More medications, fewer pills: Combination medications for the treatment of hypertension

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Achieving blood pressure targets in hypertension can be challenging. Often, patients require multiple medications to reach these targets. The Canadian Hypertension Education Program has updated its past recommendations to reflect current knowledge regarding effective antihypertensive combinations. Evidence for the use of specific drug combinations in achieving blood pressure targets has been reviewed, and the inventory of effective drug combinations has been expanded. From a clinical perspective, fixed-dose antihypertensive combinations offer certain advantages in terms of efficacy, adherence, cost, convenience, patient-perceived 'wellness' and side effects. Consequently, in the future, fixed-dose combination formulations are likely to become increasingly used in the treatment of cardiovascular disease.

Key words: *Compliance; Drugs; Hypertension*

Plus de médicaments, moins de comprimés : La polythérapie pour le traitement de l'hypertension

Pour les hypertendus, il peut être difficile de parvenir aux cibles de tension artérielle (TA). Souvent, les patients doivent prendre de multiples médicaments pour y parvenir. Le Programme éducatif canadien sur l'hypertension a mis à jour ses recommandations afin de refléter les connaissances courantes sur les polythérapies antihypertensives efficaces. On a analysé les données probantes sur l'utilisation de polythérapies précises pour obtenir les cibles de TA et accru le nombre de polythérapies efficaces. D'un point de vue clinique, les polythérapies antihypertensives à dose fixe offrent certains avantages en matière d'efficacité, d'observance, de coût, de caractère pratique, de « bien-être » perçu par le patient et d'effets secondaires. Par conséquent, à l'avenir, des formules de polythérapie à dose fixe pourraient être de plus en plus utilisées dans le traitement des maladies cardiovasculaires.

Hypertension is a common condition that sometimes proves to be challenging to treat. Existing statistics suggest that a minority of hypertensive patients in Canada achieve recommended blood pressure (BP) targets (1), although a recent upward trend in BP control has been noted (2). This positive trend has been associated with an increase in the number of antihypertensive medications prescribed; a positive finding because achieving BP control is highly cost-effective, and in people with diabetes, it can be cost-saving. Indeed, most patients with hypertension ultimately require multiple antihypertensive medications (3). However, clinicians are too familiar with the reluctance of patients taking an increasing number of pills. Moreover, hypertension commonly exists in concert with other chronic conditions, such as diabetes or dyslipidemia, each of which requires its own pharmacotherapeutic interventions. Thus, patients with hypertension are often faced with the need to take a plethora of medications.

To address the requirement of multiple medications in the treatment of hypertension, the Canadian Hypertension Education Program (CHEP) has reviewed the use of fixed-dose combination pills and developed recommendations. In the past, the pharmaceutical industry produced unhelpful combination pills for hypertension, such as hydrochlorothiazide (HCTZ) 50 mg plus triamterene 25 mg and HCTZ 50 mg plus amiloride 5 mg, which had higher doses of HCTZ than are recommended today. Many newer combinations are appearing regularly, and the question therefore arises of whether these combination antihypertensive pills are clinically useful or merely a gimmick of industry. Thus, the purpose of the present paper is to examine the clinical use of combination pills in the management of hypertension.

The need for multiple medications

Although the CHEP recommendations suggest starting antihypertensive pharmacotherapy with single agents (pages 529-538 in the current issue of the *Journal* [4]), it is acknowledged that the majority existing hypertensive patients require multiple medications to achieve BP targets. Indeed, in the most recent hypertension trials, such as the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT [5]), the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial (6) and the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT [7]), as well as in older hypertension trials, a large proportion of patients required two or even three antihypertensive medications to achieve target BPs. For example, at the conclusion of the ALLHAT, in controlled patients, approximately 30% of patients were on dual therapy and 20% of patients were on triple therapy (8). Accordingly, one can anticipate needing to use multiple antihypertensive medications in patients with

