

FIXED DOSE BETA-BLOCKER DIURETIC COMBINATIONS

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INTRODUCTION

Beta adrenoceptor blocking drugs (beta blockers) and diuretics are accepted as first line treatments for hypertension today. Furthermore most specialists who treat hypertension would agree that a combination of a beta blocker and a diuretic would be the next step in the management of a patient whose blood pressure is not satisfactorily controlled by either a beta blocker or a diuretic given alone. As a result of this practice, manufacturers have produced a number of fixed dose single tablet combinations of a beta blocker and a diuretic. Some examples are given in table 1. These combinations have been accepted by some experts as a logical and helpful development, others feel that drug combinations should never be used. The aim of this review is to consider the arguments for and against fixed dose combinations with particular reference to beta blocker-diuretic combinations.

Before proceeding to a review of the advantages and disadvantages it is reasonable to consider the theoretical basis for giving these two agents together. Figure 1 shows the role of cardiac output, peripheral resistance and blood volume in the production of blood pressure. Shown in the diagram are the pathways which transmit messages about changes in blood pressure, registered by the baroreceptors, to the sympathetic centre in the brain. It can be seen how in response for example to a fall in blood pressure, the sympathetic centre may increase heart rate, peripheral resistance and renin release. The latter then increases blood volume, via aldosterone, and peripheral resistance, via the action of angiotensin II, a powerful vasoconstrictor. Figure 1 also shows the major sites of action of four groups of drugs which may be used to treat hypertension.

As the cause of essential hypertension is not known, treatment is directed at modifying one or more of the three factors which maintain blood pressure. The treatment must be able to achieve a reduction in pressure in spite of the numerous feedback systems which will try to maintain blood pressure, albeit at an abnormally high setting. Beta blockers affect cardiac output¹, the sympathetic centre² and rennin release³ and diuretics may reduce blood volume

and act as vasodilators⁴. Thus the combination of these two agents has the potential to affect the whole system, and restore an abnormal situation towards normal. The combination of the two agents then has a sound theoretical basis. Furthermore, it involves the two most popular antihypertensive agents. It is therefore likely that the two agents will be used together very frequently, if monotherapy is insufficient. Accordingly debate about the need for a fixed dose combination is important and relevant.

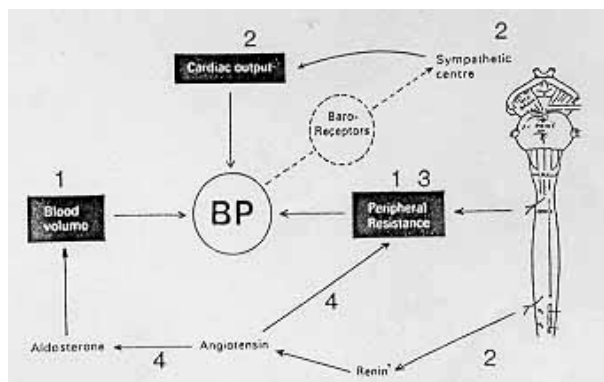


Fig. 1 - The contribution of blood volume, cardiac output and peripheral resistance to blood pressure; and site of action of commonly used antihypertensive drugs. 1 = diuretics; 2 = beta-adrenoceptor blocking drugs; 3 = vasodilators; 4 = angiotensin converting enzyme inhibitors.

ARGUMENTS AGAINST FIXED DOSE COMBINATIONS

In this section we shall consider briefly the general arguments against fixed dose combinations and then assess the relevance of these arguments to the specific instances of a fixed dose beta blocker diuretic combination.

The potential disadvantages of fixed dose combinations are:

- 1) loss of flexibility;
- 2) possible ignorance of the prescriber about the contents;
- 3) difficulty attributing blame for any adverse effects;
- 4) temptation to use two or more drugs when a single one would do;
- 5) cost.

Of those given, loss of flexibility is probably the most important. When two drugs are used together such as antibiotics given to treat multiple bacteria, to eradicate a difficult organism or to prevent the development of resistance, it is often necessary to be able to adjust the doses of the two antibiotics to suit the patients clinical problem. In this instance the reason may be that one organism is particularly resistant and therefore a larger dose may be required. More generally it may be necessary to prescribe each drug separately because they may have differing duration's of action and different routes elimination. If one drug were excreted by the kidney, then a smaller dose would be required an elderly patient or one with renal disease.

