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ORIGINAL ARTICLE

Fixed Dose Combination Antimicrobials Practices In Nepal – Review Of Literature

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ABSTRACT

Antibacterial drugs are one used commonly as fixed dose combination. The use of fixed dose combination antimicrobials is more common in developing countries. There are several studies which suggest extensive use of fixed dose combination antimicrobials drugs in Nepal. Although thousands of fixed dose combination are available in world market, WHO has approved only 25 fixed dose combination in 15th edition of WHO essential drug list. Even if some of the fixed dose antimicrobial offer some benefit in treatment of disease like Tuberculosis, Leprosy etc., majority of irrational fixed dose antimicrobials has major contribution in resistance development, decrease the flexibility of prescriber and increase the misuse by self-medication. To minimize the extensive use of fixed dose combination of antimicrobials certain measure like developing guideline for preparing of combination product, evaluation of product before registration, banning of irrational IFDC antimicrobials, strict monitoring, strict antibiotic policy, hospital antibiotic policy etc., will be helpful. In the developing world where resistance to antimicrobials is increasing, minimizing the use of irrational fixed dose combination antimicrobials can be better tool to combat with the resistance.

Key Words : Drugs, Fixed dose combination, antimicrobials, policy

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Introduction

Rational drug use means 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 [1]. Some of the common irrational drug use

problems are polypharmacy, overuse of injections, self medication, misuse of antibiotics, use of irrational fixed dose combinations (IFDCs) etc. A fixed dose combination refers to the combination of two or more drugs in a single pharmaceutical formulation [2]. The use of FDCs is common worldwide. Antibacterial drugs are one used commonly as fixed dose combination.

Some of the commonly used irrational drug combinations include antibiotics combined with other antibiotics e.g. ampicillin + cloxacillin, antibiotic combination with antiamoebic e.g. ciprofloxacin + tinidazole etc. Irrational fixed dose combination in general and the need of intervention is already been described in a review article by Poudel A et al. [3] This article focuses mainly about the fixed dose combinations of antimicrobials in Nepal.

Fixed dose combination of antimicrobials practices in Nepal

Antimicrobials are grouped in class of drugs which can be dispensed only after the valid prescription from the registered medical practitioner. The relation between the use of antimicrobials and development of resistance is well established. Despite the established relation, the self-medication with the antibiotic is common in developing as well as developed countries [4], [5]. The risk of resistance development is increased several fold by the use of irrational fixed dose combination. The use of fixed dose combination antimicrobials is more common in developing countries. There are several studies which suggest the extensive use of fixed dose combination antimicrobials drugs in Nepal. Some of studies showing extensive use of fixed dose of antimicrobials in Nepal are listed in [Table/Fig 1].

[Table/Fig 1]: Studies suggesting the use of Fixed Dose Combination of Antimicrobials in Nepal

Authors	Year of study	Study site	Incidence of Fixed Dose Combination of Antimicrobials (FDCs)
Das BP, et. al. [6]	May- 2001	Teaching district hospital of Nepal	Fixed dose combination of ampicillin and cloxacillin (12.12%) was the most commonly prescribed FDC
Sarkar C, et. al. [7]	March 2001- February 2002	Dental outpatient departments at Manipal Teaching Hospital, Nepal	The average number of drugs prescribed was 2.03 (3698 / 1820) and 66% prescriptions contained antimicrobials (1 or 2). 21% drugs were prescribed in generic names and 38% drugs were fixed dose combinations of 2 or more drugs
Sarkar C et. al. [8]	July 2000 and June 2001	Dermatology outpatient department of the Manipal Teaching Hospital in Nepal.	Of 256 antimicrobials prescribed, 63% were topical and 37% systemic, 5% were generic, 29% were from the essential drug list of Nepal, and 15% were fixed-dose combinations
Das BP et. al. [9]	January 2005	Department of Pharmacology at B.P. Koirala Institute of Health Sciences (BKHS), Dharan	There was use of expensive antimicrobial agents (AMAs) and irrational prescribing of combinations of AMAs in some prescriptions
Ravi P. Shankar et. al. [10]		Surgical Outpatients department of the Manipal Teaching Hospital in Nepal.	Two hundred and forty-four drugs (26.4%) were FDCs. Cotrimoxazole was the only FDC prescribed from the Essential drug list of Nepal. Ampicillin and cloxacillin combination was most commonly prescribed
Palitke N et. al. [11]	November- December 2003	General ward of major children hospital in Kathmandu valley	Benzyl penicillin and gentamycin / cefotaxim were found to be mostly used combination antibiotics in case of pneumonia. Simlady ceftriaxone in combination with chloramphenicol was used in case of meningitis
PR Shankar et. al. [12]	November- March 2004	Manipal Teaching Hospital, Pokhara, Nepal	Ampicillin + Cloxacillin combination comprises 3.4% of total antibiotics commonly prescribed with fluoroquinolones.

