The role of combination therapy in the management of hypertension

Joel M. Neutel

Orange County Research Center, Tustin, CA, USA

Keywords: angiotensin receptor blockers; combination therapy; goal blood pressure

The relationship of blood pressure and cardiovascular risk

Data from the largest meta-analysis of hypertensive patients clearly demonstrate that increasing systolic blood pressure (BP) in any age group is associated with very significant increases in cardiovascular disease [1]. It has been shown that for every 20 mmHg increase in systolic BP, or for every 10 mmHg increase in diastolic BP, there is a doubling in the risk of cardiovascular disease. Conversely, a meta-analysis of outcome studies in the treatment of systolic hypertension demonstrated that for every 20 mmHg reduction in systolic BP, there is an ~40–45% reduction in cardiovascular disease [2]. These studies have confirmed the very significant cardiovascular risk associated with hypertension and the impressive benefits that can be derived from the treatment of this disease process. Despite these findings, worldwide epidemiological data have shown that fewer than one-third of hypertensive patients achieve a BP of <140/90 mmHg [3].
study, for every 2 mmHg reduction in diastolic BP, there was a significant further reduction in cardiovascular disease (Figure 3) [6]. Data from these studies have now been analysed to show that for every 2 mmHg reduction in systolic BP there is a 7% reduction in coronary artery disease and an 10% reduction in stroke [6]. It is clear from these studies that treated but inadequately controlled hypertensive patients remain at risk for cardiovascular disease and it is critical that clinicians around the world focus on achieving recommended goal BP values in these patients.

**Reasons for inadequate blood pressure control**

There are currently >125 antihypertensive agents available for the treatment of hypertension; many of them are very effective drugs. Despite this, we struggle to control BP. The question must be asked, why are we doing so poorly in the management of hypertension, and what can we do differently to improve control rates? The answer may be that the stepped care approach is failing in the management of hypertension. Over the past 30 years, the Joint National Committee has advocated the stepped care approach for the management of hypertension. During this time, control rates in the USA, as reported by the NHANES group, have improved by only 5%. This clearly demonstrates that this approach is failing. The principle of the stepped care approach is sound in that it advocates treating people with a chronic illness with as few drugs as possible at the lowest doses possible. Why then is this not working in the management of hypertension?

Surveys performed on clinicians to determine which qualities of antihypertensive agents are most important in the selection of initial drugs for the treatment of hypertension repeatedly show that efficacy and safety are most important. It is here that the problem lies. If you consider the stepped care approach, the logic is that as you increase the dose of a particular agent, the efficacy increases along the dose–response curve. However, as you increase the dose of that same agent, there is a simultaneous increase in dose-dependent side effects. Thus the two criteria most important to clinicians in the management of hypertension move in opposite directions as we follow the stepped care approach [7]. This creates a clinical conundrum, since in many cases we cannot have all that we want in the treatment of our patients. The result is that we accept inadequate BP control, are ready to accept a little less efficacy in order to have tolerable side effects, and depend on non-pharmacological methods to achieve greater BP reduction. This contributes significantly to the poor control rates around the world.

**The solution: combination therapy—greater efficacy**

The solution to this problem is the use of combination therapy. In terms of efficacy, using two complementary
anti hypertensive agents in combination will always result in greater efficacy than high-dose monotherapy. Figure 4 demonstrates that small doses of hydrochlorothiazide (HCTZ) (6.25 mg) added to small doses of bisoprolol (10 mg) are more effective than high-dose HCTZ monotherapy (25 mg) and more effective than high-dose bisoprolol (40 mg) [8]. Similarly, as shown in Figure 5, uptitration of any of the angiotensin receptor blockers (ARBs) from low dose to high doses results in significantly less impact on BP than the addition of a small dose of HCTZ (12.5 mg) to the lower dose ARB [9–11]. It is clear from these data that if efficacy is important to a clinician, you will always do better, by ~3-fold, when using complementary drugs in combination than you could do by uptitration. Table 1 shows control rates from a large PROBE design study using ambulatory blood pressure measurement to demonstrate that the vast majority of patients can be controlled by simply using a combination agent [12].

