Suppression of Chronic Ventricular Arrhythmias with Propranolol

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SUMMARY The antiarrhythmic efficacy of propranolol was evaluated in 32 patients with chronic high frequency ventricular arrhythmias in a placebo-controlled protocol. After a placebo control period, propranolol was begun and the dosage increased sequentially until arrhythmia suppression was achieved, side effects appeared, or a maximum dosage of 960 mg/day was reached. Computerized analysis of ambulatory recordings was used to quantify the arrhythmias. Twenty-four patients had 70–100% arrhythmia suppression at plasma levels ranging from 12–1100 ng/ml (end of dosing interval). Eight patients in this group had frequent episodes of ventricular tachycardia that were totally suppressed at or below the dosage that produced ≥70% suppression of ventricular ectopic depolarizations (VEDs). A biphasic dose-response curve was seen in five patients who responded with a decrease in arrhythmia frequency in the lower ranges of dosages but had increased frequency of ectopic rhythms as the dosage was increased above the optimal level. Only one-third of patients responded at dosages ≤160 mg/day. However, with dosages of 200–640 mg/day, an additional 40% responded.

Propranolol appears to control ventricular arrhythmias safely and effectively in many patients. The finding that the antiarrhythmic effect in many patients required plasma concentrations greater than those that produce substantial β-adrenergic blockade raises a question whether blockade of cardiac β receptors can directly account for all of the antiarrhythmic actions of propranolol.

PROPRANOLOL is widely recognized as effective therapy for atrial arrhythmias and ventricular arrhythmias due to excess catecholamines or digitalis toxicity, but is not generally considered the drug of choice for controlling recurrent ventricular tachycardia (VT) or frequent ventricular ectopic depolarizations (VEDs). However, the dose-response relationship for propranolol has not been systematically evaluated and most of the evidence indicating efficacy in the treatment of ventricular arrhythmias comes from case reports and small or uncontrolled trials. Gibson and Sowton\(^1\) reviewed 125 uncontrolled cases treated with propranolol in doses from 25 mg i.v. or 30–120 mg/day orally. Ventricular arrhythmias were suppressed in 98 cases (44%) and decreased in 27 additional cases (total response 57%). Gianelly et al.\(^2\) did not observe benefit in any of the five patients given propranolol for ventricular arrhythmias, but dosages were less than 120 mg/day and plasma levels were not reported. Another series of 10 patients with the progressing mitral valve syndrome had only a 50% response rate with the maximum dosage of 160 mg/day.\(^3\) Winkle et al.\(^4\) observed a decrease in VEDs in only five of nine patients with mitral valve prolapse. The maximum dosages or plasma levels obtained were not reported for individual patients. Plasma concentrations of propranolol associated with suppression of VEDs were determined after intravenous administration by Coltart, Gibson and Shand.\(^5\) Eight of 12 patients responded at plasma concentrations of 40–85 ng/ml and four were not controlled at peak levels of 70, 82, 110 and 200 ng/ml respectively. Nixon et al.\(^6\) studied a group of patients with exercise-induced or augmented VEDs and found that eight of 15 patients had greater than 70% reduction in arrhythmia frequency at plasma concentrations from 40–322 ng/ml (137 ± 99 ng/ml, mean ± SD). However, each patient's dosage was titrated to >20% suppression of exercise-induced tachycardia and not to maximal arrhythmia suppression.

In view of the wide variation in plasma concentration among patients receiving the same oral dosage of propranolol,\(^7\) it cannot be assumed that all patients in previous studies received doses that delivered concentrations in plasma that were within the effective antiarrhythmic range. Furthermore, the range of plasma concentrations necessary for optimal antiarrhythmic efficacy has not been systematically evaluated. Accordingly, we used dose-ranging methods to investigate the dose-response relationship for the antiarrhythmic effects of propranolol, and determined

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the plasma concentration and response at sequentially increasing dosages in patients with ventricular arrhythmias.

