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Influence of Genetic Polymorphism on the Metabolism and Disposition of Encainide in Man[1]

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ABSTRACT

The metabolism of the new, highly effective antiarrhythmic agent, encainide, appears to be polymorphically distributed in a similar fashion to the genetically determined oxidative biotransformation of debrisoquine. Accordingly, the disposition of encainide and known metabolites was investigated after simultaneous acute i.v. (radiolabeled) and single and multiple oral (nonradiolabeled) dosing to two groups of normal subjects characterized as "poor" (PM) and "extensive" (EM) metabolizers of debrisoquine. Pronounced differences in both the plasma concentration/time curves and the 24-hr urinary excretion of encainide and metabolites were observed between the two phenotypes. In the EM group, the oral bioavailability of encainide was only about 25 to 30% because of extensive presystemic (first-pass) metabolism, and no accumulation occurred after multiple oral dosing with 50 mg every 8 hr for 3 days, as the elimination half-life of the drug was about 2.5 hr. The major metabolite formed was O-desmethylencainide which accounted for almost half of the identified urinary metabolites and represented about 10% of the administered dose. This metabolite was present in 5- to 10-fold higher concentrations in the plasma than unchanged drug and accumulated almost 2-fold after multiple oral dosing. 3-Methoxy-O-desmethylencainide also was present at higher concentrations than encainide and accumulated on multiple dosing similarly to O-desmethylencainide. N,O-didesmethylencainide was a minor metabolite only detectable in the urine and N-desmethylencainide was not measurable in either plasma or urine. In contrast, in the PM group, encainide plasma concentrations were 10- to 20-fold higher than in the EMs after both oral and i.v. administration and the elimination half-life was 3- to 4-fold longer. Only a small first-pass effect was present after oral dosing and significant accumulation of unchanged drug occurred after multiple oral administration. These pronounced differences were caused by an impaired ability to metabolize encainide as almost 40% of unchanged drug was excreted in the urine compared with only 5% in the EM group. O-desmethylencainide formation in particular was affected such that its plasma concentrations were at the most one-tenth those of parent drug after a single dose and one-fifth after multiple dosing. In addition, its urinary recovery was only about 3% compared with approximately 10% in the EM group. Particularly noteworthy was the fact that no 3-methoxy-O-desmethylencainide was apparently formed in PMs; instead, N-desmethylencainide was present in both the plasma and urine in significant amounts and accumulation occurred during multiple oral dosing. The differences in metabolism and disposition had significant pharmacodynamic consequences. In the PM group no changes in the EKG were observed during multiple dosing; however, in six of the eight EM subjects the QRS interval increased from 18 to 58% compared wtih its base-line value. This is consistent with reports showing the metabolites of encainide having cardiovascular activity equal or greater than the parent drug. These findings show the pronounced differences in the metabolism of encainide and pharmacological response that are present in deficient metabolizers. The incidence of this genetically determined trait is about 8 to 10% in American Caucasians and it affects the oxidative metabolism of a large number of drugs other than encainide. This would suggest that knowledge of a phenotype of an individual with regard to this and other separately inherited traits may have therapeutic and investigative potential.

Variability in drug responsiveness between individuals is well established and the often important role played by differences in drug metabolism has been the focus of numerous studies. In general, such differences are considered to arise from environmental factors, including concomitant drug use, and disease-states interacting with the genetic characteristics of an individual. While a plethora of studies have demonstrated the importance of the environmental and disease-state factors, only limited investigation has been made of the role of genetic constitution in determining drug metabolizing ability. A major reason for this is that it has appeared that most drug metabo-

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ABBREVIATIONS: EM, extensive metabolizers; PM, poor metabolizers; ODE, O-desmethylencainide; MODE, 3-methoxy-O-desmethylencainide; NDE, N-desmethylencainide; DDE, N-O-didesmethylencainide; AUC, area under the curve.

lism pathways are determined by several genes and such control results in a continuous (unimodal) distribution of the process, which is difficult to investigate except by twin studies (Vesell, 1975). An exception to this is the ability to N-acetylate certain arylamines, a process controlled by two alleles at a single gene locus that are inherited in a classical Mendelian fashion (Weber, 1973). Similar discontinuous traits also occur in the hydrolysis of paraoxon (Playfer *et al.*, 1976) and succinylcholine (Kalow and Staron, 1977).

