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Pharmacokinetics of *Hoasca* alkaloids in healthy humans

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Abstract

N,*N*-Dimethyltryptamine (DMT), harmine, harmaline and tetrahydroharmine (THH) are the characteristic alkaloids found in Amazonian sacraments known as *hoasca*, *ayahuasca*, and *yajè*. Such beverages are characterized by the presence of these three harmala alkaloids, where harmine and harmaline reversibly inhibit monoamine oxidase A (MAO-A) while tetrahydroharmine weakly inhibits the uptake of serotonin. Together, both actions increase central and peripheral serotonergic activity while facilitating the psychoactivity of DMT. Though the use of such 'teas' has be known to western science for over 100 years, little is known of their pharmacokinetics. In this study, *hoasca* was prepared and administered in a ceremonial context. All four alkaloids were measured in the tea and in the plasma of 15 volunteers, subsequent to the ingestion of 2 ml *hoasca*/kg body weight, using gas (GC) and high pressure liquid chromatographic (HPLC) methods. Pharmacokinetic parameters were calculated and peak times of psychoactivity coincided with high alkaloid concentrations, particularly DMT which had an average T_{max} of 107.5 ± 32.5 min. While DMT parameters correlated with those of harmine, THH showed a pharmacokinetic profile relatively independent of harmine's.

Keywords: *Ayahuasca*; Serotonin; Psychoactivity; Religion; Addiction

1. Introduction

Hoasca is a Brazilian word for a decoction of the woody liana *Banisteriopsis caapi*, which is

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pounded and then boiled with the leaves of *Psychotria viridis*. This beverage, also known as *ayahuasca*, *caapi*, *daime*, *yagé*, *natem*, and by many other local names, is found throughout the extensive river regions of Brazil, Bolivia, Ecuador and Peru. Such beverages have been used throughout the Amazon and Orinoco River Basins for both medicinal and ceremonial purposes since antiquity, and remain as sacraments to indigenous religions of these forested regions (Spruce, 1908; Schultes and Hofmann, 1992). While other plants may be added to the brew, and many variations of this beverage have been described (Schultes, 1957; Pinkley, 1969; McKenna and Towers, 1984; McKenna et al., 1984a,b; Luna and Amaringo, 1991; Schultes and Raffauf, 1992; Ott, 1994), the salient common denominator is the presence of harmala alkaloids (Rivier and Lindgren, 1972); particularly harmine, harmaline and tetrahydroharmine (THH). Aside from a brief mention in a congress abstract (Rivier and Holmstedt, 1982), pharmacological studies of this beverage in humans have not been reported.

The harmala alkaloids, obtained from *B. caapi*, were initially identified as the primary components of this beverage (Hochstein and Paradies, 1957), and were subsequently considered to be responsible for the visionary effects (Naranjo, 1967). In this regard, however, these alkaloids function primarily as specific and reversible inhibitors of type-A monoamine oxidase (MAO–A), particularly the more potent harmine and harmaline (Udenfriend et al., 1958; Buckholtz and Boggan, 1977). While not a strong inhibitor of MAO, THH possibly contributes neuroactivity by weakly inhibiting the uptake of serotonin (5-hydroxytryptamine, 5-HT) at presynaptic sites, like other 1-methyl-tetrahydro-β-carbolines (Airaksinen et al., 1980). Subsequently, concentrations of 5-HT increase in the body when both its metabolism by MAO–A and presynaptic uptake are simultaneously blocked by these harmala alkaloids.

The inhibition of MAO also allows for the oral activity of *N*,*N*-dimethyltryptamine (DMT), a potent psychedelic agent often found in these beverages and is obtained from the leaves of *P. viridis*. DMT binds to serotonergic sites in the brain and typically facilitates novel perceptions of reality with complex mental imagery (Holmstedt and Lindgren, 1967; McKenna and Towers, 1984; McKenna et al., 1984a,b, 1990; Deliganis et al., 1991; Ott, 1994; Strassman et al., 1994). The psychoactivity of DMT was first described in the medical literature over 40 years ago (Szára, 1956), at an effective dose of about 1 mg/kg intermuscularly. Ordinarily, DMT is rapidly oxidized by functional MAO to an inactive metabolise (Barker et al., 1980; Suzuki et al., 1981). For this reason it is orally inactive. Harmine and harmaline allow the oral activity of DMT by temporarily inhibiting the activity of MAO, and the resulting visionary effects are a hallmark of this unique plant combination. Fig. 1 shows the molecular structures of DMT and harmala alkaloids, illustrating their chemical similarities to 5-HT.

Aside from conferring oral activity on DMT, MAO inhibition may also contribute to actions of other psychoactive alkaloids that are sometimes found in these beverages; e.g. nicotine from *Nicotiana* species, cocaine from *Erythroxylum coca*, caffeine from *Ilex guayusa*, atropine, scopolamine and other tropane alkaloids from members of the *Solanaceae* family etc. (Schultes, 1957; Pinkley 1969; Ott, 1994). The inherently complex pharmacology of such combinations are essentially unknown to modern medicine, although their utility is indicated by a legacy of human use throughout a large geographical region (Schultes and Hofmann, 1992).

Stemming from indigenous usage, syncretic churches have developed over the last 75 years within urban populations of northern South America, particularly in Brazil. These sects evolved by blending the psychoactive effects of these beverages with Judeo–Christian, African or other Old World religious doctrines. Of these modern religions, the Santo Daime (perhaps the oldest Christian church using this beverage), the União do Vegetal (UDV, the largest unified congregation), and the Barquinha (an Afro–Brazilian church) presently have some of the largest followings. In 1987, the use of such beverages within a religious context was officially recognized and protected by law in Brazil, after lengthy investigations into its alleged threats to public health and national security (Ott, 1994).

