Ayahuasca Preparations and Serotonin Reuptake Inhibitors: A Potential Combination for Severe Adverse Interactions

James C. Callaway, Ph.D.* & Charles S. Grob, M.D.**

Abstract—The Amazonian psychoactive plant beverage ayahuasca has attracted increasing interest in recent years. Little attention has been given, however, to potentially dangerous interactions with other drugs. In particular, the interaction between the potent monoamine oxidase-inhibiting harmala alkaloids in ayahuasca and the selective serotonin reuptake inhibitor (SSRI) class of antidepressants may induce a serotonin syndrome with potentially grave outcome. Caution is advised when combining ayahuasca with certain pharmaceutical drugs.

Keywords—ayahuasca, drug interactions, harmala alkeloids, selective serotonin reuptake inhibitor (SSRI), serotonin syndrome

Ayahuasca (a Quechua word meaning "vine of the soul") is a psychoactive beverage that has been used for religious purposes throughout the Amazon and Orinoco River Basins since prehistoric times (Schultes & Hofmann 1992). Also known as *hoasca, daime, yage, caapi, natema*, and by many other local names, this beverage characteristically contains harmala alkaloids, which are derived from the vine *Banisteriopsis caapi* (Callaway et al. 1996; Ott 1994, 1993; Luna & Amaringo 1991). These alkaloids, primarily harmine and harmaline, are capable of blocking the enzymatic activity of monoamine oxidase (MAO) for several hours, and consequently inhibit the metabolic breakdown of neurotransmitters. While the inhibition of this enzyme's action is not intrinsically life threatening, lethalities from combinations of MAO type-A inhibitors (MAOIs) with specific serotonin reuptake inhibitors (SSRIs) have been reported (Neuvonen et al. 1993). Contraindications between serotonergic drugs and harmala alkaloids, however, have not been included in the medical literature.

The use of this beverage has not been limited to indigenous groups, and regular use by members of syncretic religious movements from the urban populations of Brazil was already established over 70 years ago (Ott 1994). Proponents of its use contend that ayahuasca benefits the individual, the family and society. An official investigation of ayahausca-based religions by the Brazilian health and drug authorities—the Brazilian Divisao de Medicamentos do Ministerio da Saude (Dimed) and Conselho Federal de Entorpecentes (Confen), respectively—eventually led to legislation that protects the use of ayahuasca in Brazil for religious purposes as of August, 1987.

*Department of Pharmaceutical Chemistry, University of Kuopio, Finland.

**Associate Professor of Psychiatry, Department of Psychiatry, Harbor/UCLA Medical Center, Torrance, California 90509.

Please address correspondence and reprint requests to James C. Callaway, Ph.D., Department of Pharmaceutical Chemistry, University of Kuopio POB 1627, FIN-70211 Kuopio, Finland.

Recent psychological and biomedical investigations into the long- and short-term effects of ayahuasca have not shown evidence of adverse physical or psychiatric sequelae (Callaway et al. in press; Callaway et al. 1996; Grob et al. 1996). In addition, an increased density of [3H]citalopram binding sites on blood platelets suggests a neurophysiologic compensation for the periodic increases in serotonin levels following regular (typically biweekly) use of this beverage (Callaway et al. 1994).

The detrimental consequences of combining MAOIs with certain foods or medications have been known for several decades (Goldberg 1964; Blackwell 1963). One aspect of this reaction, known as the "serotonin syndrome" (Sternback 1991), is characterized by excessive levels of the neurotransmitter serotonin (5-hydroxytryptamine, 5-HT). Symptoms are typically initial euphoria, nausea and confusion followed by tremors, vomiting, convulsions and loss of consciousness, possibly leading to death in extreme cases. Therefore, patients are warned of such contraindications before using MAOIs, and physicians typically scrutinize potential complications with known concurrent medications. Still, adverse and fatal interactions between combinations of MAOIs with SSRIs continue to be reported (PDR Editors 1996; Copland & Gorman 1993; Neuvonen et al. 1993; Peterson 1991). Paradoxically, such combinations have intentionally been used in the treatment of intractable cases of depression, where severely attenuated serotonin activity is thought to be the underlying cause (Peterson 1991). The combination of MAOIs with SSRIs blocks two essential pathways for serotonin (centrally, in the neuron): its specific metabolism by MAO-A and its reuptake into presynaptic nerve terminals, respectively. The production of serotonin continues unabated (neither increasing or decreasing); only its main pathways of metabolism are shut down, thus levels increase because nothing is metabolized, as production continues. However, serotonergic activity can pass from therapeutic to fatal levels if its unchecked production becomes excessive.

