Research Article

An evaluation of prevalence and prescribing patterns of rational and irrational fixed dose combinations (FDCs): a hospital based study

Supriya Pradhan, Abinash Panda, Sarita Sahu, Jayanti Prava Behera

Department of Pharmacology, M.K.C.G. Medical College and Hospital, Berhampur, Odisha, India.
Correspondence to: Supriya Pradhan, E-mail: drsupriyapradhan.sp3@gmail.com

Received June 19, 2016. Accepted July 4, 2016

Abstract

Background: Fixed-dose combinations (FDCs) are combinations of two or more active drugs produced in a single dosage form and are used in the treatment of a wide range of ailments.

Objective: The objective was to find out prevalence, prescribing pattern, and rationality of FDC amongst patients attending out-patients department of medicine in a tertiary care teaching hospital.

Materials and Methods: A hospital based prospective cross sectional observational study based on a convenience sample of 620 prescriptions carried out in between May 2015 and July. A seven point tool was developed based on the WHO guideline to evaluate the rationality FDCs. The format for the collection of data were to include patients demographic information such as name, age, sex, social history, family history, as well as medication information, diagnosis, and current treatment regimen given by prescriber. Collected prescriptions were screened for fixed dose combinations and analysed for prevalence, prescribing pattern, and rationality.

Result: Prevalence of FDCs in the prescription was 81.31%. Brand names were used in 82.78% of the prescriptions. FDCs containing nutritional supplements containing vitamins and minerals are prescribed for maximum numbers (20.48%). About 70% of FDCs were irrational, where 17.71% were either controversial or banned and 15.83% were rational.

Conclusion: The prevalence of irrational prescribing of FDC is high. To minimize the pattern, educating the prescribers about rational prescribing is essential. A relook and rationalization may be required in the use of combination product.

KEYWORDS: Fixed dose combinations (FDCs), rational, irrational, controversial or banned

Introduction

Prescribing more than one drug for treating an ailment has become a common practice among clinicians. There is an increasing trend to develop and market fixed dose combinations (FDCs), as a consequence, more than one-third of all the new drug products introduced worldwide during the last decade were FDCs.[1]

FDCs are combinations of two or more active drugs produced in a single dosage form. FDCs are beneficial when they have been formulated and developed on the basis of comprehensive pharmacological principles. In patients suffering from communicable diseases such as tuberculosis, malaria, and HIV, FDCs can improve clinical outcomes and patient compliance by decreasing complexity of the drug dosing schedule. In addition, the cost of a FDC may be less as the packaging cost minimizes, and there are simpler logistics of procurement and distribution, particularly in less well-resourced countries.[2] FDCs such as, synergistic combination of oestrogen with progestogen in oral contraceptives pills, combination of levodopa with carbidopa in Parkinson's disease decreases the side effects of levodopa, trimethoprim and sulfamethoxazole

Access this article online	
Website: http://www.ijmsph.com	Quick Response Code:
DOI: 10.5455/ijmsph.2017.19062016555	

combination are helpful in bacterial infection by inhibiting successive steps of bacterial folate metabolisms, amoxicillin clavulanic acid combination is very effective against beta lactamase producing organisms.[3]

The 19th world health organization (WHO) model list of essential medicines (April 2015) contains 29 approved FDCs and national list of essential medicines (NLEM) 2015 contains 23 FDCs, while there has been an alarming increase in manufacturing of numerous irrational FDCs in the recent past, particularly in India.[4, 5] Use of irrational FDCs can increase adverse effects, hospitalization, and impose unnecessary financial burden, as well as decreased quality of life due to drug–drug interactions.[6, 7]

The WHO has published a series of guidelines relating to marketing of FDCs.[8] These guidelines are intended to provide advice to countries and industries, about developing new products and the regulatory requirements associate with that. A system of screening the drug combinations that are already licensed and available in the market is implemented in many countries. In India, central drug standard control organization (CDSCO) had published guidelines in August 2010 for approving the FDCs.[9,10] Pharmaceutical companies developing many FDCs even when those combinations are unnecessary for the patients and they are influencing physicians to prescribe those products. Furthermore since, there is no clear, comprehensive and rational drug policy, these FDCs are easily available as over the counter (OTC) drugs. It is in this scenario, this study has been taken up to evaluate the prevalence, drug prescribing pattern, and identification of rational and irrational FDCs among patients attending a medicine outpatient department of a tertiary care teaching hospital in Odisha.

