Polymorphism of propafenone metabolism and disposition in man: clinical and pharmacokinetic consequences

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ABSTRACT The relationship between debrisoquine metabolic phenotype and the pharmacokinetics and pharmacodynamics of propafenone was studied in 28 patients with chronic ventricular arrhythmias (22 extensive metabolizers [EMs] and six poor metabolizers [PMs] of debrisoquine). EMs were characterized by a shorter propafenone elimination half-life (5.5 ± 2.1 vs 17.2 ± 8.0, $p < .001$), lower average plasma concentration (Cp) (1.1 ± 0.6 vs 2.5 ± 0.5 ng/ml/mg daily dosage, $p < .001$), and higher oral clearance (1115 ± 1238 vs 264 ± 48 ml/min, $p < .001$). The active metabolite 5-hydroxypropafenone, assayed in 12 patients, was identified in nine of 10 EMs but in neither of the PMs. A lower incidence of central nervous system side effects was noted in EMs (14% vs 67%, $p < .01$). The magnitude of QRS widening at any given propafenone Cp was greater in EMs than PMs. There was no significant difference between EMs and PMs in effective propafenone dose or frequency of antiarrhythmic response. Inhibition of debrisoquine 4-hydroxylation by propafenone was demonstrated both in vivo and in a human liver microsomal system in vitro. We conclude that propafenone is metabolized via the same cytochrome P-450 responsible for debrisoquine's 4-hydroxylation, and that its pharmacokinetics and concentration-response relationships and the incidence of central nervous system side effects are different in patients of different debrisoquine metabolic phenotype.
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THE ANTIARRHYTHMIC AGENT propafenone is a fast sodium-channel blocker with weak β-adrenoceptor–blocking activity and demonstrated efficacy in the treatment of a variety of ventricular and supraventricular cardiac arrhythmias.[1-9] Early studies in a small number of normal volunteers and patients have shown marked interindividual variability in elimination half-life, a wide range of effective plasma concentrations, and nonlinear presystemic clearance.[1, 2, 10, 11] Early in our clinical experience with propafenone we found that one patient, known to be a poor metabolizer of the polymorphically metabolized antihypertensive debrisoquine, exhibited an unusually long propafenone elimination half-life and high propafenone plasma concentrations. We therefore postulated that propafenone is metabolized by an hepatic oxidative pathway that is characterized by the debrisoquine metabolic phenotype. The purposes of this study were to determine in vitro and in vivo the metabolic relationships between debrisoquine and propafenone and to assess the effect of debrisoquine metabolic phenotype, not only on pharmacokinetics, but also on clinical response, concentration-response relationships, and toxicity of propafenone.

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Methods

Patient selection. Patients were eligible for the study if they were between 21 and 75 years old and had more than 30 ventricular ectopic depolarizations (VEDs) per hour. Antiarrhythmic therapy was indicated for treatment of arrhythmias symptomatic with syncope, near-syncope, dizziness, fatigue, or palpitations. Patients with hemodynamically unstable sustained ventricular tachycardia or a history of sudden cardiac death were excluded, as were patients with second- or third-degree heart block, severe congestive heart failure (functional class IV of the New York Heart Association), hepatic or renal insufficiency, or terminal illness.

Determination of debrisoquine phenotype. Debrisoquine phenotype was determined by analysis of urinary excretion of debrisoquine and its major metabolite, 4-hydroxydebrisoquine.[12, 13] A single 10 mg oral dose of debrisoquine was given

at least 2 hr after a meal, and no food was given for the next 4 hr. Urine was collected for 8 hr after the dose and concentrations of debrisoquine and 4-hydroxydebrisoquine were determined by gas-liquid chromatography.[14] Metabolic ratio (debrisoquine/4-hydroxydebrisoquine) was calculated and patients were phenotyped as extensive metabolizers (EMs) or poor metabolizers (PMs) based on metabolic ratios of 12.6 or less or greater than 12.6, respectively.[12] Debrisoquine 4-hydroxylation was also characterized by the fractional excretion of 4-hydroxydebrisoquine (FE_{HDb}, 4-hydroxydebrisoquine/[debrisoquine + 4-hydroxydebrisoquine]),[15] with FE_{HDb} of 0.08 or greater and less than 0.08 for EM and PM, respectively. All debrisoquine phenotype studies were performed at least 2 days before or after the administration of propafenone.