Materials and Methods

Thirty-two consenting patients (table 1) with chronic ventricular arrhythmias participated in this placebo-controlled evaluation. Eighteen of these patients were admitted to the Clinical Research Center of Vanderbilt University and had continuous electrocardiographic monitoring. Patients were selected for admission to the hospital for evaluation if they had a history of symptomatic ventricular arrhythmias (light-headedness, presyncope or syncope) or if they had not had prior in-patient evaluation of arrhythmia etiology and severity. All were ambulatory while in the hospital except for three patients with severe symptoms associated with VT who remained at bed rest during placebo therapy. Despite the limited activity these three patients each had 16–40 VEDs/min and short runs of VT throughout the baseline evaluation. A Hewlett-Packard Model 78100A telemetry system transmitted ECG signals to the hospital coronary care unit and also to an eight-channel tape recorder (15/16 inches/sec recording speed). On placebo days and on the second day of each dosage, 12 hours of ECG data (9:00 a.m. to 9:00 p.m.) were taped for computer analysis of arrhythmia frequency. All medications except cardiac glycosides or anticoagulants were discontinued on admission, and dietary sodium was controlled at 100 mEq daily.

Fourteen additional patients known to have stable chronic ventricular arrhythmias and without a history of symptomatic VT or angina pectoris were followed weekly in the out-patient clinic of the Clinical Research Center. Arrhythmia frequency was determined by computer analysis of ambulatory, 24-hour ECG tape recordings. Outpatients were given instructions for a 100 mEq sodium diet before beginning this study, but intake was not regulated or monitored. Compliance with drug therapy was monitored by weekly pill counts and all medications other than digitalis glycosides were discontinued during the study.

Patients

Patients with frequent VEDs (more than 500 in 12 hours) and relatively stable frequency were chosen for study. Patients who were free of VEDs for 30 consecutive minutes during control observations from 9 a.m. to 9 p.m. were excluded. No patients who were New York Heart Association functional class III or IV were included in this study. The following criteria were also used to exclude patients from this study: age less than 21 years or greater than 75 years; unstable concurrent illness; pregnancy (determined by history or urine test); arrhythmia due to digitalis excess, electrolyte disturbance, correctable blood gas abnormality or acute myocardial infarction; arrhythmia requiring acute therapy; "sick sinus syndrome"; ventricular preexcitation; atrial fibrillation or flutter; atrial

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*History of ventricular tachycardia (three or more consecutive ventricular ectopic depolarizations at a rate >100/min).
†History of resistance to two or more antiarrhythmic drugs before this study.

Abbreviations: IVA = idiopathic ventricular arrhythmia; HBP = hypertension; ASCVD = atherosclerotic coronary vascular disease; RVD = rheumatic valvular disease; PMV = prolapsing mitral valve syndrome; VT = ventricular tachycardia.

tachycardia; second-degree (or greater) atrioventricular block; myocardial infarction within 3 months; unstable angina; history of asthma; and serum urea nitrogen >30 mg%.

The 16 male and 16 female subjects are described in table 1. Five of the 32 patients had known coronary vascular disease and had a myocardial infarction 2 or more years before this study. Four patients had essential hypertension that did not exceed levels of 150/120.
mm Hg during placebo therapy. Five patients had prolapse of the posterior leaflet of the mitral valve on echocardiogram and no other identifiable causes for their arrhythmia. Seventeen patients were felt to have idiopathic ventricular arrhythmias after negative evaluations that included echocardiography and exercise test in all and coronary arteriography in two patients.

Medication

Initially, propranolol was purchased for this study as 40-mg and 80-mg tablets, and a similar but not identical placebo was supplied by Ayerst Laboratories. The last 10 patients studied received 40-mg propranolol tablets and identical placebo kindly supplied by Ayerst Laboratories, Inc.

