

Original Research Article

An evaluation of fixed dose combinations and its practices at medicine department of tertiary care hospital, Nepal

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ABSTRACT

Background: A large proportion of fixed dose combinations (FDCs) are manufactured and used widely in Nepal. This study aimed to evaluate the FDCs and its utilization in medicine department of tertiary care hospital.

Methods: A cross-sectional study was conducted for 50 days among admitted patients in the medicine department of tertiary care hospital, Nepal. A predesigned form was used to collect the data at the time of patient discharge. Only the oral FDCs were selected for study. Microsoft Excel 2007 was used for statistical analysis and data were presented as number and percentage in tabulated and figure forms.

Results: Oral FDCs were used in 27.08% of admitted patients. A total of 295 FDCs were prescribed in 208 patients with 44 FDC items in 58 different brand names. Categorically, the most commonly used FDCs were of analgesics (34.24%) followed by antibiotics (25.76%) and vitamin supplements (22.71%). The 27.27% of FDCs prescribed contain more than two active pharmaceutical ingredients (APIs) up to nine and the highest number of APIs were found in vitamin supplements. All FDCs were prescribed in the brand names. The very few 2.27% and 4.55% of FDCs were prescribed from the essential medicine list of Nepal and world health organization, respectively.

Conclusions: The use of FDCs listed in essential medicine list was very poor. Similarly, generic prescribing was also zero. The regulatory body must study the rationality of FDC before production, marketing, importing, and utilization in hospital.

Keywords: Oral FDC, Medicine department, Nepal

INTRODUCTION

Fixed dose combinations (FDCs) are defined as two or more drugs in a single formulation, each drug having independent modes of action, the combination of which are synergistic, additive, or complementary in their effect.¹ The drug combination increases the risk of adverse effects, leads to an ineffective dosage and liability for abuse, unnecessary financial burden, emergence of resistant organisms and treatment failure.^{2,3}

Several FDCs are available in the market of Nepal. The Department of Drug Administration (DDA) is the authorized body in Nepal to regulate and prepare criteria

for FDCs evaluation and registration. There are no clear or strict guidelines or criteria to suggest whether particular FDCs are rational or irrational.^{4,5} However, the previous studies assess the rationality of FDCs by considering parameter like pharmacokinetics parameter, mechanism of action, safety, efficacy, listed in essential medicine list (EML) and approval of authentic body.^{6,7} The drug and cosmetic act of India 1940 considered FDCs as a “new drug”; hence, it should undergo clinical trials.⁸ The rationality of FDC is the debated issue in today's clinical practice.⁹

Large proportions of FDCs are manufactured every year and are widely used in different health care settings of

Nepal. The irrational FDCs were found to be significantly used in previous studies of Nepal. A recent study among five cities of Nepal showed that a maximum of eight and a minimum of two drugs per combination. Medical experts have expressed serious concerns over the increased use of FDC, particularly in developing countries.⁴

Therefore, appropriate use and monitoring of FDCs has become essential. This study enables us to evaluate oral FDCs and its utilization among admitted patients in the medicine department of the hospital. The study will help us understand the FDCs practices and interventions to promote rational use of medicine.

METHODS

The cross-sectional descriptive study was carried out in the in-patient medicine department of tertiary care hospital of Kathmandu. Prior to the study, approval was taken from the study hospital. For the study, all the patients admitted to the medicine department from July 17, 2018 to September 4, 2018 (50 days) were taken. A total of 768 patients were admitted at that time period. All the prescriptions containing oral FDCs were separated and required data were copied in data collection form at the time of discharge. The instrument for the study was prepared by reviewing the literature and consultation with senior colleagues.^{6,7,10} The designed questionnaire collects demographics (age, gender), FDCs name (brand or generic name), FDC composition and total FDC prescribed. The EML list of Nepal 2016 and World Health Organisation (WHO) 2017 were used for study.^{11,12} The data for the study were manually checked after copying the details. Two separate evaluators did a

double review of collected data to avoid errors in the data entry process. The data was analysed by using Microsoft Excel 2007, and results were expressed in number and percentage by using table and bar-diagram.

RESULTS

Among 768 patients, the oral FDCs were used in 208 (27.08%) patients. In 208 patients, female patients (n=106, 50.96%) were slightly higher than male patients (n=102, 49.04%). FDCs were prescribed high to 21 to 40 years age group (42.31%), while other age groups (0-20, 41 to 60 and 60 above) were equally prescribed (19.23%).