Recently, the polymorphism of certain oxidative pathways of drug metabolism has been shown to be more common than previously considered. For example, the formation of the alicyclic 4-hydroxy metabolite of the antihypertensive, debrisoquine, is characterized by two distinct phenotypes, EM and PM (Mahgoub *et al.*, 1977; Tucker *et al.*, 1977). The deficient trait is inherited as an autosomal Mendelian recessive character (Price-Evans *et al.*, 1980) and the EM phenotype represents both the homozygous dominant and the heterozygous genotypes. In the British Caucasian population the frequency of the deficiency is about 8 to 9% (Price-Evans *et al.*, 1980) and a similar incidence appears to be present in American Caucasians (Aslanian *et al.*, 1983); however, considerable interethnic variability is present (Kalow, 1982). An increasing number of other drug oxidations has now been shown to cosegregate with the defect in debrisoquine 4-hydroxylase activity including those of sparteine (Eichelbaum *et al.*, 1982), perhexilene (Shah *et al.*, 1982), nortriptyline (Mellström *et al.*, 1981) and some *beta* adrenergic blocking agents (Dayer *et al.*, 1982; Lennard *et al.*, 1982; Alvan *et al.*, 1982).

During initial clinical studies with the investigational antiarrhythmic agent, encainide, 1 of 11 patients did not respond to therapy and was found to have a prolonged elimination half-life of parent drug and a reduced ability to form the pharmacologically active metabolite, ODE (Roden *et al.*, 1980). A subsequent family study suggested that the defect had a genetic basis and that it was associated with the impaired ability to 4-hydroxylate debrisoquine (Woosley *et al.*, 1981). The present study was, therefore, designed to determine the disposition of encainide and its metabolites in normal subjects of known oxidative phenotype with respect to debrisoquine 4-hydroxylation and to assess the pharmacological consequences of any differences.

Methods

Twelve healthy male subjects who had no abnormalities on routine physical examination, history, EKG, laboratory blood and urine tests were studied. Each individual had previously been phenotyped for his ability to 4-hydroxylate debrisoquine using the 8-hr urinary "metabolic ratio" procedure described by Mahgoub *et al.* (1977). Eight of the subjects were EM (age, 24–40 yr; weight, 50–83 kg), whereas the remaining four (age, 21–35 yr; weight, 61–85 kg) were determined to be PM. No drugs, including alcohol, were administered for at least 2 weeks before and during the study.

Subjects were placed on continuous telemetric electrocardiographic monitoring throughout the study beginning on the evening before drug administration. Electrocardiographic intervals were measured from a single EKG lead which was oriented to match the longest intervals as measured from the base-line vector cardiogram.

After an overnight fast, approximately 10.7 mg of [*carbonyl*-^{14}C] encainide hydrochloride (Amersham, Arlington Heights, IL; specific activity, 1.97 mCi/mmol; purity >99%) was administered into a forearm vein over 10 min using a constant rate infusion pump (0.5 ml/min). The actual amount of drug administered was calculated by weighing the syringe before and after the infusion. At the end of the infusion, 50 mg of encainide hydrochloride was administered orally and no food was permitted for the subsequent 2 hr. Blood samples were obtained at 10, 20, 30, 45 and 60 min and 2, 3, 4, 5, 6, 8, 11 and 14 hr after the oral dose *via* an indwelling cannula in the contralateral arm, kept patent by a dextrose infusion. The blood was placed into all-glass centrifuge tubes containing heparin (40 U) and the plasma was promptly separated and stored at −20°C until analyzed. Starting 24 hr after the initial oral dose, the subjects received 50 mg of encainide hydrochloride orally every 8 hr. The seventh such dose was administered after an overnight fast and a 10-min i.v. infusion of radiolabeled drug was given as at the beginning of the study. Blood samples were collected during the subsequent 24 hr as described above. Urine collections were made daily throughout the study and stored at −20°C until analyzed.