Excluding users from the indigenous population, the present number of regular (e.g. monthly) users within the urban populations of South America could be over 15000 individuals (Luna, 1997). In most indigenous groups only a small percentage of the total population use the tea on a regular basis, although most individuals have had it at some time during their lives. In the syncretic churches, however, it is routinely consumed by all adult members on a weekly or bimonthly basis within a ceremonial context. Some physical tolerance may develop through regular use (Callaway et al., 1994), as a reaction to the subsequent and periodic surge in neurotransmitter levels that follow the ingestion of *hoasca* (especially 5-HT), although it is not physically addictive nor has psychological dependence been demonstrated for these beverages. In fact, dedicated members of these modern religions typically lose their interest in the habitual use of alcohol, tobacco, cocaine and other addictive substances (Grob et al., 1996).

During the Summer of 1993, at the invitation of the UDV's Center for Medical Studies, a clinical study was initiated in order to investigate the psychopharmacologic properties of *hoasca*. This invitation was accepted by an international team of medical researchers who were interested in examining the contextual use of this beverage, in addition to examining its potential applications in modern medicine. Our previous articles for this investigation described the analytical methodologies that were used to assay the *hoasca* alkaloids, conduct psychologic inventories of the volunteers before, during and after *hoasca* ingestion, and identify changes in 5-HT uptake site densities on thrombocytes after long term (>10 years) periodic (biweekly) use of *hoasca* (Callaway et al., 1996; Grob et al., 1996; Callaway et al., 1994, respectively). Herein are reported the pharmacokinetic results following the ingestion of *hoasca* in healthy volunteers, and their correlation with some pharmacodynamic effects.

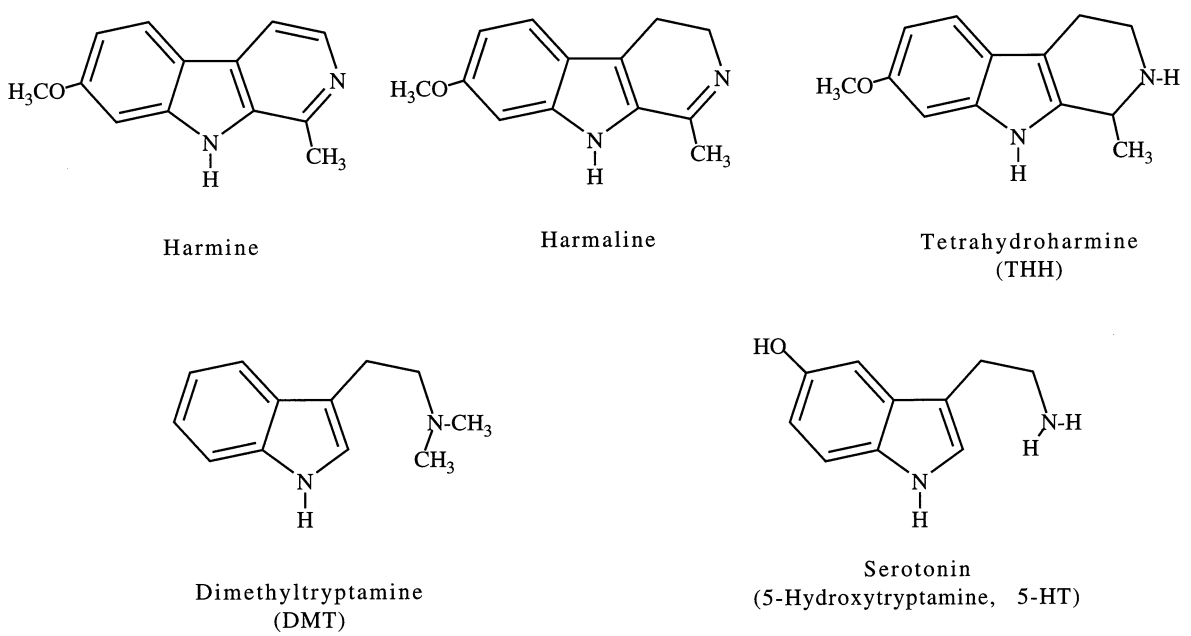

Fig. 1. Molecular structures of *N*,*N*-dimethyltryptamine (DMT) and three harmala alkaloids found in *hoasca*, along with the neurotransmitter serotonin (5-hydroxytryptamine, *S*-HT).

2. Methodology

2.1. The study site

The *Nucleo Caupurí*, a UDV temple on the outskirts of Manaus, Amazônia, was the designated site for this study. Approximately 40 years in existence, this temple is the second oldest *nucleo* of the UDV and has the highest proportion of long-term members.

2.2. The hoasca

Sufficient amounts of *B. caapi* Spruce. ex Grisebach (Malpighiaceae), known as *mariri* to the UDV, and *Psychotria viridis* Ruíz et Pavón (Rubiaceae), known as *chacrona* to the UDV, were gathered on site at the *Nucleo Caupurí* to prepare *hoasca* for the purpose of this study. Plant collection began shortly after dawn. Voucher specimens were collected and authenticated by Dr. D.J. McKenna, and subsequently deposited in the herbarium at the Puutarha Botanical Garden at the University of Kuopio, in Kuopio, Finland (*B. caapi* # 98-147, *P. viridis* # 98148). In preparing the *hoasca*, the woody *B. caapi* was carefully washed in water and pounded with wooden mallets, and the leaves of *P. viridis* were simply rinsed with water.

