

Drug combinations

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Summary

Most drugs are used at constant dosage and many are administered together. Under these circumstances, there are many advantages to patients and doctors in providing fixed combinations. Despite some official and academic criticisms, such combinations help patients to adhere to recommended regimens, and overcome the risk of unexpected drug interaction. These advantages must be balanced against the disadvantages of inflexible dosage for some patients but the majority should benefit from the additional simplicity, convenience and safety of combinations, when they need more than one drug at standard dosage.

In order to treat certain clinical conditions or to achieve a desired therapeutic effect, it is often necessary to administer more than one drug at the same time.

It is also apparent from clinical usage and prescription surveys that a great many commonly used drugs are administered at constant dosage to between 50 to 75% of adult patients.^{1,2}

Accepting these two situations, there are considerable practical advantages in giving the required drugs in single formulation. Such combination formulations give greater convenience and safety for patient and doctor and reduce the risk of errors in medication. The advantages are even greater in this modern therapeutic era, when all such combinations are not only convenient and simpler but have been carefully tested and registered as safe and efficacious. In addition, many of the existing combinations have arisen from requests by practising doctors, who are aware of these benefits.

Despite these advantages, there has been widespread criticism of combination products.^{3,4,5} Recent changes in attitude question the validity of such criticisms, especially in view of the widespread acceptance of combinations in clinical practice.

Need for concomitant therapy

There is no justification for using a fixed-dose combination where there is no medical reason for giving more than one drug. However, it is clear from all analyses of drug usage in hospital and in general practice, that more than one drug is frequently required for the optimum management of the patient.^{6,7}

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The reasons for multiple drug therapy are legion but a few of the commoner examples are listed in Table I.

Table 1.

| Rationale | Drug combination | Disease |
|------------------------------------|-------------------------------------|-------------------------------|
| Potentiation of effect | Trimethorprim and sulphonamide | Urinary infection, bronchitis |
| | Diuretic and hypotensive agent | Hypertension |
| Reduction of side-effects | Nystatin and tetracyclines | Candida prone patients |
| Prevention of drug resistance | P.A.S. + I.N.A.H. | Prolonged anti-T.B. therapy |
| Extended coverage | Antibacterial and antifungal agents | Mixed skin infections |
| Multiple effects for single entity | Oestrogen and progestogen | Oral contraception |
| Co-existing diagnoses | Folic acid, iron | Mixed anaemias of pregnancy |

Interaction between drugs given together

Whenever more than one drug is administered at the same time, either as separate formulations or a fixed combination, a number of factors operate which may influence the effect of the individual drugs and of the total therapy.

(a) Physical and chemical factors

The bio-availability of drugs can be significantly modified by the presence of other drugs, which alter pH, form chelates, allow precipitation, etc.⁸

(b) Pharmacokinetic factors

Pharmacological and toxic effects of drugs are the final results of very complicated mechanisms. Pharmacodynamic research has yielded information on the importance of the concentration of different compounds at receptor sites, changes in drug metabolism and tissue protein binding,^{9,10,11} all of which can be influenced by multiple drug therapy. Examples of drug interaction which profoundly modify these pharmacokinetic factors include barbiturates decreasing and phenylbutazone increasing the anti-coagulant action of oxycoumarols, sulphonamides altering the hypoglycaemic action of tolbutamide, etc.

Risk in prescribing

The factors listed above prompted Dollery to state¹²: "Every time a physician adds to the number of drugs a patient is taking, he may devise a novel combination that has a special risk. Frequent use of a new drug combination requires separate

investigation with animal toxicity studies and clinical observation carried out as thoroughly as the primary trial of a single drug.”

Everybody will agree with this view and the need to investigate carefully all possible aspects of drug interaction, when more than one drug is administered at the same time. This is unlikely to be achieved when more than one separate drug is prescribed as concomitant therapy in hospital or in general office practice, but is covered completely by the pharmaceutical industry in their investigation of drug interaction for a proposed combination.