Materials and Methods

Study design and site

A prospective cross sectional observational study was conducted in medicine outpatient department of M.K.C.G. Medical College and Hospital, a tertiary care teaching hospital, during May 2015 to July 2015. Study was started after obtaining the approval from the institutional ethics committee. Informed consent was waived, as it was observational study without having concern with patients and any intervention.

Sample size and sampling technique

Assuming a prevalence of FDC to be 50%, confidence interval (CI) of 95% and precision of 0.04, the sample size was calculated to be 620 prescriptions which were collected over a period of 2 months and were screened for FDCs. Among these 503 prescriptions containing one or more than one FDCs, are analysed for prescribing pattern and rationalism. The study was based on convenience sample of the patients attending the medicine OPD during the study period. In each data collection session on an average 10 patients were interviewed based on the inclusion and exclusion criteria. Prescriptions containing drugs of any category were selected irrespective of ailments, age or sex of the patients or the route of administration of the drug. We have excluded the patients who are unwilling to participate.

Study tool and data collection

The case record form consisted of two parts – the first part captured data on the patients demographic details like name, age, sex, diagnosis, current treatment regimen and the second part collected the medication data like drugs prescribed in brand or generic name by the prescriber. Data was collected by investigators themselves. There is no precise validated tool to assess the rationality of marketed FDCs. Therefore, a seven point tool was developed based on the WHO guideline to evaluate the FDCs (Table 1).[8] Score (+1 for positive and -1 for negative observation) has been given to each criterion. The FDCs were categorized as rational or irrational, on the basis of total scoring. The total score ranged from 1 to 13 and score ≥7 was considered rational.

Table 1: Tool for assessment of rationality of fixed dose combinations

1.	API along with strength listed in			
	a. WHO EML	:	Yes (+1)	
	b. NLEM	:	Yes (+1)	
	c. Both	:	Yes (+1)	
	d. None	:	Yes (–1)	
2.	Approved by:			
	a. USFDA	:	Yes (+1)	No (–1)
	b. DCGI	:	Yes (+1)	No (–1)
	c. Banned	:	Yes (–1)	
3.	Dose and dosing of API there in the FDC should be appropriate for the intended use			
	a. Appropriate	:	(+1)	
	b. Inappropriate	:	(–1)	
4.	FDC should have:			
	a. Efficacy	:	Yes (+1)	No (–1)
	b. Safety	:	Yes (+1)	No (–1)
5.	Pharmacokinetic parameters:			
	a. Favorable	:	(+1)	
	b. Unfavorable	:	(–1)	
	c. Not affected	:	(0)	
6.	Pharmacodynamic interactions-Mechanism of action of each ingredient			
	a. Complementary/Different	:	(+1)	
	b. Similar	:	(–1)	
7.	Advantage of FDC			
	a. Compliance	:	Yes (+1)	No (–1)
	b. Less costly	:	Yes (+1)	No (–1)
	c. Reduced dose	:	Yes (+1)	No (–1)

Total score: 13, Score ≥7: Rational FDC, Score ≤6: Irrational FDC
API-Active Pharmaceutical Ingredients, EML-essential medicine list, NLEM -National List of Essential Medicines USFDA- United States Food and Drug Administration, DCGI- Drug Controller General of India

The various criteria in the seven point study tool evaluated the FDC based on the WHO model essential medicine list (EML) (2015) and the NLEM (2015). The dose of the individual active pharmaceutical ingredients (API) was confirmed from standard textbooks and references in pharmacology and therapeutics.[11] The published data regarding clinical evidence of safety, efficacy, and reduction in dose, compliance and adverse effects was collected from databases such as Pubmed, Medscape, Science Direct, Google scholar, and the Cochrane library. The cost data of the individual components, as well as the FDCs, was obtained from CIMS and IDR.[12,13] The information about pharmacokinetic or pharmacodynamic parameters was verified from Medscape drug interaction checker. "Drugs banned in India. 2012" formulated by CDSCO was used to identify the API used in FDCs which are already banned.[14]

Statistical analysis

Data were tabulated and analysed in SPSS 20.0 (IBM Corp., NY.). Descriptive analytical statistics is used to analyse the data and *'p'* values less than 0.05 were considered as statistically significant.

