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Evaluation of the rationality and cost comparison of fixed dose combinations of antibiotics in a tertiary care hospital

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ABSTRACT

The development of fixed-dose combinations (FDCs) is becoming increasingly important from a public health perspective. Such combinations of drugs are being used in the treatment of a wide range of conditions. The use of fixed dose combinations of antibiotics is more prevalent in the recent years. The FDC antibiotic use must be limited because; a single antibiotic can be used effectively in most infections caused by a single organism. Furthermore, a single wide-spectrum antibiotic may be used in many mixed infections. The main objective of the study was to assess the prescription pattern and rationality of Fixed Dose Combinations of antibiotics using seven- point criteria. A Prospective- Observational Study was conducted among 102 patients for 9 months. The data from the cases were evaluated. The FDCs prescribed were thoroughly analyzed by seven point criteria to evaluate the rationality. The demographics of study population showed that male population was predominant. The diagnosis study population revealed that major infections were LRTI (26%) and UTI (20%). The culture sensitivity test was performed in 31.3% of study population to choose the appropriate antibiotic. The results of culture sensitivity tests showed that the most commonly isolated organisms were *E.coli* and *S.pneumonia*. A total number of 455 drugs were prescribed in the study population from which 22% were identified as FDC antibiotics. The commonly prescribed FDCs was Pipercillin+Tazobactum accounting for 34%. The seven point criteria analysis reveals 5 out of 8 FDCs were cost effective than their individual components and were rationally prescribed. By studying and comparing all the evidences obtained, the study concludes that the utilization of FDCs in the study site was found to be rational.

Keywords: Fixed Dose Combinations, Rational Drug Use, Antibiotics.

INTRODUCTION

Antibiotic resistance is a stark reality across the globe, including in India. The pervasive use of antibiotics in medical practice had contributed to the emergence and expansion of antibiotic-resistant strains of bacteria in divergent regions.[1] The World Health Organization has stated that drug resistance is one of the major problems we face today. Another contributor to the growth in antibiotic resistance is the irrational use of the antibiotic.[2] Irrational drug use leads ineffective and unsafe drug treatment, worsening or prolonging of illness, adverse drug reaction and increases the cost to the patient, government or insurance system. Widespread

antibiotic resistance is partly due to the irrational use of antibiotics and use of irrational fixed dose combinations (FDCs).[3] India is the country with significant drug use problems. There is concern regarding the irrational production, prescription and use of FDCs. The rationality of a FDCs is the most controversial and debated issue in today's clinical practice.[4]

Presently in India the use of FDCs of antibiotics are alarmingly high with majority of the prescriptions containing at least one FDCs. It has been found that over 80,000 formulations are marketed in India which includes several FDCs and other single drug formulations, while the 18th list of essential medicine has mentioned only about 25 FDCs[5]. The monitoring of FDCs prescription and their ideal utilization is a better approach to minimise the FDCs use. Programs to educate the pharmacists in the critical area of drug dispensing need to be designed and implemented.

MATERIALS AND METHODS

Study Site

The study was conducted in the general medicine department of Private Corporate Hospital at South India.

Study Design

Prospective- Observational Study

Study Period

The study was conducted over a period of 9 months.

Inclusion Criteria

Patients who are getting admitted during the study period with at least one FDCs of antibiotic prescribed in their prescription.

Exclusion Criteria

The patients who are not willing to participate in the study and critically ill patients.

Study Materials

Patient consent form, data entry form.

Study Procedure

The data from the cases were evaluated. The FDCs of antibiotics prescribed were thoroughly analysed by seven point criteria[6] to evaluate the rationality. The possible drug interactions and adverse drug reactions in patient prescriptions were monitored.

RESULTS & DISCUSSION

A total number of 102 patients were enrolled for the study. The demographics of study population showed that male population was predominant. The diagnosis of study population reveals 26.4% (27) of the patients suffered with LRTI, 20.5% (21) were with UTI followed by 5.88% (6) with GIT infection, 3.92% (4) with PUD, 2.94% (3) with URTI and others including prophylaxis were 36.2% (37). [Table No. 1] LRTI is the most common infection among the study population.