Combination therapy—fewer side effects

As far as side effects are concerned, you will get similar or fewer side effects with complementary drugs used in combination than with high-dose monotherapy. As is shown in Table 1, despite β-blockers and diuretics having many dose-dependent side effects, particularly at higher doses, when given in low-dose combinations there are very impressive reductions in BP with placebo-like adverse events [8]. Similarly, as shown in Figure 5, an ARB given in combination with a low-dose diuretic results in substantially greater BP reduction than with monotherapy, and the side effect profile for the combination, despite greater BP reductions, is no different from that for the monotherapy (Table 1) [11]. The addition of an angiotensin-converting enzyme (ACE) inhibitor to a dihydropyridine calcium channel blocker (CCB) results in less oedema using the combination, despite greater BP reduction, than the CCB given at the same dose as monotherapy. This is because of the complementary effect of the combination decreasing capillary pressure and thus decreasing oedema [13]. Similarly, the metabolic effects of diuretics are significantly attenuated when given with an ACE inhibitor or an ARB. Thus, by using combination therapy, we can have efficacy and safety both going in the same direction (Figure 6), providing us with the two most important criteria in the management of hypertension.
The role of fixed combinations

This concept has enabled us to use higher dose fixed combinations. It is well known that it is predominantly the inadequate control of systolic BP that has contributed to poor BP control rates. Due to the adverse events and metabolic side effects associated with high-dose use of diuretics, there is a general consensus that HCTZ should not be used at doses greater than 12.5 mg. However, many of the new combinations have included HCTZ at a 25 mg dose. The reason for this is shown in Figure 7. Uptitration of an ARB from low dose to high dose results in a small further reduction in BP along with a dose–response curve which is relatively flat for the class. The addition of 12.5 mg of HCTZ to the high-dose ARB results in a further very impressive reduction in systolic BP [14]. One may think that the addition of a further 12.5 mg of HCTZ (to 25 mg) would also result in a flat dose–response curve. However, as shown, the addition of the second 12.5 mg of HCTZ results in at least as much further reduction in systolic BP as did the first 12.5 mg [11]. This is not surprising since systolic hypertension is volume dependent and very responsive to diuretics. When considering the adverse events, the fact that HCTZ is given with high-dose ARBs results in a side effect profile which is not significantly different from that seen with HCTZ 25 mg given as monotherapy [14]. Thus, the complementary nature of these agents allows us to achieve much greater reductions in systolic BP without significantly impacting side effects.

Another important benefit of fixed dose combination therapy is improved compliance rates. It has been shown that the addition of antihypertensive agents to a treatment regimen has a very significant inverse effect on compliance, even if the drugs are given once daily [15]. The simplification of regimen of the antihypertensive agents is critical in the management of hypertension. Wherever possible, a fixed dose combination should be used by clinicians to simplify the dosing regimen. It has been shown that more rapid control of BP results in fewer cardiovascular events than BP controlled over longer periods of time. This improves patient compliance and decreases cardiovascular disease, resulting in fewer events. More rapid control is always achieved by using combination therapy than can be achieved by monotherapy, even at higher doses.

Another advantage of combination therapy is its ability to control BP similarly across all subgroups of hypertensive patients. For example, it is well known that African American patients are less responsive to ACE inhibitors, ARBs and β-blockers than Caucasian patients. However, if given in combination with HCTZ, each of these drug classes is equally effective in African American and Caucasian patients [9]. Seeing as it has also been shown that the cardioprotective effects of blockade of the renin–angiotensin system are largely independent of BP, this approach offers African American patients the benefit of the vascular protection of these agents without compromising efficacy. This increased response rate simplifies the management of hypertension.

‘Overtreatment’—a legitimate concern?

There appears to be a major concern by physicians regarding ‘overtreatment’ of hypertension. Our goal in managing this disease seems to be simply to dip our patients into the normotensive range. For example, if we have a patient with a diastolic BP of 100 mmHg, the patient is started on monotherapy and the resulting diastolic BP is 88 mmHg. Most physicians would be very pleased with this result, believing that they had taken a sick patient and made them better and they would probably stop at this point. However, a more aggressive physician would say that this same patient has grade II hypertension and start them on combination therapy. If the resulting diastolic BP was now 80 mmHg without adverse events, this physician has taken a sick patient and made them even better. This
has been shown in the HOT study—the lower the BP, the lower the risk of cardiovascular disease [6]. It could be argued that this is an overtreated patient, in that they could have been controlled on one drug; however, the use of two agents to lower BP further, provided there are no side effects, would be a much better approach. Thus, overtreatment is determined by adverse events rather than by BP and should be less of a concern to physicians, particularly if they are using complementary agents in combination.

Conclusion

In conclusion, our current approach to the management of hypertension has not provided us with the desired results. The use of combination therapy as first-line treatment, or treatment much earlier in the course of treating hypertension, appears to be much more efficient than the stepped care approach. The use of combination therapy will provide greater efficacy, fewer side effects and greater convenience than can be achieved with monotherapy and, most importantly, will significantly increase control rates. It would appear that a change in paradigm in the treatment of hypertension may be the most significant change that we can make in order to improve worldwide control rates, which will ultimately impact cardiovascular disease.

Conflict of interest statement. None declared.

References


Received for publication: 7.12.05
Accepted in revised form: 21.12.05