The effect of chronic long-term administration of propafenone on debrisoquine metabolism was assessed in nine patients. Debrisoquine was administered to these patients on two occasions: without propafenone and when a steady-state concentration of propafenone had been reached.

Pharmocokinetic and pharmacodynamic study design. Patients were admitted to the Coronary Care Unit or Clinical Research Center Arrhythmia Monitoring Unit of Vanderbilt University Medical Center, and antiarrhythmic agents and β-adrenoceptor blockers were discontinued at least five half-lives before they entered the study. Patients receiving other drugs before the study continued these medications without change in dosage during the course of the study. Patients were excluded if within 2 weeks of the study they had received drugs known to alter hepatic metabolism, such as phenytoin, phenobarbital, and rifampin, or agents known to alter the electrocardiogram, such as tricyclic antidepressants.

After a 2 day placebo baseline period, a dose-titration phase was begun during which patients received 300 mg propafenone hydrochloride every 12 hr, increased to 300 mg every 8 hr after 2 to 3 days if necessary for achievement of satisfactory antiarrhythmic response. After 3 days at the highest dosage, a final morning dose was given and serial blood samples were obtained for analysis as described below.

Electrocardiographic analysis. Predose 12-lead electrocardiograms (ECGs) were recorded at 25 mm/sec, and cycle length, PR interval, QRS duration, and QT interval were recorded as those that were the longest measured in the limb leads. QT corrected for heart rate, QTc, was calculated by Bazett's formula.[16]

Determination of antiarrhythmic efficacy. Ambulatory electrocardiographic recordings were analyzed by a user-interactive template-matching computer system previously validated at our institution.[17] Arrhythmia suppression was defined as greater than 70% reduction in the frequency of VEDs on a 24 hr ambulatory ECG during dose-ranging as compared with the frequency during the placebo period.

Propafenone plasma concentrations. Blood samples for determination of plasma concentration of propafenone were obtained before the morning dose on the final day at each dosage and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, and 36 hr after the final dose of propafenone. Plasma concentrations of propafenone were determined by high-performance liquid chromatography.[18] Propafenone elimination half-life was determined by linear regression analysis of the log concentration-time curve beginning at the time of maximum concentration. Area under concentration-time curve during a dosing interval (AUC_τ) was determined by the trapezoidal rule. Average dosage interval plasma concentration was determined as AUC_τ/τ. Apparent oral clearance was defined as dose of propafenone base per dosing interval divided by AUC_τ.

5-Hydroxypropafenone determination. The metabolite 5-hydroxypropafenone was assayed by reverse-phase HPLC as described for propafenone, with a modification in the first plasma extraction step as follows. Two hundred fifty nanograms of internal standard (2-(2'-hydroxy-3'-ethylamino-propoxy)-phenyl-5-hydroxypropiophenone hydrochloride) was added to an aliquot of 0.5 ml plasma, which was then adjusted to pH 9 with 0.1N NaOH. Ethyl acetate (2.0 ml) was added, and each tube was mixed 10 min in a tilting shaker and then centrifuged for 10 min. The organic phase was transferred to a clean conical tube, and phosphoric acid extraction and HPLC assay were performed as previously described.[18]

Control samples were prepared by addition of known amounts of freshly prepared aqueous solutions of propafenone, 5-hydroxypropafenone, and internal standard to 0.5 ml heparinized drug-free human plasma. Minimum detectable quantities of propafenone and 5-hydroxypropafenone were 25 ng for each. The curve was linear over the range of 25 to 1600 ng (50 to 3200 ng/ml using 0.5 ml plasma aliquots) for both propafenone and 5-hydroxypropafenone. Recoveries of propafenone and 5-hydroxypropafenone by this extraction procedure were 88% and 75%, respectively. Propafenone, 5-hydroxypropafenone, and internal standard used in this assay were provided by Knoll Pharmaceutical Company, Whippany, NJ.

