High Dose Propranolol in the Treatment of Angina Pectoris: Relationship of Dose to Blood Levels and Hemodynamic Consequences

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Propranolol blood levels and the effect of these levels on hemodynamic parameters were evaluated in 25 patients with coronary artery disease undergoing cardiac catheterization and coronary angiography. Fifteen patients were receiving high doses of propranolol (320–1920 mg/day) while ten patients were receiving conventional doses (80–240 mg/day). The high dose propranolol group had significantly higher plasma propranolol levels than the conventional dose group (788 ± 134 SD vs. 43 ± 7.2 ng/ml SD), and there was a direct linear relationship between propranolol dose and plasma drug levels (r = 0.85, P<0.001). There were no significant differences between high and conventional dose propranolol groups in terms of all hemodynamic parameters measured, namely ejection fraction, ventricular volume, cardiac index, or peripheral vascular resistance. Despite high drug dosage and blood levels, only mild side effects were seen.

INTRODUCTION

Although the use of propranolol generally is accepted for the treatment of angina pectoris, recommendations concerning the most appropriate drug dosage still vary [1,2,3]. On the one hand, it has been stated that drug dose be increased sequentially to tolerance, defined by bradycardia, hypotension, or fatigue; or to maximum relief of anginal symptoms [1]. Alternatively, it has been suggested that maximum therapeutic benefit occurs at relatively low doses of 160–240 mg per day and that higher doses are associated with clinical and hemodynamic deterioration [3,4]. Differences in patterns of propranolol administration appear to be due to two factors: (1) variable therapeutic responses observed over a wide range of drug doses [1,2,3] and (2) a lingering suspicion that propranolol administration may result in deterioration of left ventricular performance [4,5,6].

A number of mechanisms could account for the observed individual variability of propranolol doses required for an adequate therapeutic response. These include: (1) differences in bioavailability and drug absorption resulting in suboptimal blood
and tissue drug levels [7,8]; (2) differences in drug levels necessary to attain adequate beta blockade in individual patients, resulting from different levels of sympathetic tone or differences in the actual number of beta receptors among patients [9,10]; (3) differences in regional myocardial drug availability resulting from reductions in regional myocardial blood flow due to coronary occlusion or obstruction [11].

The issue of whether propranolol impairs ventricular function in a major negative manner continues to be debated. Previous studies of the effects of propranolol on left ventricular function have not shown uniform results [4,5,12,13,14]. Many of these investigations reported a negative inotropic effect and development of regional wall motion abnormalities following acute administration of intravenous propranolol [4,5]. However, recent studies by Marshall et al. [15] and Reduto et al. [16] have not demonstrated substantial alteration of ventricular performance by propranolol. Using radionuclide techniques, they found no change in resting ejection fraction induced by chronic oral doses of the drug. Furthermore, the epidemiologic study of propranolol usage conducted by the Boston Collaborative Drug Surveillance Program indicated that drug-induced heart failure is a relatively uncommon clinical phenomenon [17]. In addition, adverse reactions do not appear to be dose-dependent, frequently occurring at rather low doses.

The current trend of antianginal therapy in our institution involves administration of propranolol sequentially until either improvement of angina or development of limiting symptoms or signs, irrespective of total dose. Because of this therapeutic policy, we were able to evaluate a group of patients receiving a wide range of propranolol dosages. This report describes initial studies in patients receiving both high dose and more conventional doses of propranolol. The goals of the study were twofold: (1) to assess if variation in dosage was a function of differences in absorption or bioavailability and (2) to assess indirectly the hemodynamic consequences of high dose oral propranolol in patients with coronary artery disease.

MATERIALS AND METHODS

Patient Population

The study population consisted of 25 consecutive patients admitted to the West Haven VA Medical Center for evaluation and treatment of incapacitating angina pectoris. The mean patient age was 54 years with a range from 42 to 64 years. All patients were either receiving propranolol prior to hospital admission or had the drug instituted subsequent to hospitalization. In each patient, the dose of propranolol was increased until maximum tolerance, defined by heart rate less than 50 beats per minute or improvement of symptoms irrespective of the dose. In addition, all patients received nitrates in the form of either sublingual isosorbide dinitrates, nitroglycerin paste, or sublingual nitroglycerin. During the course of hospitalization, physical activity was limited and patients were frequently kept at bed rest.

