Editorial:
Calcium-entry Blockade, Beta-adrenergic Blockade and the Reflex Control of Circulation

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The increasing use of calcium-entry blocking agents requires that their pharmacologic interaction with other cardiovascular drugs be carefully investigated. Although marketed in this country for its antiarrhythmic properties, verapamil is a potent dilator of vascular smooth muscle and has proved effective in the management of stable angina pectoris, both alone and in combination with β-adrenergic blocking agents. In vitro studies have shown that verapamil has significant negative inotropic, chronotropic and dromotropic effects. Clinical studies in patients with well-preserved ventricular function have documented reflex sympathetic stimulation in response to vasodilation that usually compensates for any expected depression of left ventricular performance. However, verapamil has produced marked depression of left ventricular function in patients with poor left ventricular function. Beta-adrenergic blocking drugs also have negative chronotropic and dromotropic properties, as well as potentially negative inotropic properties. Although these effects are similar to those of the calcium blockers, their pharmacologic site of action is different. At the cellular level, calcium-entry blockers uncouple excitation-contraction, whereas β-adrenergic blockers competitively antagonize the β-adrenergic membrane receptor. There is legitimate concern about the potential deleterious effects of combination of these independently useful antianginal therapies. Addition of a β-adrenergic blocking drug may blunt the reflex β-adrenergic stimulation that occurs with calcium-entry blockers, thereby unmasking the latter drug’s myocardial depressant effect.

Two articles published in the current issue assess the effect of combined β-adrenergic and calcium-entry blockade on left ventricular performance. Kieval and associates studied patients with well-preserved left ventricular function (mean ejection fraction 59.9 ± 11.2%) who were receiving maintenance doses of oral propranolol (plasma range 65.7–81.7 ng/ml). After left ventriculography, the patients were given short infusions of i.v. verapamil, and standard hemodynamic variables and several determinants of left ventricular function were assessed. Kieval et al. found no change in left ventricular performance as assessed by cardiac index, stroke volume index, left ventricular ejection fraction and mean velocity of circumferential fiber shortening, despite several dosing regimens (total dose of verapamil 14.4–32.8 mg) and peak plasma verapamil levels of 122–214 ± 108 ng/ml. They did observe the transient and potent vasodilating properties of i.v. verapamil in 13 of 20 patients who had transient hypotensive responses (mean decrease in aortic pressure of 24 mm Hg).

Packer and associates also undertook a hemodynamic study in patients with well-preserved left ventricular function. The patients were monitored with an indwelling pulmonary arterial catheter for 3 days. Their patients had substantially higher plasma levels of propranolol at the initiation of the investigation (mean 400 ng/ml). The study design also differed in that they used incremental increases in the dose of oral verapamil, achieving mean peak plasma levels of 205 ng/ml. While receiving the same incremental doses of oral verapamil, these patients were withdrawn from oral propranolol during the second day of the study to reassess the relative contributions of verapamil and propranolol to ventricular function as plasma propranolol levels diminished. In the presence of high plasma levels of propranolol, they demonstrated that for patients with preserved left ventricular function, oral loading with verapamil (120 mg every 6 hours for two doses) caused a small decrease in left ventricular performance as evidenced by an increase in pulmonary capillary wedge pressure (2.2 mm Hg) and a decrease in cardiac index (0.38 l/min/m²). This depression in left ventricular function occurred while mean systemic vascular resistance remained without significant change. Kieval et al. detected a 24% decrease in the mean systemic vascular resistance after i.v. verapamil. This acute unloading of the left ventricle probably accounts for the absence of detectable left ventricular depression in their patients, and the small difference in the two studies. When Packer and his colleagues allowed the plasma propranolol levels to decrease to 40 ng/ml (while peak plasma verapamil levels increased to 383 ng/ml), there was a significant decrease in systemic vascular resistance and the minor decrease in left ventricular performance was normalized. No significant effect on sinoatrial or atrioventricular conduction was observed in either study.

Although Packer et al. used a five- to sixfold higher level of plasma propranolol, their results are in agreement with the results of Kieval et al. In patients with well-preserved ventricular function, these short-duration studies indicate that the combination of β-adrenergic and calcium-entry blocking therapies can be used safely for a wide range of plasma drug levels achieved by oral or parenteral administration.

Although these preliminary studies are of timely clinical importance, we reiterate that the findings pertain to an isolated group of patients with stable cor-

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Coronary artery disease, sinus rhythm and, most important, well-preserved left ventricular function. No data were available that would allow one to anticipate the use of combined \(\beta\)-adrenergic blocking therapy and calcium-entry blockade in the presence of even moderately compromised left ventricular function. Furthermore, these studies were carried out in supine patients and, although these data are relevant to patients in a coronary care unit, studies are required in the ambulatory patient. Aside from several exercise studies on patients with stable angina pectoris,\(^4,5\) we know little about the potential interaction of these two drugs in ambulatory patients.

As other calcium-entry blockers become available, one may be able to tailor the combination of \(\beta\) blockade with a specific calcium blocker. Nifedipine and diltiazem offer different and potentially useful features. Nifedipine is the most potent vasodilator of the group, and because of afterload reduction and reflex sympathetic stimulation, it causes no detectable depression of left ventricular function.\(^12\) In a canine study, when equivalent degrees of peripheral vasodilation were achieved with several calcium-entry blockers, nifedipine alone mildly increased global left ventricular ejection fraction and decreased left ventricular end-diastolic pressure, while verapamil increased the left ventricular end-diastolic pressure by 64% and depressed the global ejection fraction by 16%.\(^13\) When nifedipine is instead given in equimolar doses with verapamil (doses that greatly exceed those necessary for nifedipine-induced vasodilation), there is a significant depression of left ventricular function as assessed by \(dP/dt\) and fractional shortening of left ventricular transverse diameter.\(^14\) A similar observation has been made in human subjects when the regional effects of intracoronary nifedipine were compared with those after i.v. administration. After intracoronary nifedipine, a direct negative inotropic effect was noted, whereas the dominant effect of i.v. nifedipine at clinical doses was a lowering of systemic blood pressure and an improvement in regional left ventricular function.\(^15\)

Diltiazem has been reported to have selective activity in vitro on human coronary vascular smooth muscle at a level that produces no negative inotropic effects.\(^16\) Diltiazem may also have less effect on systemic vascular resistance. Thus, selective pharmacologic properties of individual calcium-entry blockers may provide unique advantages when combined with \(\beta\)-adrenergic blockade.

Combined blockade of calcium entry and \(\beta\)-adrenergic receptors should be approached with caution, particularly in patients with left ventricular dysfunction. Although the combination can be tolerated, tolerance can require a complex and occasionally unpredictable interaction of afterload reduction and reflex sympathetic response.

References

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