The plant materials were carefully combined, boiled and concentrated over several hours to produce approximately 120 l of the tea before midnight of the same day. This process was supervised entirely by *mestres* of the UDV, and executed by members of the UDV, according to their religious practice. The tea was tested for quality and potency, in a ceremonial context, prior to the pharmacokinetic study. Alkaloid content of the tea was later quantified by high-pressure liquid chromatography (HPLC), using fluorescence detection (Callaway et al., 1996).

Each of the 15 volunteers (74.2 ± 11.3 kg; average $\pm$ SD) ingested 2 ml/kg of *hoasca* after a baseline blood sample had been collected from a cubital vein, through an indwelling catheter. The actual dose was always rounded up to the nearest power of 10 (e.g. an individual weighing 66 kg received 140 ml of the brew, rather than 132 ml). In every case, the *hoasca* was administered by a *mestre*, in keeping with their tradition, and the entire amount was rapidly consumed (within less than 10 s).

2.3. The volunteers

Fifteen male members of the UDV, between 26 and 48 years of age (35.9 ± 6.9 years; avg. $\pm$ SD), were randomly selected from a larger group of 24 volunteers who had used *hoasca* as part of their regular religious practice for at least 10 years, and who had also passed a physical examination administered by a medical doctor. The medical evaluation included an extensive blood-chemistry panel (SMAC-24), basal cardiac measures, ECG and other standard measures of health. Psychological evaluations were made throughout the study, and these results have been published elsewhere (Grob et al., 1996). In addition to the experimental volunteers, an age matched group of 15 males who had never consumed *hoasca* were subjected to the same medical evaluation, which included blood samples, as previously described (Callaway et al., 1994; Grob et al., 1996).

UDV members typically ingest *hoasca* once every other week, though seldom more often than once a week. All volunteers used some caffeinated beverage on a daily basis. None had used alcohol, tobacco or other drugs for many years, although eleven (73%) were once dependent on tobacco, alcohol and/or other drugs prior to their regular sacramental use of *hoasca* (Grob et al., 1996). All participants gave informed consent to the study. All of the volunteers abstained from their use of *hoasca* for at least 1 week prior to the study. All studies began at 09:00 h, and volunteers were instructed to fast on the morning of their study day.

2.4. Subjective effects

The hallucinogenic rating scale (HRS) is an instrument that was developed to measure the psychotropic effects of injected DMT (Strassman et al. 1994). The HRS was administered to each volunteer before, during and after the acute pharmacokinetic study in an attempt to obtain some

numerical measure of *hoasca's* psychotropic effect, and these results have already been published (Grob et al., 1996).

2.5. Plasma collection

Whole blood was allowed to flow freely through a heparinized line and into an opened test tube that contained aqueous EDTA as an anticoagulant (13 mg EDTA per 10 ml purple top tube, Termo Oy, Espoo, Finland). Samples were capped and briefly mixed by repeated inversions, then centrifuged at $200 \times g$ for 10 min at ambient Amazonian temperatures (33–38°C). The plasma was rapidly transferred to clean glass tubes and frozen on dry ice and subsequently stored at −80°C. All samples remained frozen until analysis. A maximum of three volunteers were studied in a single day, where each administered dose was staggered by 15 min. Blood samples were collected prior to ingestion, then at the following time points (in min): 0, 20, 40, 60, 90, 120, 180, 240, 360, 480 and finally a 24 h sample on the next day. A sample was discarded if collection began over 1 min past the designated time.

2.6. Plasma alkaloid analyses

Harmine, harmaline and THH were measured from plasma using HPLC with fluorescence detection, while plasma DMT was quantified by gas chromatography using nitrogen-phosphorus detection (GC-NPD), as previously described (Callaway et al., 1996).

2.7. Pharmacokinetic calculations

The software package PCNONLIN (Version 4.0, Scientific Consulting) was used to determine concentration–time curves (AUC) for the alkaloids. This program afforded a nonparametric analysis of the pharmacokinetic data, using Levenberg's modification of the Gauss–Newton method for estimating parameters from non-linear regression analyses.

2.8. Neuroendocrine assays

Growth hormone (GH) and prolactin were measured in plasma against standards obtained from the National Pituitary Agency, as previously described (Odell et al., 1967; Poland and Rubin, 1981). GH was iodinated by the glucose-oxidase method and its suitability for radio-immuno assay (RIA) was determined by the talc-resin-TCA method. All samples were analyzed in duplicate. Assay sensitivity was 0.2 ng/ml for both GH and prolactin. Plasma cortisol was determined by RIA, using ^{125}I-cortisol and anti-cortisol antisera (Radio Assay Systems Laboratories), and analyzed as previously described (Poland and Rubin, 1982). Control samples were analyzed in duplicate at the beginning, middle and end of each assay, giving maximum intra- and inter-assay coefficients of variation of approximately 9.0 and 15%, respectively.

2.9. Autonomic measurements

Heart rate, blood pressure, respiration, oral temperature and pupillary diameter were measured after each blood draw until 240 min, each time by the same clinicians, using simple standard techniques.

3. Results

3.1. The hoasca

Emperical testing of the freshly prepared tea, by experienced members of the UDV, provided verification that the beverage was typical and suitable for the pharmacokinetic study. Subsequently, it was decided that a standard dose of 2 ml/kg body weight would be used throughout the study. In retrospect, this particular amount was considered to be somewhat mild in effect, according to the volunteers. Analytical analyses revealed the alkaloid content of the *hoasca* to be: harmine 1.70 mg/ml, harmaline 0.20 mg/ml, THH 1.07 mg/ml and DMT 0.24 mg/ml.

