Letters to the Editor


Chronobiological aspects of antihypertensive treatment with calcium antagonists

We read with interest the editorial by Staessen et al.[1], which discusses very objectively the position of calcium antagonists in the treatment of hypertension. As scientists who are familiar with calcium antagonists both in daily practice and pre-clinical experiments[2], we have had difficulty in accepting negative clinical trial results on the use of calcium antagonists in hypertension. We use calcium antagonists both in acute hypertensive crisis and in the elderly with multiple metabolic diseases, and feel that these drugs are safe and effective, although at the moment they cannot be considered as first-line drugs.

One disadvantage of most calcium antagonists are the pharmacokinetics. The first pass effect is generally variable and therefore variable plasma concentrations, as well as comparable short half-lives, may yield diurnal changes of pharmacodynamic effects. Due to the circadian course of cardiovascular events[3], the question arises: do calcium antagonists protect against the critical rise of blood pressure, including high concentrations of catecholamines, in the morning hours, when most cardiovascular events occur? Could this, at least partially, be responsible for the negative results in clinical trials with calcium channel blockers?

 Vasodilation alone may be insufficient, but from the theoretical point of view, beta-receptor blockade should be the ideal co-medication in order to reduce the double product. We ask whether it may be an advantage to administer calcium antagonists twice daily and add a once daily dose of a beta-blocker agent in the late evening hours, to protect the heart against beta-stimulation in the morning. The concept of sympathetic arousal during the morning hours also gives an additional possible explanation as to why diabetic patients have a better outcome when treated with calcium antagonists alone, as heart rate is much more rigid in those patients due to autonomic impairment and may therefore react less to sympathetic influence.

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References


A reply

Drs Koch and Raschka propose to tailor antihypertensive drug treatment according to a patient’s diurnal blood pressure profile. Unfortunately, the hypothesis that the early morning surge in blood pressure is associated with increased risk remains unproven. Indeed, in the placebo group of the Syst-Eur trial[1], the 24-hour level and the night-to-day ratio of systolic blood pressure were significantly and independently correlated with the incidence of all cardiovascular end-points. The relative hazard rates associated with a 10 mmHg increase in the 24-hour blood pressure and with a 10% higher night-to-day ratio were 1.23 (95% CI, 1.03–1.44; P=0.02) and 1.41 (95% CI, 1.03–1.94; P=0.03), respectively. Furthermore, after adjustment for daytime blood pressure, the early morning increase in systolic blood pressure was inversely correlated with the incidence of cardiovascular end-points in the placebo group. In the latter model, a 10 mmHg increase in the daytime systolic blood pressure and a 1 mmHg·h−1 steeper increase in the morning systolic blood pressure were associated with relative hazard rates of 1.22 (95% CI, 1.03–1.44; P=0.02) and 0.92 (95% CI, 0.87–0.97; P=0.003) respectively. Thus, it appears that after adjustment for the daytime blood pressure level, the early morning surge in blood pressure does not predict a worse prognosis[3].

The possibility of reducing blood pressure for 24 hours or longer with once daily dosing is an important argument in the marketing strategy of many antihypertensive drugs. Once daily dosing may increase patient compliance[1-3], but for now it remains unproven that one has to reduce blood pressure for a full 24-hour period to decrease cardiovascular risk. Thus, tailoring drug treatment according to the diurnal blood pressure profile should only be recommended after the scientific evidence has been produced by properly controlled outcome trials.

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References


Cholesterol reduction, statins and the cytochrome P-450 system

We read with interest the review in the Journal[1] which drew attention to the potential for interaction between...