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long-established hypertension. Some international guidelines, such as the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (9) and the European Society of Hypertension/European Society of Cardiology practice guidelines (10), allow for the commencement of antihypertensive therapy with combination medications in acknowledgement of this fact. So, for example, in the recommendations by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, if BP remains greater than 20/10 mmHg above target at diagnostic visits, initial fixed-dose combination therapy is acceptable, because most monotherapeutic options do not reduce BP more than this. In Canada, the CHEP has considered, but not yet adopted, this approach to antihypertensive therapy, because it has not been subjected to a clinical trial to demonstrate a benefit in hard outcomes. There is also the concern about hypotension, and particularly first-dose hypotension, in elderly patients with this approach, as well as about the potential for an adverse event to lead to the inability to use two drugs rather than one. This has been balanced, on the other hand, since 2006 by the desire for more rapid titration of antihypertensive therapy, as would be expedited with the early use of drug combinations (3). Whether this recommendation will change in the future is open to speculation. Despite the concern of hypotension with the initial use of combination therapy, the very few studies that have examined initial use of combination therapy have not reported excessive hypotensive events (11-13).

BP control with combination therapy

The therapeutic efficacy of combination therapy, either singly or in fixed-dose combination forms, has been well established. Most antihypertensive medication combinations interact in an additive or even synergistic manner, but it was always thought that adding a 'renin'-type drug (angiotensin-converting enzyme [ACE] inhibitor, angiotensin receptor blocker [ARB] or beta-blocker) to a 'volume'-type drug (diuretic or calcium channel blocker) was the most logical choice. Reflecting this, the CHEP guidelines before this year had cited the 'ABCD' rule of combining antihypertensive medications. This year's recommendations recognize that other combinations, such as a dihydropyridine calcium channel blocker and a thiazide diuretic, can be just as efficacious as other combination therapies in the management of hypertension (4). This is based on studies such as the VALUE trial (6), in which the combination of a thiazide diuretic and a dihydropyridine calcium channel blocker resulted in greater and more rapid attainment of BP targets. The only exception to the combination rule is the apparent inferiority of an ACE inhibitor plus beta-blocker combination in reducing BP. A similar situation is seen with ACE inhibitor plus ARB combinations, which lower BP less than adding a diuretic to either.

Although combination therapy and fixed-dose combination medications are certainly effective in lowering BP, the superiority of any particular combination strategy or fixed-dose combination product in reducing cardiovascular end points has not yet been firmly established. As mentioned, most patients in clinical hypertension trials have ended up on multiple medications. However, the design of these trials has been such that the comparative effectiveness of individual combination strategies has been difficult to separate from the effects of the initial monotherapeutic drugs. For example, in the Losartan Intervention for Endpoint Reduction (LIFE) trial (14), patients randomly assigned to the ARB arm fared better than those randomly assigned to the beta-blocker arm. However, in both arms, the majority of patients were also receiving a thiazide diuretic. Thus, the effect of the individual monotherapies versus the effect of the principal drug plus diuretic combination could not be differentiated. The observed effects could have been due to differences in the principal drug effects or to different effects of the ultimate drug combinations used by the patients. Indeed, there have been very few studies that examined specific combination strategies versus the effect of individual drugs in preventing cardiovascular events in hypertension. One of these few studies is the recent ASCOT – Blood Pressure-Lowering Arm (ASCOT-BPLA [15]), which compared the strategy of a dihydropyridine calcium channel blocker plus ACE inhibitor combination with that of a beta-blocker plus diuretic combination. However, the results of this trial were somewhat controversial, because the trial was stopped prematurely due to excess mortality in the beta-blocker plus diuretic arm before sufficient primary end points could be collected to make any definitive conclusions about the combination strategy in preventing the composite primary end point. This may have been due, in part, to higher BPs in the diuretic plus beta-blocker group with lower high-density lipoprotein cholesterol levels, higher low-density lipoprotein cholesterol levels, and higher glucose and creatinine levels. On the basis of the ASCOT trial, the British Hypertension Society has recommended against the use of a diuretic plus beta-blocker combination strategy for the treatment of hypertension (16). In Canada, we have taken a more conservative approach, and while the potential inferiority of a diuretic plus beta-blocker combination has been discussed, it is still listed as a potentially acceptable combination therapy.