Table No: 1 DIAGNOSIS OF STUDY POPULATION

Sl. No.	Major Diagnosis	No. of Patients (n=102)	Percentage%
1	LRTI	27	26.4
2	UTI	21	20.5
3	GI Infection	6	5.88
4	PUD	4	3.92
5	URTI	3	2.94
6	Fungal Infection	2	1.96
7	Septicemia	1	0.98
8	Meningitis	1	0.98
9	Others	37	36.2

The culture and sensitivity test has been performed for 31.3% (32) patients. The study by Ahmad et.al[7] 2012 reports 2.33% of patients in their study had culture and sensitivity report. This reveals our study has higher number of culture and sensitivity test done and the prescription were given according to culture

sensitivity reports which avoids microbial resistance. Among the sample investigated in culture and sensitivity test 43.7% (42) were sputum followed by urine 31.25% (10), blood 21.88% (7) and CSF 3.12% (1).

E.coli was the most frequent organisms isolated from the study population which account for 37.5% (12*)*, *S.pneumoniae* were 28.12% (9), Streptococcus pyogens were 12.5% (4), *Klebsiella pneumoniae* were 6.25% (2), *Staphylococcus aureus* were 6.25% (2), Enterobacter species, Helicobacter pylori, and Candida were the other organisms isolated from the samples.[Table no:2] A similar study done by Balasubrahmannian R. et al[8] 2013 also reported that *E.coli* was the most common organism isolated among the patients.

Table No: 2 ORGANISMS ISOLATED OF STUDY POPULATION

Sl. No.	Organism Isolated	No. of Patient (n=32)	Percentage %
1	*Escherichia coli*	12	37.5
2	*S. pneumonia*	9	28.12
3	*Streptococcus pyogens*	4	12.5
4	*Klebsiella pneumoniae*	2	6.25
5	*Staphylococcus aureus*	2	6.25
6	*Enterobacter*	1	3.12
7	*Helicobacter pylori*	1	3.12
8	*Candida*	1	3.12

FIXED DOSE COMBINATION OF ANTIBIOTIC PRESCRIBED

The most frequently prescribed FDC antibiotics is Piperacillin+Tazobactum which accounts for a total of 33.3% (34) of the total FDCs antibiotics prescribed. This was followed by amoxicillin+ clavulanic acid in 21.5% of cases, cefepime+ tazobactum in 16.6% (17) and cefeperazone+ salbactum in 14.7% (15) of cases. About 14% of the FDCs were prescribed in less number of patients and this includes ceftriaxone+salbactum, ornidazole+ ofloxacin, cefotaxime+ornidazole and trimethoprim +sulfamethoxazole. [Table no: 3]. A similar study by Preetha M[9] 2011 reported that Pipercillin + Tazobactum combination was the most prescribed FDC antibiotic among their study group.

Table No: 3 FIXED DOSE COMBINATIONS OF ANTIBIOTIC PRESCRIBED

Sl. No.	FDCs of Antibiotic	No. of Drug (n=102)	Percentage%
1	Pipercillin + Tazobactum	34	33.3
2	Amoxcillin + Clavulanic Acid	22	21.5
3	Cefepime + Tazobactum	17	16.6
4	Cefeperzone + Salbactum	15	14.7
5	Cefetrixone + Salbactum	8	7.8
6	Ornidazole + Ofloxacin	4	3.9
7	Cefotaxime + Ornidazole	1	0.98
8	Trimethoprim + Sulfamethaxazole	1	0.98

SEVEN POINT CRITERIA ANALYSIS:

The first step (criteria 1*) is the evaluation of the presence of each component of the FDC listed in either EML or NLEM. According to this only one FDC (Amoxicillin+Clavulanic acid) has both components in the list of EML. Among the other FDC antibiotic three FDC antibiotics has one of the individual components in the EML (ceftriaxone, cefixime and trimethoprim). Other four FDC antibiotics, both the individual components were not

listed in EML. In the NLEM list none of FDCs of our study has both the components were present. There were four FDCs in which one component was there in NLEM list and 4 FCDs both the components were not listed in NLEM. The FDCs list of antibiotics present in EML has only 2 FDCs which are prescribed in our study population, similarly the FDC list of antibiotic in NLEM also contains 2 FDCs which are prescribed in our study group. The two FDCs were amoxicillin + clavulanic acid and sulphamethoxazole+Trimethoprim. Among the FDC antibiotic prescribed only two were listed in WHO model list of essential medicines (EML) and National List of Essential Medicine (NLEM). This shows there is a need to produce necessary evidence to update them in NLEM. Study by Neetesh K J et al [10] 2009 reported that only 20% of FDC in the prescription of their study population was present in WHO and ELM.