Assay of debrisoquine 4-hydroxylase inhibition in vitro. Human liver specimens were obtained from victims of accidental death and microsomes were prepared as previously described.[19–21] A mixture comprised of 50 nM microsomal cytochrome P-450, 0.05 mM Tris-HCl buffer (pH 7.4), 0.1M sodium phosphate buffer (pH 7.4), 0.6 mM NADP, 1 unit glucose-6-phosphate dehydrogenase, 0.05 to 1.0 mM debrisoquine hemisulfate, and inhibitor (0.002 to 0.06 mM propafenone hydrochloride or 0.0625-0.25 mM sparteine sulfate) was preincubated 2 min, and then the reaction was begun by addition of glucose-6-phosphate (final concentration 10 mM). Reaction volume was 1.0 ml. Incubation and analysis of 4-hydroxydebrisoquine were performed as previously described.[22] Relationships of reaction velocity (v) and concentrations of substrate (debrisoquine) and inhibitor (propafenone) were assessed graphically by standard plotting techniques as previously described,[22] and maximum velocity (V_{max}), K_m and K_i were derived from the slopes and points of intersection of the Lineweaver-Burk plot.

Statistical analysis. Propafenone concentration-response correlations were quantified by linear regression analysis. Electrocardiogram intervals and VED frequency at different dosages during therapy were compared with baseline values by use of a two-tailed paired t test. Because of nonnormal distribution, the relationships between propafenone pharmacokinetic parameters and debrisoquine metabolic phenotype were analyzed with the Wilcoxon rank-sum test for unpaired data. The relationship of metabolic phenotype to response and adverse effects was assessed with Fisher's exact test, and that of phenotype to age was determined with an unpaired t test. Data are presented as the mean ± SD.

Results

Patient population. Twenty-eight patients, eight women and 20 men, participated in the study. Ages ranged from 35 to 73 years (mean 57). Diagnoses were ischemic heart disease (15 patients), congestive cardiomyopathy (four patients), hypertensive heart disease (two patients), mitral valve prolapse (three patients), and primary ventricular arrhythmias (four patients).

Debrisoquine phenotype. Twenty-two patients were

EMs and six were PMs. There was no significant difference between the EM and PM groups in age (57 ± 10 vs 58 ± 11 years) or sex (16/22 vs 4/6 male).

Pharmacokinetic analysis. Pharmacokinetic data were obtained from 27 patients and are presented in figure 1. EMs of debrisoquine had significantly shorter elimination half-lives, lower dose-corrected propafenone plasma concentrations, and higher oral clearance than did PMs ($p < .001$).

The correlation between dosage and predose plasma concentration was assessed in patients (13 EMs and four PMs) for whom plasma concentrations at both the 600 mg/day and 900 mg/day doses were available (figure 2). As a group, EMs showed a disproportionate rise in plasma concentration, with a 244 ± 201% rise after the 50% increase in dose. In contrast, the concentration of propafenone rose proportionally in PMs, with a mean 52 ± 23% increase in plasma concentration after the 50% increase in dose.

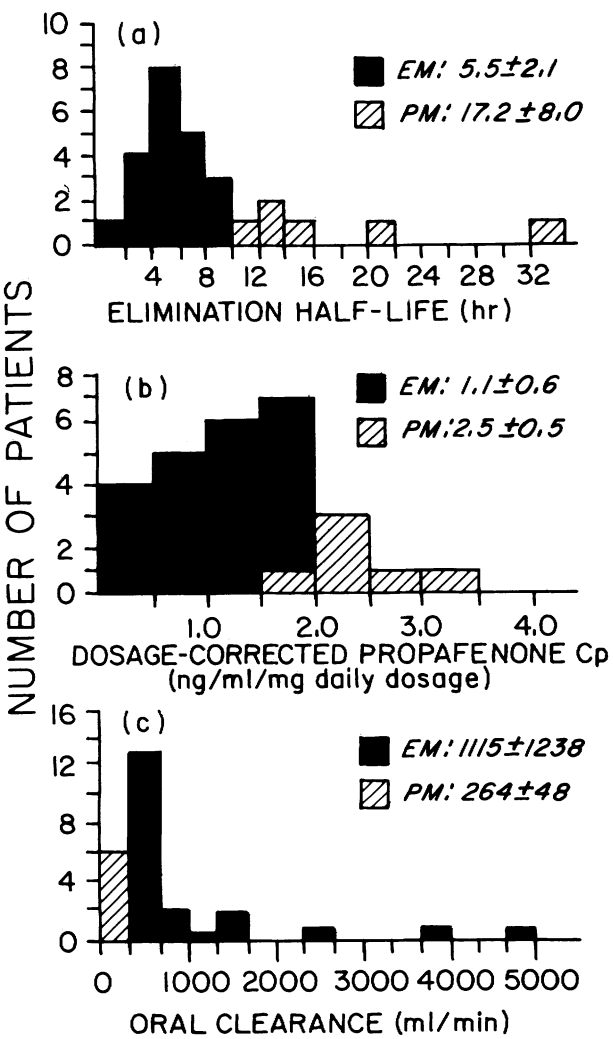

FIGURE 1. Pharmacokinetics of propafenone related to debrisoquine metabolic phenotype.