Fixed dose combination antimicrobials practice in developing countries

Studies showing extensive use of fixed dose of antimicrobials in developing countries are listed in [Table/Fig 2].

[Table/Fig 2]: Studies suggesting the use of fixed dose combination of antimicrobials in developing countries

Authors	Year of study	Study site	Incidence of FDCs
Verma I et. al. [13]	2003	Medical OPD of Guru Nanak Dev Hospital	FDCs were used for 21.92% patients.
Haza A et. al. [14]	2000	outpatient facilities maintained by the Southern Health Improvement Society, a non-governmental organization in the South 24 Parganas district of West Bengal	Frequent use of antibiotics, irrational fixed dose combinations and preparations of uncertain efficacy, were some of the problematic prescribing and dispensing trends identified through this survey.
Rehan HS et. al. [15]	March 2000.	Dental prescribers in a tertiary care teaching hospital, New Delhi	Fixed dose combination of ampicillin and cloxacillin was most commonly prescribed antimicrobial agents. Fixed dose combinations (43%), drugs by brand name (36.3%) were frequently used.
N. Kastury et. al. [16]	2001		As early as 1988 itself (based on MIMS), there were 110 vitamin formulations, 71 cough remedies, 70 anti-diarrheals, 54 antimicrobial combinations and 49 analgesic formulations available in the market. Awareness needs to be created to allow only the rational combinations based on the criteria above.
DC Lamichhane, et. al. [17]	January 2004- December 2004	Outpatient department (OPD) of the Manipal Teaching hospital, Pokhara, Western Nepal.	Ampicillin and Cloxacillin combination was most frequently prescribed fixed dose combinations.

Fixed dose combination antimicrobials suggested by World Health Organization

Although there are thousands of fixed dose combinations that are available in world market. WHO has approved only 25 fixed dose combination in the 15th edition of WHO essential drug list. Fixed dose combination of

antimicrobials approved in 15th edition of WHO essential drug list are mentioned in [Table/Fig 3].

[Table/Fig 3]: FDC antimicrobials approved in WHO essential drug list 15th Edition (March 2007)

S. N	Drugs	Form	Strength
1	Neomycin + Bacitracin	Ointment	5 mg+500 IU
2	Amoxicillin + Clavulanic acid	Tablet	500 mg+ 125 mg
3	Imipenem + Cilastatin	Injection	250 mg+ 250 mg
4	Sulfamethoxazole + Trimethoprim	Tablet	100 mg+ 20 mg 400 mg+ 80 mg
		Oral Liquid	200mg+40mg/15ml
5	Sulfamethoxazole + Trimethoprim	Injection	80 mg+16 mg/ml (in 5 ml ampoule)
6	Isoniazid + Ethambutol	Tablet	150 mg+400 mg
7	Rifampicin + Isoniazid	Tablet	150 mg+ 75 mg 300 mg+ 150 mg
8	Rifampicin + Isoniazid + Pyrazinamide	Tablet	150 mg+ 75 mg + 400 mg
9	Rifampicin+ isoniazid+ ethambutol	Tablet	150mg+75mg+275mg
10	Rifampicin+isoniazid+ ethambutol+ pyrazinamide	Tablet	150mg+75mg+275mg+ 400mg
11	Sulfadoxine + Pyrimethamine	Tablet	500 mg+ 25 mg

Fixed Dose Combination antimicrobials registered in Nepal

In Nepal, monitoring and evaluation of drugs starting from the production, marketing, distribution, export-import, storage to use of safe and efficacious drug is done by the Department of Drug Administration (DDA). Manufacturer has to register their individual product to the DDA before marketing their product. The list of registered antimicrobials in the DDA of Nepal is given in [Table/Fig 4].

