Fast and Slow Metabolizers of *Hoasca*†

J.C. Callaway, Ph.D.*

Abstract—Harmine, a major alkaloid in ayahuasca (*hoasca*), is a selective and reversible inhibitor of the enzyme monoamine oxidase-A (MAO-A). It is also a selective inhibitor of the human cytochrome P450 isozyme 2D6 (CYP 2D6), which metabolizes harmine to a more hydrophilic derivative for eventual excretion. CYP 2D6 exhibits a wide range of polymorphisms in human populations, and variations in this enzymatic activity could account for differences in effects between individuals who use *hoasca*. This report broadly describes two subgroups of CYP 2D6 phenotypes—i.e., fast and slow metabolizers of harmine—in 14 experienced male members of the União do Vegetal (UDV) who received a standardized dosage of *hoasca*. To compensate for metabolic variations in their normal religious practice, the administered dose of *hoasca* is always determined by the presiding *mestre*, who is responsible for deciding the actual amount for each individual. This age-old method compensates for metabolic variations between individuals and variations in both the alkaloid profile and strength of the *hoasca*.

Keywords—alkaloid, ayahuasca, CYP 2D6, *hoasca*, MAO, metabolism, polymorphism

The overall somatic effects of *Banisteriopsis caapi* infusions and decoctions are generally similar and dependent on dose, despite the wide range of alkaloids and alkaloid profiles that may be present in this plant and subsequent "teas" (see Callaway 2005 and Callaway, Brito & Neves 2005 in this issue). Although tens of thousands of individuals now use these beverages on a regular basis, as *hoasca*, *daime*, *ayahuasca*, *la purga*, etc., overall personal experiences are surprisingly uniform in the ceremonial context and without apparent detriment to the individual or community (Grob et al. 1996).

The pharmacokinetics of hoasca (Callaway et al. 1999; Callaway 1996) and *daime* (Riba et al. 2003) have been investigated. In the author's earlier work on the pharmacokinetics of *hoasca* (Callaway et al. 1999), considerable individual differences were noticed in the metabolism of harmine, although these individual differences were not reported in the original publication, where these results were averaged and reported for 14 out of the 15 experienced volunteers. From the original data, however, these volunteers could be evenly divided into two subcategories of relatively fast and slow metabolizers of harmine, although a likely scientific explanation for this metabolic phenomenon was unknown at that time.

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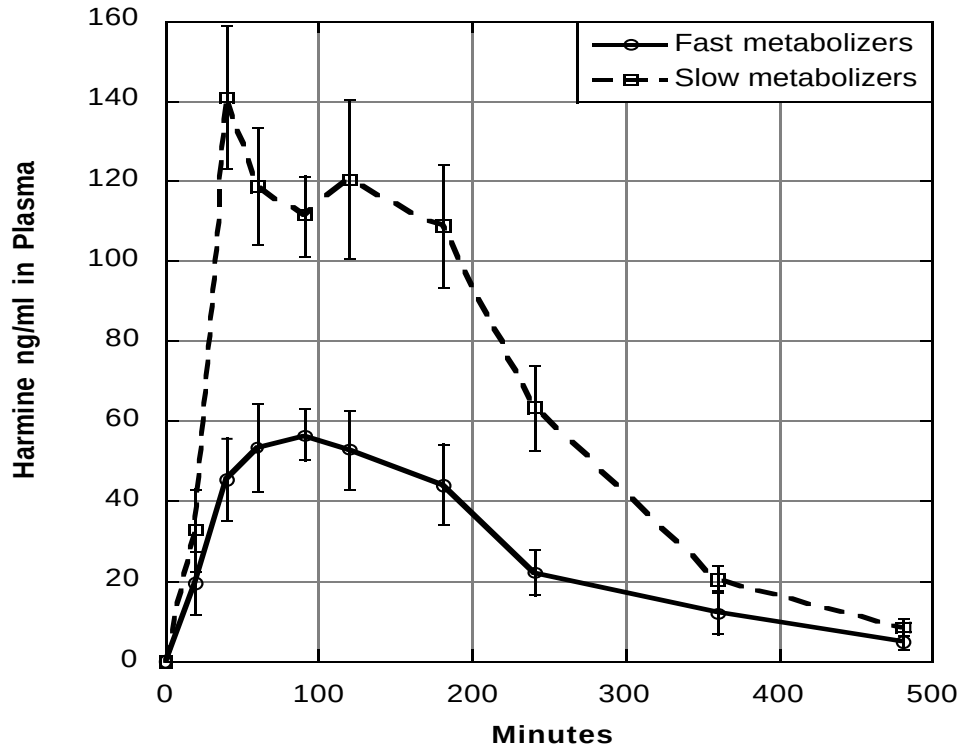
DISCOVERY OF CYP 2D6

