Title: ADRENERGIC RESPONSE TO NICARDIPINE IN THE MANAGEMENT OF POSTOPERATIVE HYPERTENSION

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Introduction: Calcium antagonists are now widely used in the treatment of a variety of medical conditions, such as ischemic heart disease, cardiac arrhythmias, and hypertension. Nicardipine, a new dihydropyridine calcium channel blocking agent structurally related to nifedipine, has been shown to produce coronary vasodilation and reduce systemic vascular resistance. The treatment of postoperative hypertension remains a therapeutic dilemma for anesthesiologists since many of the vasodilator drugs require invasive monitoring and elicit reflex sympathetic stimulation which would be deleterious in patients with ischemic heart disease. The aim of the present study was to evaluate the adrenergic response to intravenous nicardipine in the management of postoperative hypertension in the anesthetic recovery room.

Methods: Seven patients (aged 52 to 93 yr) were studied. Informed consent and institutional approval were obtained. Patients were randomly assigned to receive nicardipine or placebo on a 3:2 basis for the treatment of postoperative hypertension. Postoperative hypertension was defined as a systolic blood pressure (SBP) greater than 140mmHg. Baseline recordings of heart rate and blood pressure were made from the electrocardiogram and an automated blood pressure recording device and the patient entered a titration period in which the study drug (nicardipine or placebo) was administered in doses of 10 mg/hr, 12.5 mg/hr and 15.0 mg/hr for 5 mins, 5 mins and 15 mins respectively to achieve a sustained therapeutic response defined as a reduction of SBP of 15% or more. Once a sustained therapeutic response was achieved, the patient entered a maintenance period when the study drug infusion rate was reduced to the equivalent of 3.0 mg/hr and the dose adjusted by 1.0 to 2.5 mg/hr every 15 mins as needed to maintain blood pressure control. Patients who did not respond to the study drug had their treatment code broken and if on placebo, received open-label nicardipine. Blood samples were taken for the measurement of plasma norepinephrine (NE) concentrations by radioenzymatic assay at baseline prior to nicardipine infusion, at the time of sustained therapeutic response (ie. $\geq$ 15% reduction in SBP from baseline), during maintenance infusion, and after discontinuation of nicardipine infusion. BP and heart rate were measured at the time each blood sample was taken. Statistical analysis was by analysis of variance and paired Student's t-test and $p<0.05$ taken as the minimum level of significance.

Results: The 5 patients randomized to receive nicardipine achieved a therapeutic response. The 2 patients randomized to placebo failed to achieve satisfactory BP reduction, they then received nicardipine, when they too achieved a sustained therapeutic response. Fig. 1 shows there was no significant difference between the baseline heart rate prior to nicardipine infusion and heart rate at the time a sustained therapeutic response was achieved, during maintenance and after discontinuation of the infusion. Thus, in contrast to other hypotensive agents nicardipine did not produce a tachycardia.

Mean plasma NE concentrations at baseline prior to nicardipine infusion in patients who had developed postoperative hypertension in the recovery room were 589.3±140.1 pg/ml, (normal range 75 to 480 pg/ml). Thus, hypertensive patients in recovery room have a high degree of background sympathetic stimulation. However, nicardipine did not further increase plasma NE levels (Fig. 2). Plasma NE concentrations post nicardipine (472.6±143.8 pg/ml) were significantly lower ($p<0.05$) than during maintenance infusion (598.4±168.8 pg/ml), suggesting that rebound sympathetic stimulation does not occur on discontinuation of nicardipine.

Figure 1: HEART RESPONSE TO NICARDIPINE (mean±SEM)

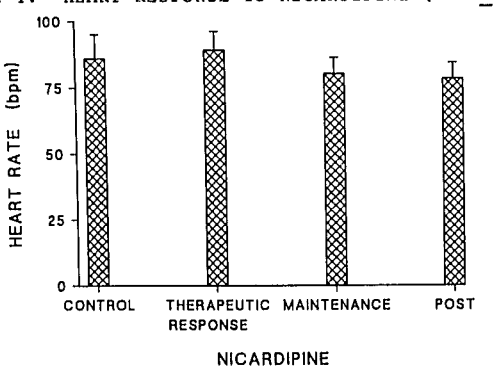
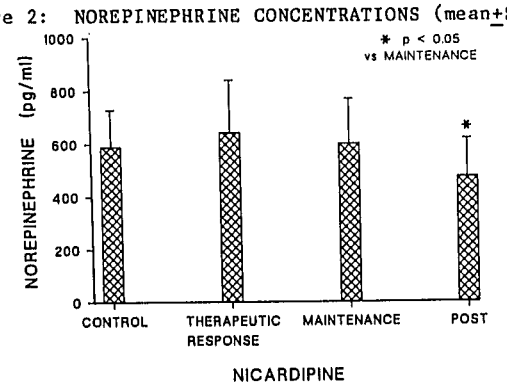


Figure 2: NOREPINEPHRINE CONCENTRATIONS (mean±SEM)



Discussion: Increases in heart rate due to reflex stimulation of the sympathetic nervous system have been demonstrated for other dihydropyridines, but in our study of patients with postoperative hypertension where resting baseline catecholamines were elevated, nicardipine did not further increase heart rate or NE levels. However, following control of hypertension and discontinuation of nicardipine, NE levels fell. The lack of a sympathetic response to nicardipine may make this agent useful in the management of postoperative hypertension.