[Table/Fig 4]: List of fixed dose combination antimicrobials registered in the DDA of Nepal

Drugs	Form	Strength
Penicillins		
Ampicillin + Cloxacillin	Cap.sule	• 290 mg + 274 mg • 250 mg + 250 mg • 250 mg + 125 mg • 125 mg + 125 mg
	Injection	• 500 mg + 500 mg • 250 mg + 250 mg • 125 mg + 125 mg
	Syrup /dtop	• 125 mg + 125 mg • 50 mg + 25 mg
Amoxicillin + Clavulanic acid	Tablet	• 875 mg + 125 mg • 500 mg + 125 mg • 250 mg + 125 mg
	Injection	• 1 g + 200 mg • 250 mg + 50 mg • 125 mg + 25 mg
	Syrup	• 200 mg + 28.5 mg • 125 mg + 31.25 mg
Amoxicillin + Cloxacillin	Cap.sule / Tablet*	• 250 mg + 250 mg • 125 mg + 125 mg*
Ampicillin + Sulbactam	Injection	• 0.5 gm + 0.25 gm • 1 gm + 0.5 gm
Benzyl Penicillin Sodium + Procaine Penicillin	Injection	• 500000 Units + 1500000 Units • 100000 Units + 300000 Units • 240 mg + 600 mg
Penicillin G sodium + Procaine Penicillin	Injection	• 500000 Units + 1500000 Units
Procaine Penicillin + Streptomycin	Injection	• 3 g + 600 mg
Imipenem + cilastatin	Injection	• 500 mg + 500 mg
Piperacillin + Tazobactam	Injection	• 4 gm + 500 mg

Usefulness of Fixed Dose Combination antimicrobials

When two or more drugs are given together as like fixed dose combination, they may either be indifference to each other or produce synergism or antagonism. When the action of one drug is increased by another drug given concomitantly, it is said to be synergism and when one drug inhibit or decreases the action of another said to be antagonism. The synergistic actions produced by the fixed dose combination drug many remains beneficial for the treatment. Some of the synergistic action of fixed dose combination antibiotics is very much beneficial role in the treatment of infectious disease especially when resistant to single drug treatment is high. In addition, clinically the use of combinations of antimicrobials is advocated for empirical therapy when cause of infection is unknown, for treatment of multiple microbial infections, for synergistic action and to prevent the resistance [18]. Examples of some of synergistic FDC antibiotics are listed in the [Table/Fig 5].

Moreover, the resistant to the treatment of disease like Tuberculosis, Leprosy is very high and is recommended to treat such disease with the multi-drug. In such condition, FDC antibiotics can decrease the complexity of dosage regimen, cost of therapy, incidence of ADR and increase the compliance of therapy.¹⁹ Thus decreases the resistance to the treatment.

[Table/Fig 5]: Examples of some of synergistic FDC antimicrobials

Drugs	Mechanism of synergism
Sulphamethoxazole + Trimethoprim	Trimethoprim is inhibitory for a wide range of bacteria, and when used in combination with a sulphonamide marked synergy has been reported [20]
Amoxicillin + Clavulanic acid	Clavulanic acid enhances the antibacterial spectrum of amoxicillin by rendering most β -lactamase-producing isolates susceptible to the drug. In clinical trials amoxicillin/clavulanic acid is clinically and bacteriologically superior to amoxicillin alone and at least as effective as numerous other comparative agents [21]
Imipenem + Cilastatin	Coadministration of Imipenem with a renal dehydropeptidase inhibitor, Cilastatin prevents its renal metabolism in clinical use. This increase the efficacy and extend spectrum covers septicemia, neutropenic fever, and intra-abdominal, lower respiratory tract, genitourinary, gynaecological, skin and soft tissues, and bone and joint infections [22]
Ampicillin + Sulbactam	Clinical findings from the past decade confirm the results of numerous older studies and together provide good evidence to support the continued use of ampicillin/sulbactam and sulbactam in hospital- and community-acquired infections both in adults and children. This is also recognized in recent published national and international guidelines, many of which recommend ampicillin/sulbactam as first-line therapy for various respiratory and skin infections [23]
Piperacillin + Tazobactam	Combining tazobactam, a beta-lactamase inhibitor, with the ureidopenicillin, piperacillin, successfully restores the activity of piperacillin against beta-lactamase-producing bacteria. Tazobactam has inhibitory activity, and therefore protects piperacillin against Richmond and Sykes types II, III, IV and V beta-lactamases, staphylococcal penicillinase and extended-spectrum beta-lactamases [24]
Sulfadoxine + Pyrimethamine	Sulfadoxine/pyrimethamine plus amodiaquine could be used as an inexpensive regimen to decrease the rate of subsequent episodes of malaria [25]

Harmfulness of IFDC antimicrobials

Although some of the fixed dose antimicrobials offer some benefit in treatment of disease like

Tuberculosis, Leprosy etc. The majority of irrational fixed antimicrobials have major contribution in resistance development. In addition, IFDC antimicrobials increase the toxicity and identification of causative drug in the combination [19]. Moreover, the combination drug decreases the flexibility of prescriber and increase the misuse by self-medication.

Are all FDC antibiotics rational?