Table 1
Averages and ranges of body weight, amount of *hoasca* ingested (2 ml/kg) and amounts of alkaloids consumed by 14 volunteers

	Body weight (kg)	Tea (ml)	DMT (mg)	THH (mg)	Harmaline (mg)	Harmine (mg)
Average	74.2 ± 11.3	148.4 ± 22.6	35.5 ± 5.3	158.8 ± 24.2	29.7 ± 4.5	252.3 ± 38.4
Range	58–90	120–180	28.8–43.2	128.4–192.6	24.0-36.0	204.0–306.0

3.2. The volunteers

From the preclinical investigations, no significant differences were found between the experimental and control groups (note: the latter group of *hoasca*-naive individuals were not included in the pharmacokinetic phase of this study). The ranges and averages of body weights for the 14 experimental volunteers included in these analyses, and averaged amounts of tea, and measured alkaloids consumed, are presented in Table 1. One of the 15 volunteers vomited during the pharmacokinetic study, approximately 45 min after ingestion, and experimental data from this individual were not included in the final analyses of this report.

3.3. The subjective effects

The duration of psychoactivity from the tea was coincidental with alkaloid plasma levels. In particular, peak plasma levels of DMT were associated with intricate and colored eyes-closed visual imagery, complex thought processes and a general state of heightened awareness. Overall perceptual, cognitive, and affective processes were significantly modified while maintaining the presence of a clear sensorium. All 15 volunteers experienced these subjective effects at this dosage (2 ml/kg).

3.4. Pharmacokinetics

Although peak plasma levels for DMT were determined in all volunteers, only 12 had sufficient concentrations for all pharmacokinetic calculations. The following data are reported as the mean $\pm$ SD, in plasma. The C_{max} for DMT ($n = 12$) was 15.8 ± 4.4 ng/ml, with a T_{max} of 107.5 ± 32.5 min. Pharmacokinetic values for harmine were determined for 14 volunteers, giving a C_{max} of 114.8 ± 61.7 ng/ml and a T_{max} of 102.0 ± 58.3 min. Levels of harmaline were already low in the beverage, thus C_{max} (6.3 ± 3.1 ng/ml) and T_{max} (145.0 ± 66.9 min) were determined for only five volunteers. Pharmacokinetic values for THH were determined for all 14 volunteers, giving a C_{max} of 91.0 ± 22.0 ng/ml and a T_{max} of 174.0 ± 39.6 min. These and other pharmacokinetic parameters of the four alkaloids are summarized in Table 2. Plasma alkaloid concentrations for harmine, THH and DMT were averaged and plotted against time for the 14 volunteers, and these data are presented in Fig. 2. None of these alkaloids were detected in blank samples collected before the ingestion of *hoasca*, nor at the zero time point. Only THH was detected, at low levels, in three of the volunteers at the 24 h time point.

3.5. Neuroendocrine effects

All measures of neuroendocrine response showed sharp increases over basal levels for each volunteer (Fig. 3). The following are reported as the mean $\pm$ SEM. After 20 min, levels of plasma growth hormone began to increase to a maximum at 90 min (9.44 ± 2.41 ng/ml), then returned to basal levels (0.54 ± 0.48 ng/ml) by 360 min (Fig. 3A). Plasma prolactin levels began to increase after 40 min, to a maximum at 120 min (33.90 ± 8.86 ng/ml), then also returned to basal levels (7.60 ± 1.26 ng/ml) by 360 min (Fig. 3B). Plasma cortisol values increased to a maximum at 60 min (132.60 ± 10.72 ng/ml), dipped below basal levels (66.80 ± 10.12 ng/ml) after 360 min, and showed a significant increase ($P < 0.05$) to 73.90 ± 11.40 ng/ml over basal values in the 24 h samples (Fig. 3C).