Result

Data were collected from 620 prescriptions, among these 503 (81.13%) prescriptions contained FDCs. A total of 909 numbers of FDCs were prescribed, by excluding the repetitions, 96 different categories of FDCs were analysed further. The average number of FDCs per prescription was 1.81 ± 0.87 (mean ± SD), whereas the average drugs per prescription were 3.48 ± 1.24 (mean ± SD). The mean age of the patient was 41–42 years, which ranges from 15 to 91. FDCs were prescribed to 50.48% of males and 49.52% of females ($p > 0.05$). Most common route of prescribing FDCs were by oral route (91.7%), followed by topical (4.1%) and parenteral (1.9%) routes ($p < 0.001$). Prescriptions contain more than one FDCs were 284 (56.57%), and poly-pharmacy of 5 or more drugs per prescription was seen in 266 (42.90%) of prescriptions. The distribution of the categories of FDCs is shown in Figure 1. FDCs containing nutritional supplements containing vitamins and minerals are prescribed for maximum numbers (20.48%), whereas drugs used in kidney and urinary disorders are the least (1.45%), and the difference in the proportion of FDC in these two groups was found to be statistically significant (<0.001) using *z* test for proportions.

Among the 96 different FDCs 15 (15.63%) were rational, 68 (70.83%) irrational, and 17 (17.71%) were either banned or controversial. Only 7.29% FDCs were listed in the WHO EML and 10.8% in NLEM and 753 (82.84%) drugs out of 909 were prescribed by their brand names.

Discussion

The trend of prescribing FDCs is increasing in clinical practice.[15] The finding of this study of 620 prescriptions showed that 81.13% of the prescriptions contain at least one FDC. These findings are highly consistent with a study conducted in Ahmedabad, India, and reported a prevalence of 82%.[16]

Most healthcare authorities including WHO recommends for using combination therapy in disease like AIDS, TB, and malaria, since these preparations increase treatment efficacy, prevent drug resistance, reduce burden of consuming more pills, and also reduce the cost of treatment.[17,18,19] Eighteenth WHO essential medicine list (EML) of April 2015 contains 29 FDCs and national list of essential list (NLEM) 2015 contains 23 FDCs. Whereas, in this study 96 different types of FDCs were prescribed, among them only 7.29% were listed in the WHO EML and 10.8% in NLEM. Most of the FDCs (82.78%), in this study were prescribed by the brand names. The finding corroborates the finding of the study done by Rayasam et al.[20], which show that 95% FDCs are prescribed by their brand names.

Out of 96 different FDCs 15 (15.63%) combinations are rational, as they scored more than ≥7 on rationality scoring

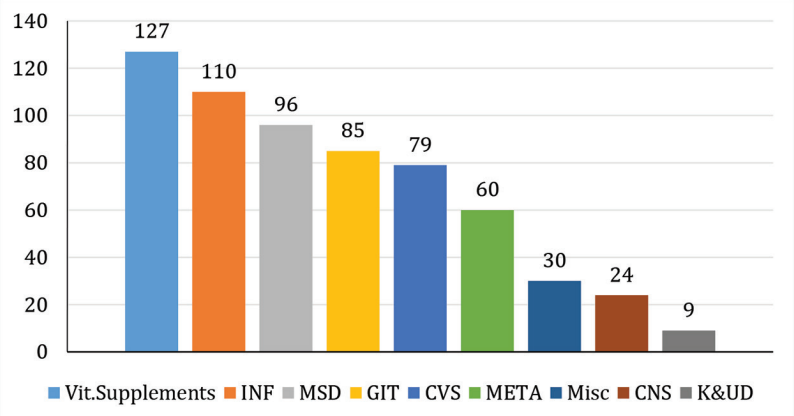

Figure 1: Category wise distribution of FDCs

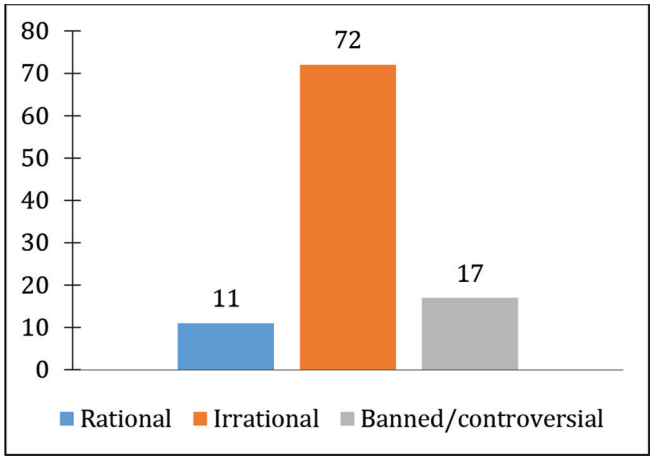

Figure 1: Distribution of FDCs according to rationality score ≥7: Rational, ≤6: Irrational.

