A Pharmacological Study of **Ayahuasca** in Healthy Volunteers

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THERE CAN BE few natural psychoactive preparations whose consumption has increased so spectacularly as has that of ayahuasca in Europe over the last decade. The Amazonian inebriant *par excellence*, whose Quechuan name means "vine of the souls" or "vine of the dead" enjoys great prestige among several intellectual circles and in certain religious practices of Brazilian origin as a medium facilitating introspection and self knowledge. The fact that it is natural is highly valued in these spheres, to the detriment of synthetic drugs with analogous properties to which, in contrast, inferior qualities or clearly harmful properties are attributed. Although ayahuasca is not as widely used by the general public as amphetamine derivatives of the MDMA type are, it has a achieved a certain popularity and is beginning to attract media attention in Spain; in Summer 1997 a weekly general interest magazine labelled it a "fashionable drug" on the Spanish island of Ibiza.

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Our study aims to be the first controlled pharmacological study of ayahuasca in humans undertaken in a Western country and with local volunteers who are familiar with its consumption. In this first phase we do not intend to discuss the possible adverse psychopathological effects derived from repeated consumption, nor to study the hypothetical therapeutic qualities suggested by some. In addition to collecting information about the preparation's pharmacokinetics and tolerability after the administration of different single doses we also aim to place special emphasis on its neurophysiological and subjective effects; quantitative pharmacoelectroencephalography and an evaluation scale of the subjective effects of hallucinogens, whose validation in Spanish will be undertaken in the course of the project, will be used respectively. We also aim to model pharmacokinetic-pharmacodynamic relationships using *N,N*-dimethyltryptamine (DMT) plasma levels and the modifications observed in the electroencephalogram.

In addition to the study's pharmacological aspects we propose to collect information regarding phenomenological aspects of the experience through interviews with the volunteers after the experimental sessions. This is a very ambitious project indeed and our group is therefore in contact with Rick J. Strassman, a psychiatrist who consulted, and James C. Callaway, a neurochemist who participated in the 1993 Hoasca Project[1] and who have kindly made valuable suggestions for the carrying out of this study.

We shall now take a brief look at the recognised pharmacological aspects of ayahuasca and comment on the objectives and methodological issues of this study.

The pharmacology of ayahuasca

As most readers will be aware, ayahuasca, a brown-reddish drink with a strong taste and smell, is a shamanic drug originating in the Amazon. It is obtained from infusing the shredded stalk of the malpighiaceous plant *Banisteriopsis caapi* with the leaves of other plants, generally *Dyplopteris cabrerana* or *Psychotria viridis*. During the cooking process, which may last for hours, a plethora of chemical compounds from these plants enter the infusion. *Banisteriopsis caapi*'s chief contribution is three alkaloids generically known as ß-carbolines, namely harmine, tetrahydroharmine and to a lesser degree harmaline, while *Dyplopteris cabrerana* and *Psychotria viridis* contribute large quantities of *N,N*-dimethyltryptamine, or simply DMT. The final chemical compositions of ayahuasca infusions show great variability owing to fluctuations in the alkaloid contents of the plants used in its preparation, the differing extraction times and different practices with regard to the greater or lesser concentration of the infusions once obtained.

Of the four main alkaloids which the drink contains it is DMT which is chiefly responsible for its hallucinogenic effects. DMT is a potent ultra-short acting hallucinogen present in numerous species of plant growing in temperate and tropical regions. Before its presence in

[1]Grob CS, McKenna DJ, Callaway JC, Brito GS, Neves ES, Oberlaender G, Saide OL, Labigalini E, Tacla C, Miranda CT, Strassman RJ and Boone KB (1996) Human Psychopharmacology of Hoasca, a Plant Halluncinogen Used in Ritual Context in Brazil, *J of Nervous and Mental Disease* 184(2):86-94.