In the second step (criteria 2*) the appropriateness of dose and proportion of each API present in the FDC was analyzed. Each component (API) of the FDC must be in correct dose and proportion for the intended use. The results reveals all the FDCs antibiotics prescribed in our study were in appropriateness of dose and proportion. In step three (criteria 3*) the established evidence of efficacy and safety of FDC over individual components administration were evaluated with the help of standard literatures. The eight FDCs antibiotic prescribed in our study has established evidence of efficacy and safety over individual components administration. In step four (criteria 4*) the cost of FDC over the cost of individual components was analyzed. Our study results shows there were 3 FDCs which are costlier than the individual components and 3 FDCs were cheaper than their individual components and two were not available in individual dosage forms. In step five (criteria 5*) reduction of dose or adverse effect by FDC over individual components was analyzed. The analysis reveals five of the FDCs antibiotics have reduction of dose or adverse effect. In step six (criteria 6*) Unfavorable pharmacokinetics or pharmacodynamics interactions between API's were analyzed with the help of literature reports. The data evaluation found none of the FDC antibiotics prescribed in the study has interaction between API's. In step seven (criteria 7*) mechanisms of action each component was evaluated. Each component of FDCs should have individual mechanism of action, the components of FDCs antibiotics prescribed in the study has their individual mechanism of action.

The evaluation of scores of seven points reveals that all the FDC antibiotics scored above 8 points which indicates all FDC antibiotics indentified in the study were satisfied the seven point criteria. Some advantage may be present with the use of FDC antibiotic but the reports suggest that FDC antibiotic may result in microbial resistance. Study by Kadir A et al[11] 2010 reported that minimizing the use of irrational fixed dose combination antimicrobials can be a better tool to combat antimicrobial resistance. The use of rational combination not only prevents the microbial resistance also will reduce the cost and adverse drug reaction. A similar study by Poudel A et al[12] 2008 concluded that rational combination can be of immense help to the health care system. These combinations may improve the quality of life in many people.

Table No: 4 SCORES OF FDC ANTIBIOTICS BY SEVEN POINT CRITERIA ANALYSIS

Sl. No.	FDC	1*				2*	3*	4*	5*	6*	7*	Total Score
		EML		NLEM								
1	Pipercillin + Tazobactum	×	×	×	×	Yes	Yes	Yes	No	No	Yes	10
2	Amoxicillin + Clavulanic Acid	√	√	√	×	Yes	Yes	No	Yes	No	Yes	12
3	Cefepime + Tazobactum	×	×	×	×	Yes	Yes	No	Yes	No	Yes	10
4	Cefeperzone + Salbactum	×	×	×	×	Yes	Yes	Yes	Yes	No	Yes	12
5	Cefetrixone +	√	×	√	×	Yes	Yes	Yes	No	No	Yes	11

	Salbactum											
6	Ornidazole + Ofloxacin	×	×	√	×	Yes	Yes	No	No	No	Yes	9
7	Cefixime + Ornidazole	√	×	×	×	Yes	Yes	Yes	Yes	No	Yes	13
8	Trimethoprim + Sulfamethaxazole	√	×	√	×	Yes	Yes	Yes	Yes	No	Yes	13

CONCLUSION

The present study demonstrates the prescription pattern of fixed dose combinations of antibiotics and assessed the rationality of FDCs with the help of seven- point criteria. The study describes various challenges in prescribing FDCs like the rapid emergences of resistant species of micro-organism. The present study also compared the cost of various FDCs and thereby analysed the effectiveness of choosing FDCs. This study also analysis the occurrence of various drug interactions in the prescription of study population. By studying and comparing all the evidenced obtained, the study concludes that the utilization of FDCs in the studies site is found to be rational.

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