The cytochrome P450 isozyme 2D6 (CYP 2D6) was already identified over 25 years ago, and has served as a prototype in studies on the genetic polymorphism of cytochrome p450 isozymes (Mahgoub et al. 1977). More recently, CYP 2D6 was shown to efficiently metabolize 5-methoxy-*N*,*N*-dimethyltryptamine (5-MeODMT) and 6-methoxy-tetrahydro-*beta*-carboline (6-MeOTHBC, "pinoline") to their corresponding hydrophilic derivatives (Eichelbaum 2003; Yu et al. 2003a). Such a variation in metabolic action could have a significant influence on both mood and behavioral actions that result from these

FIGURE 1
Pharmacokinetic Profile of Plasma Harmine Levels for Fast (N = 7) and Slow (N = 7) Metabolizers in Healthy Men (Mean ± Sem) after 2 ml/kg *Hoasca*



endogenous indoles (Callaway et al. 1994a; Callaway 1988). Moreover, CYP 2D6 was also found to have high affinity for the metabolism of both harmine and harmaline (Yu et al. 2003b).

The purpose of this article is to examine the original pharmacokinetic data from the 15 Hoasca Project volunteers (Callaway et al. 1999; Callaway & Grob 1998; McKenna, Callaway & Grob 1998), and look for possible differences in the metabolisms of *N*,*N*-dimethyltryptamine (DMT), tetrahydroharmine (THH) and harmine from the original data set.

MATERIAL AND METHODS

The pharmacokinetic study design, volunteer profile and sample analyses and results of the Hoasca Project have already been described (Callaway et al. 1999, 1996; McKenna, Callaway & Grob 1998; Grob et al. 1996). The entire sample set included 15 experienced individuals who ingested a standard amount of hoasca (2 ml/ kg of body weight); time-synchronized plasma samples were collected and analyzed for DMT, THH and harmine as described (Callaway et al. 1996). Each volunteer received 3.4 mg of harmine, 0.4 mg harmaline, 2.14 mg THH and 0.48 mg DMT/ kg of body weight.

Kaleidagraph version 3.6 was used to statistically analyze and plot the original pharmacokinetic data for harmine, THH and DMT. These data were further analyzed by paired student-t comparisons. Only 14 of the 15 volunteers were included in the final data analyses. One volunteer had vomited early into the study and was not included in the final analysis.

"Fast" metabolizers were defined as those individuals who had a maximum plasma harmine concentration (Cmax) of 100 ng/ml or less, while "slow" metabolizers were those who had a plasma harmine Cmax over 100 ng/ml. This level of division allowed for a clear and even distribution of seven volunteers into each group.

RESULTS

The difference in pharmacokinetic profiles between the fast and slow metabolizers of harmine are illustrated in Figure 1. The statistical difference in area under the curve (AUC) between these two groups was highly significant for harmine ($p = 0.002$; see Table 1). There were no statistically significant differences or trends for the AUC between fast and slow metabolizers for either THH or DMT (Figures 2 and 3, Table 1). Plasma levels of harmaline were too low to be included in the present analysis.

TABLE 1
Area Under the Curve (AUC, in microgram minutes/ml ± Standard Deviation) of Hoasca Alkaloids for Fast (N = 7) and Slow (N = 7) Metabolizers of Harmine; Paired Student's *t* Comparison

	Fast	Slow	*p*
Harmine	13.62 ± 6.92	32.13 ± 6.95	0.002
THH	37.83 ± 21.29	57.74± 27.68	0.153
DMT	5.74 ± 3.80	5.46 ± 5.54	0.913

DISCUSSION

Individual differences in drug metabolisms are common, and drug combinations are even used to characterize phenotypic responses to cytochrome P450 metabolism (Christensen et al. 2003). The CYP 2D6 isozyme allele frequency is known to vary significantly between geographic populations (Bradford 2002), with Asians and Pacific Islanders having a lower expression and Caucasians a higher expression of this enzyme. Lower enzymatic expression, and subsequent activity, results in slower metabolic rates while higher expression allows for faster metabolism of harmine by CYP 2D6. Such a phenotypic division between fast and slow metabolic activities of CYP 2D6 has recently been described and characterized for debrisoquinone and sparteine (Yu, Idle & Gonzalez 2004).