ayahuasca was discovered it had in fact been identified, along with other indole derivatives in *Anadenanthera* hallucinogenic snuffs which had been used in South America since before Columbus. The compound is remarkable within the hallucinogen family because of its pharmacological characteristics; when administered parenterally it produces extremely strong effects which are felt almost immediately (intravenously) or within around ten minutes (intramuscularly), to disappear within the space of about half an hour or forty-five minutes. Surprisingly, when the drug is administered orally it provokes no psychoactive effects whatsoever, even in doses as high as a gram, appearing to be entirely destroyed in the intestines and at hepatic level by monoamine oxidase (MAO), an enzyme which is widely distributed throughout the body, and thus prevented from reaching systemic circulation and the brain. Because of DMT's inactivity when taken orally several other methods of parenteral administration have been used; *Anadenanthera* and *Virola* snuffs are taken through the nose and synthetic DMT has circulated in a free base form for smoking.

On a molecular level DMT interacts equally with serotonin 5-HT1a and 5-HT2a/2c receptor sites, just like LSD does. Unlike LSD, however, repeated administration of DMT does not lead to tolerance of the subjective effects, or at least it has not done so in studies carried out to date. Furthermore, DMT does not show cross tolerance with this classic hallucinogen; that is, an individual who has developed tolerance to the effects of LSD through repeatedly taking the drug will experience full hallucinogenic effects if administered a dose of DMT.

What is truly extraordinary about ayahuasca is that in a single preparation it combines DMT which is inactive when taken orally with the ß-carbolines referred to above. These tricyclic compounds, to which proserotonergic and prodopaminergic properties are attributed, lack hallucinogenic activity but *in vitro* they display a potent inhibiting activity with respect to the MAO enzyme, or to be more precise, the isoenzyme MAO-A. In line with the generally accepted hypothesis the ß-carbolines' inhibiting of this enzyme would prevent the oxidative deamination of the DMT, which could then reach and exercise its effects on the central nervous system. The experience which follows the ingestion of ayahuasca differs from the effects of parenterally administered DMT by being less intense and of greater duration; the onset of its effects is not instantaneous but occurs approximately an hour after ingestion and the effects usually last for a maximum of two hours, to disappear altogether after around three or four hours. In addition, adverse events such as nausea and vomiting, which are not observed in the parenteral administration of DMT and which are attributable to the action of the ß-carbolines, frequently occur. The inhibiting of the MAO brings with it an increase in endogenous catecholamine and serotonin levels which would modulate the effects of the DMT, either reinforcing them or, as has also been postulated, reducing them given that the DMT now has to compete for the 5-HT2 receptor with higher serotonin levels.

Design of the study and objectives

The study will be carried out at Hospital St. Pau in Barcelona and has been approved by the hospital's Ethics Committee and by the Spanish Ministry of Health, which is responsible for approving clinical studies undertaken in the country. A total of 18 healthy volunteers of both sexes will participate, all of whom are acquainted with the effects of ayahuasca, or if not, with other hallucinogens. The study has been designed to take advantage of the presence of local people who are aware of the effects of ayahuasca and are in principle willing to take part in a study of this nature. The inclusion of individuals with experience of these drugs was decided on at the outset; using subjects who were not familiar with them seemed to us ethically unacceptable, a criterion which would doubtless be shared by any ethics committee, granted that the use of such drugs is not entirely without risk. To minimalize the risk of adverse reactions appearing during the sessions special emphasis will be placed on the psychiatric examination of volunteers during the selection stage, and they will be put in contact with team members and able to familiarise themselves with the facilities in which the study will be carried out before the sessions begin. They will also be fully informed as to the nature and objectives of the study and will be required to give prior written consent to their participation.

During the course of the investigation two doses of ayahuasca (0.5 and 0.8 mg/kg of DMT) and one placebo will be administered. The study has been designed as a double blind, that is, neither the subject nor the researcher will know whether the drug administered is ayahuasca or a placebo, and if it should be ayahuasca they will not know the size of the dose. The double blind condition will be maintained until the information gathered is analyzed. The investigation will be cross-over and randomized, which is to say that the 18 participant subjects will receive the three preparations in totally random order, and a washout period of two weeks between experimental sessions will also be established.