Table 2: Rational FDCs as per the study tool

FDCs	Score
Amoxicillin + Clavulinic acid	13
Oral Rehydration Salts	13
Artesunate + mefloquine	12
Artemether + lumefantrine	12
Levodopa + Carbidopa	13
Artesunate + Sulfadoxine + Pyrimethamine	12
Iron + folic acid	12
Piperacillin + Tazobactam	10
Aluminium Hydroxide + Magnesium Hydroxide	11
Tramadol Hcl + paracetamol	9
Beclometasonedipropionate + salbutamol	9
Budesonide + formoterol	9
Sitagliptin + simvastatin	8
Amlodipine + valsartan+ hydrochlorothiazide	8
Pioglitazone Hcl + metformin Hcl	8

(Table 2). Many FDCs which are listed neither in WHO EML nor in NLEM were also categories as rational.[21]

The findings are also consistent with previous studies that a large number of FDCs prescribed were irrational 68 (70.83%).[22] The most common prescribed irrational FDC in this study was combination of vitamin and mineral supplements (20.48%). WHO and the drug controller general of India (DCGI) has banned the combination of vitamin supplements, however many other authors also mentioned this observation. Some of the other combinations are; FDCs containing two NSAIDs, anti-bacterial drugs with anti-amoebic drugs, cephalosporins with clavulanic acid and amoxicillin or ampicillin with cloxacillin as they have no synergistic or additive effect, rather the side effects are additive.

Approximately 17 (17.71%) of the FDCs prescribed were either controversial or banned. Some examples are; dextromethorphan and guaiphenesin combination in cough has antagonizing pharmacodynamics properties, where guaiphenesin acts as expectorants and dextromethorphan as antitussive. Similarly, combinations of NSAIDs with antispasmodic agents are also found in this study. The NSAIDs promotes sweating and the antispasmodic (anticholinergic) drug inhibits sweating. They are not only irrational but also could be dangerous. CDSCO has categorically prohibited combining of two NSAIDs special paracetamol (500mg) combined with other NSAIDs, but we observed 96 times these combinations are prescribed. Nimesulide preparation has been withdrawn from USA, UK, Australia and most of the European countries, however there are many combinations prescribed containing nimesulide. Similar finding was observed by many authors.[15, 22]

Some of the FDCs are not included in the EML or NLEM, but still be justifiable, such as combination of antihypertensive, anti-hypercholesterolemic, anti-glaucoma and drugs used in diabetes.[23] Many of the combinations are recommended by United States Food and Drug Administration (USFDA) and European Union (EU). Piperacillin and tazobactam, which is not included in WHO EML whereas included in NLEM 2015. Other combinations e.g. antacid mixture of aluminium and magnesium salts, combination of bronchodilators with corticosteroidsor anti-muscarinics for synergistic effect in asthma and COPD, drugs used in *Helicobacter pylori* eradication and combination of centrally acting and peripherally acting analgesics.

Strength and limitations of the study: The seven point study tool was used to evaluate the FDC based on the WHO model list of EML (2015) and the NLEM (2015), which is the strength of the study. Whereas, non inclusion of indoor patients was a limitation of this study and may not be totally generalized to all prescriptions.

Conclusion

The prevalence of FDC in the prescriptions was high and most of the FDC were from the vitamins and mineral supplements. Most of the FDC were irrational as per the guidelines. In view of the findings of this study and in the current scenario of the increasing popularity of the use of FDC in India in the last decade, the therapeutic justification of all the marketed FDCs is a controversial issue. In spite of the recent ban of 350 FDC preparations in the country more irrational FDC need to be identified and regulated.

References

1. Combination Products. Food and Drug Administration, USA. Available from: http://www.fda.gov/CombinationProducts/GuidanceRegulatoryInformation/ucm109108.htm. Last accessed on 2014 Sep 17.
2. Davies N E C G. Fixed-dose combination for adults accessing antiretroviral therapy. SAfr J HIV Med 2013;14 (1 Suppl):41–3.
3. Goswami N, Gandhi A, Patel P, Dikshit R. An evaluation of knowledge, attitude and practices about prescribing fixed dose combinations among resident doctors. Perspect Clin Res. 2013;4:130–5.

