Genetically determined drug-metabolizing activity and desipramine-associated cardiotoxicity: A case report

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Desipramine is an effective tricyclic antidepressant but at high doses it can cause cardiotoxicity. There is wide variation in plasma concentrations for a fixed dose because of intersubject variation in metabolism. Most of the drug is metabolized by cytochrome P450 to 2-hydroxydesipramine, and this oxidation exhibits a genetic polymorphism that cosegregates with the debrisoquin hydroxylation phenotype catalyzed by cytochrome P4502D6.[1] The 8-hour urinary ratio of debrisoquin/4-hydroxydebrisoquin will predict the steady-state plasma concentration of desipramine. Thus individuals with the poor metabolizer phenotype for debrisoquin have significantly higher concentrations of desipramine than those who are extensive metabolizers.[2] Occurrence of cardiotoxicity at conventional doses of desipramine is rare.[3,4] Even though it would be anticipated that individuals with poor metabolizer status would be at higher risk of toxicity, we are unaware of any reports of individuals identified as poor metabolizers who manifest cardiotoxicity.

The patient described in this report developed cardiac symptoms and signs of myocardial ischemia with conventional doses of desipramine. An extensive cardiac evaluation excluded underlying heart disease. To explain toxicity and to plan future therapy, the patient was studied with the drug-metabolizing probes, debrisoquin and mephenytoin, which probe for cytochrome P4502D6 and P4502D$_{MP}$ activity, respectively, and dapsone, which probes for N-acetylation

and cytochrome P4503A4 activity.[5-7] In addition, three generations of the patient's family were also studied.

METHOD

The index patient and family members were phenotyped with the three probe drugs: debrisoquin, mephenytoin, and dapsone. At the time of the phenotyping study, the patient was taking 20 mg fluoxetine twice daily, but this was withheld for 48 hours before phenotyping. Additional subjects studied included the patient's mother and father, his sister and brother, and two sons, ages 21 and 20 years. The patient's daughter, age 15 years, received only mephenytoin. The protocol was approved by Vanderbilt University's ethical review committee.

Urine was collected for the 8 hours after debrisoquin (10 mg), mephenytoin (100 mg, 450 μmol), and dapsone (100 mg) were administrated. Also at this time, 5 ml heparinized blood was collected and the plasma was separated. Debrisoquin and 4-hydroxydebrisoquin were determined in urine by a modification of the method of Wedlund et al.[8] by use of gas chromatography–mass spectrophotometry. The urinary debrisoquin/4-hydroxydebrisoquin ratio is greater than 12.5 for poor metabolizers and less than 12.5 for extensive metabolizers.[8] The enantiomeric ratio for mephenytoin in the 8-hour urine sample was measured as described previously.[8,9] Extensive metabolizers have R/S ratios greater than 1.8, and poor metabolizers have ratios close to unity. The quantity of 4-hydroxymephenytoin was also measured by high performance liquid chromatography.[10]