The ability of MAOIs to activate novel drug combinations has recently been described to audiences in Europe and North America, through popular magazines, books and internet discussion groups related to recreational drug use (Dobkin de Rios 1994; Ott 1994; Krajick 1992). The potential for adverse and possibly lethal consequences from combinations of ayahuasca with serotonergic medications, however, has received little consideration. In addition, an insidious potential for adverse effects from active metabolites may remain up to five weeks after discontinuing certain SSRIs (Copland & Gorman 1993). Under these circumstances, it is conceivable that some of the increasing numbers of individuals who have already had SSRIs prescribed for them and also try ayahuasca—perhaps as an adjunct to psychotherapy or in the hope of personal development—may consequently develop an adverse or lethal serotonin syndrome.

Initially, emergency medical procedures may not appear to be indicated, as the initial symptoms of euphoria or confusion, vomiting and tremor are also common with typical doses of ayahuasca (according to the authors' observations). In serious cases, antidotal therapy is indicated, and treatment should be aggressive, as death can follow within only a few hours. A serotonin antagonist, such as methysergide or cyproheptadine, may be used to block symptoms of serotonin syndrome (Copland & Gorman 1993). Additional measures may include cooling blankets for hyperthermia, artificial ventilation for respiratory insufficiency, and the administration of anticonvulsants for possible seizures (Sternback 1991). Dantrolene may also be indicated to reduce muscle rigidity and hyperpyrexia (Feighner et al. 1990).

CASE STUDY

J.M, a 36-year-old white male, had been undergoing treatment for mild depression for several months with fluoxetine (20 mg taken orally each morning) when he participated in a ceremonial ayahuasca session. One hour after ingesting approximately 100 ml. of ayahuasca, J.M. began to experience tremors, sweating, shivering and confusion. As his symptoms rapidly intensified, he staggered out of the religious ceremony and collapsed on the ground outside. For the next three hours J.M. reported that he continued to sweat profusely, display gross motor tremors and experience severe nausea and vomiting. In addition to being disoriented, J.M. also later reported that he had endured profound despair and anguish which were associated with mental imagery of his wife. J.M. stated "I experienced being my wife during the time I had been unfaithful to her, and I went through this horrible pain which I knew was the pain she had experienced." J.M. would later describe his experience as having been overwhelming, yet valuable in catalyzing a rapprochement with his wife. Although J.M. reports having been physically incapacitated for several hours and having received no treatment, he rapidly became asymptomatic after the four-hour post-ayahuasca ingestion point. There were no apparent long-term adverse sequelae.

CONCLUSION

With the growing popularity of ayahuasca throughout the Americas and in Europe, there is a need to establish clear parameters for optimal efficacy and safety. Although a pilot Phase 1 study of short- and long-term effects of ayahuasca in the Brazilian Amazon found subjects to be in good psychological and physical health (Callaway et al. in press; McKenna, Callaway & Grob 1998; Grob et al. 1996; Callaway et al. 1996; Callaway et al. 1994), further investigation is called for. One particular area in need of scrutiny is the risk of adverse interaction between the monoamine

oxidase-inhibiting harmala alkaloids and other drugs. Given that millions of individuals worldwide are currently undergoing treatment with selective serotonin reuptake inhibitors, the potential for incurring a dangerous serotonin syndrome is not insignificant. Those interested in using ayahuasca are strongly cautioned not to combine this ancient plant medicine with certain classes of modern psychoactive drugs.

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