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Calcium channel blockers and alpha-blockers in hypertension: what is the evidence ?

There are reservations about short-acting calcium channel blockers and alpha-blockers

Hypertension is the commonest cardiovascular disorder encountered by medical practitioners in primary and secondary health care. Safety in the drug treatment of hypertension can only be seen in relation to efficacy, which has now come to mean not just blood pressure reduction, but improvements in endpoints, including mortality. Diuretics and beta-blockers are two classes of antihypertensive agents with clearly proven benefits in mortality and morbidity studies (1). Although there are ongoing studies, there are no published outcome trials measuring endpoints for most of the other antihypertensive agents currently in use.

Based on available evidence angiotensin converting enzyme inhibitors are safe and effective, and are particularly recommended for diabetics with hypertension and albuminuria, because they slow the rate of progression of renal failure (2). They are also the drugs of choice for hypertensive patients with heart failure or left ventricular dysfunction (3). However, it must be noted that although angiotensin converting enzyme inhibitors have been shown to reduce morbidity and mortality in patients with heart failure in general, there are few data available about the effects of blood pressure lowering specifically in hypertensive patients with heart failure.

Results of several recent studies indicate that long term treatment with short-acting dihydropyridines such as nifedipine and isradipine may increase coronary artery morbidity and mortality in hypertensive patients (4). The risk was greatest at high doses, and sympathetic stimulation appears to be a likely explanation for the increased cardiovascular events (5). Despite some criticism of these studies, overviews of controlled trials raise serious concerns regarding the use of short-acting nifedipine in hypertensive patients, particularly in those with concomitant ischaemic heart disease.

As for long-acting calcium channel blockers (CCB), findings with short-acting preparations cannot be automatically transferred to long-acting CCB. Indeed, long-acting and short-acting calcium antagonists differ significantly in regard to cardiovascular outcomes (6). The newer second generation calcium channel blockers, for example amlodipine, felodipine and nisoldipine, show greatly improved vascular selectivity and longer duration of action. Once daily dosing with these longer-acting agents improves patient compliance and sustained and smooth blood pressure control. However, based on a new meta-analysis presented at the European Society of Cardiology meeting in Amsterdam, there is some preliminary evidence that seems to suggest that calcium channel blockers in general may be inferior to less expensive antihypertensive drugs in preventing cardiovascular complications of high blood pressure (7). According to these data, although calcium channel blockers were found to be as effective as other antihypertensives in lowering blood pressure, they failed to provide additional protection that cheaper antihypertensives did in preventing heart attacks and congestive heart failure. This meta-analysis has certain shortcomings, and results of other ongoing studies will help to clarify the contentious issues.

It needs to be mentioned here that there is adequate data to continue the use of heart rate lowering calcium antagonists such as verapamil and diltiazem as antihypertensives in post-myocardial infarction patients intolerant of beta-blocker therapy (8).

The use of alpha-blockers also needs to be reviewed in the light of emerging scientific evidence. Early this year the Data Safety Monitoring Board for the Antihypertensive and Lipid Lowering Treatment to prevent Heart Attack Trial (ALLHAT) decided to discontinue its doxazosin arm of the study. The decision was based on the finding that a significantly higher percentage of patients on doxazosin developed congestive cardiac failure (9). The ALLHAT trial involves 42 448 patients enrolled through 623 clinics and centres across the USA, Canada, Puerto Rico and the US Virgin Islands. Based on the findings of this trial doxazosin should no longer be considered as first line antihypertensive therapy. Indeed, recommendations of several notable guidelines, such as those of the US Joint National Committee, WHO/ISH, the British Hypertension Society and the Canadian Medical Association on the management of hypertension, which recommend alpha-adrenergic antagonists as first line antihypertensive drugs, will need to be revised in the light of this emerging evidence.

With no other data available for guidance it seems reasonable to assume that these findings should apply to all other drugs in the alpha-adrenergic antagonist group including prazosin. Whether doxazosin, prazosin and other drugs in the group should continue to be used as a second or third line antihypertensive drugs remains to be determined by future trials. When alpha adrenergic antagonists are used for treatment of prostate hypertrophy, caution should be exercised if such patients have manifest or latent congestive heart failure or are at high risk of developing failure because of previous myocardial infarction or left ventricular dysfunction. Since diabetic patients also are at increased risk of developing congestive heart failure this group of drugs is best avoided in them until further information becomes available.

These findings have special implications for Sri Lanka. Short-acting nifedipine is currently a commonly used antihypertensive in clinical practice in public and private sector health institutions, particularly in the periphery. This is probably due to its widespread availability in hospital settings and its potency in lowering blood pressure. Prazosin is sometimes used by medical practitioners as a first line drug in the treatment of hypertension. In the light of the above evidence short-acting calcium channel blockers should not be used for the long term treatment of hypertension, and prazosin cannot be recommended as a first line antihypertensive.

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