A single FDC was most commonly used (66.35%), sequentially followed by two, three and four FDC. The total 44 types of FDC were used in 208 admitted patient. Among them, FDCs having two active pharmaceutical ingredients (APIs) were high (n=32, 72.73%); they were mainly of analgesics, antibiotics, antihypertensive and anti-diabetics preparations. The three APIs containing FDC were of cough preparations. Six and nine APIs containing FDCs were belonged to vitamin supplements (Table 1).

The 295 FDCs were prescribed to 208 patients with 44 different types of FDC in 58 different brand names. Moreover, all 295 FDCs were prescribed in the brand name. Categorically, analgesic group of FDCs were highly used followed by antibiotics and vitamin supplements (Table 2). Among of all, ibuprofen 400 mg and paracetamol 500 mg tab were the most frequently prescribed one (n=81, 27.46%) (Figure 1).

Table 1: FDC per patient and APIs per FDC.

Number of FDC per patient	Patient number (%)	Number of APIs per FDC	Generic FDCs number (%)
One	138 (66.35)	Two	32 (72.73)
Two	54 (25.96)	Three	4 (9.09)
Three	15 (7.21)	Four	3 (6.82)
Four	1 (0.48)	Five	0 (0)
		Six	3 (6.82)
		Seven	0 (0)
		Eight	0 (0)
		Nine	2 (4.55)
Total	208 (100)	Total	44 (100)

*FDC = Fixed dose combination; API = Active pharmaceutical ingredient.

Table 2: FDCs prescribed details to 208 patients.

FDC category	Number of generic FDCs items under each category (%)	Number of brand used under each category (%)	Number of FDCs prescribed (%)	Number of FDCs prescribed in brand name (%)
Analgesic	4 (9.09)	6 (10.34)	101 (34.24)	101 (34.24)
Antacid	1 (2.27)	1 (1.72)	3 (1.02)	3 (1.02)
Antibiotics	9 (20.45)	18 (31.03)	76 (25.76)	76 (25.76)
Antidiabetics	8 (18.18)	9 (15.52)	13 (4.41)	13 (4.41)
Antihypertensive	5 (11.6)	7 (12.07)	19 (6.44)	19 (6.44)

Continued.

FDC category	Number of generic FDCs items under each category (%)	Number of brand used under each category (%)	Number of FDCs prescribed (%)	Number of FDCs prescribed in brand name (%)
Antiparkinsonism	1 (2.27)	1 (1.72)	1 (0.34)	1 (0.34)
Antitubercular	3 (6.82)	3 (5.17)	10 (3.39)	10 (3.39)
Cough preparation	3 (6.82)	3 (5.17)	5 (1.69)	5 (1.69)
Vitamin supplements	10 (22.73)	10 (17.24)	67 (22.71)	67 (22.71)
Total	44 (100)	58 (100)	295 (100)	295 (100)

*FDC = Fixed dose combination.

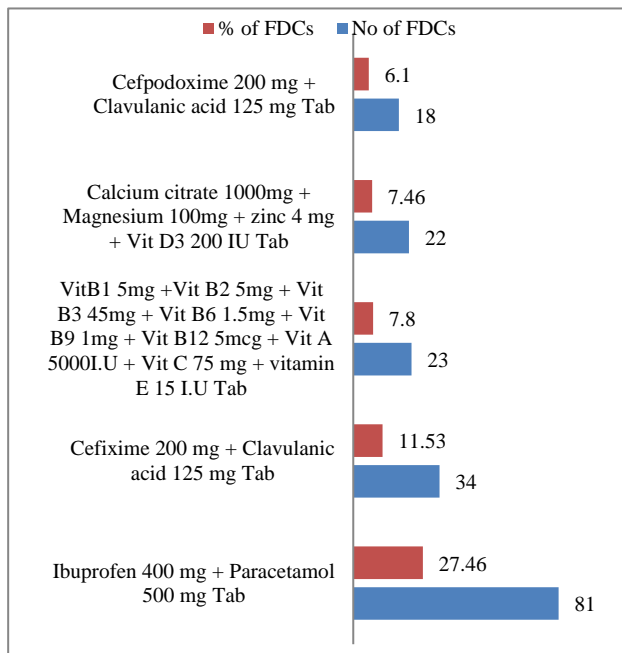


Figure 1: Most commonly prescribed five FDCs.

