EDITORIAL

FIXED DOSE COMBINATIONS

The phrase "multidrug therapy" (MDT) refers to concurrent use of two or more drugs to treat a single disease. This approach is commonly used in the treatment of hypertension, tuberculosis and diabetes, among other several diseases. There are different variations of MDT. In one variation, drugs are administered singly in different dosage forms either at the same time or at different intervals. In another variation, two or more drugs are co-packaged and taken at the same time interval (od, bd, tds, etc). In yet another variation, two or more active pharmaceutical ingredients (APIs) are co-formulated as a single dosage form commonly referred to as fixed dose combinations (FDCs) and administered at appropriate intervals. This editorial will focus on the merits and demerits of FDCs.

Fixed dose combinations are justified only where there is a well-defined large population in need of such combinations and when a FDC has distinct advantage over single drugs administered separately. The advantage may be with regard to enhanced efficacy, safety or more often, improved medication compliance. The adverse drug reaction of a FDC should not be more than of individual components. In real practice, FDCs are promoted as new products for treatment of a particular disease to gain advantage over competitor drugs. This is particularly true of disease conditions such as HIV/AIDS, hypertension and diabetes where no single dosage regime is recognized as superior to the others. In such a situation, a new product in form of FDC is given the benefit of doubt. The standard of proof needed to discredit any dosage regime is very high. The World Health Organization (WHO) model list of essential drugs (March 2005) includes 312 products of which 18 are FDCs. Among them are sulphamethoxazole/trimethoprim, rifampicin/isoniazid and levodopa/carbidopa. The reasons for formulating the above three FDCs are well documented in literature. Although many other FDCs are not included in the WHO list of essential drugs, they are well accepted in clinical practice. For example, the following FDCs are commonly used in HIV/AIDs: zidovudine/lamivudine (Combivir); abacavir/zidovudine/lamivudine (Trizivir); lopinavir/ritonavir (Kaletra); emtricitabine/tenofovir (Truvada); efavirenz/emtricitabine/tenofovir (Atripla); and rilpivirine/emtricitabine/tenofovir (Complera). Among the six FDCs, only Kaletra is recommended by the WHO. This serves to show that FDCs are much more widely used even though only a few are approved by the WHO.

There are some basic requirements to be met in formulating two or more APIs into a FDC. These include: (1) the APIs should preferably act by different mechanisms; (2) the pharmacokinetic profiles of the APIs should not be widely different; and (3) the combination should not have enhanced toxicity compared to individual components. These requirements appear to be met in the combination of sulphamethoxazole/trimethoprim (cotrimoxazole), one of the oldest FDCs. Both APIs act sequentially to block dihydropteroate synthetase (DPS) and dihydrofolate reductase (DHFR), hence blocking synthesis of folic acid in bacteria. Further, sulphamethoxazole and trimethoprim have about the same elimination half-life of approximately 11-12 h. The combination of sulphonamide and pyrimethamine (SP) used as antimalarial has the same advantages as cotrimoxazole. In the case of artemether/lumefantrine (artemisinin-based combination therapy), the half-life of the two APIs is very different leading to accumulation of the latter. However, this is considered advantageous in that it helps to clear parasiteamia over an extended duration. Nevertheless, some of the FDCs are controversial. For example, the triple antibiotic combination of neomycin/bacitracin/polymyxin used topically is not accepted by dermatologists for different reasons. Similarly, a FDC of three antihistamines used as a cough mixture is irrational.

Fixed dose combinations have some demerits. An obvious one is that the clinicians cannot alter the dose of one drug relative to the other as would be the case if the two components were administered as different dosage forms. It is also rare to find two or more drugs used for the same disease having similar elimination half-life. By far, the most important disadvantage is that there are no official monographs to validate label claim of FDCs or monitor quality assurance parameters of such products. Generally, analyses of FDCs are difficult and time consuming. In the majority of cases, reverse phase high performance liquid chromatographic (HPLC) and spectrophotometric methods have been developed to assay FDCs. In other cases, microbiological diffusion methods have been used. In this issue of the journal, Gachangaga *et al*. have described a HPLC method for simultaneous determination of amlodipine, valsartan and hydrochlorothiazide formulated as an antihypertensive FDC. The authors have cited published literature (see references 5 and 6 in the article) in which similar FDC products were analyzed using HPLC but under different conditions. The order of elution of the components and run time were significantly different from those reported by Gachangaga *et al*. in the present article. The question then is, for a laboratory wishing to analyze a FDC product containing amlodipine, valsartan and hydrochlorothiazide, which of the three analytical methods reported in the literature would be preferred and why? For many FDCs, the physicochemical properties of APIs are not significantly different making separation difficult. This would certainly be true of neomycin/bacitracin/polymyxin combination.

An article by the United States Department of Health and Human Services (www.fda.gov/regulatoryinformation/guidance, accessed June 2014) provides guidance for industry on how to formulate FDCs for HIV/AIDs. These guidelines would apply for FDCs used in other disease conditions.

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