



## BENEFICIAL COMBINATIONS OF TWO OR MORE ANTIHYPERTENSIVE AGENTS

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### Introduction

In a preceding communication we described the most relevant interactions between antihypertensive drugs and other therapeutics [1]. In the present paper we will deal with the combination of different types of antihypertensive drugs. Approximately half of the hypertensive patients can be satisfactorily controlled by a single drug, with the usual advice for appropriate changes in lifestyle. This means that the other 50 % of the patients require 2 or even more antihypertensive drugs for the adequate control of their blood pressure. The need for drug combination therapy has long been neglected or dismissed in academic medicine. In particular the use of tablets containing 2 or 3 different drugs in a fixed dose, has been strongly criticized. This view has been clearly reverted towards an appreciation of combined treatment, as expressed in more recently issued guidelines (1999 WHO-ISH [2] and JNC VI [3]). In these guidelines, combination therapy is advocated more explicitly for certain types of hypertensive disease, such as:

- isolated systolic hypertension (ISH);
- accelerated hypertension;

- in patients where blood pressure (BP) values lower than 140/90 mmHg are required to prevent target organ damage (e.g. in diabetes mellitus: <130/85 mmHg, chronic parenchymatous nephropathy: <125/75 mmHg).

The combination of 2 or more drugs may be expected to offer a more pronounced lowering of increased blood pressure and this has indeed been observed in numerous, usually rather small clinical studies. For very few drugs, their combination has been included deliberately in large randomised intervention studies, (e.g. the combination of diuretics and  $\beta$ -blockers [4,5]). Furthermore, the use of *fixed combination*, in a single tablet, is more and more appreciated since it significantly reduces the number of tablets to be taken daily, thus improving patient compliance, a most relevant source of insufficient therapeutic efficacy in hypertensive patients. Fixed dose combinations have recently been enriched by *very low dose combinations*, which may now be considered as first-line therapy.

### Effective combinations of two different antihypertensive drugs

Over the years, several combinations of antihypertensive drugs have been studied and shown to be effective in lowering elevated blood pressure. In this chapter we will discuss a series of combinations which are assumed to be effective and probably beneficial in certain groups of patients. Although not all are based upon large intervention studies required for evidence-based decisions, we have chosen these combinations on the basis of haemodynamic and pathophysiological considerations, mostly supported by studies as well as by our own experience.

- a. *Thiazide-diuretics + beta-blockers*: this combination has long been favoured by guidelines for patients with uncomplicated hypertension without target organ damage. This combination has been included in several large-scale intervention studies (e.g. STOP [4]; MRC [5], ALLHAT [12]) and can be considered as firmly established.
- b. *Thiazide-diuretics + ACE-inhibitors*: useful in patients with hypertension and congestive heart failure (CHF), ISH, as well as hypertension in the elderly (which is frequently ISH). This combination is considered to be a very potent antihy-

pertensive medication, and the addition of an ACE-inhibitor to a diuretic (or vice versa) should be performed cautiously, in order to prevent a too rapid decrease in BP. Furthermore, both, ACE-inhibitors and diuretics are considered as standard therapy in CHF.

- c. *Diuretics + AT<sub>1</sub>-blockers (ARB)*: this is proved to be a more effective combination for the treatment of hypertension with left ventricular hypertrophy, than beta-blocker + diuretics [10]. ISH is also a condition where this combination could successfully be applied [11]. It may also be beneficial for those with hypertension and CHF.
- d. *Diuretics + imidazoline (I<sub>1</sub>) receptor agonists*: this combination, which has not been studied on any larger scale, can be thought of if a beta-blocker cannot be added to a diuretic agent because of contra-indications.
- e. *Diuretics + calcium antagonist (dihydropyridines)*: dihydropyridine calcium antagonists, known to be potent vasodilators, can concomitantly be administered with diuretics in ISH-patients, who are usually elderly. There exists evidence both for diuretics [4,5] and for dihydropyridine calcium antagonists [6] (although not so clearly for their combination) that they are effective in lowering BP in ISH, as well as for protective activity towards the complications of hypertensive disease.
- f. *Alpha-blockers + beta-blockers*: this combination may be used in accelerated hypertension. There is little evidence for the efficacy of this combination. Accelerated hypertension is probably based on sympathetic hyperactivity and its sequelae. For this reason sympatholytic activity, as caused by both drugs of the combination, appears to be a logical therapeutic approach. For sympathetic overactivity centrally acting antihypertensives (clonidine, imidazoline I<sub>1</sub> receptor stimulants) and non-dihydropyridine calcium antagonists may also be thought of.
- g. *Beta-blockers + ACE-inhibitors*: although the antihypertensive effect of this combination is less than that of diuretics + beta-blockers [12], it could be used in hypertensive patients after myocardial infarction (MI), in those with coronary heart disease (CHD) or with CHF [8].
- h. *Calcium antagonists (dihydropyridine-type!) + beta-blockers*: patients with hypertension and CHD can be treated by this combination. Both types of drugs, apart from being efficacious antihypertensives, are known to display beneficial activity in CHD patients. The fixed combination of the two types of drugs can help improve patients' therapeutic compliance [17].
- i. *Calcium antagonists + ACE-inhibitors*: this combination can be suggested for the treatment of hypertensive patients with nephropathy, CHD or established atherosclerosis. The combination displays pronounced antihypertensive activity. Calcium antagonists are known to have anti-ischaemic activity in CHD. ACE-inhibitors are proved to be renoprotective, particularly in patients with diabetic nephropathy. Calcium antagonists, as shown for lacidipine in the ELISA study [9], amlodipine in PREVENT study [13] and nifedipine-GITS in the INSIGHT study [14] are proved to display anti-atherogenic activity. For ACE-inhibitors this effect has also been revealed (SECURE study) [15].
- j. *Calcium antagonists (dihydropyridines) + AT<sub>1</sub>-blockers*: the