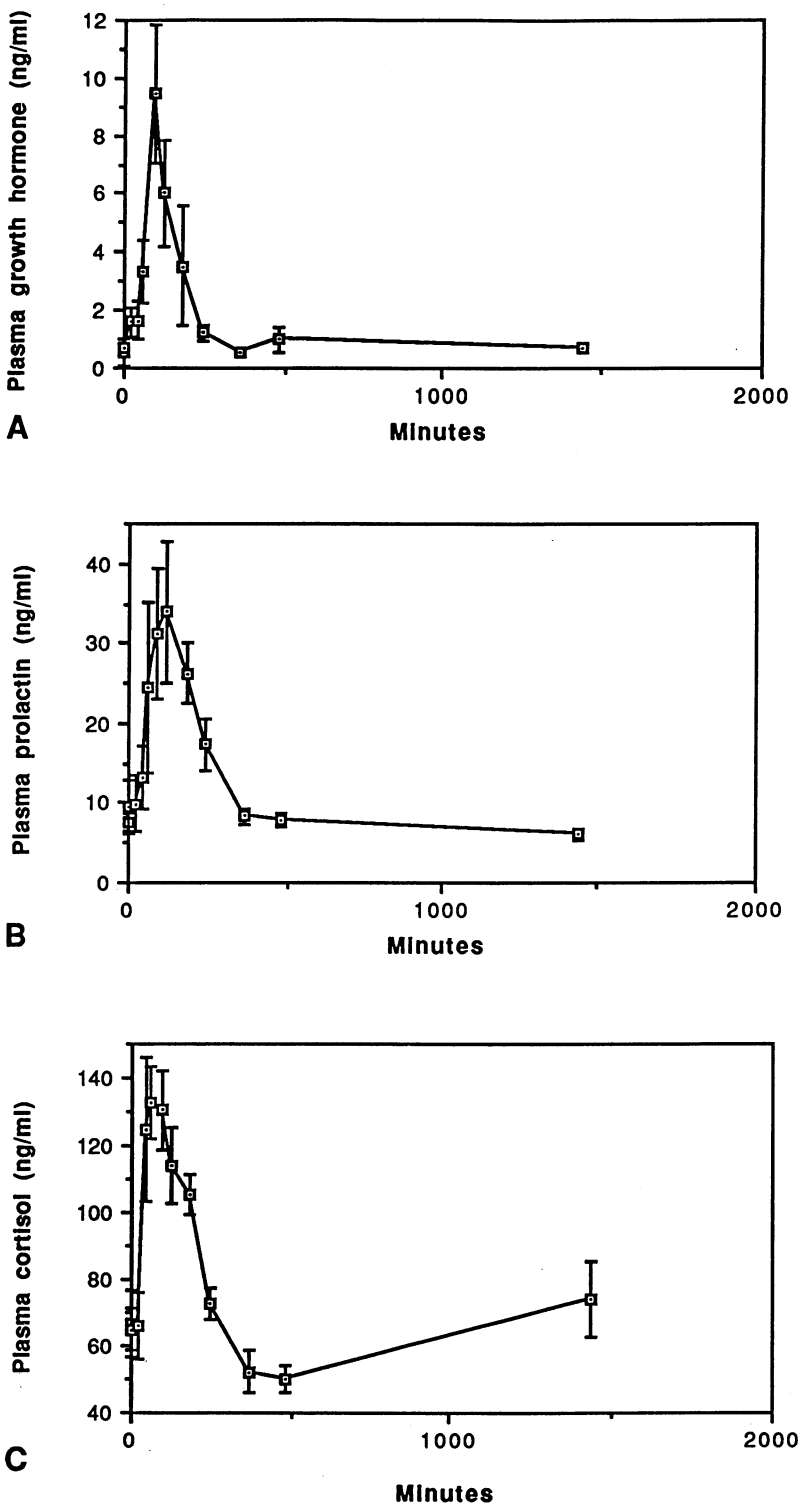

Fig. 3. Averaged values and standard errors for the following neuroendocrine values, in ng/ml plasma, are shown for the 14 volunteers after *hoasca* (2 ml/kg); growth hormone 3A, prolactin 3B, and cortisol 3C.

3.6. Autonomic effects

All measures showed increases over basal levels for each volunteer (Fig. 4). The following results are reported as the mean ± SEM. Pupillary diameter increased over basal values (3.7 ± 0.2 mm) after 40 min, to a maximum of 4.9 ± 0.2 mm at 180 min, and pupils remained dilated after the last measurement at 240 min (Fig. 4A). Pupil size typically returned to normal after approximately 6 h at this dosage (2 ml/kg). Respiration rate increased slightly over basal values (18.4 ± 0.7 breaths/min), to a maximum of 21.5 ± 1.0 at 90 min, and fluctuated throughout the study, showing an overall increase after 240 min (Fig. 4B). Oral temperature increased slightly over basal measures (37.0 ± 0.1°C), reaching a maximum of 37.3 ± 0.1°C by 240 min (Fig. 4C). It should be noted here that ambient room temperature also increased (33–38°C) throughout each day as the study sessions progressed from morning to afternoon.

3.7. Cardiovascular effects

All measures showed increases over basal levels for each volunteer. The averaged values and SEM of all 14 volunteers are illustrated in Fig. 5. The following results are reported as the mean ± SEM. Heart rate initially increased over basal values (71.9 ± 2.9 bpm) to a maximum of 79.3 ± 0.3 bpm by 20 min, decreased to a minimum of 64.5 ± 2.2 bpm by 120 min, then increased towards basal levels by 240 min. Both systolic and diastolic pressures increased to maxima after 40 min (137.3 ± 3.2 and 92.0 ± 3.0 mmHg, respectively) over basal values (126.3 ± 3.9 and 82.7 ± 2.9 mmHg, respectively), gradually returning to basal levels by 180 min. At 240 min, the systolic pressure was 123.9 ± 3.2 mmHg and the diastolic pressure was 81.1 ± 2.8 mmHg.

Table 2
Pharmacokinetic parameters (avg. ± SD) of *hoasca* alkaloids from 14 volunteers

	C_{max} (ng/ml)	T_{max} (min)	$T_{1/2}$ (min)	k_{obs} (min^{-1})	C1/F (ml/min/kg)	V_{ss}/F (l/kg)	AUC_{inf} (mg min/ml)	MRT (min)
Harmine ($n = 14$)								
Avg.	114.8	102.0	115.6	0.016	271.7	49.6	22.88	180.2
± S.D.	61.7	58.3	60.1	0.027	180.3	40.4	11.69	55.7
Harmaline								
Avg.	6.3	145.0	—	—	—	—	—	—
± S.D	3.1	66.9						
THH ($n = 14$)								
Avg.	91.0	174.0	531.9	0.003	63.3	43.5	47.78	548.9
± SD	22.0	39.6	290.8	0.002	21.9	8.0	25.88	404.2
DMT ($n = 12$)								
Avg.	15.8	107.5	259.4	0.008	221.8	54.8	5.60	357.7
± SD	4.4	32.5	207.2	0.016	129.9	14.8	4.53	271.5

Due to low concentrations, parameters for DMT could only be determined in 12 volunteers, while only C_{max} end T_{max} could be calculated for harmaline in five volunteers.
Avg, average.