In terms of fixed-dose combination therapies, a number of options exist in Canada, and this number is increasing. Currently, the vast majority of fixed-dose antihypertensive combinations are represented by ACE inhibitor plus diuretic or ARB plus diuretic formulations. However, an ACE inhibitor plus verapamil combination also exists, and based on other countries' experiences, we are likely to see further fixed-dose combination therapies appearing on the Canadian market. Considerable interest has been engendered around the concept of a 'polypill', and perhaps we will see the introduction of novel cardiovascular fixed-dose combination products. A recent introduction in this area is a dihydropyridine plus statin combination, which, for the first time, aims at two of the major reversible components of cardiovascular risk reduction. Using such a combination, along with an ACE inhibitor (or an ACE inhibitor plus diuretic combination) or ARB (or an ARB plus diuretic combination), hypertensive patients, such as those with diabetes who require multiple antihypertensives and a statin, can achieve this with only two pills.

Adherence

With the fixed-dose combination therapies, one must ask whether they offer any advantage over the same drugs given as individual pill combinations. One area in which fixed-dose combinations may have an advantage is adherence. It is well recognized that medication adherence is a significant impediment to BP control in hypertensive patients. Regimens with fewer pills or once-daily dosing are more likely to be associated

with enhanced adherence than more complicated regimens (17-19). Thus, one strategy that may be effective in promoting adherence is reducing the number of pills by using fixed-dose combination therapies. Accordingly, the current CHEP guidelines advocate the use of fixed-dose combination therapy for this purpose (4).

Cost

Another barrier to achieving effective BP control is the cost of medications. From an individual perspective, patients may be unable to afford multiple antihypertensive medications. From a system perspective, drug costs are a major contributor to overall health care costs. In Canada, the use of fixed-dose antihypertensive combinations offers cost savings to patients and some payers over the use of the same agents prescribed individually but not to pharmacies.

'Wellness'

There is also a psychological aspect to the use of fixed-dose combination medications in chronic diseases such as hypertension. There is an association between the number of pills patients take and their self-perceived health (20-22), which has implications for both mental well-being and physical health. By reducing the number of pills, patients' mental and physical health may actually be improved without altering the actual medications being taken.

Convenience and safety

Unrelated to direct health benefits is the aspect of patient convenience. Using a single formulation in place of two individual drugs means that fewer pills need to be swallowed. This can be of benefit to elderly patients, presuming that the fixed-dose combination is as easy, or easier, to swallow than the individual pills. It also offers the added aspects of safety and efficacy, because the use of a single pill reduces the chance of a patient forgetting to take one of the prescribed individual pills in a multidrug regimen or through confusion, taking a double dose of an individual medication. Indeed, the use of blister packs, pill containers and other devices has been developed to avoid such confusion. Fixed-dose combination therapies, in addition to these strategies, should help to further improve drug adherence.

TABLE 1
Potential advantages of fixed-dose antihypertensive combination medications

- Preserved or enhanced efficacy
- Increased medication adherence
- Convenience
- Reduced individual and system costs
- Enhanced patient 'wellness'
- Increased safety
- Reduced side effects

Side effects

A final aspect of the use of combination therapy and fixed-dose combinations is that a combination therapy strategy can reduce medication side effects. In a large but heterogenous meta-analysis, Law et al (23) concluded that the use of low-dose combination therapies was just as efficacious as, but associated with fewer side effects than, the use of high-dose monotherapies. This, in turn, may offer both health and compliance advantages to patients.

CONCLUSIONS

The need for combination therapy for the treatment of hypertension is now accepted as the rule rather than the exception. Principles of guideline implementation mandate that strategies that enhance antihypertensive efficacy, acceptability, tolerability and adherence should be used. Fixed-dose combination formulations for the treatment of hypertension offer many of these potential advantages. Accordingly, many hypertension organizations, including the CHEP, encourage the use of fixed-dose antihypertensive formulations.

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