Rationality of fixed dose combination is always remains questionable. When it comes to antimicrobial, it may be rational sometimes but not always. Many irrational fixed dose combinations of antimicrobials are available. One of the examples is Ampicillin + Cloxacillin. None of the evidence supports the combination of these two drugs combinations [26]. Moreover, there are so many other irrational combinations are available in the market. Some of them are Metronidazole + Tinidazole, Metronidazole + Diloxanate furate + Diphenhydramine, Doxycycline + Neomycine sulphate, Furazolidone + Metronidazole, Ofloxacin + Tinidazole, Ciprofloxacin + Metronidazole, Norfloxacin + Ornidazole, Tinidazole + Ciprofloxacin etc.

Strategies to minimize IFDC antimicrobials

The various strategies to minimize the IFDC antimicrobials are

1. Developing guidelines for preparing of combination product: Many irrational drugs get registered because of lack of guideline for combination products. Hence developing guideline for preparing fixed dose combination will be effective in minimizing irrational fixed dose combination of antimicrobials.

2. Evaluation of product before registration: The complete evaluation of fixed dose antimicrobials before registration will be helpful in minimizing irrational fixed dose combination antimicrobial.

3. Banning of irrational FDC antimicrobial: Banning of irrational fixed dose combination antimicrobials will be helpful in minimizing irrational fixed dose combination antimicrobial.

4. Strict monitoring of use of antimicrobial: Strict monitoring of specially fixed dose

combination antimicrobials use can decrease the irrational fixed dose combination.

5. Strict antibiotic policy: Many countries have their antibiotic policy and the strict implementation of it has minimized the use of not only irrational fixed dose combination antimicrobials but also the use of antimicrobial and there was decrease in resistance.

6. Hospital antibiotic policy: In addition to antibiotic policy of the countries, many hospitals have their own antibiotic policy which monitors the use of antimicrobials at the hospital level. Hence the formation of hospital antibiotic policy to individual hospital may be helpful to minimize not only the use of IFDC antimicrobials also the excessive use of antimicrobial.

Initiatives to minimize the IFDC antibiotics in Nepal

In Nepal, some of the initiatives taken in the past to minimize the IFDC antimicrobials are

1. Banning of Irrational fixed dose combination antimicrobials: in the past DDA has banned several irrational fixed dose antimicrobial periodically [27]. Some of them are

- Combinations of antihistamines with antidiarrhoeals or with antiamoebic
- Combinations of penicillin with sulfonamides
- Combinations of vitamins C with tetracycline
- Combinations of chloramphenicol except in combination with streptomycin
- Combinations of vitamins with antitubercular drugs except in combinations of antitubercular drug isoniazide with vitamin B6.
- Combination of Antidiarrhoeal/Antibacterial with Electrolytes
- Combination of Two or More Antibacterials Except the Following
 - Combination Used for the Treatment of Tuberculosis
 - Combination Used for the Treatment of Leprosy

- Combination of Two Antibiotics of the Penicillin Group
- Combination of Two or More Therapeutic Agents as Recognized by Standard Pharmacopoeia
- Combination of anti-amoebic or anti-diarrhoeal drug except the following
 - Combination of Metronidazole or Tinidazole with Diloxanide furoate
 - Combination of diphenoxylate 2.5mg with Atropine 0.025mg in a tablet

2. Re-evaluation of registered products: DDA re-evaluate the registered product time to time to find the harmful registered drugs, irrational combinations and drugs/combinations of doubtful therapeutic value [28]. The evaluation is done by some of the NGO. Base on their recommendation DDA ban the harmful and irrational drugs. First time the drug was banned in 1983 followed by banning items in 1986, 1990, 1992 and 1997.

3. Incorporation of prudent use of antimicrobials in National Drug Policy (NDP): Although there is no separate antibiotic policy, Govt. of Nepal has added prudent use of antimicrobials in NDP as a one of the component under rational drug use which suggest about the supervision and monitoring of antimicrobial use to control the misuse of antimicrobial.

4. Drug Act 1978: Drug Act 1978 was brought into action which prohibits the misuse of drugs and also has categorized the antimicrobial into class of drug which can be sold only with prescription from the registered medical practitioner.

Conclusion

The misuse or over use of antimicrobial can lead to antimicrobial resistance. The use of irrational fixed dose combination antimicrobials can increase the antimicrobial resistance. To minimize the extensive use of fixed dose combination of antimicrobials certain measures like developing guidelines for manufacturing of combination products, evaluation of new products before registration, banning of IFDC antimicrobials, strict monitoring, strict antibiotic policy, hospital antibiotic policies etc., will be helpful. In the developing world where

resistance to antimicrobial is increasing, minimizing the use of irrational fixed dose combination antimicrobials can be a better tool to combat antimicrobial resistance.

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