Combination products – love them or loathe them?

R.F.W. Moulds, Associate Professor in Clinical Pharmacology, University of Melbourne, Melbourne

SYNOPSIS

The introduction of new combination products requires prescribers to decide whether or not to include these formulations in their personal formulary. Although there is little firm evidence to guide us, factors in favour of their use include better patient compliance, simplicity for prescribers, and in some cases reduced cost. Factors against their use include the inability to adjust the dose of each component separately, exposing the patient unnecessarily to more than one drug, and incompatible kinetics. Prescribers should only consider prescribing a combination product if it will facilitate treatment according to generally accepted guidelines.

Index words: compliance, cost of drugs.

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Introduction

Prescribers have recently been presented with an array of new combination products, such as the combination of a thiazide diuretic and an ACE inhibitor. Australia has been slow to allow the marketing of these products. They have been available for years in Europe, where physicians are confronted with a bewildering array of combinations. Indeed sometimes it seems all the different drugs for treating hypertension have been combined in as many different permutations as possible.

So what should our attitude be to these products? Should we welcome the fact that Australia has finally been dragged into the modern world of therapeutics, or should we bemoan the fact that one of the bastions of rational prescribing has finally been breached?

Combination products are not new in Australia. They are widespread, indeed almost the norm, in the 'over-the-counter' area. Combination analgesics (e.g. paracetamol with codeine) have been available for years. Special cases have also been made, and accepted, in the past for combinations such as sulfamethoxazole with trimethoprim, or amoxycillin and clavulanic acid to broaden their antimicrobial spectrum, or the combination of L-dopa plus a peripheral decarboxylase inhibitor, to decrease the peripheral adverse effects of L-dopa. However, the recent approval of a large number of combination products seems to signal that the Australian Drug Evaluation Committee and the Therapeutic Goods Administration have relaxed their opposition to these formulations.

Pros and cons

The main arguments for and against combination products are summarised in Table 1. Unfortunately, the clarity of the arguments is not always accompanied by equal clarity of evidence. Each argument needs to be looked at critically rather than simply accepted.

Compliance

It seems intuitively obvious that patients are more likely to take one tablet than two or more tablets. However, the evidence for this assertion involves extrapolation from old compliance studies showing that there is in general an inverse relationship between compliance and the frequency and complexity of medication regimens.[1,2] This extrapolation may be invalid at the lowest end of the complexity range when going from two tablets daily to one tablet daily. The extrapolation also might not hold when patients are taking many drugs and only a small change is made to the complexity of their regimen.

Simplicity of prescribing

In general, it is more convenient to prescribe a combination product than it is to prescribe the individual components separately. However, there is no evidence that the simpler it is to prescribe a drug, the more likely it is to be done well. In fact experience suggests the opposite. 'Simple' prescribing can all too easily slip into 'lazy' prescribing. For example, in hospitals there has long been concern that compound analgesics (such as paracetamol and dextropropoxyphene) are overprescribed when the compound formulation is easier to prescribe than the individual components.

Cost

The cost of drugs is an important factor. It is an argument for using a combination product which costs less than the sum of its components. However, prices are fickle and go up and down, so cost should not be used as the basis for long-term prescribing policies. Patient co-payments are less for a single combination item than for two separate items.

Table 1

Arguments for and against combination products

For	*Against*
• Improved patient compliance	• The inability to adjust the doses of the individual components
• Convenience for prescribers	• Exposing the patient to more than one drug unnecessarily
• Reduced expense	• Different pharmacokinetics of the components

Dose adjustment

The inability to adjust the doses of the individual components is a strong argument against the use of combination products. It is only relevant, however, if both components are dose sensitive. A combination may be appropriate if the prescriber and patient have determined that each component is required at the dose contained in the combination. However, how often will the dose of each drug be titrated, before starting the combination?

If only one component in the combination is dose sensitive, then the overall dose can be adjusted to reflect the patient's particular dose requirement for that component, and it will not matter that the dose of the other component(s) automatically changes as well. However, no drug is totally dose insensitive, particularly for adverse effects. So the inability to adjust the individual components will always be a disadvantage.