5-Hydroxypropafenone concentrations. Simultaneous trough plasma concentrations of propafenone and 5-hydroxypropafenone at the final dose were determined in 12 patients (10 EMs and two PMs). Trough plasma concentrations of 5-hydroxypropafenone (not normalized for propafenone dose) ranged from 30 to 513 ng/ml (mean 236 ± 154) in those EMs (nine of 10 patients) with simultaneous plasma concentrations of propafenone of greater than 50 ng/ml. In contrast, the metabolite was not detected in either PM, despite high plasma concentration of propafenone in both patients (1688 and 1484 ng/ml, respectively).

Antiarrhythmic efficacy. Arrhythmia suppression was achieved in 16 of 22 EMs and four of six PMs (difference not significant). There was no significant difference in effective dose in the EM (828 ± 131 mg/day) as compared with the PM group (800 ± 155 mg/day).

Electrocardiographic changes. PR, QRS, and QTc intervals were increased at the highest propafenone dose as compared with those at baseline ($p < .05$), but JTc interval (QTc minus QRS duration) and resting heart rate were not significantly changed. There were no significant differences in the magnitude of change in electrocardiographic intervals in PMs and EMs.

Concentration-response relationships. The predose plasma propafenone concentrations at which more than 70% suppression of VEDs was achieved in responders ranged from 42 to 1801 ng/ml (figure 3). This range could be divided into two groups on the basis of debrisoquine metabolic phenotype: 42 to 1356 (mean 334 ± 131) ng/ml for EMs and 1408 to 1801 (1579 ± 172) ng/ml for PMs ($p < .002$).

For the group of patients as a whole, there was no significant correlation between propafenone concentration and change in QRS intervals (figure 4, *a*). However, when these data were analyzed as a function of metabolic phenotype, there was a good correlation for EMs ($r = .74$, $p < .001$), with PMs demonstrating a smaller change in QRS at a given propafenone concentration (figure 4, *b*).

Adverse effects. Central nervous system side effects, including visual blurring, dizziness, and paresthesias, were noted in seven patients. These side effects were in most cases associated with predose plasma propafenone concentrations of 900 ng/ml or more (figure 3). Predose propafenone concentrations were significantly higher in patients with these central nervous system side effects (1460 ± 749 ng/ml) than in patients without such adverse effects (451 ± 517 ng/ml, $p < .002$). The incidence of central nervous system side effects in PMs, 67%, was significantly greater than that in EMs, 14% ($p < .01$).

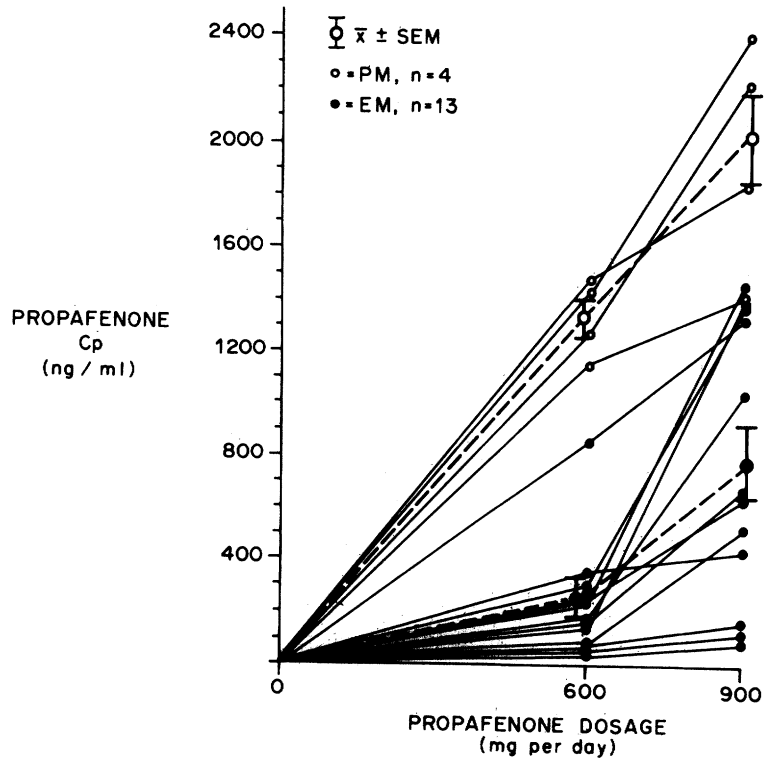

FIGURE 2. Relationship of daily propafenone dose to trough plasma concentration (Cp). Note that the increase in plasma concentration is disproportional to dose for EMs, but proportional for PMs.