The patient population was divided arbitrarily into two groups based upon the propranolol dosage: (1) those receiving propranolol doses $\geq 320$ mg per day, constituting the high dose group ($n = 15$), (2) those receiving $\leq 320$ mg per day, constituting the conventional dose ($n = 10$).

Fourteen patients had evidence of previous myocardial infarction (eight transmural and six nontransmural). No patient had sustained a myocardial infarction within the month preceding the study. The diagnosis of coronary artery disease was obvious clinically in all patients. Coronary angiography was performed in each patient. No patient required intraaortic balloon placement as an adjunct to either therapy or
angiography. Propranolol was administered for treatment of angina (17 patients had Class III angina; eight patients had Class IV angina). Nine patients had a history of congestive heart failure and were being treated with digitalis and/or diuretics (five patients in the high dose group and four in the conventional dose group), although all were compensated clinically at the time of study. On physical examination, no patient manifested a third heart sound or significant pulmonary rales. Two patients had mild liver abnormalities characterized by mild elevation of liver enzyme. None of the patients had renal dysfunction.

Cardiac Catheterization and Angiography

Right and left cardiac catheterization was carried out by standard techniques. Intracardiac pressure measurements, cardiac output determinations by the thermodilution method, left ventricular cineangiography, and coronary cineangiography were obtained in each individual. Single plane end-diastolic volume, end-systolic volume, and ejection fraction were determined by the method of Dodge et al. [18].

Plasma Propranolol Levels

Blood samples for propranolol plasma levels were obtained six hours after administration of the drug on the day of cardiac catheterization. Serum was frozen and maintained at 0°C until assayed using the spectrophotofluorometric method of Rao et al. [19]. This technique uses samples of 1 ml and has good reproducibility. Data on serum propranolol measured by this technique correlate closely with measurements obtained in the same sample by the method of Shand et al. [20] (n = 25 samples, r = 0.98) (Zito R: unpublished data).

Statistical Analysis

Data are expressed as the mean ± SD. The correlation coefficients between dose and plasma levels were calculated from linear regression analysis. The differences between the means were calculated using an unpaired t test.

RESULTS

Mean plasma levels ± SD of propranolol in the group of patients receiving high dose of propranolol was 788 ± 134 ng/ml (range 132–920) and for the group on conventional doses was 43 ± 7.2 ng/ml (range 10–85). A highly significant difference (P < 0.001) existed between the mean plasma level of propranolol in the two groups. Furthermore, a direct linear relationship (r = 0.85) was demonstrated between dose administered and propranolol plasma levels (Fig. 1). Specifically, high doses of propranolol were associated with high plasma levels. Despite the high doses utilized and the high blood levels attained, only mild side effects were seen (mostly fatigue) with the exception of one patient who developed clinical evidence of cerebral vascular insufficiency which improved when the dose was reduced. Congestive heart failure was not detected in any patient. Seven of the 15 patients obtained symptomatic relief of their angina when high doses of propranolol were utilized as compared to therapy at low dose range.

The clinical characteristics of the patient population classified with respect to propranolol dosage are shown in Table 1. No significant difference was found between high and conventional dosage groups for age, sex, degree of angina, history of myocardial infarction, and extent of coronary artery disease. The hemodynamic data for the two groups are shown in Table 2. Again, no significant differences were
DOSE/PLASMA CONCENTRATION RELATIONSHIPS

FIG. 1. Relationship of oral propranolol dose in mg/day to plasma concentration in 25 patients. The circles (o) represent the patients on conventional doses and the exes (x) the patients on high dose propranolol.

found for heart rate, cardiac index, left ventricular end-diastolic pressure, peripheral vascular resistance, end-diastolic volume, end-systolic volume, or ejection fraction.