As has been described,¹³ the ingredients of combinations are carefully studied separately and together in animal pharmacology and toxicity experiments, in human pharmacology and in controlled clinical trials to the same standard as single new drug entities. The pharmaceutical industry does this to comply with its own standards and to fulfil the requirements of registration authorities around the world.

Official comment

Although there has been widespread academic and semi-official criticism of drug combinations in many countries,^{3,14} it is only recently that an official regulatory body has given explicit views⁵ and then further detailed comment¹⁵ after considering evidence on combinations brought forward by their statements.

The Commissioner of Food & Drugs (F.D.A.) in the United States originally stated⁵ that combinations could only be approved if they had properties additional to those of the active ingredients and if they were operative for most patients for the duration of treatment and finally declared: “It is generally advisable to administer therapeutic agents separately.” This was endorsed by the Council on Drugs,¹⁴ which pronounced: “Combinations or mixtures combining two or more active ingredients in fixed ratios are, in most cases, not recommended by the Council.”

These restrictive and generally condemnatory statements produced a wealth of opinion and evidence on the value of combinations in clinical practice with a resultant reconsideration of their status.¹⁵

In the subsequent F.D.A. publication,¹⁵ it was acknowledged that, if the components contributed to the overall effect and the dosage was suitable for a significant patient population, then a combination would be considered for approval.

This change in official attitude suggests that others might wish to reflect on earlier empiric statements and consider carefully the shortcomings and advantages of combinations in the light of available evidence.

Disadvantages

The possible disadvantages of combinations are taken from those listed by various critics^{5,14,16} and fall into the following main categories:

(a) Inflexible dosage

It is suggested that patients need individual dose adjustments for each drug used and that this cannot be done with a fixed dose combination,

Such arguments certainly apply to some patients, such as the uraemic and seriously ill, and to certain drugs, such as digitalis, insulin and some anti-hypertensive agents that require careful and critical adjustment of dose. However, as pointed out by McMahon¹⁷: “. . . for the vast majority of patients who come to a physician's office, titration of dose beyond the range available in most fixed combinations is not important or necessary”.

Dollery¹² also stressed that many drugs are usually prescribed in a fixed dosage or a narrow dosage range and that combinations of such drugs “may be justified”. Prescription surveys confirm this general uniformity of dosage in clinical practice, whether the drugs are given separately or in combination.^{1,2}

Lasagna¹⁸ also pointed out that, in practice, the physicians prescribing drugs are not likely to change their established pattern of usage and no change in flexibility would result if drugs were used separately instead of in combinations. This is a conclusion borne out by an independent survey, which showed that most prescribing doctors continue with the same pattern of medication irrespective of the availability of certain combinations and of cost.¹⁹

Beckett²⁰ and Lasagna²¹ also suggest that flexibility of dosage is less important than many experts contend because precise bio-assay in patients is often difficult to accomplish and attempts often do nothing other than delay effective therapy. It is apparent from these observations that the need for flexible dosage has been exaggerated. In any case, the active ingredients are always available as separate items to add to a combination or substitute for it. This will give complete flexibility, even though it may be at the cost of patient safety, convenience and economy.

(b) Increased risk of drug interaction

This suggestion conflicts with the admission of the F.D.A.⁵ that possible drug interaction between the ingredients of fixed-dose combinations has been investigated and allowed for and that information on interaction is available.

It is, perhaps, paradoxical that many people who quote the risk of drug interaction as a reason for avoiding drug combinations are, in fact, making that risk greater by pushing practising doctors away from a tested and approved ratio of drugs in a single formulation to more random concomitant use that has not been investigated or come before any regulatory body and must have a greater degree of risk.^{12,17}

Another point worth noting is that additional drugs are much less often given to patients receiving combinations. Prescription surveys¹³ show that doctors use combination products as the only form of therapy for a patient approximately three times as frequently as they use a single drug entity for the sole form of therapy. This means that the combination is not only the safest and most thoroughly tested way of giving two drugs together to the same patient, but is usually the total regimen. This further lowers the risk of drug interaction, as no other drugs are involved.

