Hypertension

Single-pill combinations to improve blood pressure control

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examines the rationale for increased use of single-pill combinations, which he believes can contribute significantly to achieving BP control in a cost-effective manner

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Resistant hypertension is a major problem affecting 10-15% of hypertensive patients on medication

Hypertension has been more thoroughly investigated than most illnesses and well conducted research studies, costing many billions of dollars, have shown unequivocally that the cardiovascular consequences of elevated blood pressure (BP) – most notably stroke and heart attack – can be prevented. Moreover, these research studies have provided cost-effective drugs with relatively few adverse effects capable of restoring normal BP levels in the majority of people with hypertension.

Why is it, then, that raised BP is the major cause of morbidity and death in the world? Why are the inevitable, albeit preventable cardiovascular consequences of uncontrolled hypertension, which include not only stroke and heart attack, but also cognitive impairment, dementia, atrial fibrillation, heart failure and renal failure among other vascular complications, not being at least contained by treatment?

And finally, the damning question; why is it that despite having superlative drugs, less than one-third of patients with hypertension has elevated BP restored to normal?

There are a number of answers to these questions, but undoubtedly poor adherence to treatment and so-called therapeutic inertia are major contributors.

Therapeutic inertia

Therapeutic inertia can be defined in a number of ways, but in short it is the failure to prescribe enough medication to achieve BP control. The prescribing doctor is usually held accountable for the phenomenon, and though there is some substance to this accusation there are other influences contributing to failure to prescribe adequate drugs. There is, for example, the contribution of the patient to therapeutic inertia.

If, as is often the case, the first prescribed BP lowering drug is ineffective, the doctor is then faced with the option of adding another drug. Neither he nor the patient is anxious to embark on this course, which means that the patient has to take more tablets and so the process of therapeutic inertia is shared by both patient and doctor.

Let me offer a way out of this dilemma of choice by considering an option that allows the prescribing physician to titrate medication upwards in a number of permutations without increasing the tablet intake for the patient.

Single-pill combinations

The rationale for producing a number of drugs within one tablet is based on well established premises; most patients with hypertension will require more than one drug to achieve BP control; combination preparations improve BP control; prescribing low-dose drugs in combination causes fewer adverse effects than prescribing maximum doses of any one drug; patient adherence to medication is improved by combination tablets, and finally, the combination approach is cost-effective.

I initially termed these drugs as 'flexipill combinations', but the term single-pill combination (SPC) has gained general popularity in the literature and indicates preparations that contain two or more drugs in flexible dosages within one tablet.

There are SPC combinations of angiotensin receptor blocker (ARB) and angiotensin converting inhibitor (ACEI) drugs with calcium-channel (CCB) blocking drugs, ARBs or ACEIs with thiazide diuretics, and beta-adrenergic blocking drugs and renin inhibitors with thiazide diuretics in varying dose increments. The majority of SPCs incorporate hydrochlorothiazide (HCTZ) as the diuretic component in differing strengths. Thiazide-like diuretics, such as chlortalidone and indapamide, which may be more efficacious BP lowering drugs, are used much less often.

An example of a SPC incorporating an ARB, a CCB and HCTZ in the largest dosage range is shown in Table 1 and a SPC with an ACEI and CCB and indapamide is shown in Table 2.

The ideal SPC

If we accept that there is strong evidence that SPCs can contribute significantly to achieving BP control in a cost-effective manner, we must next ask if SPCs can be improved? Or put another way, given the state of knowledge today, what is the ideal SPC for tomorrow?

ARB or ACE inhibitor?

The issue as to whether an ACEI or an ARB should be the main BP lowering medication in a SPC is dependent on the comparability of the drugs. There is evidence that ARBs are equivalent to ACEIs in reducing BP. The issue of equivalence on the vasculoprotective benefits, however, is not so clear-cut. Whereas there may be small benefits for ARBs in stroke prevention and for ACEIs in reducing cardiac events, the overall difference is likely to be small.

When it comes to clinical practice, the most important issue is tolerability of the drug prescribed and in this regard the ARBs are superior to ACEIs in that they induce far less cough, a major reason for discontinuing ACEI treatment.

On balance, therefore, my preference would be that an ARB should be a component of an ideal SPC.

HCTZ or thiazide-like diuretics?

The majority of SPCs that include a diuretic component use HCTZ, but evidence has been growing over recent years suggesting that thiazide-like diuretics, such as chlorthalidone and indapamide, may be superior to HCTZ both in lowering BP and preventing cardiovascular events. Chlorthalidone is only available in a SPC in this country in combination with beta-blockers, which are not now recommended as first-line therapy for hypertension, whereas indapamide is available in combination with an ACEI. (Table 2)

Spironolactone for resistant hypertension?

Resistant hypertension is a major problem affecting 10 to 15 per cent of hypertensive patients on medication. The effectiveness of aldosterone antagonists, such as spironolactone or eplerenone, in lowering BP in patients with resistant hypertension has been demonstrated in a number of studies. In other words, patients whose 24-hour ABPM pressures remain elevated with a SPC containing maximum doses of an ARB, a diuretic and a CCB, would benefit from a SPC containing an aldosterone antagonist.

Conclusion

Based on evidence, a strong case can be made for the use of SPCs to overcome therapeutic inertia on the side of the doctor and to improve compliance with treatment on the side of the patient. Armed with a range of SPCs, the prescribing doctor has a number of permutations within one tablet allowing up-titration of medication without the need to prescribe multiple tablets.

Perhaps the pharmaceutical companies, which have advanced the management of hypertension greatly by providing the present range of SPCs, will now reappraise the ingredients of future SPCs so as to provide prescribing physicians and patients with a mechanism for increasing drug dosage and enhancing therapeutic effect in a mutually acceptable manner.

Table 1:
Example of SPC with ARB, CCB and HCTZ

	Olmesartan	Amlodipine	HCTZ
Omesar	20 mg	-	12.5 mg
Plus	20 mg	-	25 mg
	40 mg	-	12.5 mg
	40 mg	-	25 mg
Konverge	20 mg	5 mg	-
	40 mg	5 mg	-
	40 mg	10 mg	-
Konverge	20 mg	5 mg	12.5 mg
Plus	40 mg	5 mg	12.5 mg
	40 mg	10 mg	12.5 mg
	40 mg	5 mg	25 mg
	40 mg	10 mg	25mg

Table 2:
Example of SPC with AEI, CCB and Indapamide

	Perindopril	Amlodipine	Indapamide
Coversyl	2.5 mg	-	0.625 mg
Plus	5 mg	-	1.25 mg
	10 mg	-	2.5 mg
Acerycal	5 mg	5 mg	-
	5 mg	10 mg	-
	10 mg	5 mg	-
	10 mg	10 mg	-