Hoasca and analogous beverages are seldom consumed more often than once a week in regular use. In a religious context, hoasca is dispensed by a presiding *mestre* who is familiar with both the tea and the individual, and adjusts the dosage accordingly. This beverage has no demonstrated acute or long-term toxicity, nor do withdrawal symptoms appear after its regular use is suddenly terminated. However, it is not uncommon to experience nausea and even vomiting after its ingestion. From a metabolic point of view, serotonin levels increase after MAO inhibition, stimulating the vagus nerve in the brain, which innervates the digestive tract. Increased serotonin in the lower intestinal tract also stimulates motility. Evacuation of both the upper and lower parts of the digestive tract may occur with sufficient overdoses of hoasca, probably more so in poor metabolizers of harmine, which is a natural reflex that acts as a fail safe mechanism against the possibilty of a fatal overdose in this case. Although some tolerance may develop to hoasca, emesis is still not uncommon even in experienced individuals (Callaway et al. 1994b).

It is assumed that any pharmacologic contribution from harmaline will be effectively the same as harmine, as both are metabolized by CYP 2D6 at a similar rate (Yu et al. 2003b). Harmaline is present in only small amounts in hoasca and related beverages (Callaway 2005), and has similar actions as harmine on MAO-A. Although there were significant differences for the metabolism of harmine in the present study, there were no significant differences in the metabolism of either DMT or THH. Plasma harmine and DMT levels were already decreasing after 120 minutes (see Figures 1 and 3), and for THH after 180 minutes in most cases for both groups (Figure 2).

The similar pharmacokinetic profiles for THH in this study (Figure 2) and large standard deviations in AUC (Table 1) indicate that it may be metabolized by another pathway entirely, or that the metabolism of THH is not greatly affected by CYP 2D6 polymorphisms at these levels. The similarity between harmine and DMT profiles (Figures 1 and 3) clearly illustrates the direct dependency of DMT on plasma harmine levels (Holmstedt & Lindgren 1967), although it is surprising to see so little difference between the plasma DMT levels for these two groups (Figure 3). This is probably due to the fact DMT can be metabolized by enzymes other than MAO, such as kynureninase (Hryhorczuk et al. 1986).

One could argue that harmine might be metabolized to a significant degree by MAO (Benedetti 2001), but harmine functions as a reversible inhibitor of MAO, meaning that it blocks this enzyme without being metabolized or destroying the enzyme (Kim, Sablin & Ramsay 1997). Thus, its primary metabolic fate is likely to reside with CYP 2D6. Results from a recent study on the pharmacokinetics and metabolism of *ayahuasca*, as *daime*, support this position (Riba et al. 2003).

A NOTE OF CAUTION

Selective serotonin reuptake inhibitors (SSRIs) are antidepressants that have high affinity for CYP 2D6 (Bourin, Chue & Guillon 2001), in addition to the serotonin reuptake site. Many antipsychotic medications are also metabolized to a significant extent by CYP 2D6, and prescription recommendations have already been made with this in mind (Oscarson 2003; Dahl 2002). Thus, harmine's metabolism by CYP 2D6 provides another good reason to avoid the combination of SSRIs and other monoaminergic medications with hoasca (Callaway & Grob 1998). More common drug substances, such as tobacco smoke, are also known to affect CYP 2D6 metabolism (Tiihonen et al. 2000), although the use of tobacco is common among indigenous users of *B. caapi* infusions, both smoked and as an admixture to the decoction, where it is claimed to modulate the effect (Wilbert 1991).

FIGURE 2

Pharmacokinetic Profile of Plasma Tetrahydroharmine (THH) Levels for Fast (N = 7) and Slow (N = 7) Metabolizers in Healthy Men (Mean ± Sem) after 2 ml/kg *Hoasca*