DISCUSSION

The study indicates that high doses of oral propranolol are associated with concomitant elevation of plasma drug levels. These high plasma concentrations of

| TABLE I | Clinical Characteristics of Patient Groups |
|---------|------------------------------------------|
|         | High Dose (N = 15)                        |
|         | (> 320 mg/day)                            |
| Mean    | Range                                    |
| Age     | 54 yrs                                   |
| Sex     | 14 male                                  |
| Angina  | Class III 10/15                          |
|         | Class IV 5/15                            |
|         | Previous MI 8/15                         |
| Extent of CAD | 1.5/15                                          |
| Number of Vessels | 2.6                                           |
| Conventional Dose (N = 10) (< 320 mg/day) |
| Mean    | Range                                    |
| Age     | 53 yrs                                   |
| Sex     | 10 male                                  |
| Angina  | Class III 7/10                           |
|         | Class IV 3/10                            |
|         | Previous MI 6/15                         |
| Extent of CAD | 2.4                                           |
| Number of Vessels | 2.4                                           |
propranolol may be necessary to obtain appropriate antianginal responses in individual patients. Although high doses are employed frequently for the treatment of hypertension, little data is available concerning the effect of these dose ranges in patients with coronary artery disease and a greater tendency to intrinsic left ventricular dysfunction. In this selected group of patients, important therapeutic effects appeared to occur without associated major side effects. No congestive heart failure or further hemodynamic deterioration was precipitated by the doses of propranolol employed in the high dose group. In addition, hemodynamic parameters in patients treated with high doses of propranolol were not significantly different from those seen in patients treated with conventional doses.

Work with antiarrhythmic agents such as quinidine and procainamide has established distinct relationships between drug dose, drug blood levels, therapeutic effectiveness, and toxicity. No such simple set of relationships exist for propranolol. Many previous investigations have noted a wide variation in the drug dose necessary for the treatment of both angina and hypertension [1,2,3,7,8]. Physiologic studies likewise have demonstrated wide variations in the propranolol blood concentration necessary to induce appropriate responses to isoproterenol infusion or exercise [9,21]. As opposed to other drugs evaluated, there does not appear to be a clearly defined therapeutic and toxic range of blood levels for propranolol. This should not be too surprising, since the physiologic effects of propranolol are dependent upon the interaction of the drug with the endogenous beta receptor population in the individual patient. The number of cardiac receptors and the level of intrinsic beta adrenergic activity on both a regional and systemic basis will have wide individual variability. George et al. [10] have shown in dogs that there is a direct relationship between propranolol and isoproterenol sensitivity. Animals more sensitive to intravenous propranolol are far more sensitive to isoproterenol infusion, implying a common receptor response. Recently an increase in the number of receptors has been demonstrated in animals and humans chronically treated with propranolol [22,23]. These could explain the need of high dose of propranolol in some patients.
Propranolol is metabolized primarily by the liver. Paterson et al. [8] have demonstrated an active metabolite of propranolol (4-hydroxypropranolol) in the serum after oral propranolol administration. This metabolite was not measured in our study. However, this metabolite does not appear to be present after chronic oral therapy and would therefore not influence the results of our study [24]. Nevertheless, it is possible that other, as yet not measured or defined, metabolite, may play a role in the hemodynamic consequences of propranolol therapy.

Despite the high dosage utilized in many of our patients, only mild side effects were seen. Only one patient of the high dose group developed a major complication, that of cerebral vascular insufficiency. This improved when the dose was reduced. Congestive heart failure was not detected in any patient. The latter results are in agreement with those of the Boston Collaborative Surveillance Program [17]. However, it must be noted that the majority of patients in our study had severe angina and were consequently symptom-limited and hospitalized. It is conceivable that at higher levels of physical activity, evidence of altered cardiac reserve might develop.

The present study employed doses as high as 1920 mg per day. Even at these high doses there was no evident demonstration of major abnormalities in cardiac function different from those seen in comparable patients on conventional doses. Clearly, it would have been optimal also to study patients during exercise stress at the onset of therapy and then again as the dosage was increased. However, this option was not available because of the symptomatic status of the patients studied and the fact that hemodynamic measurements were made on only one occasion, at rest at the time of cardiac catheterization and angiography. Nevertheless, our data support recent preoperative observations made by Marshall et al. [15] and Reduto et al. [16], both of whom failed to demonstrate any major deterioration in left ventricular function induced by propranolol in patients with coronary artery disease studied sequentially.

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