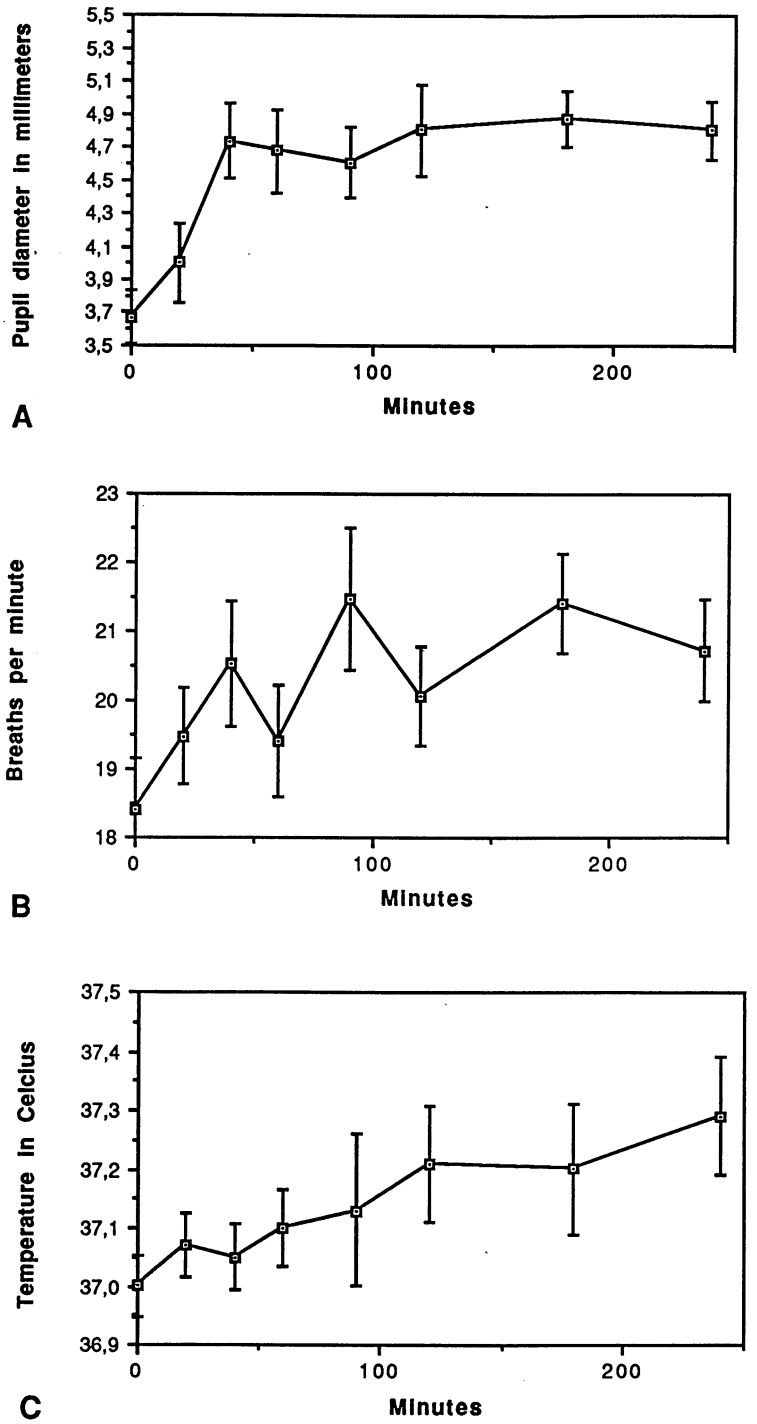

Fig. 4. Averaged values and standard errors for the following autonomic responses, after *hoasca* (2 ml/kg), are shown for the 14 volunteers; pupillary diameter 4A, respiration rate 4B, and oral temperature 4C.

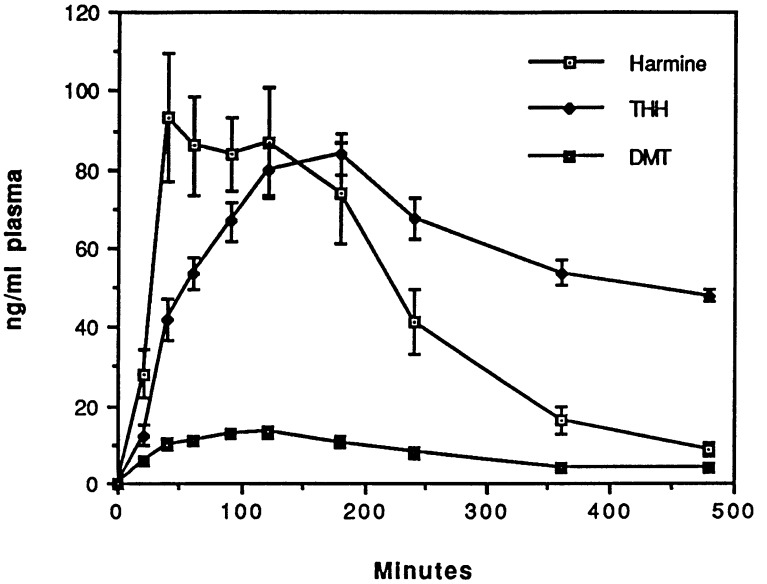

Fig. 2. Averaged values and standard errors of harmine, THH and DMT concentrations, in ng/ml plasma, are shown for the 14 volunteers after *hoasca* (2 ml/kg).