Study Procedure

Inpatients

Patients in this study were admitted to the Clinical Research Center and any previous antiarrhythmic therapy was discontinued for at least 2 days (or more than four drug half-lives) or until symptomatic arrhythmias (rapid VT causing symptoms of light-headedness, presyncope or syncope) prompted initiation of therapy. Once the patient's arrhythmias were stable or required treatment, propranolol therapy was given every 6 hours in a total oral dosage of 80 mg/day. If antiarrhythmic efficacy was not seen after 48 hours, the daily dosage was increased sequentially to 160 mg, 320 mg, 480 mg, 640 mg, 800 mg, or to the point of efficacy, adverse effect or a maximum daily dose of 960 mg. Efficacy was defined as described below, comparing the number of VEDs in a 12-hour period (9 a.m. to 9 p.m.) on the second day of each dosage with that during predrug placebo therapy. Plasma samples were obtained at the end of the dosage interval on the second day of each dosage level for determination of propranolol concentration by a previously described, high-performance liquid chromatographic method.  

Plasma protein binding of propranolol was determined by equilibrium dialysis techniques described previously. After the dosing interval, propranolol was discontinued and an equal number of placebo tablets substituted. Placebo therapy was continued for 2-3 days until ectopic frequency returned to control level (± 20%) or until VT recurred, necessitating reinitiation of therapy. Four patients were excluded and their data are not presented because their arrhythmia failed to return during the final placebo period.

Outpatients

Patients with stable ventricular arrhythmias were seen weekly in the out-patient department. At each visit, patients were examined and a plasma sample was obtained 5-6 hours after a dose of either placebo or active drug. A 24-hour ambulatory ECG recording was obtained each week using Medcraft Accutape Holter-type recorders. These tapes were analyzed by a computerized system described below. After two clinic visits on placebo therapy, each patient's treatment was changed to active propranolol 80 mg/day taken in divided doses at 6-hour intervals. If antiarrhythmic efficacy was not seen at the end of one week, the daily dosage was increased to 160 mg, 320 mg, 480 mg, 640 mg, 800 mg, or to a maximum dosage of 960 mg/day. If efficacy was observed at any point, the previous dosage was continued for an additional week before the treatment was then converted to an equal number of placebo tablets for 2 weeks. If an adverse reaction or side effect occurred, propranolol was discontinued and an equal number of placebo tablets begun.

The occurrence of side effects was assessed in all patients by means of a questionnaire that was read to each patient by a nurse daily (inpatients) or weekly (outpatients). A positive response to any question was graded by the patient as either mild, moderate or intolerable.

Arrhythmia Detection and Analysis

A semiautomated arrhythmia detection and quantification system has been developed by the Division of Biomedical Engineering Services at Vanderbilt University. The system consists of a series of computer programs executed on a Digital Equipment Corporation PDP 11/40 Laboratory Computer. The accuracy of the computer system was verified by comparison of computer-generated counts of VEDs and runs of VT (three or more VEDs with rate >100/min) made from the recorded ECG with visual counts made by trained observers using paper records. Validation of this system showed that the computer correctly identified 614 ectopic depolarizations (99.8%) on a test tape containing 10,715 heart beats from patients in the Johns Hopkins Myocardial Infarct Research Unit. Thirty-five false positives (5.7%) and one false negative (0.16%) were detected. Each recording is verified during the analysis, as previously described.

Definition of Response and Statistical Analyses

Antiarrhythmic efficacy was determined by comparing hourly VED counts during the 12-24-hour placebo control period with the hourly counts for the same hours at each dosage. These were compared using the Wilcoxon rank-sum test; an unusually small p value (<0.005) was required for assignment of significant differences. Because small but consistent changes may have high degrees of statistical significance, assignment of drug response also required a >70% reduction in total VED counts.

Results

The characteristics of the 32 patients in this study are shown in table 1. Patients were selected to have stable arrhythmia frequency as expressed by the finding that in the control periods the 95% confidence limits for daily spontaneous variability was only


±16.3% for the group (based upon 80 days of data from 32 patients). Twenty-eight of 32 patients (88%) had 50–100% reduction in VED frequency as assessed by ambulatory monitoring. This reduction was highly significant (p < 0.005) when the hourly VED counts were compared by means of the Wilcoxon rank-sum test. Twenty-four patients (75%) had ≥70% suppression of VEDs (table 2); 10 of these patients had nearly complete (≥95%) arrhythmia suppression at maximal dosage. Arrhythmia returned after discontinuation of propranolol and reinstitution of placebo therapy in all cases (table 2).

