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SPECIAL ARTICLE

Report of a Workshop on Fixed-Ratio Drug Combinations

On October 16-18, 1974, a group of scientists convened at Ascona, Switzerland, to discuss problems in the use of combination drugs.* Fixed-ratio combination drugs (hereinafter referred to as FRCD) are popular with the medical profession and with patients. In some instances, they represent a continuation of ancient prescribing traditions. Whereas some FRCD are rational, others are irrational because one or more of the components serves no purpose or the dose of one or more ingredients is inappropriate, or are objectionable because their effects do not correspond to the claims made for them. Some of these FRCD are of older vintage whereas others are of more recent derivation.

The workshop discussed the limitations and merits of FRCD in general, of the theoretical requirements for useful and rational combinations, and the problem of how to meet these requirements in practice. There was a further attempt to decide whether a separate approach was required for combinations that have been available for some time as opposed to those that have been newly recommended, and for FRCD obtainable for self-medication without a prescription.

There is little disagreement about the need in medicine for multiple drug therapy in the management of many conditions. In the management of hypertension, by concomitant use of drugs that decrease blood pressure via different mechanisms, one may produce a greater lowering of pressure with fewer untoward effects. In the treatment of tuberculosis, multiple drugs may improve the efficacy of treatment and prevent or delay the emergence of resistant organisms. All of these principles also apply to the FRCD, although it is worth noting that FRCD for hypertension are considered by many to be rational, whereas therapy for infections requiring more than one antibiotic is generally better achieved by individualizing the dosage of the selected antibiotics rather than by using FRCD. (Combination therapy is, for example, generally preferred for the treatment of tuberculosis of all types, but FRCD are not as yet widely used for this purpose.)

Pros and Cons

A number of arguments in favour of FRCD usage were listed. These products provide, at the very least, increased convenience for doctor and for patient. They are likely to improve compliance, i.e. adherence to prescribing directions. For the most part, FRCD provide their ingredients at a cost less than would be required were the ingredients to be prescribed separately. The use in the FRCD of a ratio of ingredients that may have been tested for both therapeutic efficacy and safety may provide better performance than is achieved with ratios constructed ad hoc by individual prescribing physicians. For some of the ingredients in FRCD, these products occasionally represent the only available source (e.g. trimethoprim is not available except in combination with a sulphonamide). Finally, the FRCD provides potentially not only a way of decreasing unwanted effects (such as potassium loss with thiazide diuretics), but lessens abuse of individual ingredients by the purposeful combining of drugs, one of which will produce side-effects (if taken in excess) that will decrease the likelihood of euphoriant effects from the abusable ingredient. (An example would be the combination of an anticholinergic with a narcotic anti-diarrheal.)

A number of arguments can be mounted against FRCD. These combinations limit flexibility and individualization in dosing. The availability of a FRCD may result in an inappropriate widening of the target population to include individuals who are not optimally treated by the combination but in fact become the recipients of it. For those individuals who do not require all of the ingredients in a specific FRCD, needless exposure (and perhaps sensitization) to an ingredient may occur. Ignorance by physicians of all the ingredients in a FRCD may result in harm to patients through sensitivity to one of the ingredients or to the overlooking of a contraindication. The availability of FRCD that treat a multiplicity of symptoms may encourage imprecision in diagnosis. If side-effects occur in a patient receiving a FRCD, there may be greater difficulty in ascribing the side-effect to a specific ingredient, and intelligent selective non-compliance on the part of patients will be rendered impossible. (Inappropriate or improper co-prescribing of several medications is not a reason for introducing a fixed ratio combination, simply to provide convenience to physicians who prescribe badly, yet it is paradoxical that such bad co-prescribing may only appear for formal examination when an attempt is made to register a FRCD.)

There was no controversy among the participants about the requirement that the combined pharmaco-

*Participants (see page 154). The meeting was sponsored by Sandoz, Ltd., Basle, Switzerland.

dynamic actions of the ingredients of a FRCD should provide advantages over the use of a single drug, and that these advantages should not be outweighed by any increase of hazard. There was agreement about the need for a readily identifiable and describable target population. On the other hand, extended discussion ensued on such matters as the pharmacokinetic aspects of FRCD, the importance of individualization of dosage, and the question of compliance or adherence.