The second major problem is ignorance of tablet composition. When a doctor prescribes a conventional drug, he states the name, the dose and the frequency of administration. Combinations are often referred to by trade names and one or two tablets are taken, once or twice daily. When this happens the doctor may not be fully aware of the contents of the tablet and may not take the proper precautions or give the patient the right advice. Cotrimoxazole is a well known combination of trimethoprim and sulphamethoxazole and is used to treat urinary infections. When this is prescribed using a trade name it could easily be given to a patient who is sensitive to sulphonamides without either patient or doctor appreciating the risk that is being taken.

The remaining three disadvantages of combinations are self evident and do not merit further discussion.

Do the general disadvantages of combinations apply to beta blocker diuretic combinations?

Flexibility

In this context the relevant questions are: Is it desirable to be able to increase or decrease the doses of the two agents independently? Are the duration's of action of the two types of drug materially different? Do differing patient characteristics such as renal function or respiratory disease require individualisation of dosing?

Diuretics are moderately effective antihypertensive agents⁵⁻⁷. Figure 2 shows the effect of gradually increasing the dose of some of the commonly used thiazide diuretics. From this it can be seen that there is no particular therapeutic advantage to be gained from the higher dose. Indeed this may be counterproductive as further increases may be associated with a greater incidence of both hypokalaemia^{8,9} and hyperglycaemia^{10,11}.

Comparable data on beta blockers is more difficult to obtain and there may be some variation between different beta blockers. Using the reduction in exercise heart rate as measure of beta blockade, there is evidence that increases in dose above metoprolol 100 mg, propranolol 120 mg, and nadolol 80 mg do not produce further

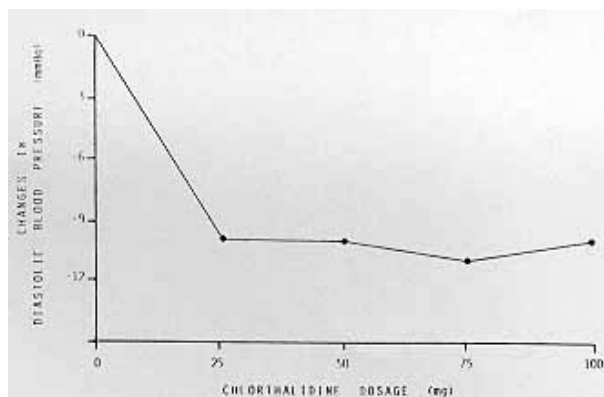


Fig. 2 - The response of diastolic blood pressure to increasing the dose of chlorthalidone (from Russell et al⁷).

proportional reductions in heart rate¹⁰⁻¹⁴. In relations to the treatment of hypertension it would also seem that doses over 100 mg metoprolol¹⁵ or 40 mg b.i.d. propranolol¹⁶ do not confer much additional benefit.

Therefore if a reasonable dose of a beta blocker and a thiazide diuretic are chosen there should not be a need to increase the dose of either.

The second question under the heading of flexibility relates to duration of action. Most thiazide diuretics have a fairly long half life and are given once daily⁶. Some beta blockers, such as atenolol, nadolol and sotalol also have long half lives and are therefore suitable for once daily administration. Other beta blockers such as propranolol, pindolol and metoprolol have shorter half lives and might be considered less suitable for inclusion with a thiazide diuretic in a tablet or once daily administration. However, although in volunteer studies the beta blocking effect seems to wear off in 8-12 hours, there is evidence that these agents can be used once daily to treat hypertension^{17,18}.

Combination preparations may cause problems if significant dosage regulation of one agent is required by a particular group of patients. Thus the combination of a penicillin and an aminoglycoside antibiotic (such as gentamycin) would be difficult to use since moderate renal impairment would require that the dose of aminoglycoside be markedly reduced. Beta blockers may be metabolised (propranolol, metoprolol, oxprenolol) or excreted unchanged by the kidney (atenolol or nadolol) but moderate impairment of hepatic¹⁹ or renal function^{20,21} respectively does not require any change in dose. Furthermore beta blockers appear to be well tolerated by the old²² and have been used without undue difficulty in pregnancy²³. Excluding serious severe renal disease and pregnancy, situations in which beta blocker diuretic combinations would almost certainly not be used, the combination would seem to be acceptable in terms of not requiring special dosage modification of one agent when the drug is given to a specific subgroup.