Evidence that arrhythmia reduction is due to drug efficacy is seen in the dose-response curves for each patient (fig. 1). Of the 24 patients with >70% arrhythmia suppression, 20 received multiple doses enabling assessment of the dose-response relationship. Of these, 19 had a unidirectional dose-response curve, i.e., an increase in dosage was associated with a progressive decrease in arrhythmia frequency (fig. 1).

By interpolation from the individual dose-response curves, it was possible to estimate the plasma concentration required for 50% arrhythmia response (EC50). The EC50 for each patient ranged from 11–800 ng/ml (99.5 ± 37 ng/ml, mean ± SEM).

One patient with >70% suppression had a bidirectional dose-response curve, with marked suppression of arrhythmia (94%) at a dosage of 240 mg/day, demonstrated a loss of effect as the dose was increased above that level (fig. 2). In this patient, the suppression at the optimal dose level was reconfirmed on three occasions (p < 0.001 each time). Furthermore, the worsening of control with doses above that level was also confirmed on three occasions (p < 0.001). Four other patients who had a less marked reduction of VEDs at lower dosages of propranolol had an increase in arrhythmia frequency when the dosage was raised above that level. As shown in figure 2, the increased ectopy in these patients occurred at plasma concentrations >100 ng/ml. In each case, arrhythmia frequency returned to baseline (±20%) when therapy was discontinued. One patient (no. 28) did not have suppression of VEDs at any dosage, but developed increased ectopy and coupling of ectopic depolarizations during treatment with both 80 and 160 mg/day.

The range of plasma concentrations required to achieve >70% reduction in VED frequency is shown in figure 3. Response to therapy was observed over the range of plasma concentrations from 12–1100 ng/ml. Although the range for outpatients was narrower than
that for inpatients, there was no significant difference between the two.

Eleven of the 18 patients with a history of VT had multiple runs of VT (three or more successive VEDs) during this study. The dose-response curves for eight of these patients who had suppression of VT are shown in figure 4 and also are normalized to the lowest dosage that produced >70% suppression of VEDs. Three patients with frequent VT did not have VED or VT suppression at any dosage. Suppression of VT occurred at or below the dosage that produced a 70% decrease in VED frequency in all patients. Three of the patients continued to have paired VEDs (couplets). All eight patients had suppression of the symptoms of light-headedness, syncope or presyncope in conjunction with the complete suppression of the runs of three or more VEDs.

Although there was a general relationship between oral dosage and response (fig. 5), there was considerable interindividual variability in plasma level obtained from a given dose (fig. 6). Only 11 of 32 patients (34%) responded at a daily dosage ≤160 mg, while an additional 13 patients responded to a dosage >160 mg/day. The degree of plasma protein binding of propranolol was determined in the six patients who required plasma concentrations >200 ng/ml for efficacy and was found to be 90–95%, the range previously reported for propranolol.

The degree of maximal arrhythmia suppression for each patient is shown in table 2. When propranolol was discontinued, 21 patients who had responded had a return of their arrhythmia to a frequency that was ±20% of control levels (table 2). Three patients had a return of short runs of VT within several hours after discontinuing propranolol and restarting placebo therapy, and propranolol therapy had to be reinstituted before VED frequency could have been expected to return to baseline.

During propranolol therapy, none of the patients developed symptomatic hypotension or bradycardia, even though heart rate and blood pressure were reduced during therapy. When propranolol was discontinued, none of the patients had an increase in VED frequency, blood pressure or heart rate that was substantially higher than control, nor did they develop any symptoms other than those experienced during the initial placebo therapy.

Propranolol was relatively well tolerated; only one patient developed a severe adverse reaction. Patient 6, a heavy smoker (60 pack-years) who had no history of asthma or atopy, developed severe bronchospasm at a
dosage of 160 mg/day that required discontinuation of therapy. Seven patients developed fatigue during propranolol therapy; it was an intolerable symptom in five patients who required discontinuation of therapy.