Propafenone was discontinued in five patients, three EMs and two PMs, because of adverse effects. The reasons for discontinuation, debrisoquine phenotypes, and trough propafenone concentrations were as follows: acute psychosis (EM, plasma concentration 57 ng/ml), aggravation of arrhythmia with a 14-fold increase in VED frequency (EM, plasma concentration 434 ng/ml), worsening bronchospasm in a patient with chronic obstructive lung disease (EM, plasma concentration 1386 ng/ml), second-degree atrioventricular

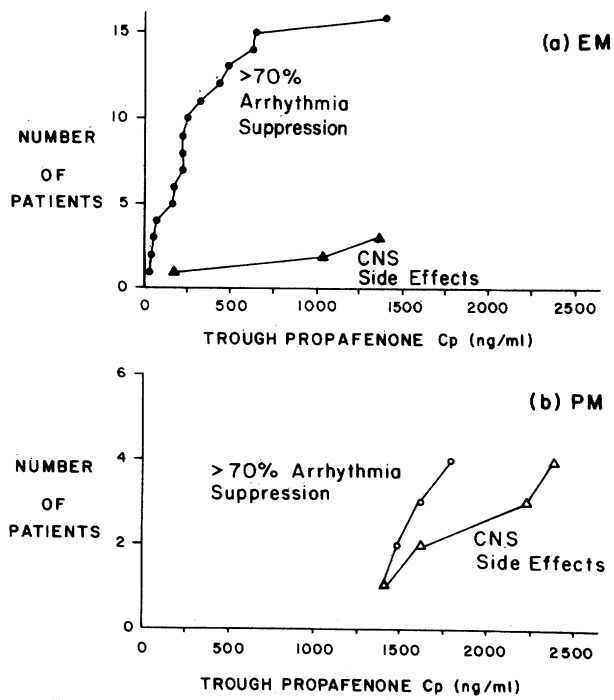

FIGURE 3. Predose plasma concentration of propafenone vs cumulative frequency of antiarrhythmic response and central nervous system side effects (excluding psychosis).

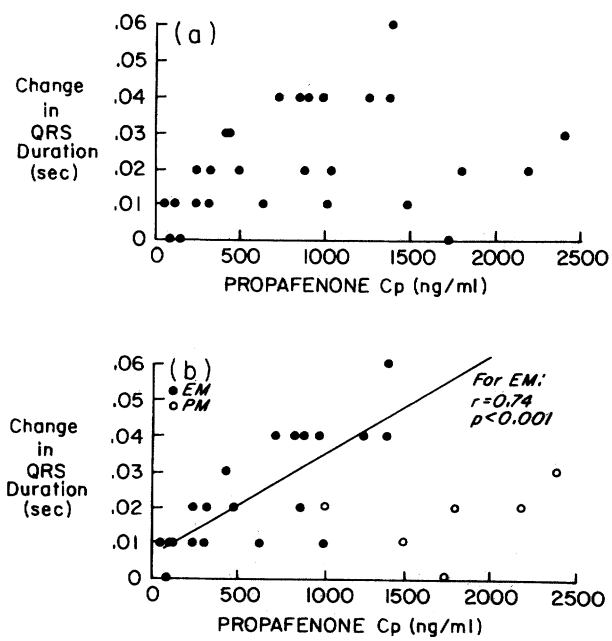

FIGURE 4. Change in QRS duration as a function of plasma concentration of propafenone. *a*, Data for all patients; *b*, data for PMs (closed circles) and EMs (open circles), with linear regression fit for EMs. Cp = plasma concentration of propafenone.