presumed beneficial effects of this combination are globally the same as for the combination calcium-antagonists + ACE-inhibitors [16]. The renoprotective activity in diabetic (type 2) nephropathy appears to be well established [9]. Dihydropyridine-type calcium antagonists and the AT<sub>1</sub>-blocker losartan are known to display uricosuric activity, which may be advantageous also in patients with gout.

- k. *ACE-inhibitors + AT<sub>1</sub>-blockers*: this combination can be thought of in hypertensive patients with diabetic nephropathy as well as with glomerulonephritis, since both types of drugs have been shown to decrease proteinuria more than the individual components, so they may display renoprotective activity.
- l. *ACE-inhibitors + imidazoline receptor agonists*: theoretically this combination could be thought of if it would be desirable to simultaneously suppress the activities of both the renin-angiotensin aldosterone system (RAAS) and the sympathetic nervous system (SNS). The metabolic syndrome has been proposed as a target for SNS-suppressant drugs such as moxonidine or rilmenidine, since this syndrome is believed to be partly the result of SNS-hyperactivity.

### Triple combinations

A few suggestions have been put forward for triple combinations involving different antihypertensive drugs. These combinations are put together on merely theoretical grounds, virtually without formal clinical evidence. Arguments in favour of the use of 1 particular category of drugs are the same as those discussed above for the components of combinations of 2 differ-

ent drugs. The following drug combinations are conceivable:

- m. *Diuretics + beta-blockers + calcium antagonists*: a very potent combination which could be used in treatment of accelerated hypertension.
- n. *Diuretics + calcium antagonists + ACE-inhibitors*, potentially beneficial in the treatment of diabetic hypertensive patients, of those with accelerated hypertension or ISH.
- o. *AT<sub>1</sub>-antagonists + calcium antagonists + diuretics*: this triple combination may help reaching the target BP (<130/85 mm Hg) in hypertensive patients with type-2 diabetes mellitus, or with ISH.
- p. *ACE-inhibitors + alpha1-adrenoreceptor antagonists + imidazoline agonists*: potentially beneficial in the treatment of diabetic hypertensive patients or for those with metabolic syndrome, in particular when beta-blockers are contra-indicated or not well tolerated.
- q. *ACE-inhibitors + Ca-antagonists + beta-blockers*: potentially beneficial in hypertensive patients with coronary heart disease.

### Conclusions

Combination therapy has become widely accepted for the management of hypertensive disease and a substantial fraction of patients is best treated by 2, or frequently 3 antihypertensive drugs. Tablets with fixed combination of 2 drugs will facilitate the therapeutic schedule and thus improve patient compliance. The choice of drug combinations is mainly based upon haemodynamic and metabolic criteria, and for most combination formal evidence has not (yet) been put forward.

Drugs	Potential use
β-blockers + diuretics	Uncomplicated hypertension without target organ damage
Diuretics + ACE-inhibitors	Hypertension + congestive heart failure (CHF)
Diuretics + AT <sub>1</sub> -blockers	Isolated systolic hypertension (ISH) + CHF Possibly: ISH
Diuretics + imidazoline (I <sub>1</sub> )-receptor agonists	To be used when a β-blocker (contra-indications) cannot be added to a diuretic
Diuretics + calcium-antagonists (dihydropyridines)	ISH (usually elderly patients)
β-blockers + α-blockers	Accelerated hypertension
β-blockers + ACE-inhibitors	Hypertensives: post MI (sec. prevention) CHD, CHF
Ca-antagonist + β-blockers	Hypertension + CHD
Ca-antagonist + ACE-inhibitors	Hypertension + nephropathy, CHD or atherosclerosis
Ca-antagonists+AT <sub>1</sub> -blockers	Hypertension+ nephropathy, CHD or atherosclerosis (?)
ACE-inhibitors + AT <sub>1</sub> -blockers	Hypertension + nephropathy
ACE-inhibitors + imidazoline (I <sub>1</sub> )-receptor agonists	Patients with activated RAAS and SNS
Diuretics + β-blockers + calcium antagonists	Accelerated hypertension
Diuretics + calcium antagonists + ACE-inhibitors	Accelerated hypertension ISH, hypertension + diabetes mellitus
Diuretics + calcium antagonists + AT <sub>1</sub> -antagonists	Ibid.
ACE-inhibitors + α <sub>1</sub> -blockers + imidazoline (I <sub>1</sub> )-receptor agonists	Hypertension + diabetes mellitus. Metabolic syndrome
ACE-inhibitors + Ca-antagonists + β-blockers	Hypertension + CHD

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