Dapsone (DDS), monoacetyldapsone (MADDS), and dapsone hydroxylamine concentrations in plasma were determined by high performance liquid chromatography.[7,11] The acetylation ratio was expressed as plasma MADDS(8 hour)/plasma DDS(8 hour). Poor acetylators were defined as individuals with an acetylation ratio less than 0.4, whereas rapid acetylators
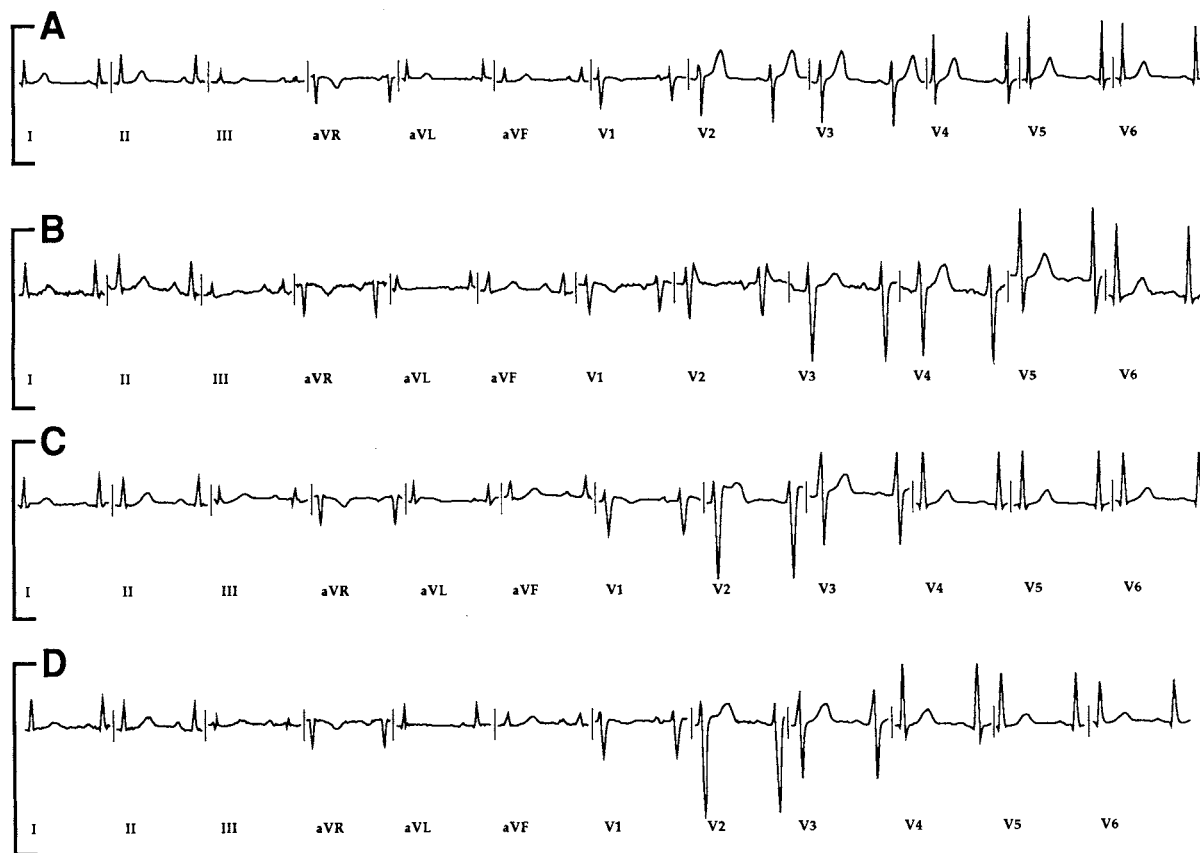
Fig. 1. ECG tracings of proband at four time intervals. A, Before the start of desipramine therapy. B, Fifteen days after desipramine therapy was begun. C, Day 45 of desipramine therapy, during evaluation for chest pain. D, Thirteen hours after previous tracing (C). Chest pain had resolved.

had an acetylation greater than 0.4.[8] Dapsone hydroxylation ability was measured as the relative recovery of dapsone hydroxylamine (HDA) and was determined in urine as HDA(8 hour)/[HDA + total DDS](8 hour). Total DDS measured included acid labile and acid stable fractions in urine.

CASE HISTORY

The patient was a 46-year-old white man, with a DSM-III-R diagnosis of major depression, chronic, by the Structural Clinical Interview for Diagnosis—Patient Version.[12,13] His depression had been first diagnosed 30 years earlier. He had received no previous pharmacotherapy for his depression. He was voluntarily enrolled and randomly assigned to desipramine treatment as part of a safety and efficacy study of desipramine. His baseline physical examination, ECG (Fig. 1, A), and laboratory tests were normal. He received a placebo in the morning and desipramine as a

single dose in the evening just before supper time. Desipramine was begun at a dose level of 50 mg daily and was gradually increased to 250 mg over approximately 1 month. At this highest dose, he experienced his first episode of squeezing sternal chest pain at rest, associated with minimal shortness of breath but no diaphoresis, nausea, or vomiting. This discomfort was brief and resolved spontaneously. On four subsequent occasions during the next several weeks, he noted chest tightness occurring about 2 hours after taking his desipramine dose, always while he was at rest. Heavy exertion during the day did not precipitate chest pain. On the day before hospitalization, and 2 hours after taking desipramine, the chest pain occurred and lasted approximately 1 hour. On the subsequent morning, which was 45 days after beginning desipramine, he reported these symptoms to his doctor and was hospitalized for evaluation. At the time of admission to the hospital, while he did not have symptoms, his ECG