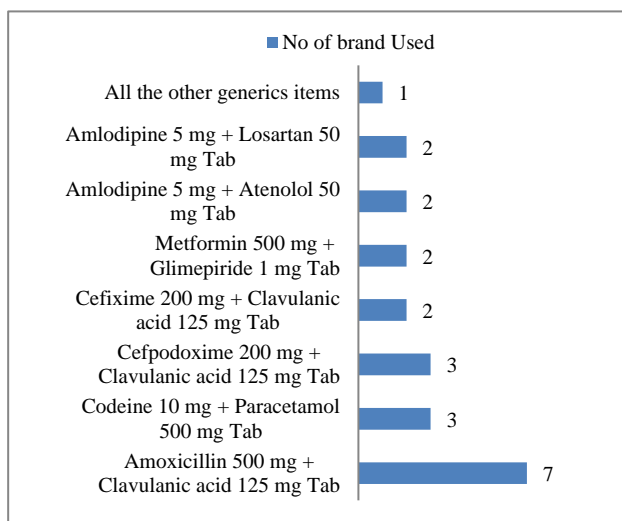


Figure 2: Brand number per FDC item.

The high numbers of different FDCs were of vitamin supplements group followed by antibiotics and anti-diabetics. The highest numbers of brand were used in antibiotics (Table 2). While viewing brand names, except

for seven FDCs, all the other FDCs in the study were prescribed by a single brand name. The brand name used for amoxicillin 500 mg and clavulanic acid 125 mg tab was very high (n=7) (Figure 2).

The only one FDC, that is amoxicillin 500 mg and clavulanic acid 125 mg tab, was included in both EML of Nepal and WHO. Moreover, levodopa 100 mg and carbidopa 25 mg were also present in the EML of WHO but in Nepal. The dose combination of levodopa and carbidopa prescribed was not similar to the dose combination present in EML of Nepal. Similarly, the combination of amoxicillin and clavulanic acid liquid oral preparation was available in EML of WHO but the combination dose was different. The FDCs of antitubercular drugs were present in both EMLs but their combination dose was different. The majority of APIs of FDC were not listed in either EML (Table 3).

Table 3: FDCs presence as per EML of Nepal and WHO.

FDCs presence	No. of FDCs in EML of Nepal 2016 (%)	No. of FDCs in EML of WHO 2017 (%)
Present	1 (2.27)	2 (4.55)
Absent (total)	43 (97.73)	42 (95.45)
At least one API present	16 (34.09)	13 (25)
None API present	28 (63.64)	31 (70.45)
Total	44 (100)	44 (100)

Table 4: Mechanism of action of API in FDCs.

Mechanism of action of API in FDCs	No. of FDCs (%)
Similar	3 (6.82)
Different	41 (93.18)
Total	44 (100)

There were only three FDCs that are paracetamol 500 mg and ibuprofen 400 mg tablet, paracetamol 125 mg and ibuprofen 100 mg per 5 ml suspension and ampicillin 250 mg and cloxacillin 250 mg capsule have a similar mechanism of action. All other APIs of FDC have separate mechanism of action (Table 4).

DISCUSSION

In our study, FDCs were comparatively found to use higher in female (50.96%). In contrast, a study among geriatric patients (58.7%) and pharmacy stores of Ahmedabad, India (54.4%), showed high FDCs use in male.^{10,13} Generally, adult age groups are considered healthier; however, FDCs were found to prescribe more to adults aged 21 to 40 years in our study. Similarly, a study of Ahmedabad, India showed high number of FDCs prescribed to 31 to 49-year patients (23.7%).¹³ The reason could be the higher availability of adult dose FDCs or the higher number of an adult aged patient admitted to the medicine department.

The study carried out in the out-patient department of medical college reported 32.57% of FDC containing prescription, which is similar to our study 27.08%.¹⁴ The 33.65% of patients received more than one FDC up to four, and 27.27% of prescribed FDCs contain more than two APIs up to nine in our study. A study carried out in India reported increased in adverse reaction in more than half of FDCs, while the FDCs in that study and of our is not compared.¹⁵ Therefore, the appropriate need-based selection and use of FDC is required. However, a study among dental clinicians and residents reported that they had poor knowledge and awareness of FDC.⁴ The pharmaceutical company encourages physicians to prescribe their FDC even though they are not required by patients.⁵ Therefore, the prescriber should be equipped with appropriate knowledge and skill to rationally prescribe FDCs, and the hospital pharmacist is a desired professional to provide appropriate information regarding medicines in hospital.⁹

Vitamin supplements were most commonly used (22.71%) in our study; among them, vitamin B combination and calcium combination were the majors. Vitamin supplements were commonly used in other studies as well.^{7,13,15,16} In case of vitamin supplements, the combination drug was very much similar to each other, but their combination dosage was different. There were ten brands and equally ten generic items in vitamin supplements. The unique combination compels patients to search for a particular brand. The slight changes in API and dose are probably the marketing strategy of manufacturers to promote their brand. Therefore, patients must be assessed thoroughly about their nutritional deficiency and the requirement of a specific dose of vitamins. The regulatory body must study combinations and doses of FDC before giving approval for marketing. Higher use of nutritional FDCs without proper study can increase financial expenses, unwanted toxicities, and interactions.