Unnecessary risk

The issue of exposing the patient to more than one drug unnecessarily only pertains if the patient does not require one or more of the components of the compound product. Ideally this should not occur, as the patient should only be prescribed a combination product when both components are required.

In real life it is likely that an initial judgement, presumably based on the severity of the problem, will often be made that two drugs will be required. The decision to start treatment with a combination may not always be correct. Some patients may therefore be exposed to an extra drug, and thus unnecessarily run the risk of adverse effects.

Pharmacokinetics

If the time course of the clinically important effects of the components of a combination follows their individual kinetics, there will be a major problem if the components have substantially different pharmacokinetics. If the kinetics of both components are relevant to their effects, it will be impossible to have a regimen for repeated doses that does not result in either underdosing or overdosing of one of the components.

If only one component has an effect which follows its kinetics then the dose frequency can be set to better reflect the kinetics of that particular component. It will not then matter that the other component is being taken either too frequently or not frequently enough.

To use or not to use?

An important factor influencing our decision on whether or not to prescribe a particular combination product is how well it enables us to prescribe according to generally accepted therapeutic guidelines. To put this in perspective, it might be helpful to consider the example of a hypothetical compound product, e.g. bendrofluazide 5 mg plus enalapril 10 mg, for hypertension.

Both drugs are usually given once daily, so in terms of their pharmacokinetics the combination is reasonable. However the maximum dose of bendrofluazide is normally only 5 mg daily to minimise metabolic adverse effects, whereas enalapril may need dose adjustment up to 20 mg, or even 40 mg, daily. You cannot titrate the individual doses of a combination product, so from a dose adjustment point of view, this combination product is not good.

If the prescriber has already established that a particular patient requires both bendrofluazide 5 mg daily and enalapril 10 mg daily to control their blood pressure, it would obviously be reasonable to switch the patient to the combination product. Cost will presumably be the main factor influencing this decision, although compliance might also be better with the combination product. However, the consequences of missing a tablet will be greater than when the patient was taking the drugs individually and only missed one of them.

A significant problem is likely to be the temptation to prescribe the combination as first-line treatment for hypertension. Current guidelines recommend thiazide diuretics or beta blockers as first-line treatment. Although the use of an ACE inhibitor may be reasonable, combinations are not recommended as first-line treatment.

To justify the use of the combination as first-line treatment the prescriber must decide if the particular patient is going to need two drugs rather than one. No one should trust their judgement on that issue! Although there is a relation between the severity of hypertension and the number of drugs required for satisfactory control, not all patients, even those with moderately severe hypertension, will require two drugs. There is at present no evidence on how to make the judgement in individual patients as to whether or not they will eventually require two drugs rather than one drug to control their blood pressure.

A reasonable approach in all but a very severe case would be to commence treatment with bendrofluazide 2.5 mg daily alone. If the response is not ideal, then an ACE inhibitor, in this case enalapril, could be added. If this controls the hypertension the use of the combination product might then be appropriate. However if the response is very poor, or if the patient develops any adverse effects, it would be more logical to substitute another drug for the thiazide, and a beta blocker might be more consistent with guidelines than an ACE inhibitor.

If a patient is already taking bendrofluazide or enalapril, and control is unsatisfactory, the prescriber should decide, before changing to the combination product, whether or not the second drug would normally be added to, or substituted for, the first drug. If addition is reasonable, then using the combination product might be appropriate, but if substitution is indicated then the combination product would not be appropriate.

Conclusion

Combination products require us to think carefully about our prescribing. In some circumstances they might simplify, or even improve, therapy. However there is a real possibility they will tempt us into 'lazy' prescribing.

We should consider if using a combination product helps us to prescribe according to accepted guidelines. Paradoxically, an innovation which at first sight seems to simplify prescribing will perhaps make it more complex.

