Alpha-blockers in the Treatment of Hypertension

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Selective alpha$_1$-blockers act as vasodilators, both on arteries and veins. The specificity for alpha-adrenoreceptors induces relaxation of vascular smooth muscle with little reflex stimulation of cardiac output because catecholamine release is modulated via nonblocked alpha-receptors. As a result, peripheral resistance falls during rest and during various cardiovascular stresses, while cardiac output remains unchanged or slightly increased and cardiovascular reflex-control mechanisms are well maintained. These favorable haemodynamic effects have been demonstrated during exercise, when they particularly contrast with the effects of beta-adrenergic receptor blockers, which are often poorly tolerated by athletes.

The various selective alpha$_1$-blockers differ from each other according to their pharmacokinetic and pharmacodynamic properties. These properties have been examined for prazosin, the first and for over 10 years the only member of this class available; terazosin, introduced in 1987, and doxazosin, which became available in 1991.

Terazosin and doxazosin are less lipid soluble and have half or less of the affinity for alpha$_1$-receptors than does prazosin. For these and other reasons, they induce a less rapid and less profound initial fall in blood pressure, particularly after standing, than does prazosin. These may translate into differences in the propensity for first-dose and subsequent hypotensive symptoms and certainly provides for a longer duration of action for the second-generation alpha$_1$-blockers.

More recently, a controlled-release doxazosin gastrointestinal therapeutic system (GITS) have been developed. This GITS system in an osmotic pump that slowly releases the active drug so that peak levels are achieved 10 to 12 hours after oral intake. The plasma drug concentration declines more gradually for the doxazosin GITS formulation than the standard doxazosin tablet, providing high blood levels even at the end of 24 hours.

These long-acting alpha-blockers have been found to lower both systolic and diastolic blood pressure by approximately 10 mm Hg in multiple groups of patients with mild-to-moderate hypertension. In a multicentre trial, doxazosin was equally effective in patients over the age of 65 years and in younger patients, as well as in both black and nonblack patients.

In double-blind randomized parallel group comparisons made between the newly marketed doxazosin GITS formulation and the standard doxazosin tablets, doxazosin GITS was well tolerated and fewer patients on the GITS formulation discontinued therapy because of side effects and syncope was not seen with the GITS preparation.

Unfortunately, alpha-blockers have not been included in the multiple randomized placebo-controlled trials performed over the past 30 years that have proved the ability of antihypertensive therapy to reduce cardiovascular morbidity and mortality.

The situation is in process of changing. In particular, the massive Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), which will be completed in 2003, is comparing the ability of a calcium channel blocker (amlodipine), an ACE inhibitor (lisinopril) and an alpha-blocker (doxazosin) with a diuretic to reduce cardiovascular mortality and morbidity in almost 45,000 high-risk hypertensives.

In the meantime, alpha-blockers are widely recommended for the initial choice of therapy in hypertensives with one or more comorbid conditions, including dyslipidaemia, diabetes and prostatism.

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