Eighteen of the 24 patients responding during the dose-ranging portion of the study have continued on therapy with adequate control of their arrhythmias and without the occurrence of side effects necessitating discontinuation of therapy. Ten of these patients previously had documented VT. All 18 patients have been followed for 2–32 months (14.2 ± 10 months, mean ± sd). Patient 12 had excellent arrhythmia control for 6 months, but stopped taking her medication for personal reasons unrelated to any drug effects and died of her arrhythmia.

**Discussion**

As anticipated, there is no optimal dose of propranolol that suppresses ventricular arrhythmias in all patients. The wide variation in plasma propranolol concentrations at a given dosage is a factor known to influence the therapeutic response. This variability was again confirmed in this study by the five- to tenfold variation in plasma concentrations obtained even under conditions of hospital-assisted compliance. A second and equally important source of interindividual difference in the response to propranolol was the variation in the antiarrhythmic effect associated with a given plasma concentration. This may be a reflection of differences in the underlying electrophysiologic abnormality or due to the expression of more than one mechanism whereby arrhythmia is suppressed.

In previous studies of antiarrhythmic drugs, investigators have arbitrarily designated a level of VED suppression of 50, 70, 80 or 90% as a significant drug response.\(^\text{15-16}\) However, the importance of a certain level of suppression depends upon 1) the statistical probability that it is a true drug effect and not due to random variation in arrhythmia frequency, and 2) that the level is associated with a clinically significant drug effect (symptomatic improvement). Morganroth et al.\(^\text{19}\) described the degree of arrhythmia suppression necessary for assignment of drug efficacy when comparing data from a control ambulatory monitoring period with data from an equal period taken after initiation of drug therapy. These investigators caution that their criteria are only applicable for patients compared in this way and may not apply to patients with high arrhythmia frequency, because the spontaneous variation in arrhythmia frequency is less in the latter patients.

Patients with lower arrhythmia frequency and greater variability might be more (or less) responsive to propranolol than those in this study. However, no one has shown a relationship between arrhythmia frequency and responsiveness to drug therapy.

Requirements for entry into this study were such that spontaneous variability was minimized and enabled the use of > 70% VED suppression to designate drug efficacy. That this designation is a reflection of drug effect in this selected group of patients is supported in several ways:

1) Comparison of control hourly VED frequency with that at the dosages that produced ≥ 70% VED suppression was highly significant using a nonparametric statistical test felt to be an appropriate test for analysis of this type of data (Wilcoxon rank-sum test).\(^\text{18}\)

2) Patients in this study were selected to exclude low arrhythmia frequency, thereby reducing the
chance of spontaneous variation mimicking drug efficacy.  

3) Patients were treated with placebo after propranolol, and return of arrhythmia was required for designation of true drug efficacy.  

4) The presence of a dose-response relationship in the 20 patients requiring multiple dosages for arrhythmia suppression (fig. 1) supports the conclusion that the changes in arrhythmia frequency were due to propranolol.

The second and important consideration is the clinical significance of any reduction in arrhythmia frequency. Again, the selection of ≥70% reduction is supported by the fact that the dosage providing this level of VED suppression was effective in suppressing runs of VT (fig. 4) and controlling symptoms associated with their arrhythmia. The continued control of these patients during prolonged out-patient follow-up further supports the clinical significance of this level of arrhythmia suppression.

The higher level of efficacy in this study (75% response rate) was clearly related to a more individualized approach to dosage requirements; many patients were controlled at plasma concentrations above the range usually considered to produce high degrees of β-adrenoceptor blockade. For example, suppression of renin release and prevention of angina pectoris are pharmacologic effects of propranolol, whose dose-response curves are generally similar to the steep portion of the curve for suppression of exercise-induced tachycardia. All these effects have been attributed to the peripheral β-receptor blocking action of propranolol, and some information on effective plasma concentration is available. For example, Coltart and Shand found that 50% inhibition of exercise tachycardia occurred with about 30 ng/ml plasma propranolol and that almost maximal inhibition was produced by 100–150 ng/ml. Chidsey et al. found

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**Figure 4.** Individual dose-response curves for reduction of episodes of ventricular tachycardia (VT) (three or more consecutive ventricular ectopic depolarizations [VEDs] at a rate >100 beats/min). The ordinate is percent of control frequency of ventricular tachycardia vs dosage expressed as the percent of the dosage that produced ≥70% VED suppression for that patient.