Given the study's double blind nature the ayahuasca used will not be administered in its normal liquid form, as the preparation's appearance, color and flavor would prevent its being administered without the subject's knowledge. To achieve efficient masking the following process will be carried out: the ayahuasca will undergo a lyophilization process in which the water in the infusion is eliminated in a high vacuum chamber at low temperature, after which the solid obtained will be homogenised and analyzed. In this way the different alkaloid concentrations per gram of lyophilized product can be determined and the doses adjusted according to the main active element, DMT. Finally, a quantity of the lyophilized substance corresponding to 0.5 mg/kg and 0.8 mg/kg of DMT will be encapsulated for each subject; the quantity of ß-carbolines administered in each dose will also inevitably vary. Instead of obtaining natural ayahuasca, lyophilizing and encapsulating it, we initially considered the option of administering a synthetic analogue which combined variable quantities of DMT with fixed quantities of ß-carbolines. This would have permitted the elimination of the "background noise" of increasing levels of ß-carbolines and other undesirable effects predominantly attributable to these compounds, but would have yielded results that could not have been applied to the natural preparation, which is ultimately the subject of the study. So, the study's objectives are as follows:

1. Description of the pharmacokinetics of *N,N*-dimethyltryptamine and ß-carbolines, the main alkaloids in ayahuasca, after the oral administration of increasing doses of the preparation.
2. *In vivo* determination of MAO inhibition provoked by ayahuasca.
3. Quantification of ayahuasca's pharmacological effects on the central nervous system: neurophysiological and subjective effects.
4. General tolerability of the preparation.
5. Study of the concentration-response relationships (PK/PD).

Pharmacokinetics

The aim is to study the pharmacokinetics of the four main alkaloids present in ayahuasca, that is their absortion, distribution and elimination through determining their plasma levels at regular intervals. So, having administered two single different doses the plasma levels of *N,N*-dimethyltryptamine, harmine, harmaline and tetrahydroharmine will be quantified.

The MAOI effect

On a peripheral level the pharmacodynamic effect studied will be the inhibiting of the monoamine oxidase enzyme previously referred to. Blocking noradrenaline, dopamine and serotonin's natural metabolic breakdown pathway leads to measurable variations of these compounds in plasma and, in the case of dopamine and noradrenaline, to variations in the relationships between the metabolites obtained through this pathway and those deriving from the action of another degrading enzyme named catechol-O-methyl-transferase or COMT. One of this study's objectives is the *in vivo* verification of the inhibiting of MAO associated with ayahuasca, the effect which is generally assumed to be responsible for DMT's activity when administered orally. An alternative method traditionally used to study MAOI activity consists of determining the degree of platelet MAO inhibition; in comparison with the determination of monoamines and their metabolites in plasma, this approach does not have the drawback of requiring a complex analytical technique. However, its use in the study of selective inhibitors of MAO has been called into question as the predominant isoenzyme in the platelets is MAO-B, which consequently would only be inhibited by drugs with either non-selective blocking activity or one specific to isoenzyme B.

Effects on the Central Nervous System

There are many problems inherent in studying the effects of hallucinogens on the central nervous system. Their eminently subjective nature hinders quantification and the fact that they are highly incapacitating makes it difficult for volunteers to undertake tasks or communicate with the evaluator. The evaluation of drugs' effects on the central nervous system is usually carried out via psychomotor performance tests and by using questionnaires to which the subject responds at regular intervals before and after taking the drug, or which may be completed by the evaluator according to the volunteer's responses.

These tests and scales have been used with numerous psychoactive drugs which, although potent, do not completely prevent the subject from performing tasks nor from interacting with the evaluator. However, given the profound alteration of consciousness experienced by the subject after a hallucinogen has been administered and the overwhelming nature *per se* of the effects of hallucinogens, asking the subject to actively collaborate by completing these scales is not feasible. Certain Visual Analogic Scales (VAS) which require minimal cooperation from the subject, and questionnaires which may be completed once the drugs' effects have worn off, are perhaps an exception.