Conflict of interest: none declared

E-mail: rfwm@unimelb.edu.au

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2. Greenberg RN. Overview of patient compliance with medication dosing: a literature review. Clin Ther 1984;6:592-9.

New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may have been little experience in Australia of their safety or efficacy. However, the Editorial Board believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Board is prepared to do this. Before new drugs are prescribed, the Board believes it is important that full information is obtained either from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Dexmedetomidine

Precedex (Abbott)

2 mL ampoules containing 100 microgram/mL

Approved indication: sedation

Australian Medicines Handbook Section 2.2

For several years it has been known that the antihypertensive drug clonidine can reduce the required dose of anaesthetic drugs. It does this by stimulating alpha$_2$ adrenoceptors. Dexmedetomidine also acts as an agonist at these receptors. This action has analgesic effects and, possibly because of an effect on the locus ceruleus, also causes sedation.

Dexmedetomidine has been approved for the sedation of intubated post-surgical patients during treatment in intensive care. It has been compared with placebo for this indication in a British study. Patients who were given dexmedetomidine required 80% less midazolam for sedation and 50% less morphine for analgesia.[1] A study comparing dexmedetomidine with propofol found that both drugs adequately sedated the patients. Those given dexmedetomidine required significantly less morphine for analgesia. Dexmedetomidine has an advantage because it causes little respiratory depression, so patients can be extubated without having to wait for their respiratory function to recover.

As dexmedetomidine is given by infusion, it must be diluted before use. A loading dose is given over 10 minutes followed by a maintenance infusion which is adjusted according to the clinical response. The infusion should not exceed 24 hours.

Dexmedetomidine has a half-life of two hours. It is almost completely metabolised with most of the metabolites being excreted in the urine. Dose reductions may be needed for patients with renal or hepatic impairment. Although cytochrome P450 2A6 is involved in the metabolism clinically significant interactions are thought to be unlikely.

Dexmedetomidine does interact with anaesthetic drugs, opioids and sedatives so it should only be used in intensive care. Patients require monitoring of their electrocardiogram, oxygen saturation and blood pressure.

Hypotension is the most common adverse reaction, occurring in 22% of patients, however some patients will become hypertensive. Dexmedetomidine can also cause bradycardia. Patients who are elderly, or who have diabetes or heart failure, have an increased risk of these adverse effects because of changes in their autonomic nervous systems. Lower doses are recommended for the elderly.

Dexmedetomidine has been approved on the evidence gathered from fewer than 600 patients. It may take more clinical experience to determine whether its benefits are outweighed by the adverse reactions.

REFERENCE

1. Venn RM, Bradshaw CJ, Spencer R, Brealey D, Caudwell E, Naughton C, et al. Preliminary UK experience of dexmedetomidine, a novel agent for postoperative sedation in the intensive care unit. Anaesthesia 1999;54:1136-42.

Imatinib mesylate

Glivec (Novartis)

50 mg and 100 mg capsules

Approved indication: chronic myeloid leukaemia

Australian Medicines Handbook Section 14.3.9

Most patients with chronic myeloid leukaemia have a translocation of chromosomes 9 and 22. The abnormal chromosome, known as the Philadelphia chromosome, results in the production of an abnormal tyrosine kinase. This enzyme contributes to the production of malignant cells.

Imatinib aims to inhibit the abnormal tyrosine kinase. This action stops cell proliferation and can induce apoptosis of tumour cells.

The drug is well absorbed so it can be given by mouth. It has a half-life of 18 hours and is mainly cleared by metabolism. This metabolism involves cytochrome P450 3A4 so there is a potential for interactions with inhibitors of this enzyme such as grapefruit juice, erythromycin and ketoconazole. Although there have been no studies, drugs such as phenytoin, carbamazepine, dexamethasone and St John's wort may reduce the concentrations of imatinib by inducing P450 3A4. Imatinib has other potential interactions because it also inhibits P450 2D6 and 2C9.

In a pilot study 58 patients with chronic myeloid leukemia who were in blast crisis, were treated with daily doses between