Encainide{4-methoxy-[2′-(N-methyl-2-piperidyl)ethyl]benzanilide} and its metabolites (fig. 1), ODE, MODE, NDE and DDE were determined in plasma and urine by high-performance liquid chromatography after extraction (Mead Johnson Pharmaceuticals Division, Evansville, IN, personal communication). Briefly, this consisted of the addition of 0.8 ml of 0.5 M Tris-HCl buffer (pH 8.5) and 2 ml of distilled water to 4 ml of plasma, and then extraction by shaking with 40 ml of 5% isopropanol in *n*-butyl chloride. For urine, all volumes were reduced to one-fourth and 2 M Tris-HCl buffer was used to adjust the pH to 8.5. After centrifuging, the organic layer (36 ml) was transferred to a conical glass tube and evaporated to dryness under nitrogen at 40°C. The residue was then reconstituted with 100 μl of ethanol and an aliquot injected into the chromatograph. The latter consisted of a U6K universal injector, a M6000A solvent delivery system, a normal phase 10-μ silica radial compression column (5 mm × 10 cm) (Radial PAK SI) and a model 440 absorbance detector set at 254 nm (Waters Associates, Milford, MA). The mobile phase consisted of 0.1 ml of methane sulfonic acid-30 ml of distilled water-500 ml of ethanol at a flow rate of 1.5 ml/min. Under these conditions the peaks of interest had retention times of 4.2 min (DDE); 5.7 min (NDE); 12.0 min (ODE); 15.0 min (MODE) and 17.7 min (encainide). Eluant fractions corresponding to these peaks were collected in scintillation counting vials and evaporated to dryness under air at 55°C. The residue was reconstituted in 0.9 ml of distilled water and 10 ml of Aquasol (New England Nuclear, Boston, MA) was added. The radioactivity was then determined by scintillation counting with quench correction by an automatic external standardization method (ISOCAP-300, Searle Analytical, Chicago, IL). The concentrations of total encainide and each metabolite were estimated from linear standard curves based on peak height. A similar approach was used to determine the radioactivity in each eluant fraction based on the standard curve obtained with [^{14}-C]encainide and the determined extraction efficiency of each metabolite. Subtraction of the contribution of radioactive compound from the total concentration provided a measure of unlabeled drug.

The plasma binding of [^{14}-C]encainide (2.82 nCi/ml, equivalent to 500 ng/ml) was determined in a prestudy sample by equilibrium dialysis for 3 hr using a previously described method (Johnson *et al.*, 1979). Preliminary studies indicated that equilibrium was achieved within this time period.

The plasma concentration/time curves for unlabeled and radioactive encainide and metabolites were analyzed by model-independent approaches (Wagner, 1976). AUCs were determined by a combination of the linear and logarithmic trapezoidal methods (Chiou, 1978). The systemic and oral clearances of encainide were then estimated from the respective Dose/AUC ratios of the radiolabeled i.v. and unlabeled oral data. Oral bioavailability was determined from the ratio of systemic to oral clearance. Additionally, the plasma concentration/time curve after i.v. administration was fitted to appropriate open compartmental models using the iterative, nonlinear computer program SAAM-23 (Berman and Weiss, 1966), and the apparent terminal half-lives of the metabolites in plasma were estimated by linear regression. Pharmacokinetic parameters of encainide and metabolites were compared after acute and chronic dosing using the paired Student's *t* test and between

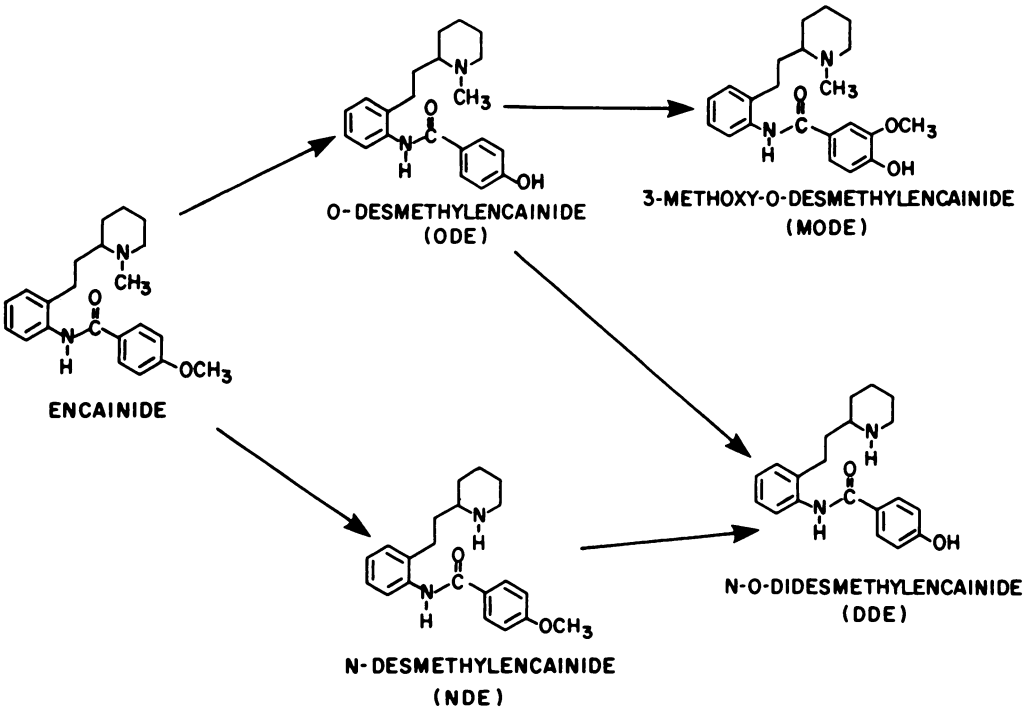

Fig. 1. Putative metabolic pathways of encainide in man.

groups using the Wilcoxon group rank sum test, with $P < .05$ as the minimal level required for significance.