Subjective effects study

The subjective effects will be studied through the use of scales which permit the ayahuasca's effects to be quantified. However, the subjects will not respond to the questions until the effects of the ayahuasca have worn off. One of the scales for use is the Hallucinogen Rating Scale developed by Rick J. Strassman, which has been translated by our group and whose validation in Spanish forms part of the study. The scale contains 100 items grouped according to six clinical factors which are characteristically affected by hallucinogens: cognition, volition, somaesthesia, intensity, perception and affect. According to its author, this scale describes the effects produced by DMT more accurately than pre-existing scales, which were compiled on the basis of data gathered after the administration of LSD.

This scale does not permit the time sequence of the drug's effects to be followed and it will not therefore be possible to establish correlations with plasma levels, but it does allow the overall quantification of these effects to obtain numerical values which in principle will be in relation to the dose of the drug administered. One of the study's objectives, therefore, is to verify the validity of a scale which, despite being designed for a specific compound (DMT) and a specific means of administration (intravenous) also aims to be of use with other hallucinogenic drugs and other methods of administration.

Neurophysiological study

An alternative method which does not require the volunteer's cooperation and is therefore free from the limitations mentioned above is quantitative pharmaco-electroencephalography. This neurophysiological method, which is totally painless, non-invasive and causes minimal distress to the individual, permits the continuous registration of variations in the electrical activity of the brain cortex caused by drugs which act on the central nervous system. The electrical activity picked up by electrodes placed on the scalp is measured at regular intervals and can then be digitalized and submitted to a frequency analysis from which a series of variables is extracted. These then undergo statistical analysis to determine whether any of the 32 variables characteristically generated by the brain's electrical activity has been significantly altered with the administration of the drug, and whether the variation is dose-dependent.

The relative simplicity of registering this electrical activity allows information to be obtained continuously throughout the experimental session. This permits the subsequent correlation of the plasma levels of the drug administered (pharmacokinetic variable), in this case DMT, with the effect it sets in motion on the cortex's electrical activity (pharmacodynamic variable) in an integrated pharmacokinetic-pharmacodynamic model.

Tolerability

Tolerability refers to the modifications observed in the subject's vital signs after the drug's administration and any event, either physical or psychological, regarded as unpleasant by the

subject. The following vital signs will be measured at varying intervals during the experimental sessions: systolic and diastolic blood pressure, heart rate and body temperature; as all these variables can be modified by the different activation of the serotonergic pathways, variations in their rates and levels can be expected. All adverse events which may be produced will also be registered.

In addition, electrocardiograms and clinical analyses will be carried out between the experimental sessions to check whether these parameters have been affected by the administration of the ayahuasca.

Pharmacokinetic- pharmacodynamic modelling

We intend to approach the task of correlating pharmacokinetics and pharmacodynamics through using data on the evolution of the DMT plasma concentrations and information from the encephalography, in such a way that will enable us to describe the evolution of the ayahuasca's effects for each individual. This approach aims to go beyond classical dose-response curves, which are subject to great individual variability because of factors which may not be of a pharmacokinetic nature. Using this approach in the present study is particularly attractive because we are faced with a prototypical case of theoretic applicability in that the biophase (CNS) of the main active constituent (DMT) is clearly outside the denominated central compartment (plasma) so the maximum plasma concentrations and maximum central effect can be expected to be out of phase to a certain extent.

Conclusion and acknowledgements

To summarise, this study aims to contribute to knowledge of the acute effects of ayahuasca, a plant hallucinogen which is widely used in South America and is becoming increasingly popular in our culture. Including highly-motivated volunteers who are acquainted with its effects will ensure the safety of the experimental sessions as far as possible and will permit the study of the pharmacokinetics at increasing dose levels, central neurophysiological and subjective effects, tolerability, and peripheral effects of a preparation whose characteristics are highly interesting from a pharmacological point of view and which has scarcely been studied up to the time of writing. We wish to express our gratitude to Dr. Rick J. Strassman at the University of British Columbia (Canada) for his advice on translating the Hallucinogenic Rating Scale, and to Dr. James C. Callaway at the University of Kuopio (Finland) for his useful suggestions and support in this early stage of the study and for offering to analyze the ayahuasca samples which will be used. Finally, we would also like to thank Rick Doblin and Sylvia Thyssen at MAPS for kindly inviting us to make our project known to the *Bulletin*'s readers. •

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