HEMODYNAMIC RESPONSES TO DIFFERENT LEVELS OF ALPHA-ADRENERGIC INTERRUPTION IN CONGESTIVE HEART FAILURE

SUMMARY. The effects of prazosin, clonidine, and indoramin on central and regional hemodynamic parameters and left ventricular performance were analyzed in a congestive heart failure population to compare the pharmacodynamic responses to different levels of alpha-adrenergic interruption in this condition. The sympathetic nervous system is blocked at the peripheral alpha,-receptor by prazosin, at central nervous system alpha-receptor sites (via alpha-adrenoceptor agonism) by clonidine, and at peripheral and central sites by indoramin. Prazosin and indoramin produced reductions in total systemic and pulmonary vascular resistances, mean systemic and pulmonary artery pressures, and pulmonary capillary wedge pressure with little change in heart rate. Both agents selectively increased hepatic blood flow. Clonidine also decreased pulmonary artery pressure and vascular resistance, but evoked negative inotropic and chronotropic activity and did not alter regional blood flow. In contrast to prazosin, indoramin and clonidine did not augment cardiac output or stroke volume. In the setting of congestive heart failure, the central and regional hemodynamic effects and the responses in left ventricular performance vary considerably depending on the site of alpha-adrenergic interruption.

KEY WORDS. alpha-adrenergic blockade, prazosin, clonidine, congestive heart failure, indoramin

Current therapy in congestive heart failure is in large part aimed at reducing pathophysiologic mechanisms that contribute to perpetuating left ventricular dysfunction. Many of these mechanisms are mediated through activation of the sympathetic nervous system [1]. The elevated sympathetic-induced vascular tone (causing ↑ preload, ↑ vascular resistances, and ↑ afterload) found in congestive heart failure can be interrupted at several levels. Peripheral alpha,-adrenergic receptor antagonists (e.g., prazosin); central alpha-receptor agonists (e.g., clonidine); and agents with a proposed combination of peripheral and central activity (e.g., indoramin) have all been evaluated as potential therapeutic agents [2–6]. The aim of this report is to bring together much of these previously reported data from our laboratory for the purpose of comparing the responses of central hemodynamic variables, left ventricular performance, and regional blood flow to different levels of interruption of the alpha-adrenergic system in congestive heart failure. The intent is not to suggest or promote alpha-adrenergic agents for the treatment of heart failure because pharmacodynamic tolerance to repeated dosing is a limiting feature of many of these drugs, but to offer additional information concerning the physiology and pharmacophysiology of heart failure as derived from pharmacologic manipulation.

Patient Populations

Fifty-eight patients with moderate to severe heart failure were studied; all were categorized as functional class III or IV as defined by the New York Heart Association. Many of the patients enrolled in this study were subjects participating in other ongoing pharmacologic protocols (as reported in [2–5]) for congestive heart failure. Prazosin was evaluated in 22 patients (17 men and 5 women, mean age 56 years); clonidine in 24 patients (20 men and 4 women, mean age 50 years); and indoramin in 12 patients (9 men and 3 women, mean age 53 years). With the exception of mean pulmonary artery pressure (higher for the clonidine group at p < 0.1), the clinical and hemodynamic profile of three treatment groups were not significantly different.

All patients had their diagnosis confirmed by cardiac catheterization within 3 months of this study. The etiology of congestive heart failure consisted of idiopathic dilated cardiomyopathy in 37 patients, ischemic congestive cardiomyopathy in 17, and status post-valvular replacement in 4. The relative distribution of each diagnosis was comparable for the three

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drug groups. Diuretics were either discontinued or shifted to evening dosing. Vasodilator agents and related drugs were discontinued at least 48 hours prior to the start of the study.

Protocol

All studies were performed in the resting post absorptive state. For each drug group, baseline control data were collected on day 1 and active drug studies were performed on days 2 and 3. On each day, central hemodynamic measurements were made predose and hourly for 6 hours after dosing; the central and regional hemodynamic measurements and the noninvasive left ventricular performance data attained 2 to 3 hours postdosing are presented in the report.

For prazosin (n = 22), 11 patients received 2 mg and 11 patients 5 mg on day 2. All clonidine-treated patients (n = 24) received 0.2 mg on day 2. Twenty-one patients also received the 0.4-mg dose on day 3 because 3 patients developed marked somnolence and/ or hypotension on the 0.2-mg dose. Each of the 12 indoramin-treated patients received 50 mg on day 2; 9 were advanced to 75 mg on day 3.

Procedures

One day prior to baseline hemodynamic studies, a flow-directed thermodilution catheter was placed in the pulmonary artery for central hemodynamic monitoring. The catheter was interfaced with Becton-Dickinson PR-18A pressure amplifiers and recording systems. Cardiac outputs were measured by thermodilution using a Gould SP1435 cardiac output computer. Systemic blood pressures were measured by auscultation using a standardized cuff and mercury column sphygmomanometer. Heart rate was obtained from continuous electrocardiographic monitoring.

Hepatic blood flow was determined by indocyanine green clearance and renal blood flow by para-aminohippurate (PAH) clearance [2]. The hepatic and renal blood flow values were corrected for body surface area. Upper limb blood flow was determined by venous occlusive plethysmography using a MedaSonics SP-16 amplification system interfaced with an SG-12 gallium-indium strain gauge [5].

Noninvasive evaluation of ventricular performance was made by measuring systolic time intervals, obtained from simultaneous recordings (100 mm/sec) of the carotid pulse, precordial phonocardiogram, and an electrocardiogram (ECG); calculations were performed and corrected for heart rate as previously described from this laboratory [7].

The data within a drug group were analyzed by Students' T-test for paired data.

Results

The results are presented in Figures 1 through 7. Prazosin alone produced a significant increase in cardiac and stroke volume index (Figure 1). Prazosin and indoramin had no significant effect on heart rate, while clonidine produced a significant decrement at both doses studied (see Figure 1). Each agent decreased pulmonary capillary wedge pressure (Figure 2). Prazosin at 5 mg and clonidine and indoramin at both doses produced reductions in the mean arterial pressure (see Figure 2). This was accompanied by significant reductions in total systemic vascular resistance after prazosin and indoramin (Figure 3). Prazosin at 2 mg and clonidine and indoramin at both doses reduced pulmonary artery pressure, and each agent decreased pulmonary vascular resistance (Figures 2, 3).

Prazosin (5 mg) and indoramin increased left ventricular ejection time; these drugs did not change the pre-ejection period (Figure 4). Clonidine did not alter ejection time, but significantly lengthened the pre-ejection period. The pre-ejection period/ejection time ratio (PEP/LVET) dropped significantly after prazosin (5 mg) and indoramin, indicating improved left ventricular performance (Figure 5). In contrast, clonidine at both doses produced an increase in this ratio.

Prazosin and indoramin increased hepatic flow and reduced hepatic vascular resistance (Figures 6, 7).

Fig. 1. Cardiac index, stroke volume index, and heart rate responses presented as baseline versus postdrug response.