Results

The debrisoquine metabolic ratios of the two groups of subjects were widely different, ranging between 0.18 and 1.25 in the EM and 33.7 to 74.5 in the PM. This was associated with pronounced differences in the disposition of encainide between the groups regardless of route or duration of drug administration. With respect to encainide, *per se*, the most obvious of these after acute administration were the much higher plasma concentrations and the 3- to 4-fold longer elimination half-life of the drug in the PM (fig. 2; table 1). The major reason for these differences was the large dissimilarity in the clearance of encainide, largely attributable to metabolism. After i.v. administration the PM had only about 10% of the EMs ability to irreversibly remove unchanged drug from the systemic circulation (table 1). When the drug was given orally considerable interindividual variability was present, especially in the EM, but the difference between the two groups in metabolizing ability as indicated by the mean oral clearance was 50-fold (table 1).

The two groups of subjects also exhibited different distributional characteristics which contributed to the differences in plasma concentrations. In the EM the plasma concentration/time profile of encainide after i.v. administration was clearly biexponential in contrast to the situation in the PM in which an essentially monoexponential decline was apparent. Accordingly, the distribution volume after pseudo-tissue equilibration in the PM was only about one-third of the value in the EM (table 1).

Because of the differences in metabolizing ability, presumably hepatic, encainide exhibited significant presystemic elimination and low bioavailability after oral administration in the EM whereas the opposite occurred in the PM (table 1).

Major quantitative differences were also apparent between the two groups in the biotransformation of encainide. The plasma concentration of the O-desmethyl metabolite was over 10-fold higher in the EM compared with the PM (figs. 2 and 3). The other major circulating metabolite in the EM was MODE; however, this compound was not detectable in the plasma of the PM. Instead, the PM had significant amounts of the N-desmethyl metabolite in their plasma, whereas this was not detectable in the EM. In neither group was DDE measurable. The plasma binding of encainide was slightly greater in the PM (table 1).

The pronounced differences in biotransformation were confirmed by the urinary excretion studies. After the first i.v. administration of radiolabeled encainide in the EM, 49.6 ± 3.5% (mean ± S.D.) of the radioactivity were excreted in the urine in 24 hr which increased to 58.7 ± 3.0% after 72 hr. Recovery values in the PM were slightly higher, 59.0 ± 0.7 and 78.0 ± 2.0%, respectively. However, only 43.4 ± 8.6% (EM) and 84.7 ± 9.5% (PM) of the 24 hr urinary radioactivity corresponded to identifiable compounds (table 2). In EM the major urinary metabolite, contributing approximately 50% of the identified, excreted radioactivity, was ODE. About 5% of the dose was excreted unchanged, a somewhat lesser percentage as MODE, and a small amount as the didesmethyl metabolite. Detectable amounts of NDE, however, were not present. In contrast, in the PM almost all of the identifiable radioactivity was excreted as unchanged drug. The recovery of ODE was only about one-fourth of that in the EM, although that of DDE was similar. A further important difference was that no detectable MODE was present but significant quantities of the N-desmethyl metabolite were excreted (table 2). Additional urine collections through 72 hr after drug administration showed that further excretion beyond 24 hr was minor. Also, the overall 24 hr urinary excretion pattern after oral administration of unlabeled encainide was similar to that observed after i.v. dosing except that the recovery of unchanged drug (0.92 ± 0.58%) was