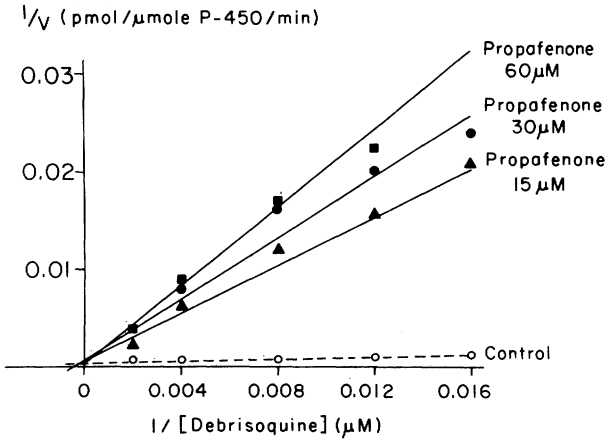

FIGURE 5. Lineweaver-Burk plot of debrisoquine 4-hydroxylation in the presence of 0 to 60 μM concentrations of propafenone.

block with 2:1 conduction during concomitant therapy with verapamil and digoxin (PM, plasma concentration 2398 ng/ml), and intolerable lip paresthesia (PM, plasma concentration 2228 ng/ml).

Inhibition of debrisoquine 4-hydroxylation in vitro and in vivo. The Lineweaver-Burk plot of data from the assay in vitro (figure 5) was consistent with competitive inhibition of debrisoquine 4-hydroxylation by propafenone, with estimated K_m, V_{max}, and K_i of 86 mM, 1544 pmol/μmol P-450/min, and 0.7 μM, respectively.

Results of the study in vivo are shown in figure 6. Of the nine patients, six were EMs and three were PMs. In EMs FE_{HDb} was significantly reduced, from 0.34 ± 0.31 with debrisoquine alone to 0.08 ± 0.10 in the presence of propafenone ($p < .05$). This reduction would have led to erroneous phenotyping of four of the six EMs as PMs had determination of phenotype been performed during administration of propafenone. There was no significant change in FE_{HDb} during administration of propafenone in PMs. Similarly, metabolic ratio was increased during propafenone in all EMs but was not significantly altered in PMs.

Discussion

We have demonstrated that propafenone is a potent inhibitor of debrisoquine 4-hydroxylation in vitro and in vivo. Also, we have shown that patients can be divided on the basis of debrisoquine metabolic phenotype into groups of "extensive propafenone metabolizers," characterized by a relatively short elimination half-life, low plasma concentration, high oral clearance, disproportional dose-concentration relationship, and detectable quantities of the metabolite 5-hydroxypropafenone, and "poor propafenone metabolizers," characterized by a long elimination half-life, high plasma concentration, low oral clearance, proportional dose-concentration relationship, and absence of detectable 5-hydroxypropafenone. These findings support our hypothesis that propafenone and debrisoquine are metabolized by the same hepatic cytochrome P-450 isozyme(s). The debrisoquine PM phenotype is an autosomal recessive trait[12, 13, 23] present in approximately 7% to 9% of the British, Swedish, and American populations.[23–25] Based on our data, one would expect similar portions of these populations to be poor metabolizers of propafenone.

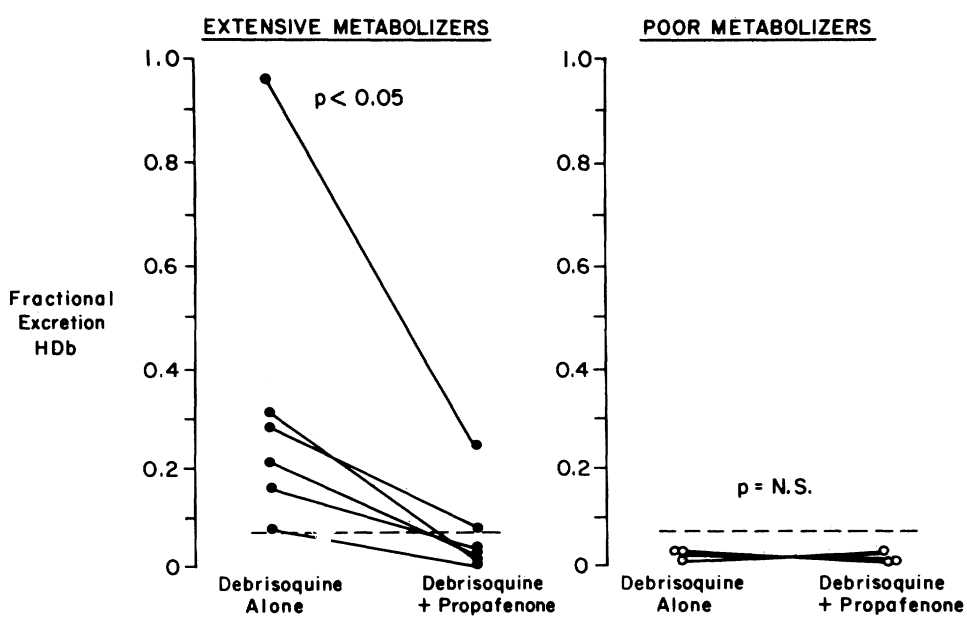

FIGURE 6. Fractional excretion of HDb in patients before and during administration of propafenone. FE_{HDb} is markedly reduced by propafenone in EMs, but is not altered in PMs.