4. Discussion

The purpose of this study was to examine the pharmacokinetic effects of *hoasca* in healthy humans. The alkaloid content of the *hoasca* used in this study are in agreement with published reports of tea dosages from other sources (McKenna et al., 1984a; Liwszyc et al., 1992; Casale and Koles, 1995; Don et al., 1998), and the beverage itself was considered typical of *hoasca* by experienced volunteers. While the dosage of *hoasca* in this study was considered mild, by comparison, the plasma alkaloid levels were sufficient for analytical detection, and larger amounts of the tea could have increased the risk of nausea and vomiting. The *hoasca*-naive agematched control group was not included in the acute pharmacokinetic study. The control group was only used in this study to provide a standard baseline measure of health, and a measure of platelet uptake site density in a *hoasca*-naive population of the region (Callaway et al., 1994).

Changes in DMT pharmacokinetic profiles were reflected in autonomic and neuroendocrine responses, and subjective effects, as previously reported (Strassman and Qualls, 1994; Strassman et al., 1994). The intensity and duration of subjective effects between *hoasca* versus intravenous DMT, however, differed considerably. In the present study, the most intense visionary effects were reported to occur between 60 and 120 min after ingesting the tea, which corresponds with the average T_{max} for DMT (Table 2). Moreover, the results from our psychological inventory with *hoasca* use (Grob et al., 1996) indicate qualitative differences between comparable levels of injected DMT, where the onset of maximal effect tended to be more rapid, singular in effect, and of shorter duration (Strassman et al., 1994). The quantitative difference is obviously due to the inherent differences in routes of administration; i.e. intravenous versus orally activated DMT. The qualitative differences can be explained by the suggestion that the visionary effects of DMT manifest through interactions at central serotonin receptor sites (Deliganis et al., 1991), where subjective effects are modified by increased levels of 5-HT, which provides competition for DMT at these sites.

The purgative effects of *hoasca* are considered to be tonic, rather than toxic, according to those who use this beverage with regularity. Variable

degrees of nausea, vomiting, and occasionally simultaneous diarrhea, are not uncommon. These effects vary according to the individual, dosage, and alkaloid composition of the tea. They are probably symptomatic of the increasing levels of unmetabolized 5-HT throughout the acute phase of this experience, which is a consequence of MAO-A inhibition by both harmine and harmaline (Buckholtz and Boggan, 1977). Vomiting, for example, results from increased vagal stimulation by central 5-HT, and increased peripheral 5-HT can stimulate intestinal motility to the point of diarrhea. A fine transient tremor and nystagmus were also observed in some cases. This may be due to receptor mediated interactions of harmala alkaloids on tryptamine binding receptors (Rommelspacher and Bruning, 1984; Airaksinen et al., 1987).

Increased heart rate and blood pressure may be due to unmetabolized catecholamines after MAO inhibition, where increasing levels of central 5-HT later attenuate this effect by decreasing cardiac response through vagal stimulation (Udenfriend et al., 1958). Similar modifications in cardiac performance have already been reported in humans and other animals for both harmine and harmaline (Goldberg and Sjoerdsma, 1959; Sjoerdsma et al., 1959; Pletscher et al., 1960). While increases in cardiac responses were remarkable, they were not hypertensive. Four individuals presented heart rates less than 60 bpm at 120 min after *hoasca* ingestion (59, 59, 58 and 52 bpm), where the two lowest measures had basal heart rates below the group average (65 and 62 bpm, respectively).

With the regular use of *hoasca*, subsequent periodic increases in levels of 5-HT may signal a compensatory upregulation of 5-HT uptake sites on blood platelets (Callaway et al., 1994). Since none of the volunteers showed signs of active or current depression (Grob et al., 1996), which might be expected from a net lack of synaptic 5-HT activity through its increased uptake, it is conceivable that such an upregulation could actually stimulate 5-HT production to fill these receptor sites during the times between *hoasca* sessions.

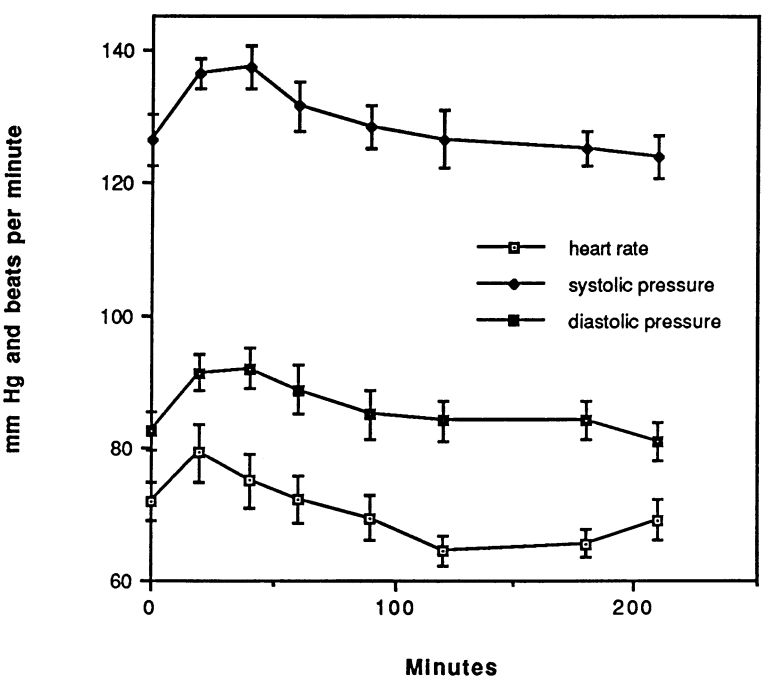

Fig. 5. Averaged values and standard errors of heart rate, systolic and diastolic pressures, after *hoasca* (2 ml/kg), are shown for the 14 volunteers. Heart rate, in beats per min (bpm) and pressure in mmHg share the same numeric scale on the vertical axis.