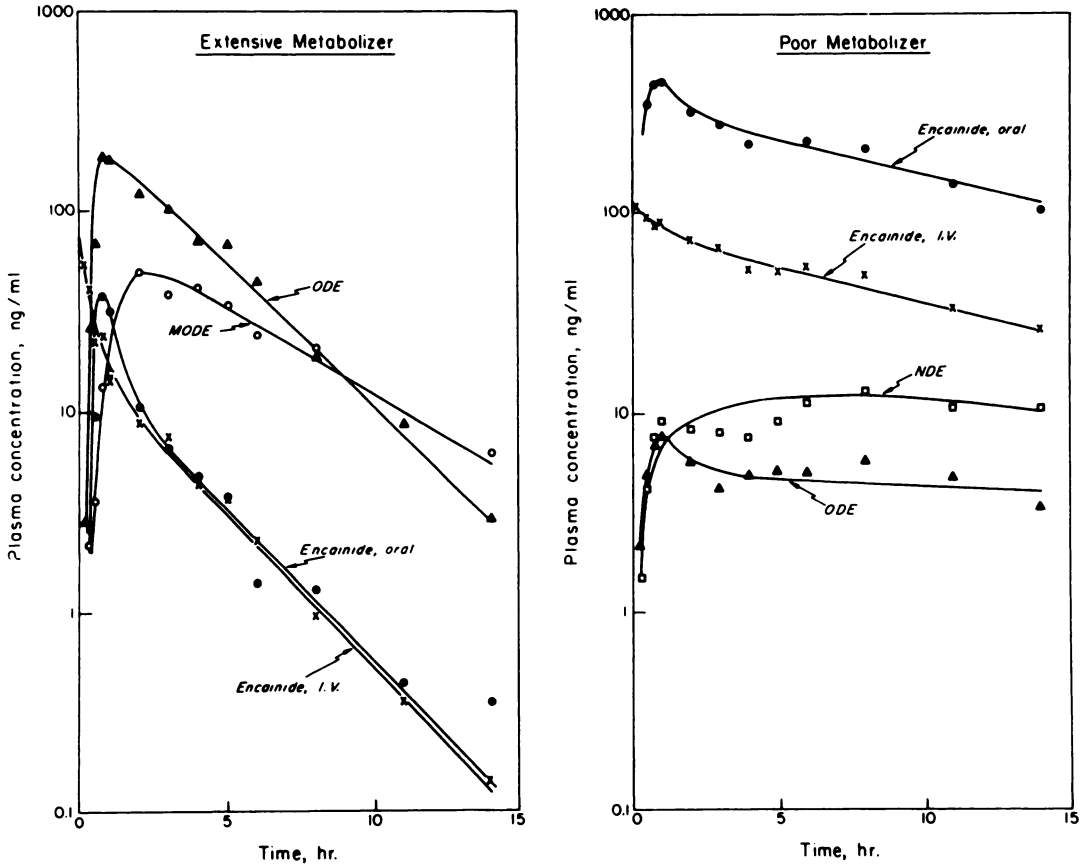

Fig. 2. Plasma concentrations of encainide and its metabolites after i.v. administration compared with the encainide concentration after an oral dose in representative EM and PM.

TABLE 1

Disposition parameters (mean ± S.E.) of encainide after i.v. administration in EM and PM after a single dose and subsequent to oral dosing for 3 days

Differences between the acute and chronic values in the two groups are not statistically significant. Differences between the two groups under either dosage conditions are all statistically significant ($P < .05$).

	EM		PM	
	Acute	Chronic	Acute	Chronic
Elimination half-life, hr	2.66 ± 0.33	2.34 ± 0.35	8.09 ± 1.08	11.28 ± 0.30
Systemic clearnace, l/min	1.80 ± 0.165	1.89 ± 0.20	0.215 ± 0.022	0.177 ± 0.002
Oral clearance, l/min	12.44 ± 4.29	11.71 ± 4.25	0.245 ± 0.033	0.225 ± 0.035
Initial volume of distribution, l	194.4 ± 19.6	213.1 ± 24.5		
Steady-state volume of distribution, l	264.0 ± 22.1	270.5 ± 32.4		
Pseudo-equilibrium volume of distribution, l	421.4 ± 38.2	375.5 ± 47.9	150.5 ± 18.6	172.2 ± 12.7
Oral bioavailability, %	26.32 ± 6.72	30.00 ± 6.84	88.43 ± 4.32	83.18 ± 9.44
Plasma binding, %	70.46 ± 2.18		78.06 ± 0.58	

significantly lower in the EM than that determined after an i.v. dose (4.93 ± 2.30%).

The disposition of encainide was unaltered after chronic administration for a sufficient period to establish steady state regardless of the drug metabolizing ability of the subjects (table 1). Accordingly, it was not unexpected to observe that encainide plasma concentrations reflected by the 0 to 8 hr AUC accumulated by almost 3-fold in the PM receiving 50 mg of encainide every 8 hr but no such accumulation occurred in EM receiving the same regimen (fig. 3). Significant accumulation also occurred with all of the plasma metabolites in both groups of subjects as assessed by the 0 to 8 hr areas under the plasma concentration/time curve (fig. 3). This presumably reflected the longer apparent elimination half-lives of the metabolites relative to encainide. For example, this value for ODE in the EM after a single oral dose was 2.81 ± 0.16 hr. The plasma concentrations of MODE declined more slowly than this, but it was not possible to determine an accurate elimination half-life from the available samples. A similar situation occurred with both ODE and NDE in the PM group where plasma concentrations of these metabolites were essentially constant over the sampling periods. The urinary excretion of drug and metabolites after i.v. administration of radiolabeled encainide after chronic oral dosing also were similar to those obtained after the first dose.