Pharmacokinetic Aspects

A number of pharmacokinetic considerations were discussed. For many drugs, clinical investigation has demonstrated that the plasma level or half-life varies greatly from individual to individual in the population. For such drugs, the use of a fixed dose for all patients will result in considerable variation in the plasma level achieved, not only after single dosage, but at steady-state, since both levels are related to half-life. There is also considerable evidence that the metabolism of different drugs may show little co-variance in a given individual, so that the patient who is a rapid metabolizer of one drug is not necessarily a rapid metabolizer of the second. There will thus be problems with the difference in time required to reach steady-state of drugs having different half-lives, and the concentration ratios seen during the intervals between dosing will also vary depending on half-life, both during acute dosage and while achieving steady-state. Drugs differ with respect to the effect of renal insufficiency on their half-life, and such pathological derangements call for special care, and may make the use of certain FRCD unwise.

On the other hand, it was pointed out that certain drugs (e.g. those eliminated by hydrolytic processes) do not necessarily show great inter-subject variability in biological half-life. In addition, one must beware the temptation to confuse half-life with the duration of biological effect, since for certain drugs there is no apparent relationship between the level of active drug in biological fluids at a given moment and the therapeutic or toxic effects of interest.

The following questions were deemed worthy of consideration in deciding on the merits of a FRCD:

1. What is the magnitude of inter-subject variation in the biological half-life of the drugs to be used in combination?
2. Is there a relationship between the biological half-life of the two or more drugs intended as components of a combination product?
3. What is the magnitude of the inter-subject variation in the therapeutic drug concentration range?
4. What is the slope of the dose-response relationship?

There was general agreement that it was not essential for drugs to have similar biologic half-lives for them to be combined, and that where problems were generated by differences in half-lives of the individual components, the proper application of pharmaceutical formulation to achieve appropriate controlled release rates could minimize or obviate problems. Many of the above considerations, moreover, are unimportant in certain clinical situations. For example, in the combined use of reserpine and diuretics, differences in the pharmacokinetics of these two ingredients are of little moment.

Individualized Dosage

The importance of individualization of dosage and flexibility in the approach to dosage is often cited as an argument against combination drugs. It is a fact, however, that such flexibility of dosage is not commonly practised by physicians. One important explanation of this fact is that flexibility in dosage is impossible if one does not have an easy pharmacologic or therapeutic end-point or if one is taking a drug in only one or a few doses. Some chronic situations, such as the use of indirect anticoagulants or the treatment of hypertension, allow for flexibility of dosage because of readily measurable biological end-points. Many diseases and complaints, however, do not fall into this category, but instead have end-points that are difficult to measure. Furthermore, experience in the management of certain important diseases (such as bacterial infections) attests to the frequent success of a non-flexible approach. A further example would be the use of chemicals to prevent pregnancy, where the very success of the method can be said to rest on the ease with which a fixed dosage and non-flexible approach succeeds in practice By the same token, however, it would seem undesirable to make available a FRCD including one ingredient that is aimed at a symptom or disease that lacks an easily measurable end-point while another ingredient is directed against a symptom or disease that provides a readily interpreted end-point. An example would be a combination of an antibiotic and an analgesic, where for the latter ingredient an end-point is readily perceived by the patient and may primarily determine the motivation of the patient to take the combination, resulting either in overdosage of the antibiotic or premature cessation of therapy if the pain disappears.