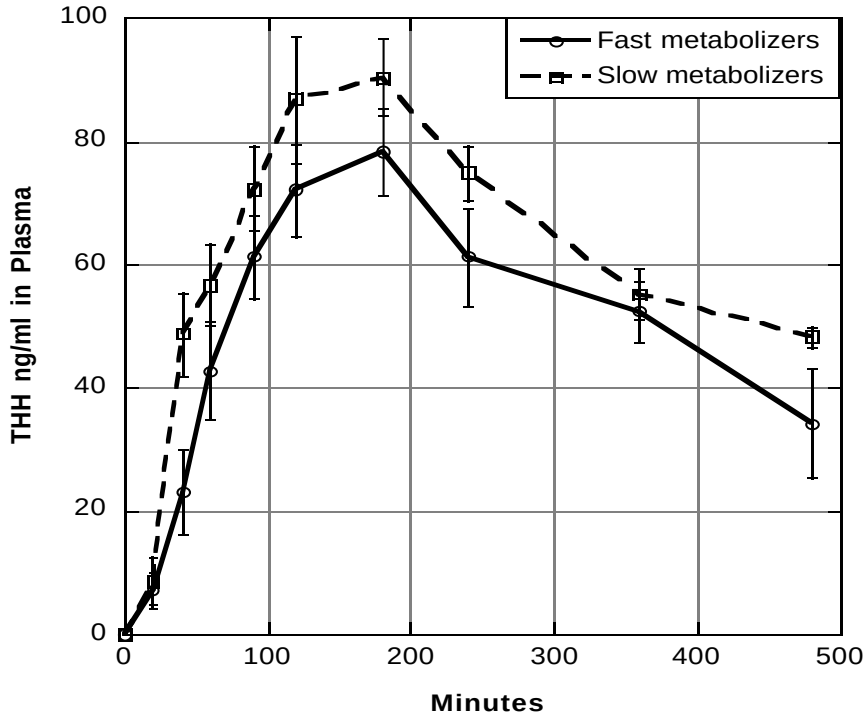
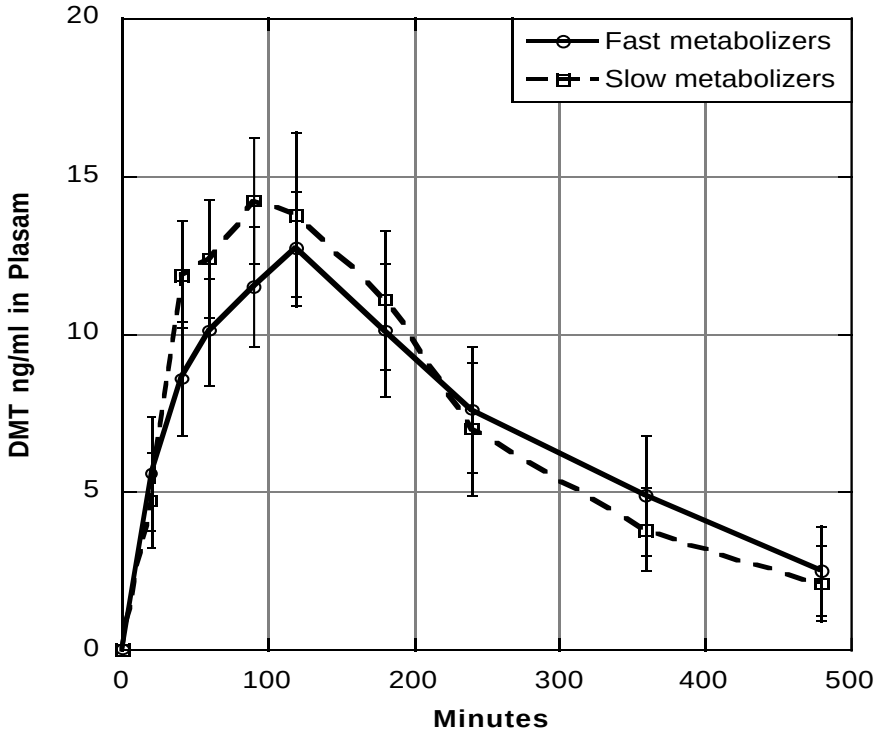


FIGURE 3

Pharmacokinetic Profile of Plasma *N,N*-Dimethyltryptamine (DMT) Levels for Fast (N = 7) and Slow (N = 7) Metabolizers in Healthy Men (Mean ± Sem) after 2 ml/kg *Hoasca*



The purpose of this article has been to describe a natural variation in the metabolism of harmine by healthy men, which was already observed empirically by those who use hoasca and related beverages on a regular basis. It is perhaps more important to keep in mind that the *mestre*, *shaman* or *padrinho* is responsible for knowing both the strength of the tea and the general constitution of the individual receiving it. As with other pharmacologic substances, this is simply a matter of adjusting the administered dose after careful consideration. In any case, it is hard to imagine a lethal overdose when the effective dose is so near the point of emesis, unless other medications are involved.

CONCLUSIONS

Considerable variations were observed for the metabolism of harmine in healthy men after ingesting a standard dose of *hoasca*. From the current available information, it seems that this difference in effect can be explained by individual differences in CYP 2D6 enzymatic activity. The metabolism of DMT by MAO is blocked by harmine, although DMT is probably still metabolized by kynureninase, while THH may be metabolized by other enzymatic actions.

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