Fixed-Dose Combination Therapy in the United States, Britain and Israel

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Abstract

Background: Fixed dose combination therapy varies among countries.

Objective: To compare the list of fixed-dose combination therapies used in the USA, UK and Israel.

Methods: The total list of drugs and FDC drugs were counted manually from a list of generic names. We also counted the number of drugs in four characteristic subgroups: cardiovascular, anti-infective, gastrointestinal, and dermatological. Data for drugs in the USA, UK and Israel were taken from the Physician's Desk Reference (PDR 1997), the British National Formulary (BNF March 1997) and the Monthly Ethical Drug Indexed Compilation (MEDIC July 1997) respectively.

Results: The global percentage of FDC drugs in the USA and UK was higher than in Israel (20%, 25% and 15% respectively). A similar trend was found in all subclasses of FDC drugs except for the anti-infective category in which the percentage of FDC drugs was low and similar in all countries.

Conclusion: The list of FDC drugs varies greatly between the USA, UK and Israel, reflecting the differences in the outcome of debate between the pharmaceutical companies and the regulatory authorities.

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At the beginning of the 1970s, combination drugs accounted for over half the pharmaceutical products and for 40% of the best-selling drugs in the USA [1]. Since then, much controversy has been generated regarding their use. While some physicians have fiercely defended their right to prescribe combined preparations [2], regulatory authorities have attempted to restrict their use.

In the late 1960s a drug efficiency study was conducted in the USA by the National Academy of Science and the National Research Council to review the efficacy of all drugs marketed between 1938 and 1962. They found that only 45 of some 1,200 fixed dose combination drugs were rated as effective [3]. In 1971 the Federal Drug Authority combination drug policy, as officially stated in the Federal Register, included the following three fundamental requirements: first, each component must make a contribution to the claimed effect; second, the dosage of each component must be such that the combination is safe and effective for use; and third, where appropriate, and as a special application of the first requirement, a component may be added, either to enhance the safety or effectiveness of the principal active ingredient, or to minimize the potential for abuse of this ingredient. The FDA restriction was reflected in the World Health Organization's list of 250 essential drugs that included combinations of only seven drugs [4]. The American Council on Drugs then stated: "combination or mixtures containing two or more active ingredients in fixed ratio are, in most instances, not recommended" [5]. In fact, the list of approved drugs in each country reflects the outcome of debate between the pharmaceutical companies and the regulatory authorities and the prescribing habits of the physicians [6].

The issue of fixed-dose combination therapy has been reviewed in the past [7–9], however little has been published on the subject during the last 15 years. The aim of the present study was to compare the list of drugs and the proportion of FDC therapy for different drug subgroups in the USA, Britain and Israel.

Methods

The list of drugs and FDC drugs as well as their numbers in four characteristic subgroups were counted manually from a list of generic names. The four subgroups of drugs to be assessed were: cardiovascular, anti-infective, gastrointestinal, and dermatological. Data of the USA, Britain and Israel were compared. Data on U.S. drugs were taken from the Physician's Desk Reference (PDR 1997) published annually by the Medical Economics Data [10]. The list of generic names was taken from section 2 – Brand and Generic Name Index, and the list of FDC drugs from section 3 – Product Category Index. Data on drugs prescribed in the UK were taken from the British National Formulary (BNF March 1997) [11], which is published twice yearly by the British Medical Association and the Royal Pharmaceutical Society of Great Britain. This list includes generic drugs and combinations. Data on Israeli drugs were

FDC = fixed-dose combination

FDA = Federal Drug Authority

taken from the Monthly Ethical Drug Indexed Compilation (MEDIC, July 1997) published by Shirol publications Ltd. [12]. This index includes a section containing all the generic names, with the FDC drugs marked by an asterisk. The BNF and MEDIC drug indexes also include over-the-counter drugs. Data on OTC drugs in the USA were assessed separately from the PDR of non-prescription drugs [13].

Results

Table 1 lists the number of generic drugs and the number and percentage of fixed-dose combinations for the different drug subgroups in the USA, Britain and Israel. In the USA, taking into account OTC FDC drugs, no difference was found in the cardiovascular and anti-infective category. In the gastrointestinal and dermatological category however, the percentage of FDC drugs increased from 21% to 36% and from 17% to 42% respectively [Figure 1].

The global percentage of FDC drugs in the USA and Britain was higher than in Israel (20%, 25% and 15% respectively). This trend was found in all subclasses of FDC drugs except for the anti-infective category in which the percentage of FDC drugs was low and similar in all countries. The percentages of FDC in the USA, UK and Israel respectively were 19%, 15% and 4% in the cardiovascular category, 36%, 38% and 19% in the gastrointestinal category, and 42%, 38% and 28% in the dermatological category. In the anti-infective category the percentage of FDC drugs was low and similar in the USA, UK and Israel – 7%, 9% and 5% respectively.