As a separate argument in this regard, the proposition was considered that careful individualization of dosage, perhaps with the aid of plasma level measurements, might be preferable to the use of multiple treatment from the very start. Proponents of this view suggested that it was better practice to take full advantage of the therapeutic capability of a single ingredient before exposing the patient to several drugs. Opponents of this view pointed out, however, that a decision along these lines required one to weigh the empiric performance of the "optimization approach" versus the multiple drug approach. For example, in those clinical conditions where time is not of the essence and where one has the op-

portunity and ability to engage in optimization, such an approach may be feasible. If, on the other hand, such experimentation with dosage results in intolerable prolongation of disability or discomfort, and it can be adequately documented that the simultaneous use of several drugs either in free combination or in a FRCD provides an overall superior performance, it would seem desirable to forego the optimization, single drug approach in favour of the multiple treatment approach. For example, the availability of dopa-decarboxylase inhibitors provides the doctor with two options — to start a Parkinsonian patient on L-dopa, titrating the dosage to optimal levels, and using a FRCD of L-dopa and inhibitor only if treatment is then suboptimal, or using the FRCD from the start, which will result usually in lower L-dopa dosage, fewer side-effects, and better therapeutic response, but carries the hazard of possible untoward effects from the inhibitor.

There was additional consideration of the desirability of having available multiple ratios of ingredients instead of a single FRCD, as well as of the use of FRCD in a given condition after the desirable ratio had been arrived at by preliminary manipulation of dosage of the individual ingredients given separately. Some FRCD may thus have a role to play as initial therapy, whereas others are perhaps most wisely used after a preliminary period of individualized dosage of the separate ingredients.

For mild to moderate hypertensive patients requiring therapy, it may be equally rational to start with one or another FRCD and then switch to more potent agents (generally requiring flexible, non-FRCD regimens for success) in the event of failure to control the hypertension, or to begin therapy with the free combination of individual drugs before proceeding to a FRCD.

Compliance

The complexity of modern prescribing and the need for many drugs to be taken simultaneously by many patients pose special problems in regard to compliance with prescribing directions and the proper taking of medicaments. It seems self-evident that the less complicated the dosage regimen, and the fewer number of medicines to be taken daily, the less likely there is to be a problem with compliance. In addition to the reasonableness of this supposition, studies such as the one by Vere[1] and by Crooks et al.[2] do provide documentation at least for the importance of complexity in determining nursing errors. Clark and Troop[3], in a retrospective study, found that patients receiving an antihypertensive FRCD with three ingredients were actually better controlled, and suffered no more side-effects, with the FRCD than from the flexible use of one, two, or all three of the single ingredients. One possible explanation for these observations is that when the patients were taking the FRCD, they more often took all their medications than when following more complicated regimens. Ayd[4] and Gatley[5] have also reported on the superior success of regimens requiring fewer medications daily. Members of the Workshop pointed out, however, that despite the existence of many papers in the literature (Haynes and Sackett[6]) suggesting that complexity of regimen increases problems of patient compliance (primarily but not exclusively errors of omission), the situation with regard to FRCD deserved special study of its own. Unfortunately, one of the difficulties in studying compliance is that when one begins to study it, the behaviour of patients may be altered by the very fact that investigation is going on, so that the true magnitude of the problem is difficult to assess.

A special aspect of compliance is the situation where one wishes to "lock together" several medications because the taking of one without the simultaneous taking of the other obviates the very reason for prescribing them together. (It is pointless, e.g. to take a dopa-decarboxylase inhibitor for Parkinsonism without also taking L-dopa.) When such compliance failures occur either because of forgetfulness on the part of the patient or due to economic considerations (resulting in the filling of one prescription but not another, for example), difficulties in regard to inadequate treatment or to abuse of medications are more likely with separately prescribed drugs, than with FRCD.

Socio-economic Considerations

Surveys of drug combination usage in the U.S. (Kemp[7], de Haen[8]) suggest that for the most part FRCD provide the consumer with ingredients at a cost less than would be required if the individual ingredients in these combinations were to be prescribed and purchased separately. For instance, a survey of the 200 most often prescribed U.S. drugs showed that 37% of them were FRCD. Of the 71 most popular combinations examined, the price for the ingredients contained within them was on average 59% higher if the ingredients were purchased separately.

Specific Therapeutic Areas

A number of specific therapeutic areas were discussed. The principles emerged that the existence of comorbid states or coexistent symptoms, and the need to attack diseases or symptoms at different sites, represent strong arguments in favour of combination drug therapy.