There are several clinical implications of our findings. The first is that PMs should have higher plasma propafenone concentrations than the majority of the population. We have shown that PMs are at increased risk of developing central nervous system side effects while receiving propafenone, presumably due to the high plasma propafenone concentrations achieved in these patients. Also, the high propafenone concentrations attained in PMs might be expected to lead to clinically evident β-blockade. Although the β-adrenergic–blocking potency of propafenone is only one-fortieth that of propranolol in man,[1] plasma concentrations of propafenone of 2000 ng/ml in PMs are 20 to 100 times the β-blocking concentrations of propranolol (20 to 100 ng/ml).[26] The worsening of bronchospasm in one patient with a plasma propafenone concentration of 1386 ng/ml may have been via this mechanism. A systematic evaluation of β-adrenoceptor antagonism during administration of propafenone will be required to answer this question.

A second point of clinical importance is that the concentration of the metabolite 5-hydroxypropafenone in PMs is much lower (undetectable) than that in EMs. This metabolite has been shown in animal studies and those in vitro to possess antiarrhythmic and β-blocking potency similar to that of propafenone.[27, 28] The concentration-response relationships for arrhythmia suppression and electrocardiographic changes are disparate in patients of different metabolic phenotypes, possibly due to variability in concentrations of 5-hydroxypropafenone and perhaps other unmeasured active metabolites.

A third clinical implication of our findings is that monitoring of plasma concentrations of propafenone may be clinically useful for the prediction of central nervous system side effects. Because of the variability in concentration-response relationships in patients of different metabolic phenotypes, plasma concentrations of the drug will be of limited usefulness in predicting efficacy or electrophysiologic changes in a group of patients of unknown phenotype. Determination of metabolic phenotype before treatment might allow better use of propafenone levels. Based on our data, this determination of phenotype might be made preliminarily by either measurement of plasma concentration (all patients with dose-corrected plasma concentrations >2 ng/ml/mg daily propafenone dosage were PMs) or by measurement of plasma 5-hydroxypropafenone (not detected in our PMs). Before firm therapeutic recommendations based on plasma concentrations of propafenone or metabolic phenotype can be made, better definition of the role of active metabolites in the therapeutic and adverse effects of propafenone and further experience with a larger number of patients will be required.

A fourth clinical implication of our data is that the time to steady-state, and hence of the optimal intervals at which efficacy can be assessed and dosage adjustments made, will vary in patients of different phenotypes. For EMs, approximately 24 to 30 hr is required to reach steady-state plasma concentrations of propafenone, while 72 hr or more is required for PMs. It would seem prudent to institute increases in dose at least 72 hr apart to avoid unexpected accumulation of propafenone or metabolites.

A final implication of polymorphic metabolism is that the dose of propafenone should be increased in relatively small increments (i.e., ≤50% at each increase) because of the disproportionately large rise in plasma concentration of this drug as dose is increased. This nonlinear relationship between dose and plasma concentration is likely due to saturation of the involved cytochrome P-450 isozyme(s).

Based on our results in this relatively small group of patients, we conclude that metabolic phenotype is important in the toxicity of propafenone, but its importance with respect to the electrophysiologic effects of the drug is unclear. It is possible that at the high plasma concentrations achieved in PMs, clinically important β-adrenergic blockade will be observed that could contribute to both adverse reactions and antiarrhythmic efficacy. However, no significant reduction in resting heart rate was noted in our small group of PMs. Also, in our group of relatively stable patients, no difference in antiarrhythmic response rate of EMs and PMs could be demonstrated and there was no clear difference in the frequency of serious adverse effects, such as a proarrhythmic effect, in the two groups. Further study in patients with ventricular tachycardia or sudden cardiac death will be required to answer these questions about overall efficacy and toxicity of propafenone in a more clinically relevant population.

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