The pharmacodynamic significance of the differences in the metabolism of encainide in the two phenotypes was determined by examining the electrocardiographic changes that occurred. Measurement of EKG changes after 3 days of oral encainide administration showed that in the EM there was a significant

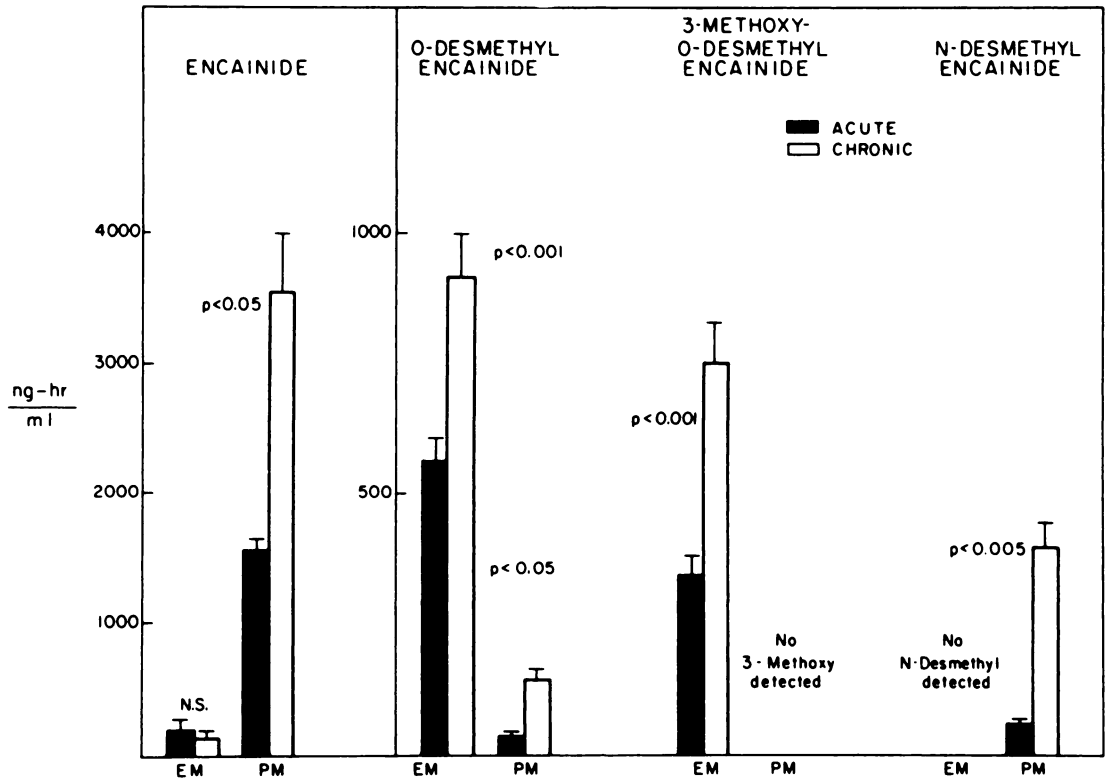

Fig. 3. Areas (0–8 hr) under the plasma concentration/time curves for encainide and its metabolites in EM and PM after single (solid bars) and multiple (open bars) oral doses (mean ± S.E.).

TABLE 2

Percentage of administered i.v. dose (mean ± S.D.) excreted in 0 to 24 hr urine as unchanged encainide and metabolites in EM and PM

Differences between the two groups, except for DDE, are all statistically significant ($P < .05$).

	EM	PM
Encainide	4.93 ± 2.30	39.33 ± 5.61
ODE	10.58 ± 3.04	3.03 ± 0.15
MODE	3.55 ± 2.76	Not detected
NDE	Not detected	1.75 ± 0.60
DDE	0.68 ± 0.50	0.50 ± 0.36
Total identifiable compounds	19.74 ± 5.2	44.61 ± 5.04
Total recovered radioactivity	49.6 ± 3.5	59.0 ± 0.7