In the area of oral contraceptives, we have drugs that provide perhaps the most dramatic example of exceptions to the notion that one drug is always to be preferred to two. (This field also supplies an exception to the principle that healthy individuals should not be given drugs.) With oral contraceptives, we have an unusual state of affairs in that the first drug in the field was a combination drug, and that later ones (including single drug entities) turned out to be less effective and less desirable than the first

preparation. Finally, oral contraception represents a situation where flexibility in dosage invites a comparison with Russian roulette.

In the field of hypertension, the majority of patients requiring therapy suffer from mild to moderate disease that is asymptomatic until such time as medications are prescribed to lower the blood pressure, whereupon drug-induced symptoms may be produced. (In some ways the taking of antihypertensive drugs by asymptomatic hypertensives may be said to offer about as much attraction as the taking of oral contraceptives by a woman shipwrecked by herself on a desert island.) This situation thus poses problems in regard to motivation, so that long term compliance can only be achieved by making the drug regimens as simple, non-toxic and inexpensive as possible (with few drugs given infrequently during the day). These patients often suffer from comorbid states, thus requiring still other medications (i.e. more tablets), which further aggravate the problem of long-term compliance.

Finally, in such therapeutic areas as cough-cold remedies and analgesic mixtures, examples are available where there is a coexistence of various symptoms, a need for acute medication (thus obviating titration of dose) and the common practice of self-diagnosis and self-treatment. Here too, therefore, certain FRCD have an important role to play, providing the possibility of increased convenience, decreased cost, improved efficacy, decreased toxicity, and a diminution in abuse of certain ingredients.

Requirements

The theoretical requirements for a rational FRCD are as follows:

1. There should be a pharmacological rationale that the simultaneous application of the several ingredients provides results superior to those achieved with one ingredient alone, and that each ingredient in the FRCD contributes to the final therapeutic effect.
2. It must be possible to incorporate the ingredients into a single dosage form that is satisfactory from the standpoint of the chemistry of the components, their bioavailability, the absence of unwanted interactions, and the selection of doses for each ingredient. (In this regard, it was pointed out that one may combine ingredients with long and short half-lives, since one can, by adjusting the dosage interval to accommodate the ingredient with the shorter half-life, still utilize the two components in one FRCD.) It was felt that, in general, if one of the ingredients of the FRCD had a low therapeutic index or a steep dose-response curve, it would be preferable if the other ingredient or ingredients had a high therapeutic index or a flat dose-response curve.
3. Another theoretical requirement is that a FRCD should be suitable, in both pharmacodynamic and pharmacokinetic respects, for a significant proportion of the target population in question.

Drug Registration

In reviewing data on FRCD, to see whether the theoretical requirements are satisfied, a flexible approach is indicated, depending on whether one is dealing with relatively innocuous, long-used, and apparently efficacious products, modern combinations based on an attempt to integrate into one pharmaceutical dosage form two or more drugs commonly co-prescribed, or new combinations involving at least one ingredient that has not been previously marketed.

In regard to long-used, apparently safe and effective products, for example vitamin tablets intended as food supplements or an aspirin-codeine combination, it may not be necessary to demand any additional information unless there is reason to doubt the safety of the combination or of one ingredient (as in the case of phenacetin-containing analgesic mixtures) or its efficacy (as in the case of certain nostrums containing botanicals with unestablished clinical utility).

In regard to modern combinations of drugs commonly co-prescribed, it would seem reasonable to demand evidence of bioavailability, as well as data on the pharmacokinetics and clinical performance, i.e. efficacy and safety, of the proposed ratio, plus perhaps limited animal experimentation. As to the human and animal data for drugs in this category, it would on some occasions be rational to expect actual comparisons of the combination with each of the individual ingredients, but in other situations this would appear not to be a sensible approach, because such a requirement would involve a great deal of time, effort, and discomfort for patients without producing any useful information (as for example in combining a vasodilator and betablocker, or putting together an enzymatic preparation to deal with an excretory pancreatic insufficiency, or combining a diuretic with a potassium supplement). Animal or human experimentation with compounds in this category might be limited to studies to document the fact that no significant change in pharmacokinetics is produced by the co-administration of the compounds. There was inadequate time in the Workshop to deal with the utility and design of studies in animals, but the feeling was expressed that use of the same fixed ratio in animals as was contemplated for man would not necessarily be rational, since different species may metabolize compounds, or respond pharmacodynamically to them, in different ways.