Table I. Hospitalization admission data

Test	Proband's result	Reference range
Plasma desipramine (ng/ml)	764	50-250
Serum creatinine (mg/dl)	1.1	0.7-1.5
Serum albumin (gm/dl)	4.3	3.5-5.0
Serum aspartate aminotransferase (IU/L)	31	4-40
Total serum bilirubin (mg/dl)	0.4	0.2-1.2
Serum alkaline phosphatase (IU/L)	66	40-110
Blood lactate dehydrogenase (IU/L)	230	125-250
Blood creatine phosphokinase (IU/L)	72	30-210

was consistent with acute anterior wall myocardial ischemia (Fig. 1, *C*). Physical examination was unremarkable except for a pulse rate of 100 beats/min. At the time of admission, the patient's only medication was desipramine 250 mg in the evening, and he had taken the last dose on the evening before admission. Thereafter the drug was discontinued. He denied the use of alcohol, he did not smoke, and he used no other drugs. Renal and liver function tests were normal, and cardiac enzymes were not elevated. However, his plasma desipramine level (764 ng/ml) was elevated (Table I).

At cardiac catheterization 72 hours after admission, the patient had normal coronary anatomy and left ventricular function, and there was no spasm during an ergonovine challenge. When the ECG was repeated 13 hours later, the ischemic changes had almost completely resolved (Fig. 1, *D*). These findings were similar to tracings taken 50 (Fig. 1, *A*) and 35 (Fig. 1, *B*) days earlier. It may be noted that tracing A is entirely normal and tracing B showed a decrease in T wave amplitude and an incomplete right bundle-branch block.

The phenotype findings of the proband and family for debrisoquin are shown in Fig. 2, A.The proband's father, brother, sister, and a son (age 21) all had urinary metabolic ratios that were less than 12.5, indicative of the extensive metabolizer phenotype. The proband, his mother, and another son (age 20) had ratios that were greater than 12.5, which would be classified as the poor metabolizer phenotype.

Determining the ratio for the *R*-mephenytoin/*S*-mephenytoin enantiomers (Fig. 2, *B*, data in parentheses) identified that the proband and his mother had ratios close to unity (1.2 and 1.8, respectively) and thus were classified as the poor metabolizer phenotype. The ratios of the proband's father (5.9), brother (11.4), sister (11.1), two sons (8 and 7.5), and daughter (10.3) were all greater than 1.8; they were there-
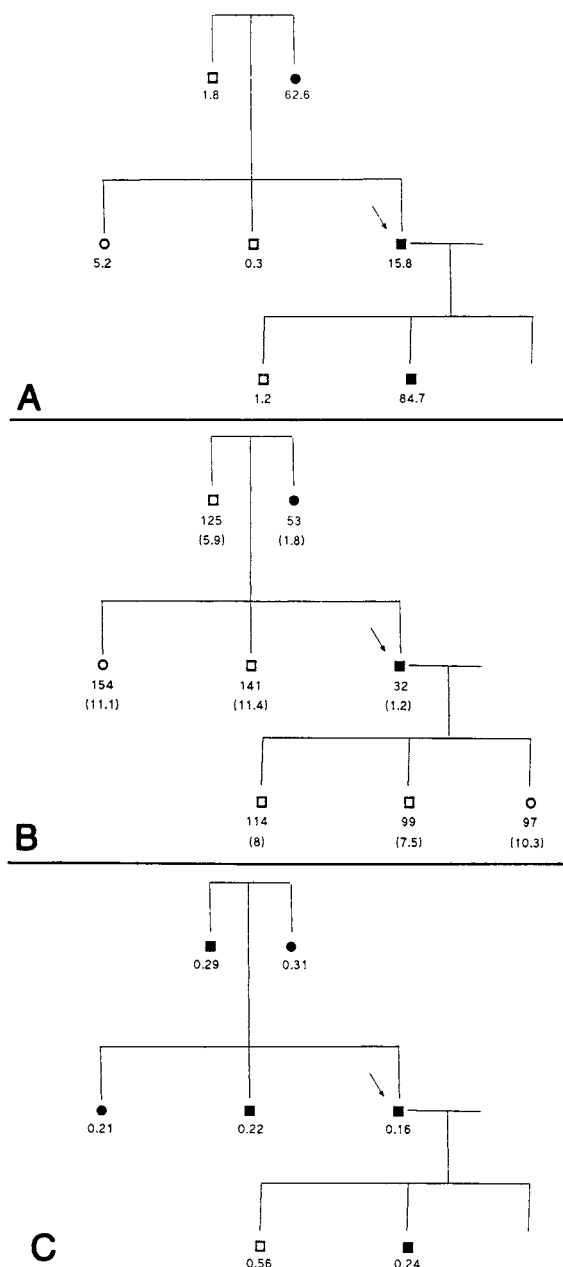