**Figure 5.** Propranolol dose-response relationship: percent of patients with >70% arrhythmia suppression vs daily propranolol dosage.

**Figure 6.** Plasma propranolol concentration vs oral 6-hourly dosage during dose-ranging study in inpatients only.
that concentrations of 14 and 8 ng/ml were associated with 50% reduction in renin levels and exercise-induced tachycardia, respectively. They also showed that the plasma concentration-response curve for reduction in anginal attacks and exercise heart rate were superimposable. In their experience, almost maximal suppression of renin, exercise heart rate and anginal attacks occurred at levels of about 100 ng/ml. Because the relationship between plasma level and β blockade is known to be reproducible between individuals, it was not deemed appropriate to evaluate β blockade with isoproterenol testing or suppression of maximum exercise tachycardia in this group of patients with VT. The plasma concentrations associated with suppression of VEDs were clearly higher than those cited for a very high level of β blockade. In 21 of the 24 responding patients, sufficient data were available to estimate the plasma propranolol concentration present at 50% arrhythmia suppression. This was found to range from 11 to 800 ng/ml (99 ± 37 ng/ml, mean ± SEM) and is clearly higher and far more variable than that producing 50% of maximal β blockade. The plasma concentrations associated with favorable response (>70% suppression of VEDs) were higher than 100 ng/ml in nine of 24 responders. These measurements were made at the end of the dosing interval and represent the lowest concentration rather than the average therapeutic concentrations through the 24 hours.

The high plasma concentration required in some patients raises the possibility that a mechanism of action other than, or in addition to, β blockade may contribute to arrhythmia suppression in these patients. By analogy, propranolol exerts a further antihypertensive effect as the dosage is increased above that required for maximal suppression of β-adrenoceptor-mediated release of renin.

Even though many of the patients required a relatively high dosage of propranolol, most patients have been able to remain on propranolol as outpatients with chronic suppression of their arrhythmia, indicating that the clinical efficacy of propranolol is associated with reasonably high level of acceptability by patients. The relatively high level of patient acceptance in this group reflects, in part, the exclusion from this study of patients with overt cardiac failure and asthma. These patients had chronic, stable arrhythmias, and the findings in this study should not be construed as evidence that intravenous propranolol is indicated for conversion of VT; other drugs or electrical conversion are much safer and more effective for this purpose. In fact, most would consider the intravenous administration of propranolol to be contraindicated in patients with persistent VT. Rather, propranolol should be considered for chronic suppression of ventricular arrhythmias in patients who do not have overt congestive heart failure, asthma or chronic obstructive pulmonary disease.

The dosage of propranolol should be individualized for each patient. The biphasic nature of the dose-response curves of some patients dictates that propranolol cannot be dose-ranged casually. The dose-response curve must be precisely assessed at higher plasma concentrations. A logical approach based upon the results in this study would be titration up to 160 mg/day, the dose below which none of the patients exhibited recrudescence of their arrhythmia. In patients in whom the therapeutic effect has been inadequate, plasma-level determination could be used as a guide to dose-ranging up to plasma levels of approximately 100 ng/ml. At higher plasma levels, the dose-response relationship should be carefully evaluated by means of quantitative analysis of arrhythmia frequency over several hours of monitoring to insure that the arrhythmia is not increasing at these higher dosages. Such quantification is only feasible through computerized analysis of ambulatory ECG data.

The overall results in this study with propranolol have implications that can be extended to the evaluation and clinical use of any antiarrhythmic drug. Dose-ranging with quantification of arrhythmia suppression at each level together with assessment of plasma concentration is likely to be the optimal approach to the use of antiarrhythmic drugs.

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