredient in the formulation should be taught. Selection of P drugs, rational drug
use, use of rational drug combinations and ethical laboratory practices should be inculcated within the student's curriculum during their clinical training. Limitation of this study is no adverse effects were identifiable during the analysis due to irrational FDCs from the Pharmacy prescription copy as it was a retrospective study.

Conclusion:
The results of this study clearly demonstrate that majority of FDCs dispensed in the pharmacy were found to be rationale in accordance with WHO seven-point criteria. However still irrational FDC’s are still prescribed. All physicians and students should be trained about how to evaluate a fixed dose combination using WHO seven-point criteria to minimize the chances of prescribing an irrational FDC.

References:
9. ICH E4 Dose response information to support drug registration (CPMP/ICH/378/95).


Annexure

Data collection form

Serial number:

Prescription number:

Department:

Sex of Patient:

Prescribing department:

Composition of FDC:

Pharmacological group:

WHO criteria score:

Rational/Irrational/Absurd/Banned:

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