Fig. 2. Proband (indicated by *arrow*) and three generations of his family: male members are indicated by *squares*; female members by *circles*. **A,** Urinary ratio for debrisoquin/4-hydroxydebrisoquin, poor metabolizers (ratio >10) are *solid symbols,* and extensive metabolizers (ratio <10) are *open symbols.* **B,** Quantity in micromoles of 4-hydroxymephenytoin and, in parentheses, the metabolic ratio for the *R/S* enantiomers of mephenytoin. *Solid symbols* indicate poor metabolizer (metabolic ratio near unity); *open symbols* indicate extensive metabolizers (>1.8). **C,** Ratio of monoacetyldapsone to dapsone. *Solid symbols* are slow acetylators (<0.4); *open symbol* is rapid acetylator (>0.4).

Table II. Dapsone hydroxylation of proband and family

	Age (yr)	Cigarette smoker	Dapsone hydroxylation ratio
Mother	74	No	0.564
Father	75	No	0.629
Proband	46	No	0.596
Sister	40	No	0.598
Brother	45	Yes	0.689
Son	21	No	0.731
Son	20	No	0.490
Daughter	15	No	—

fore classified as extensive metabolizers. Although the proband and his mother also had the lowest quantities of 4-hydroxymephenytoin (Fig. 2, *B*, 32 μmol and 53 μmol, respectively), these concentrations are greater than those observed for poor metabolizers in whom the excretion of this metabolite has been reported to be negligible.[5] Thus by the enantiomeric ratio the proband and his mother would be classified as the poor metabolizer phenotype, but by the measurement of the production of 4-hydroxymephenytoin, they may considered the intermediate phenotype.[14,15]

Determination of the acetylation phenotype in this family identified that the ratio of plasma MADDS(8 hour)/plasma DDS(8 hour) was less than 0.4 in the proband, his mother, father, brother, sister, and one son (age 20) (Fig. 2, *C*). Thus all these individuals were slow acetylators. The proband's elder son had a ratio greater than 0.4 and was a fast acetylator. Data for dapsone hydroxylation are within 2 standard deviations of a population mean (Table II).[16]

DISCUSSION

The electrophysiologic effects caused by tricyclic antidepressants can be noted in the ECG early during treatment in most patients. These changes include a decrease in T wave amplitude, prolongation of the PR, QRS, and QT_c, and an increase in heart rate.[4] Although an optimal range of plasma levels has not been established, serum levels of desipramine within a range of 50 to 300 ng/ml may be considered therapeutic, and clinically significant conduction delays occur as the plasma concentration increases above 1000 ng/ml.[17-19] This patient showed ECG effects (T wave amplitude decrease) within several weeks of beginning desipramine and, although an intraventricular conduction abnormality was also identified at that time, these conduction delays are usually not considered clinically significant.[3] Subsequently, at a time when the desipra-

mine level was approximately three times the therapeutic range, the patient had the symptoms and an ECG pattern of cardiac ischemia. This adversity in association with desipramine is highly unusual because even in patients who take an overdose, the predominant manifestation of toxicity is arrhythmia and conduction abnormalities.[20] However, myocardial infarction is cited by the manufacturer of desipramine as a potential adversity.[17] It has also been suggested that patients with underlying heart disease are predisposed to the development of cardiac toxicity at therapeutic doses of tricyclic antidepressants.[3] However, extensive clinical evaluation of this patient excluded underlying heart disease. The most likely explanation for the symptoms and changes in the ECG was coronary artery spasm.

