BJCP British Journal of Clinical Pharmacology

DOI:10.1111/j.1365-2125.2007.03089.x

Letter to the Editors

Fixed dose drug combinations (FDCs): rational or irrational: a view point

Chandler S. Gautam & Lekha Saha

Government Medical College and Hospital – Pharmacology, Government Medical College and Hospital, Chandigarh, India

Combination products, also known as fixed dose drug combinations (FDCs), are combinations of two or more active drugs in a single dosage form. The Food and Drug Administration, USA defines a combination product as 'a product composed of any combination of a drug and a device or a biological product and a device or a drug and a biological product or a drug, device, and a biological product' [1]. It is widely accepted that most drugs should be formulated as single compounds. Fixed ratio combination products are acceptable only when the dosage of each ingredient meets the requirement of a defined population group and when the combination has a proven advantage over single compounds administered separately in therapeutic effect, safety or compliance [2]. FDCs are highly popular in the Indian pharmaceutical market and have been particularly flourishing in the last few years. The rationality of FDCs should be based on certain aspects such as [3]:

- The drugs in the combination should act by different mechanisms.
- The pharmacokinetics must not be widely different.
- The combination should not have supra-additive toxicity of the ingredients.

Most FDCs have the following demerits:

- Dosage alteration of one drug is not possible without alteration of the other drug.
- Differing pharmacokinetics of constituent drugs pose the problem of frequency of administration of the formulation.
- By simple logic there are increased chances of adverse drug effects and drug interactions compared with both drugs given individually.

The recent 14th model list of essential drugs prepared by the WHO (March 2005) includes 312 formulation of which 18 are fixed dose drug combinations [4]. The World Health Organization's (WHO) Model list of Essential Drugs provides examples of some rational FDCs such as [5]:

- sulfamethoxazole + trimethoprim
- antitubercular FDCs like rifampicin + isoniazid, isoniazid + ethambutol, etc
- antiparkinsonism FDCs like levodopa + carbidopa

Unfortunately, many FDCs being introduced in India are usually irrational. The most pressing concern with irrational FDCs is that they expose patients to unnecessary risk of adverse drug reactions, for instance, paediatric formulations of nimesulide + paracetamol. Nimesulide alone is more antipyretic than paracetamol, more anti-inflammatory than aspirin, and equivalent in analgesia to any of the NSAIDS alone [6], so efficacy gains are unlikely with added paracetamol. However, the patients may be subject to increased hepatotoxic effects from the combination. FDCs of diclofenac + serratopeptidase do not offer any particular advantage over the individual drugs despite the claim that serratopeptidase promotes more rapid resolution of inflammation [3]. On the other hand, the patient is exposed to greater risk of gastrointestinal (GI) irritation and serious bleeding from unsuspected peptic ulceration. FDCs of quinolones and nitroimidazoles (e.g. norfloxacin + metronidazole, ciprofloxacin + tinidazole, ofloxacin + ornidazole) have not been recommended in any standard books [7, 8], but continue to be heavily prescribed drugs in GI infections, pelvic inflammatory disease, dental infection, etc., to cover up for diagnostic imprecision and the lack of access to laboratory facilities. Such 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. A glaring example is the emergence of ciprofloxacin-resistant *Salmonella typhi* strains which have made treatment of typhoid fever a difficult and expensive proposition in India today [3].

In India, a variety of NSAID combinations are available, often as over the counter products [9]. These combinations are an easy way to sell two drugs when one (or even none) may be needed for the patient. The 'combined' pills are marketed with slogans like 'ibuprofen for pain and paracetamol for fever' and 'ibuprofen for peripheral action and paracetamol for central action'. It is indeed very unfortunate that the medical fraternity in India has fallen prey to such gimmicks. The gullible patient then has to pay for the doctor's complacence in terms of extra cost and extra adverse effects. There is no synergism when two drugs acting on the same enzyme are combined. Thus combining two NSAIDs does not and cannot improve the efficacy of treatment. It only adds to the cost of therapy and more importantly, to the adverse effects [10] and the 'muscle relaxants' in some of these combinations are of questionable efficacy.

