Counter-regulatory effects of combined ACE inhibition and calcium antagonism

We read with interest the paper by Bellet and colleagues (1987) describing the 'buffering' effect of an angiotensin converting enzyme (ACE) inhibitor on the counter-regulatory responses to the acute vasodilator activity of the calcium antagonist, nicardipine. However, we would suggest that caution be exercised against over-interpretation of their data, with their implication that the ACE inhibitor has significant adrenergic blocking activity.

In their report the use of percentage changes conceals the fact that the maximum heart rates would (approximately) be 76 ± 8 with ACE inhibition and 82 ± 8 beats min^{-1} (mean $\pm$ s.d.) with placebo. It is additionally noted that these maximum heart rates occurred at the end of the 30 min nicardipine infusion, whereas the peak noradrenaline concentrations occurred at 40 min (i.e. 10 min after the cessation of nicardipine), by which time heart rates were falling progressively. It is incidentally observed that statistical significance for the repeated measurements of the noradrenaline results depends on the single 40 min time point, comparing 1.8 ± 0.7 vs 3.1 ± 2.0 pmol ml^{-1} . We would question, therefore, their claim of 'marked stimulation of the sympathetic nervous system'.

In similar studies combining an ACE inhibitor with a calcium antagonist we have been unable to demonstrate a significant 'buffering' effect. For example single oral doses of nicardipine superimposed upon enalapril treatment produced maximum increments (against placebo) in supine and erect heart rate of 7 and 11 beats min^{-1} respectively (Donnelly *et al.*, 1986). This compares with increments of 7 and 9 beats min^{-1} when the same dose of nicardipine was admin-

istered alone (Pasanisi *et al.*, 1985). Similarly, with lisinopril and nifedipine (Lees *et al.*, 1987) there was a maximum increment in supine heart rate of 9 beats min^{-1} with nifedipine alone compared with 13 beats min^{-1} in the presence of the ACE inhibitor.

These observations suggest that ACE inhibition does not significantly attenuate the sympathetically-mediated component of the heart rate response to the vasodilator activity associated acutely with calcium antagonist drugs. Furthermore, it has been shown that ACE inhibitors do not impair the sympathetic neuronal release of noradrenaline (William *et al.*, 1986). It is possible, since Bellet and colleagues (1987) studied only recumbent patients, that their observations mainly reflect parasympathetic withdrawal and the possible parasympathomimetic activity of the ACE inhibitor. We suggest that their data do not substantiate their claim that ACE inhibition with CGS 14824A 'is able to minimise stimulation of the sympathetic nervous system induced by acute calcium blockade'. Instead, while an ACE inhibitor may buffer the reflex responses to its own vasodilator activity there is no convincing evidence that it will attenuate the counter-regulatory, sympathetically-mediated heart rate response to a significant additional vasodilatory stimulus.

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