The very few 2.27% and 4.55% FDCs were prescribed from EML of Nepal and WHO, respectively, in our study. While it was 12% from EML of WHO and 6.4% from EML of India in the study of South India.¹⁴ There were few FDCs which have a similar composition to EML but

their doses were not matched. And, most commonly used five FDCs were also not present in either EMLs. Similarly, the majority of APIs that are 63.41% and 70.75% were not present in EML of Nepal and WHO, respectively. WHO encourages essential medicines use as they are safe, efficacious, cost-effective and able to meet the priority health needs of patients. From the above result, it can be said that either the commonly used FDCs were not safe, efficacious, and cost-effective for priority condition or they were not studied properly and updated EML on a regular basis.¹² The current study emphasised the need to find the rationality and importance of FDCs practiced in the market and update the EML accordingly.

There was a higher number of different brands used in the case of antibiotics, analgesic, anti-diabetic and antihypertensive FDCs. The highest numbers of different brands were found in antibiotic drugs and specifically in the case of amoxicillin 500 mg and clavulanic acid 125 mg tab. The EML of Nepal and WHO both considered this FDC as essential. This combination is considered rational by other studies also.^{6,7} Generally, higher use of medicine has higher brand and market competition. On the other hand, the most used antibiotic cefixime 200 mg and clavulanic acid 125 mg tab had two brands; this combination is not listed in both EML of Nepal and WHO. Additionally, this FDC is considered irrational because clavulanic acid is supposed to prevent the destruction of beta-lactam ring of penicillin antibiotics only.^{11,17} The regulatory body is responsible to make criteria and check the rationality of FDCs scrutinously before manufacturing and marketing authorisation.

All FDCs (100%) were prescribed by brand names in this study, while a study of teaching hospital of India showed 95% of FDCs prescribed by brand names and reported that the prescriber was unaware about the APIs of the 29% FDCs they prescribed.¹⁵ FDC prescribing in brand name seems to be easier than in generic. Generic writing requires mentioning doses of composition but the brand name writing directly indicates composition as the specific brand name has specific doses of composition. However, the absence of true knowledge about the composition and dose of API of FDCs leads to harmful consequences. The brand prescribing makes it difficult to arrange and dispense a particular brand by the hospital pharmacy. The generic prescribing and dispensing is desirable in developing countries as it reduces the expense of patients.

According to WHO, FDCs are rational when the combination has a proven advantage over single compounds administered separately in therapeutic effect, safety, and adherence or in delaying the development of drug resistance.¹⁰ The combination should act by different mechanism and act as a booster for another.¹⁸ However, 6.81% of FDCs (n=3) that are paracetamol 500 mg and ibuprofen 400 mg tablet, paracetamol 125 mg and ibuprofen 100 mg per 5 ml, and ampicillin 250 mg and cloxacillin 250 mg capsule have a different mechanism of

action and no complementary action. These combinations are considered irrational because the combination does not have synergistic or additive action, rather the side effects are additive.^{7,19,20} Additionally, analgesics (34.24%) were the mostly used FDC among all other categories; and Ibuprofen 400 mg and paracetamol 500 mg (27.46%) was the highly used FDC among them. A study conducted in India showed that NSAIDs combination had covered two-thirds of FDCs sold in 2011 to 2012. The combination of two NSAIDs is considered highly undesirable, as it has been found to be associated with gastrointestinal risk.²¹ The study of marketed FDCs rationality is becoming a major concern. The drug and therapeutic committee of the hospital has to be alert and conduct a rigorous study to promote appropriate use of FDC. The Manipal teaching hospital of Nepal initiated this role and banned the combination of ampicillin and cloxacillin, multivitamins and B-complex preparation containing multiple combinations considering them to be irrational.¹⁹

The study had limitations of only conducted in the medicine department of single tertiary hospital for a short period; therefore, the study lack to find the real picture of FDCs use in hospitals of Nepal.

CONCLUSION

More than one-fourth of admitted patient was found to use oral FDCs. The FDC consisting of two APIs was the most common one. The analgesics, antibiotics and vitamin supplements were the most commonly used categories of FDCs. The use of essential medicine was very rare. FDCs of vitamin supplements have similar compositions with different doses. The generic prescription was zero. The study recommended therapeutic need-based use of FDC, along with promoting essential medicines and generic prescribing. The regulatory body must study the rationality of FDCs and its combined doses before production, marketing, importing and utilization in hospital.

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