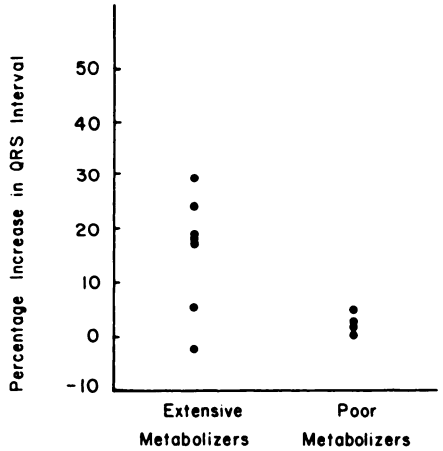

Fig. 4. Percentage of increase in QRS interval during an 8-hr dosing period after multiple oral doses of encainide in EM and PM.

intraventricular conduction delay. In 6 of the 8 EM the average QRS interval during the 8-hr dosing period increased by more than 10% with a range of 17.7 to 58.2% (fig. 4). In contrast, none of the PM exhibited any significant prolongation of the QRS interval.

Discussion

The role and importance in man of polymorphic drug oxidation have been of increasing interest since the discovery of the deficient trait to 4-hydroxylate debrisoquine (Mahgoub *et al.*, 1977; Tucker *et al.*, 1977) and determination of its genetic character (Price-Evans *et al.*, 1980). The metabolism of almost 20 drugs, representing a variety of different metabolic reactions, have subsequently been shown to cosegregate with the debrisoquine phenotype (Park, 1982), suggesting that the trait is determined by a common genetic factor(s). *In vitro* studies using biopsied human liver samples point toward the involvement of a form of cytochrome P-450 that is defective or deficient in individuals with the PM phenotype (Davies *et al.*, 1981), although other mechanisms are possible. The present study using the "phenotype panel" approach (Sloan *et al.*, 1978) strongly indicates that the O-demethylation of encainide is also regulated by identical or closely related genetic factor(s).

Oxidative phenotyping by use of the urinary metabolic ratio for debrisoquine does not distinguish betwen the homozygous dominant and heterozygous genotypes. However, relative to the modal and antimodal values of approximately 1 and 12, respectively (Price-Evans *et al.*, 1980), the low values obtained in the eight subjects characterized as having an "extensive metabolizing" phenotype suggest that they probably do represent the homozygous genotype and, therefore, the pronounced differ-

ences in the present findings likely reflect the two genotypic extremes. In this regard it is noteworthy that interindividual variability in drug metabolizing ability, as reflected by oral clearance, is significantly greater in EM; such variability has been noted in the limited number of patients in whom the antiarrhythmic efficacy of the drug and toxicity has been reported (Roden *et al.*, 1980; Winkle *et al.*, 1981; Kates *et al.*, 1982).

The differences in the pharmacokinetics of encainide *per se* in the two phenotypes were pronounced with respect to all the dispositional processes. The similarity in the 24-hr urinary recoveries of encainide and measured metabolites after i.v. and oral dosing suggests that absorption by the latter route was essentially complete. Accordingly, the poor oral bioavailability observed in the EM reflects a significant amount of presystemic (first-pass) elimination that is probably associated with liver metabolism. This is consistent with the high systemic clearance and would characterize encainide as a drug with a high total intrinsic clearance in EM (Wilkinson and Shand, 1975). Because O-demethylation is an important route of metabolism, major impairment of this pathway, as occurs in PM, leads to a large reduction in total intrinsic clearance to such an extent that in such individuals encainide is poorly extracted by the liver and undergoes a minor first-pass effect. These significant and important differences not only account for phenotype differences in encainide plasma concentrations after acute oral administration but also for the accumulation of unchanged drug seen in PM but not in EM after chronic dosing.

The biexponential shape of the plasma concentration/time course after i.v. encainide in EM compared with the essentially monoexponentially declining profile in PM could suggest a difference in the distribution of drug to the body tissues. However, such an interpretation must be made cautiously. Biexponential plasma disappearance curves are usually explained by a two-compartment open model with both drug administration and elimination occurring from the same compartment. For a drug with the distribution characteristics of encainide, it is well-recognized that impairment of elimination leads to reduction in the biexponentiality of the curve and elevated plasma levels, despite there being no change in actual distribution of the drug (Jusko and Gibaldi, 1972). This effect, along with the blood sampling times, probably accounts for the observed difference in the i.v. plasma concentration/time profiles between the phenotypes rather than an actual difference in tissue distribution. However, the latter cannot be excluded because the initial plasma concentration after i.v. administration was generally higher in the PM, suggesting a smaller initial distribution volume than in the EM. This could be related in part to the greater extent of plasma binding in the former group, the reason for which is presently unclear.