At a dose of 250 mg daily, the patient's serum level of desipramine was 764 ng/ml. In comparison to the levels achieved by the patient, Friedel et al.[21] reported that patients taking daily doses of 200 mg desipramine had an average serum concentration of 173 ng/ml, with a range from 28 to 882 ng/ml.[21] Genetic polymorphism of desipramine metabolism to 2-hydroxydesipramine has been recognized to cosegregate with the polymorphism of conversion of debrisoquin to debrisoquin 4-hydroxylation. In white subjects, approximately 90% of the population are extensive metabolizers and 10% are poor metabolizers of debrisoquin.[22] When given equivalent doses, individuals with the poor metabolizer status achieve higher levels of desipramine at steady state than individuals who are extensive metabolizers.[2] The patient in this report had a urinary debrisoquin/4-hydroxydebrisoquin ratio of 15.9. He would therefore be considered a poor metabolizer, which provides an explanation for the finding of an elevated desipramine level. To our knowledge, this is the first case report of a clinically observed adverse effect to desipramine in a poor metabolizer for this phenotype. We are unaware of previous reports of the occurrence of cardiac toxicity in a patient identified as being a poor metabolizer while receiving desipramine or other tricyclic antidepressants.

At the time of the phenotype study, but not while taking desipramine, the patient was treated with fluoxetine. It has recently been reported that the metabolism of fluoxetine to its metabolite, norfluoxetine, also cosegregates with this phenotype. This raises the possibility that fluoxetine inhibited P4502D6 at the time of the phenotypic study, and this may confound the interpretation of the debrisoquin phenotyping study.[23] Because the mother and son of the patient were also found to be poor metabolizers of debrisoquin and nei-
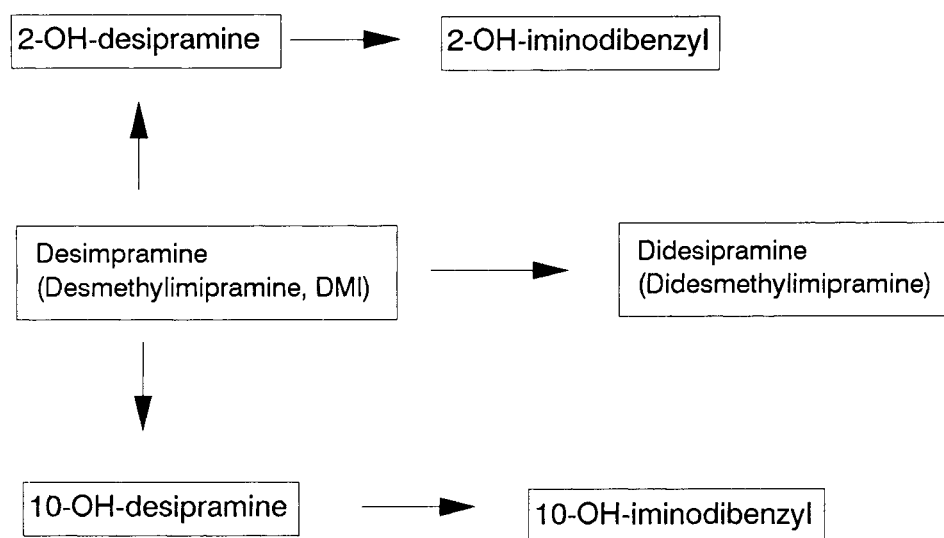
Fig. 3. Metabolic scheme that illustrates the steps in the metabolism of desipramine in humans. Steps shown may be followed by glucuronidation.[1,25]

ther had received fluoxetine and because the patient was withdrawn from this drug for 48 hours before the study, it is reasonable to believe that the patient was genotypically a poor metabolizer of debrisoquin.