(c) Hidden ingredient

This is clearly a problem if doctors do not make themselves familiar with the ingredients of the combinations which they prescribe. There is really no complete answer to the doctor who will not take this elementary precaution. Certainly, trade names should not be selected in any manner which might intentionally mislead but labels, package inserts, data sheets, drug lists and other prescribing information should, and do, list all active ingredients and the dosages present.

Some speak of hidden ingredients in combinations with reference to allergic or other adverse reactions from one of the constituents but, as stated by Lasagna¹⁸ “. . . Tracking down the cause of an adverse reaction is no easier when multiple drugs are given separately than when they are given in a pre-packaged mixture.”

(d) Unsuitable for some patients

It has been stated that the fixed-dose combination products are not suitable for all patients. This is undoubtedly true but a combination which is suitable for many patients is still a valuable contribution to the management of those people. The individual ingredients are always available for others, for whom the combination is less satisfactory.

If drug combinations do have advantages to offer, it would be a pity to deny these advantages to some patients because of others who can always be given alternative forms of therapy.

It is reassuring to see that this principle is now well accepted and that the F.D.A., which originally concluded that the dosage schedules of combinations must apply to *most* patients,⁵ now feel that they should be safe and effective for a *significant patient population*.¹⁵

Advantages

(a) Adherence to prescribed regimen

Doctors want to ensure that the treatment which they consider necessary is actually taken as prescribed. Many studies have shown that a high percentage of patients do not take the medicaments prescribed for them and the failure rate was as high as 50% in some series.²²⁻²⁵

Such a high failure rate is more likely to occur with complicated regimens of different types of medication and less likely with simple programmes, which can often be achieved by using combination formulations instead of individual medicaments.

Even in hospitals, Vere²⁶ has shown that errors increase in relation to complexity of regimens and that this is even more probable in the unsupervised conditions of general practice. This has been confirmed by Malahy²⁷, who investigated the effects of drug labelling, patient instruction, patient age and education and the number of drugs prescribed on the incidence of errors in home administration. Despite the many factors studied, only the number of medicaments significantly influenced the number of errors and the author stated: “The more medications taken by the patient, the more likely he is to make errors.”

A correlation between errors in taking prescribed drugs and the number of items prescribed was also shown in out-patients, following discharge from hospital by Clinite and Kabat,²⁸ and Latiolais and Berry²⁹ found similar results with an overall error rate of 42%.

In a study of drug defaulting in general practice, Porter³⁰ found that errors were proportional to the number of medicaments given and stated: "The number of different drugs prescribed should be reduced to a minimum."

(b) Increased convenience

The acceptance of patient convenience as a valid reason for allowing combinations has been given grudgingly and often described as "mere convenience", but must be well understood by all practising doctors prescribing and explaining treatment regimens to patients.

As stated by Dollery¹²: "Most people dislike taking several kinds of tablets and capsules and are more likely to forget some of them if the regimen is complicated. From the patient's viewpoint, the ideal regimen would be a single tablet which combined all the desired pharmacological effects even if it contained more than one drug". He then went on to describe therapeutic accidents which have occurred due to patients misunderstanding complicated therapeutic regimens.

There is little doubt that patients prefer the convenience of combined formulations instead of many different tablets and capsules. This is most marked for ambulant patients without gross symptoms to increase their motivation.

Doctors also appreciate the convenience of a simplified explanation to patients, as one survey showed an average consultation time available of only 6.6 minutes,³¹ which gives little time for complicated instructions.

It is also well recognized that complicated instructions are poorly understood by patients. Drug and Therapeutics Bulletin³² has suggested that practitioners ask too much of their patients in this regard but poor communications are partly responsible as doctors make errors in describing difficult multi-tablet regimens.