Combinations of NSAIDS/analgesics with antispasmodic agents are also available in India [9]. They are not only irrational but also could be dangerous. The antipyretic drug promotes sweating and thereby helps in heat dissipation. On the other hand, the anticholinergic antispasmodic drug inhibits sweating. Combining these two can result in dangerous elevation of the body temperature [3]. Some such fixed drug combinations are now banned in India [11].

Over the years the Indian Drug Control Authority has issued banned notifications on many FDCs like analgin + pitofenone, vitamins B1 + B6 + B12, cyproheptadine + lysine, etc. [11]. But are these measures sufficient? Obviously not, since these notifications have not deterred manufacturers from coming out with new irrational FDCs. At this crucial juncture, when the global community, represented by WHO, is making an all out effort to propagate the concept of essential drugs amongst consumers throughout the world, our official stance could be viewed as too meager. India, as the world's second most populous country, should demand a more rational approach and not pay mere lip service to the global campaign.

Irrational FDCs also impose unnecessary financial burden on consumers. Medical practitioners who patronize such combinations could be the centre of controversy when subjected to litigation in consumer forums, as these combinations do not find mention in standard text or reference books and reputed medical journals. Pharmaceutical manufacturers, however, continue to reap the benefits of huge sales, and therefore continue to promote combinations with vigour.

The time has come for all practitioners and consumers to raise this matter vociferously through all possible avenues. Drug regulatory bodies should take urgent action to mitigate the free flow of irrational FDCs.

REFERENCES

1 Sreedhar D, Subramanian G, Udupa N. Combination drugs: are they rational? Curr Sci 2006; 91: 406.

2 World Health Organization. The use of essential drugs. WHO Technical Report Series 825. Geneva: World Health Organization, 1992.

3 Amitava S. Indian market's fixation with fixed dose combinations (Editorial). Rational Drug Bulletin 2002;12: 1.

4 World Health Organization. The Use of Essential Drugs. WHO Technical Report Series 933. Geneva: World Health Organization, 2006.

5 World Health Organization. The Use of Essential Drugs. WHO Technical Report Series 850. Geneva: World Health Organization, 1995.

6 Gautam CS, Aditya S. Irrational drug combination: need to Sensitize undergraduates. Ind J Pharmacol 2006; 38: 167–70.

7 Margaret AP, Samuel LS Jr. Chemotherapy of protozoal infections. In: Goodman and Gilman's the pharmacological basis of therapeutics, 11th edn, eds LL Brunton, JS Lazo, KL Parker. New York: McGraw-Hill, 2006; 1049–50.

8 Rosenthal PJ. Antiprotozoal drugs. In: Basic and clinical pharmacology, 9th edn, ed. Katzung BG. Boston, MA: Mc Graw-Hill, 2004; 875–8.

9 Gulhati CM. Monthly index of medical specialities, India. MIMS INDIA 2005; 25: 81–94.

10 Burke A, Smyth E, Gerald GAF. Analgesic-antipyretic agents; pharmacotherapy of gout. In: Goodman and Gilman's the Pharmacological Basis of Therapeutics, 11th edn, eds Brunton LL, Lazo JS, Parker KL. New York: Mc Graw-Hill, 2006; 685.

11 Tripathi KD (ed). Appendix 2. Drugs and fixed dose combinations banned in India. In: Essentials of medical pharmacology, 5th edn. New Delhi: Jaypee Brothers, 2004; 847–8.

RECEIVED
6 May 2007

ACCEPTED
23 October 2007

PUBLISHED *OnlineEarly*
21 February 2008

CORRESPONDENCE
Dr C. S. Gautam, Government Medical College and Hospital – Pharmacology, Government Medical College and Hospital, Sector 32, Chandigarh, India 160030.
Tel.: + 91 172 264 5262
E-mail: csgautam_06@yahoo.co.in