It was observed that this patient also had impaired metabolism of mephenytoin (Fig. 2, *B*). As determined by a urinary *R/S* enantiomeric ratio of mephenytoin close to unity, the patient may be classified as a poor metabolizer of mephenytoin.[24] However, in individuals classified as the poor metabolizer phenotype for mephenytoin, the urinary recovery of 4-hydroxymephenytoin is usually less than 2 μmol.[8] Because the urinary recovery of 4-hydroxymephenytoin was measurable but less than 85 μmol, this patient may be considered an intermediate phenotype.[14,15] That this was not attributable to a general impairment of all routes of oxidative metabolism was established by the patient's ability to form the hydroxylated metabolite of dapsone, a reaction that is catalyzed by the enzyme P4503A4.[6] In addition, the patient had no evidence of liver disease. Dapsone acetylation, a probe of *N*-acetyltransferase, a serum enzyme that shows a genetically bimodal distribution, was also found to be slow in the patient.

The metabolic profile for desipramine has not been fully characterized in humans (Fig. 3). The major oxidative metabolite of desipramine is 2-hydroxy-desipramine, although a small amount of 2-hydroxy-iminodibenzyl is also produced. Subsequently, 2-hydroxydesipramine is conjugated with glucuronic acid.[25] Another identified minor metabolic pathway is

10-hydroxylation, which is catalyzed by other unidentified P450 isozymes.[1,25] The importance of these minor paths of metabolism in desipramine elimination in poor metabolizers of cytochrome P4502D6 is unknown.

The dual contribution of debrisoquin and mephenytoin enzymes to the disposition of propranolol and imipramine has been described and in both of these examples the rare occurrence of dual metabolic defects resulted in substantial increases in the AUC of the parent compound.[26,27] Although mephenytoin oxidation polymorphism is partially responsible for the *N*-demethylation of imipramine, it is unknown whether this isozyme contributes to the *N*-demethylation of desipramine to didesipramine (Fig. 3).[27] Thus in patients receiving desipramine the effect of deficiency in the mephenytoin oxidation phenotype requires further study.

The significance of the deficiency in the metabolic paths probed by dapsone acetylation on desipramine metabolism is not apparent, but it may be speculated that other metabolic paths may play a role in clearance of desipramine and that when also deficient they may contribute to the manifestation of cardiotoxicity.

The family study identified the patient's mother as sharing a similar phenotype with the patient (Fig. 2). She was the only family member with a history of an adverse drug reaction, which occurred after she received morphine and was described as general weakness.

This limited family study is consistent with the pre-

vious observations that both debrisoquin and mephenytoin poor metabolizer traits are inherited as autosomal recessive inheritance patterns.[28,29] Even though the proband and the proband's mother shared their debrisoquin and mephenytoin poor metabolizer traits, there was a dissociation of the poor metabolizer phenotypic traits in the proband's second son. This is consistent with previous reports that the traits are independent.

The poor metabolizer status for debrisoquin, mephenytoin, and dapsone acetylation identified within this family is a rare anomaly. The combined deficiency of mephenytoin and debrisoquin metabolism has been identified previously, and it is estimated that it may be expected to occur in two of 1000 subjects.[26,27,30] That a combined defect predisposes to adverse drug reactions is supported by the severe but reversible cardiotoxicity experienced by the patient. Thus a combined defect may create a greater risk to conventional dose therapy. The contribution of this combined metabolic deficiency to the underlying depressive disease in the proband remains unknown.

We thank the patient and family for participation in this study.

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CORRECTION

Please note the following correction in the Results section of the article, "Comparison of the pressor effect of tyramine after treatment with phenelzine and moclobemide in healthy male volunteers" (Simpson GM, Gratz SS. CLIN PHARMACOL THER 1992;52:286-91). On page 288, the phrase beginning on the fourth line of the Results section should read: "and diastolic blood pressure >60 and <85 mm Hg."