Ignorance of the Contents

This is of particular importance with these two groups of drugs as both have specific contra indications. Most beta blockers and thiazide diuretics are recognised as such and doctors hopefully know that they must not give the former to asthmatics and patients in heart failure and the latter to those without. However, a new combination with an uncharacteristic sort of name, which is marketed for hypertension could be prescribed for an asthmatic without the relevance of this being appreciated. Since this could be a fatal mistake, the failure to give a combination a name which suggests its contents, could justifiably give beta blocker-diuretic combinations a bad name.

Attributing blame for adverse reactions

This general criticism of drug combinations, which might be a cause of concern if a patient on a combination of two antituberculous drugs develops a fever, a rash or abnormal liver function tests, could not easily be made against beta blocker diuretic combinations. The adverse effects of the two drugs are quite different and relatively easily recognised. In fact the effects of one may tend to minimise the adverse effects of the other, a point we shall return to later.

The use of two drugs unnecessarily

The ready availability of a combination which is marketed effectively might easily push doctors to use the combination first. Since it is a good general principle of therapeutics to keep drug treatment as simple as possible, such a trend would be most undesirable. Since the availability of combinations makes this possible and easy, they might be considered undesirable. On the other hand, it would not be considered reasonable by most doctors to restrict the availability of drugs to prevent their misuse, particularly if their misuse could not be construed as being seriously harmful.

Cost

The additional pharmaceutical development required to produce a combination and the efforts required to assess it pharmacokinetically and clinically will add to its cost. A doctor who chooses to prescribe a combination instead of the two agents separately will have to weight up the additional cost and balance it against the potential benefits set out below.

ARGUMENTS FOR FIXED DOSE COMBINATIONS

In general, the reasons for wanting to prescribe a combination are:

1) to increase the therapeutic effect; 2) to reduce adverse effects either by allowing lower doses of the different

agents to be used whilst still achieving the same overall therapeutic effect or by combining drugs which tend to counteract each others adverse effects; 3) to increase the chance that the two agents are given in the optimum ratio of one to the other; 4) to ensure pharmaceutical compatibility; 5) to simplify the treatment regimen and thereby hopefully improve compliance.

We shall now consider whether the various arguments apply if the combination contains a beta blocker and a diuretic.

Increase in therapeutic effect

A combination of beta blocker and diuretic might be considered to be an advantage if adding a second drug could be shown to be more effective than simply increasing the dose of the first drug.

The majority of studies have simply shown that a combination is better than either of the single agents given alone. These studies include: propranolol and chlorthalidone²⁴; propranolol and polythiazide²⁵; atenolol and bendrofluzide²⁶; pindolol and clopramide²⁷; metoprolol and hydrochlorothiazide²⁸.

However even some of the earlier studies on beta blockers and diuretics given together indicated that increased efficacy could result. This was noted by Dollery in 1977²⁹ who referred to the study by Angervall and Bystedt (1974)³⁰ in which hypertensive patients on a diuretic were changed to alprenolol and the dose was titrated (to mean of 426mg daily) to achieve a comparable anti-hypertensive effect. The patients were then put on one quarter of the dose of diuretic plus one quarter the dose of beta blocker previously shown to be required. On this reduced dosage blood pressure control was improved. Subsequently Bengtsson in 1979³¹ followed a group of 14 hypertensive females who had been on a mean dose of metoprolol of 161mg daily and changed 12 to a single dose of CO-Betaloc (2 requiring 2 tablets) so that the mean daily dose of metoprolol was reduced to 114mg. Nevertheless they achieved an improvement in mean blood pressure of 145/85 instead of 159/92.

Penman and Smith³² have also demonstrated the superiority of the combination over a higher dose of beta blocker. In their study elderly patients received one and two combination tablets and one and two 100 mg metoprolol tablets, the order being randomised. On 200 mg metoprolol blood pressure was reduced from 185/106 to 178/95 but on one combination tablet (i.e. only 100/mg metoprolol plus diuretic) the mean blood pressure was 168/93. This was a significant ($p < 0,05$) further reduction in pressure.

Dafgard and colleagues³³ investigated the value of the combination the other way. In this case the addition of a beta blocker was found to be more effective than giving a larger dose of diuretic. In a double blind comparative group study, patients whose blood pressure had been partially controlled on hydrochlorothiazide 25mg daily were randomly

allocated to receive either 50/mg hydrochlorothiazide or to have metoprolol 200/mg added to their original regimen. The latter proved much more effective. Furthermore 6 of 13 patients whose response to the larger dose of diuretic was poor did respond satisfactorily to a lower dose of diuretic together with a beta blocker.