In his review of prescribing in general practice Gatley³³ stated: "It follows that, in many of the illnesses treated at home, the need is for increased simplicity of administration rather than for newer and better drugs." Combinations certainly give the simplicity pleaded for here.

(c) Economy

The cost factor for combinations will clearly vary according to the availability of generic forms of the constituent drugs and the regulations governing dispensing fees in individual countries. The majority of combinations with the reduction in overheads of individual tablets and packs and the smaller number of dispensing fees will constitute a considerable economy.

One survey in the United States found that, "Fixed drug combinations generally cost about 20% less than the single components separately purchased".¹⁷

Another independent survey in the same country¹⁹ confirmed the economy factors in the use of combinations and estimated an increased expenditure of over three million dollars if all the combinations in the top 200 prescribed products were withdrawn and their constituent ingredients were ordered separately.

(d) Incompatibilities investigated

This aspect has already been dealt with under 'Disadvantages (b)' above, but it is worth pointing out that the rapid advances in therapeutics have made many doctors unaware of possible drug interaction^{9,10,16} and a tested and approved combination gives reassurance on safety and freedom from untoward drug interaction. If doctors experiment for themselves with concomitant use of single drugs, they will be conducting trials of drug interaction and efficacy in the unsupervised conditions of patients' homes, instead of making use of the experience from animal experiments and carefully controlled trials carried out by the pharmaceutical industry before marketing a combination.

Professional acceptance

The value of combinations in patient care is clearly appreciated by practising physicians. McMahon¹⁷ conducted a random survey of the opinions of 130 clinicians on 20 of the most popular combinations. There was a tendency for the combinations to have a lesser degree of acceptance by the 25 professors, who are less concerned with unsupervised therapy, but the overall picture was in favour. Seventeen of the 20 combinations were considered rational by more than 80% of the physicians.

This general professional acceptance was confirmed by a more extensive independent random survey.¹ Unlike McMahon's study, this professional survey showed that specialists were almost as much in favour of combinations as general practitioners (76% to 92%). It also listed effectiveness, convenience and economy as the main attributes of combinations used by the medical profession.

Prescription surveys in 1968 in England, Italy, Germany, France¹³ and the U.S.A.¹⁴ show the extensive use of combinations (19 to 78%) in the common diagnostic categories, and a previous survey four years earlier in England³¹ demonstrates that this is a constant pattern of drug usage.

Conclusions

After years of antagonism to combinations by academic and official bodies around the world, the recent declaration of 'guide-lines' by the F.D.A.,^{5,15} however cautiously worded, suggests that the practical therapeutic advantages of combinations in certain circumstances are now being appreciated by regulatory authorities. The usage statistics^{13,14,31} show that these advantages have long been appreciated by practising physicians.

In his critical review of the arguments for and against combinations, Lasagna¹⁸ states that combinations should:

- (a) contain ingredients that deserve to be used together
- (b) work satisfactorily for a significant body of patients, and
- (c) have no pharmaceutical incompatibility.

He goes on to say: "If the above are met by a fixed-ratio combination, the public welfare should be best served by the marketing of such a mixture. Patients would

benefit in terms of accuracy and convenience, nursing and pharmacy costs and time and medication error should decrease, and the sick might even get a break in terms of drug bills.”

Drug combinations are not a homogenous group and sweeping generalizations, whether favourable or unfavourable, cannot be valid. It is certain that all combinations cannot be recommended but concomitant therapy, with more than one drug entity, is common practice and for drugs frequently given together in standard dosages, a combination gives the following advantages:

- (a) gives doctor and patient greater convenience
- (b) reduces risk of error in administration
- (c) increases likelihood that prescribed treatment will be followed
- (d) lessens risk of drug interaction
- (e) gives greater confidence in tested and approved therapy
- (f) often offers economy over separately prescribed medication.

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