Table 1. The number of generic drugs, and the number and percentage of fixed-dose combinations for the different drug subgroups in the USA, Britain and Israel

	USA			Britain			Israel		
Drug category	No.*	FDC	%	No.	FDC	%	No.	FDC	%
Cardiovascular	118	22	19	181	27	15	71	3	4
Anti-infective	163	12	7	131	12	9	119	6	5
Gastrointestinal	75	16	21	89	34	38	67	13	19
Dermatological	124	21	17	136	52	38	95	27	28
Total**	1468	250	17	1750	435	25	978	145	15

* Number of drugs in the drug subgroup
** Total number of drugs in all categories

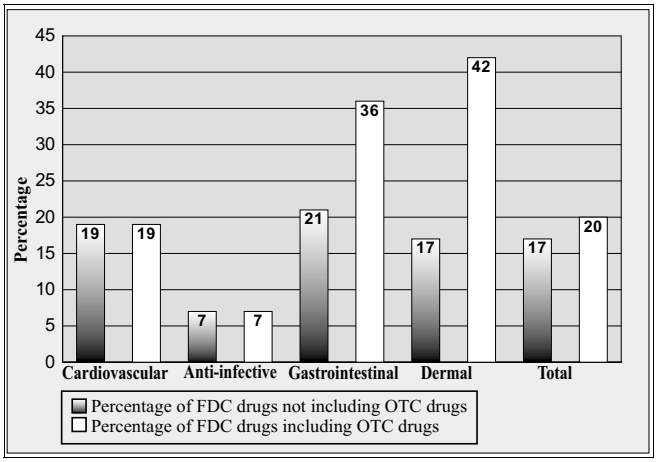

Figure 1. Percentage of fixed-dose combinations in the USA for different subgroups with and without OTC drugs.

Discussion

The purpose of this survey was to compare the list of FDC drugs in the USA, Britain and Israel. Since Israel is a small country we were not surprised to find that the number of its generic drugs is lower than that in the UK and the USA. Comparing between two large countries and a small country illuminates the differences in approach to FDC manufacturing.

The percentage of the total number of FDC drugs in the USA and Britain was higher than in Israel. This trend was found in all subclasses of FDC drugs except for the anti-infective category in which the percentage of FDC drugs was low and similar in all countries.

The highest percentage of FDC drugs was found in the gastrointestinal and dermatological categories. This can be explained by the fact that many of these drugs include OTC preparations. This high percentage in the dermal and gastrointestinal category may be explained by the strict rules of the FDA concerning these prescribed drugs.

In the cardiovascular category most of the combinations were antihypertensive agents. The differences between the USA, Britain and Israel in the cardiovascular category reflect differences in attitude to antihypertensive treatment. In the USA the first line of antihypertensive treatment will only include a diuretic or a beta-blocker [14]. In the UK however, the first line of antihypertensive treatment usually includes a diuretic, beta-blocker, calcium channel blocker, anticonverting enzyme inhibitor and alpha 1 blocker. Similarly, there has been a recent debate in the USA about the use of calcium channel blockers [15]. Only three FDC drugs are found in the cardiovascular category in Israel, where concern regarding inflexibility of treatment and drug economics has led to a limitation of FDC use for antihypertensive medications.

In the anti-infective category the use of FDC drugs is low and similar for all three countries. This finding may be explained by the goal of antibiotic treatment – namely, to avoid the use of broad-spectrum antibiotics. A good example is the combination of trimethoprim and sulphamethoxazole, which is one of the seven combinations approved by the World Health Organization [4].

The present study presents the current situation of FDC listing in different parts of the world. It is not a utilization study, which is, of course, very difficult to perform. However, a

BNF = British National Formulary
OTC = over the counter
PDR = Physician's Desk Reference

reflection of FDC use may be seen in the list of FDC drugs in each country. While it is difficult to conclude which is the best policy for FDC therapy, one of the most important factors in opting for FDC drugs is to weigh the benefits and drawbacks of their use. Improved compliance is a major advantage of FDC therapy. Patients on a multi-drug regime are prone to poor compliance. For medications prescribed for once, twice, three or four times a day, compliance has been shown to be 87%, 81%, 77%, and 39% respectively [16]. Another advantage of FDC therapy is synergism. The combination of trimethoprim and sulphamethoxazole, for example, allows each drug to selectively interfere with two successive steps in bacterial folate mechanism [17]. Enhanced efficacy can also be an advantage, as in the combination of levodopa and carbidopa. The use of this combination reduces both the dose of levodopa required and thus the incidence of side effects that occur outside of the central nervous system [18]. The addition of another drug can sometimes minimize the side effects of a drug. Amiloride, for example, may prevent hypokalemia caused by hydrochlorothiazide. The potential for abuse may also be decreased by drug combination. Excess use of the narcotic antidiarrheal diphenoxylate is discouraged by the anticholinergic side effects of atropine in the combination of atropine and diphenoxylate.

Inflexibility – as in the case of fixed insulin combinations – and incompatible pharmacokinetics are major drawbacks of FDC therapy. The use of two drugs may also increase the risk of idiosyncratic adverse reactions that lead to increased toxicity. In addition, a patient may also develop a reaction to one of the components of a combination drug, such as a rash due to sulphamethoxazole in co-trimoxazole, and may choose to avoid using the innocent trimethoprim on its own in the future. Furthermore, in many cases physicians may not be familiar with the contents of a prescribed fixed-dose combination drug [19]. As a result the symptoms may be masked, leading to an imprecise diagnosis since the physician will depend on the wide spectrum of activity of the combined drug.

In conclusion, the list of FDC drugs varies greatly between the USA, Britain and Israel, reflecting the differences in the outcome of debate between the pharmaceutical companies and the regulatory authorities. Regulatory authorities as well as physicians need to assess both the benefits and the drawbacks of FDC usage in each country.

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