The mechanism of action for *hoasca* and analogous beverages apparently begins with the inhibition of MAO by harmine and, to a lesser extent, harmaline. This action allows for the oral activity of DMT, a mechanism suggested over 30 years ago (Holmstedt and Lindgren, 1967). Where the T_{max} of injected DMT (0.4 mg/kg) was only about 2 min with a resulting C_{max} of 15.8 ng/ml (Strassman and Qualls, 1994), gastrointestinal absorption and subsequent MAO inhibition lengthened T_{max} to 108 ± 32.5 min and increased C_{max} to 90.0 ng/ml at a comparable oral dose of DMT from 2 ml/kg *hoasca* (i.e. 0.48 mg DMT/kg). Ordinarily, DMT is not orally active, even at 25 times the oral dosage used in the present study (Ott, 1994).

The oral activity of DMT in *hoasca* is apparently facilitated by the presence of harmala alkaloids. This has been tested in man (Ott, 1994) by achieving *hoasca*-like psychoactivity through the simultaneous oral ingestion of pure harmine (1.5 mg/kg) with DMT (0.44 mg/kg). The same has been demonstrated for 5-methoxy-DMT (Callaway, 1993), which is also orally inactive. An earlier study using iproniazid, a non-specific MAO inhibitor, had already demonstrated that DMT is primarily metabolized by MAO (Barker et al., 1980). As the harmala alkaloids are known to preferentially inhibit MAO-A (Buckholtz and Boggan, 1977), it follows that DMT would be the preferred substrate for this particular isozyme (i.e. MAO-A). However, one report has suggested that DMT is preferentially metabolized by MAO-B (Suzuki et al., 1981), while 5-methoxy-DMT is preferentially metabolized by MAO-A (Squires, 1975). A metabolic study on DMT showed this alkaloid to be rapidly metabolized in the blood to dimethylkynuramine by an unknown enzymatic reaction (Hryhorczuk et al., 1986). Moreover, it is also conceivable that increasing levels of 5-HT could compete with DMT for any of these reactions, and effectively slow its eventual metabolism in that way.

The EC_{50} for the inhibition of MAO-A has been reported to be 8×10^{8} M for harmine, 6×10^{-8} M for harmaline and 1.4×10^{-5} M for THH, and at higher concentrations both harmine and harmaline begin to inhibit MAO-B (Pletscher et al., 1960; Buckholtz and Boggan, 1977). In the present study, plasma concentrations of harmine alone were several orders of magnitude greater than its reported EC_{50}. By considering the high concentrations of harmala alkaloids in *hoasca* that are typically ingested, it could be argued that this amount is aufficient to inhibit both isozymes of MAO.

Due to its weak affinity, and in the presence of high harmine concentrations, THH may not play a significant role in the inhibition of MAO. Instead, THH may contribute psychoactivity indirectly by inhibiting the uptake of 5-HT in platelets and presynaptic neurons (Airaksinen et al., 1980), further increasing extracellular 5-HT levels over those seen from MAO inhibition alone, as significant amounts of this alkaloid are known to occur in *B. caapi* (Rivier and Lindgren 1972; Callaway et al., 1996). The pharmacokinetic profile of THH (Fig. 2) and related parameters (Table 2) also suggests some independence from interactions between harmine and MAO. It is possible that the activity of THH may even be potentiated by MAO inhibition.

All changes in neuroendocrine responses correlated with subjective effects. Growth hormone and prolactin are under the influence of the serotonergic system, and serve as indicators of increased serotonergic action (Van de Karr, 1991). The neuroendocrine challenge by *hoasca* provides information on the functionality of the serotonergic system. Increased cortisol and prolactin levels were comparable to previously reported values after injected DMT, although the action of MAO inhibition seems to have prolonged the time response by a factor of 4–5 in the present study. Increased levels of growth hormone followed, as well, which was also seen after injected DMT (Strassman and Qualls, 1994). The increased levels of prolactin and growth hormone that were observed in the present study probably reflect increased activation of 5-HT receptors, again through increased levels of 5-HT (Scheinin et al., 1990). Increased cortisol levels also follow this sudden surge in neurochemical activity.

Increased pupillary diameter, oral temperature and cardiac effects were also reported earlier for 0.4 and 0.2 mg/kg i.v. doses of DMT (Strassman

and Qualls, 1994), but these effects were of shorter duration than the increases seen in the present study.

5. Conclusions

A long and continuous history of regular use indicates the utility of *hoasca*. Signs of physical or psychological deterioration were not observed as a consequence of its use. Instead, the regular use of *hoasca* in a ceremonial context seems to increase one's ability to psychologically adapt to the larger process of life (Grob et al., 1996).

By investigating human reactions to psychotropic agents, we begin to bridge the gap between neurochemistry and cognition. The clinical and pharmacokinetic data obtained from this prospective study provide some direction for further investigations into the complex psychopharmacology of *hoasca*, and related substances, in healthy human volunteers. Although preliminary in nature, the results from this study suggest that such neurochemical agents are powerful tools that can enable a more comprehensive study of the mind.

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