There were also large differences in the metabolic profile of encainide in the two phenotypes. The most significant finding was the presence and absence, respectively, of MODE and NDE in the plasma and urine of EM and the completely opposite situation in PM. This could represent an actual qualitative difference in the metabolism of encainide, however, it more likely reflects the pharmacokinetic differences and the sensitivity limits of the analytical techniques. For example, the formation of ODE and MODE could be catalyzed by the same enzyme, or alternatively a sequential series of processes may be involved. In either case a deficiency in ODE generation would result in MODE concentrations below the sensitivity of the assay. Similarly, it is likely that NDE is not formed in measurable amounts in EM as the activity of the involved enzyme system is low relative to the other competing metabolic pathways. However, with the higher circulating concentrations of unchanged encainide present in PM a detectable amount of the NDE metabolite is formed. Interestingly, almost equal amounts of DDE were present in the urine regardless of phenotype. It is also noteworthy that only about 50 to 60% of radioactive dose was recovered in the 72 hr urine and in EM, less than one-half of this could be accounted for by known compounds. The identification of the unknown metabolites and their pharmacological characteristics are clearly required. Also, the genetic control of these pathways relative to that of ODE formation is important to establish. It also is apparent that the differences in urinary excretion of encainide and its metabolites are sufficiently large as to provide a relatively simple means of assessing the metabolic capacity of an individual to biotransform not only this antiarrhythmic agent but also those other drugs whose metabolism is genetically controlled in a similar fashion.

The phenotypic differences in the metabolism of encainide are important relative to the plasma concentration/time profiles and the overall pharmacological effects elicited after drug administration. This is because the various metabolites have cardiovascular activities that are qualitatively similar to those of the parent drug. For example, animal studies have demonstrated that ODE is a more potent antiarrhythmic agent in a number of models (Gomoll *et al.*, 1981; Roden *et al.*, 1982; Kerr *et al.*, 1983) and similarly this metabolite elicits comparable electrophysiological effects relative to encainide but at lower concentrations (Elharrar and Zipes, 1982). On the other hand, MODE and NDE appear to be about equipotent to encainide (Gomoll *et al.*, 1981; Elharrar and Zipes, 1982; Kerr *et al.*, 1983; Mead Johnson Pharmaceutical Division, personal communication) and no information is currently available on the activities of DDE. Differences in cardiovascular effects after a single dose of encainide compared with chronic oral therapy in patients have also pointed toward an important role of the metabolites of encainide in the overall effects (Sami *et al.*, 1979; Winkle *et al.*, 1981; Carey *et al.*, 1983). Particularly noteworthy are the observations that the antiarrhythmic activity of encainide and its metabolites are paralleled by characteristic electrocardiographic effects, namely an increase in QRS duration (Carey *et al.*, 1983). For example, there is a good relationship in patients between the suppression of ventricular arrhythmias and the increase in the QRS interval, and both effects are best correlated with the plasma concentration of ODE (Carey *et al.*, 1983). It is not surprising, therefore, that no changes in the QRS interval were observed in any of the PM but pronounced prolongation was apparent in six of the eight EM. Such differences in response suggest that little if any antiarrhythmic effects would be expected in PM who are given doses of encainide which are usually effective in EM. However, encainide *per se* does have antiarrhythmic activity and there is a 10- to 100-fold greater accumulation of unchanged drug in PM. Accordingly, it appears that arrhythmia suppression is possible in this population at dosages similar to those that are effective in EM (Carey *et al.*, 1983).

These findings in two genetically determined phenotypes provide an understanding of some of the differences in responsiveness to encainide that have been observed in patients. They also are indicative of the pronounced quantitative and quali-

tative differences in drug oxidation that may be present in the substantial portion of the population characterized as PM. The oxidative metabolism of an increasing number of drugs is being linked to the genetically determined ability to 4-hydroxylate debrisoquine (Park, 1982). Other oxidative polymorphisms are becoming defined; for example, those of tolbutamide (Scott and Poffenbarger, 1979) and mephenytoin (Aslanian *et al.*, 1983; Kupfer *et al.*, 1981). In those instances where metabolism is strongly influenced by a major gene effect there are often pronounced differences in drug effects, especially the incidence of adverse reactions (Mellström *et al.*, 1981; Shah *et al.*, 1982; Dayer *et al.*, 1982; Lennard *et al.*, 1982; Alvan *et al.*, 1982). These are generally more frequent in the PM but encainide is an example where the "extensive" phenotype may be more predisposed as the metabolites of the drug are pharmacologically active. Such a situation suggests that knowledge of the phenotype of an individual may be necessary for optimal therapy with the involved drugs. It is also apparent that the initial clinical evaluation of new drugs should take into account the possibility that polymorphic drug oxidation may significantly alter drug efficacy and toxicity.

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