4. Model List Essential Medicine 19th list. Geneva. World Health Organization; 2015.
5. National List of Essential Medicines of India 2015. Available from: http://www.apps.who.int/medcinedocs/documents/s18693en/s18693en.pdf. (accessed on 18th August 2015).
6. Poudel A, Palaian S, Shankar PR, Jayasekera J, Izham MIM. Irrational fixed dose combinations in Nepal: Need for intervention. Kathmandu Univ Med J 2008; 6(3–23): 399–405.
7. Pradhan S, Panda A, Mohanty M, Behera JP, Ramani YR, Pradhan PK. A study of the prevalence of potentially inappropriate medication in elderly in a tertiary care teaching hospital in the state of Odisha. Int J Med Public Health 2015; 5:344–8.
8. Guidelines for registration of fixed-dose combination medicinal products. Geneva. World Health Organization 2005. Report number 929.
9. Guidelines for Industry on Fixed dose combinations draft guidelines: New Delhi. Ministry of Health and Family Welfare. Government of India 2010, p.38.
10. Government of India- Ministry of Health and Family Welfare (MOHFW). Notification G.S.R 218(E) internet.. New Delhi: Government of India; 2011 March 16. Available at http://www.cipi.in/GSR218(E).pdf.
11. Brunton LL, Chabner BA, KnollmannBjörn C, Eds., In: Goodman and Gilman: *The Pharmacological Basis of Therapeutics*, 12th Edition, McGraw- Hill, New York, 2011.
12. Current Index of Medical Specialties Updated Prescribers' Hand - Book, July 2015, Atmedica Private Limited, Bangalore, India.
13. Indian Drug Review (IDR), July-Aug 2015, Mediworld Publication Private Limited, New Delhi, India.
14. Central drugs standard control organization. Drugs banned in India. 2012. Available from: http://cdsco.nic.in/html/drugs-banned.html Last accessed on 2015 Aug 20..
15. V. Shivashankar, Thomas P, Muhammed AVP, Pooja KS, Simin SJ, Sojan PP. Evaluation of the rationality and cost comparison of fixed dose combinations of antibiotics in a tertiary care hospital.IJAMSCR 2015;3(2):85–9.
16. Patel S, Desai P, Shah RB, Desai SV. Prescribing pattern of cough and cold medicines in central Gujarat. Int J Med Sci Public Health. 2013; 2(2): 196–203.
17. Rathnakar UP, Shenoy A, Ullal SD, Shivaprakash, Pemminati S, Shastry R, Ahsan S. Prescribing patterns of fixed dose combinations in hypertension, diabetes mellitus and dyslipedimia among patients attending a cardiology clinic in a tertiary care teaching hospital in india. Pharmacie Globale (IJCP) 2011;6(5).
18. Department of Health and Human Services (DHHS). AIDS Info: Clinical Guidelines portal. Available at: http://www.aidsinfo.nih.gov/Guidelines/. Accessed January 10, 2010.
19. Amin et al. Determination of artemether and lumefantrine in anti-malarial fixed-dose combination tablets by microemulsionelectrokinetic chromatography with short-end injection procedure. Malaria J 2013 12:202.
20. Rayasam SP, Dudhgaonkar SS, Dakhale GN, Hire RC, Deshmukh PS, Gaikwad NN. The irrational fixed dose combinations in the Indian drug market: An evaluation of prescribing pattern using WHO guidelines. Int J Basic ClinPharmacol 2013; 2:452–7.
21. Akazawa and Fukuoka. Economic impact of switching to fixed-dose combination therapy for Japanese hypertensive patients: a retrospective cost analysis. BMC Health Serv Res 2013;13:124.
22. Shah S, Patel J, Desai M, Dikshit RK. Critical analysis of antimicrobial and respiratory fixed dose combinations available in Indian market. Int J Med Public Health 2015; 5:161–4.
23. Balasubramanian J, Radhika N, Badarinath AV. The crave of fixed dose combination in Indian market. Asian J Pharm Clin Res 2014;7(4):.

How to cite this article: Pradhan S, Panda A, Sahu S, Behera JP. An evaluation of prevalence and prescribing patterns of rational and irrational fixed dose combinations (FDCs): a hospital based study. Int J Med Sci Public Health 2017;6:58-62

Source of Support: Nil, **Conflict of Interest:** None declared.