Finally, in regard to combinations where one of the ingredients has not been marketed before, all of the data required in regard to the second classification would be indicated plus, in all likelihood, additional animal toxicological data. The question of what kind of animal toxicity data should be demanded in this whole area could not be dealt with effectively and represents a reasonable future area of concern for the work party to be proposed later in this report.

The requirements for ethical drugs that will be dispensed only on prescription may well be different from those required for proprietary, over-

the-counter medications that will be primarily employed during the processes of self-diagnosis and self-treatment and thus will of necessity require a special concern for the problem of safety. A further consideration is that over-the-counter remedies will have to be labelled with special care in language that will be understandable by the layman.

General Remarks

It is clear that a variety of strong opinions militate against a dispassionate discussion of FRCD. These include opinions based on opposition to industrial monopoly, or that result from the existence of irrational or dangerous FRCD or that reflect the belief that bad prescribing by physicians because of poor education is aggravated further by the availability of irrational combination drugs.

It would also appear that because of differences in professional systems, regulatory agencies, reimbursement schemes, etc. in different countries, different approaches to evaluating and licensing FRCD are inevitable. Nevertheless, it is to be hoped that the scientific and medical principles underlying such evaluation and regulation should be generally similar from country to country, and that when non-scientific considerations are involved in decisions, they be clearly separated from the scientific issues.

The education of physicians in regard to the use of all drugs requires improvement, and the area of FRCD is no exception. The specific educational problems include informing physicians about the appropriate target populations for FRCD, the ingredients of specific combination products and their actions, and the elimination of improper co-prescribing habits (whether they involve combination drugs or individual drugs). In addition, when the physician is guilty of under-prescribing (for example in patients with mild to moderate hypertension), he needs to be educated about the need for adequate pharmacotherapy. Physicians must be taught that a new FRCD should not necessarily displace, but often should complement, existing single entity drugs, and that FRCD should be used as the result of an affirmative, specific decision and not by reflex.

There are a variety of research possibilities with regard to FRCD that may improve the current situation. One is the role of the clinical pharmacologist and pharmacokineticist, employing sophisticated biochemical tools, clinical techniques, and biomathematical methodology in establishing therapeutic approaches and dosage regimens which can then be implemented by the practicing physician who does not have access to sophisticated laboratory facilities. A second research area concerns ways of improving the delivery of multiple drugs such as the use of "sequential packages" (similar to the oral contraceptive package). A third involves the use of surveillance techniques after marketing to check on the proper and improper use of duly approved FRCD. Post-marketing surveillance, for example, might be specially useful to detect at an early stage an inappropriate broadening of the target population for which a FRCD was originally approved, or for studying the possible protection of the public from toxicity when a given ingredient is only available in a FRCD. (An example of the latter might possibly be the lack thus far of reported cases of acetaminophen-induced hepatic necrosis in Germany where this drug is not available as such but can only be obtained in analgesic combinations, in contrast to the UK, where acetaminophen is available per se and has often been the cause of hepatic necrosis, including many fatalities.)

The Workshop was characterized by lively debate, provocative discussion and a remarkable consensus on many issues. Nevertheless, areas of disagreement or uncertainty remain (especially in regard to what constitutes reasonable requirements regarding animal and human data on drug combinations). The participants ended their deliberations with the unanimous recommendation that an international work party be assembled to pursue these matters further, so as to elaborate non-rigid, but nevertheless useful guidelines for the pharmacologists, toxicologists, clinical investigators, drug firms and regulatory agencies of all countries. Such a meeting could be sponsored by WHO, IUPHAR, or the European Society of Toxicology.

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