Giving a beta blocker and diuretic together is therefore always more effective and some studies suggest it is more efficient in that better control is achieved with lower doses than either drug given alone.

Reduction in Adverse Effects

The potential adverse effects of thiazide diuretics are well known and include a tendency to increase plasma concentrations of glucose^{10,11}, uric acid^{5,7,8}, lipids^{34,35} and to lower the serum potassium^{5,7,9}. In the case of glucose and potassium there is reasonably good evidence that the effect is dose related⁷⁻⁹. Furthermore since there is a flat dose response curve for diuretics in the treatment such that doses of hydrochlorothiazide 12,5mg and chlorthalidone 25mg may be sufficient to produce almost maximal blood pressure reduction^{7,8}, there is no therapeutic gain to be derived from using large doses. Thus combination preparations may help to reduce adverse effects by allowing/encouraging the use of lower doses.

Of the various potential adverse effects of thiazide diuretics, the reduction in serum potassium, with the possible associated risk of arrhythmias^{36,37} is the most serious. It is therefore of interest that combination with a beta blockers may not only reduce the risk by reducing the dose needed, but may also tend to counteract the hypokalaemic effect. Catecholamines through beta receptors may lower serum potassium by their effect on the renin angiotensin system but also by stimulating the uptake of potassium into cells³⁸. Theoretically beta blocking agents might counteract both mechanisms, and there is some evidence to support this. Volunteers given terbutaline (a beta antagonist) show a fall in potassium which can be partially blocked by beta blockers³⁹. Hettiarachchi et al. have shown that the addition of timolol to bendrofluazide reduces the rise in aldosterone and the fall in potassium induced by the diuretic⁴⁰.

Indeed beta blocker therapy tends to cause a small rise in serum potassium³⁸ and some but not all patients transferred from diuretic monotherapy to a diuretic-beta blocker combination have shown a rise in serum potassium⁴¹. There is thus some evidence that combination with beta blockers may reduce some of the adverse effects of diuretics.

There is less evidence to suggest that the addition of a diuretic may reduce the risk of an adverse reaction caused by being on a beta blocker. It is possible however that because a lower dose may be required this reduces the risk and it is also possible that the

diuretic may play a small role if the beta blockers showed any tendency to produce mild heart failure.

The use of optimum doses

As indicated above, maximum benefit and minimum adverse effects are probably achieved by the administration of low doses of diuretics and beta blockers. By carefully researching the compounds involved drug companies are likely to develop fixed dose combinations which contain the dose of beta blocker and the dose of diuretic likely to produce a significant antihypertensive effect. Co-betaloc for example contains metoprolol 100/mg and hydrochlorothiazide 12,5/mg, tenoretic contains atenolol 100/mg and chlorthalidone 25/mg. These should achieve a nearly maximal therapeutic effect. It may well be worth giving two tablets daily but probably not more.

Pharmaceutical compatibility

One of the problems associated with the use of increasing numbers of drugs is that an interaction may occur. Two drugs may interact outside the body or in the gut, one may alter the body's handling of the other or there may be a pharmacodynamic interaction in the body. When a specific fixed dose preparation is produced, the drug company has to perform the appropriate investigations to ensure that there are no pharmaceutical or pharmacokinetic interactions^{24,43}. The hope, then, is that any pharmacodynamic interaction will be beneficial.

Simplification of the regimen and improved compliance

Patients with hypertension often feel well and yet are required to take tablets long term which may cause problems. These latter include not only adverse effects but also the unwelcome problem of being made to feel 'a patient' and to have to remember to take tablets. One of the ways doctors can help is by trying to ensure that the drugs they prescribe are well tolerated and also that the drug regimen is as simple as possible. Most studies on compliance conclude that the fewer the number of tablets to be taken and the less often, the more likely is the treatment schedule to be followed. Accordingly if a patient with hypertension cannot be controlled either by a diuretic or beta blocker alone, and needs to have both therapeutic agents, it is desirable to give him or her a single once daily fixed dose combination.

CONCLUSION

Whether or not beta blocker-diuretic fixed dose combinations are considered desirable will remain a matter of opinion. In this review have tried to present most of the major arguments for and against these preparations. Their increasing use by doc-

tors suggests that many feel that the arguments for outweigh those against. Certainly the ability to give a once daily combination which is more effective and less likely to cause side effects than either drug given alone seems eminently desirable. However marketing which pushed combinations as a first line treatment or the use of names which tend to obscure the nature of the contents could push the balance the other way.

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