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Short Communication

Pharmacokinetics of the Plant-Derived κ-Opioid Hallucinogen Salvinorin A in Nonhuman Primates

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ABSTRACT Salvinorin A, a potent hallucinogen isolated from the leaves of *Salvia divinorum*, has gained popularity among adolescents in the USA. No detailed study of the pharmacokinetics has been conducted in vivo. The present study investigates the in vivo pharmacokinetics of salvinorin A (0.032 mg/kg, i.v. bolus) in rhesus monkeys ($n = 4$, 2 male, 2 female). The elimination $t_{1/2}$ was rapid (56.6 ± 24.8 min) for all subjects. Pharmacokinetic differences (distribution $t_{1/2}$, elimination $t_{1/2}$, and AUC) were observed between males and females, suggesting potential sex differences in its pharmacologic effects. Salvinorin B, the presumed major metabolite, is observed to accumulate ex vivo; however, in this study it never reached the limit of detection. **Synapse 58:208–210, 2005.**

In recent years, the hallucinogenic sage *Salvia divinorum* has become widely available throughout the world, via numerous internet suppliers, either as leaves or as concentrated extracts. Young adults and adolescents have begun to smoke the leaves and leaf extracts of the plant to induce powerful hallucinations. Reports on its use within the USA have emerged (Hazelden Foundation, 2004), and recently, the Drug Enforcement Administration (DEA) has placed *S. divinorum* on the list of drugs of concern (NDIC, 2003). Currently, it remains unregulated in most countries, including the USA.

The main active constituent in *S. divinorum* is salvinorin A (Siebert, 1994; Valdes, 1994). Recent work has shown salvinorin A to be a potent and selective κ-opioid receptor agonist in vitro and in vivo (Butelman et al., 2004; Roth et al., 2002; Zhang et al., 2005). At present, there are no studies on the in vivo pharmacokinetics of salvinorin A in any species, to our knowledge. It has been suggested that salvinorin B is an inactive metabolite of salvinorin A (Roth et al., 2004; Valdes et al., 2001); however, this has never been investigated in vivo. Here, we describe for the first time the in vivo pharmacokinetics of salvinorin A in nonhuman primates (specifically rhesus monkeys), an animal model for which a substantial amount of in vivo κ-opioid pharmacology is available.

Gonadally intact, adult, captive-bred rhesus monkeys (*Macaca mulatta*; two males and two females), weighing between 6.5 and 10 kg, were administered a bolus injection at the highest concentration of salvinorin A (0.032 mg/kg, i.v.; in a vehicle composed of ethanol:Tween 80:sterile water [1:1:8 by volume]). Subjects had complex histories with opioid and nonopioid compound administration, but no history of chronic drug administration. Each individual received salvinorin A previously, but no salvinorin A was administered to these individuals for at least one month prior to the study. Salvinorin A was injected over 30 s through an acutely placed catheter in the saphenous vein, and samples were drawn through another catheter, placed in the contralateral leg. Blood was collected into EDTA tubes, at baseline (preinjection) and 0, 1, 5, 15, 30, and 60 min after injection of salvinorin A, where time 0 is defined as the end of the injection and catheter flushing. Concentrations of salvinorin A were determined by high performance liquid chromatography with a recently described method (Schmidt et al., 2005). Salvinorin A

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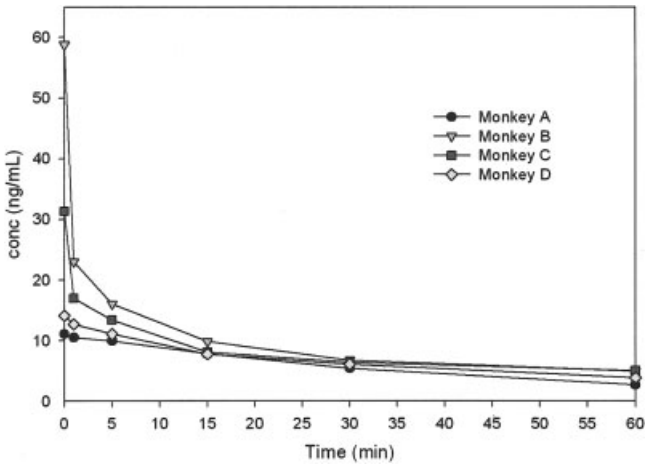

Fig. 1. Plasma concentration versus time profiles of salvinorin A following 0.032 mg/kg i.v. bolus to nonhuman primates. Subjects A and D are males.

area under the concentration–time curve (AUC) was calculated using the trapezoidal rule. Distribution and elimination $t_{1/2}$ was calculated using standard equations (Shargel et al., 2005) and the first two and last two concentrations, respectively (see Fig. 1).

Overt behavioral effects (e.g., sedation-like) were observed immediately after i.v. injection of 0.032 mg/kg of salvinorin A and dissipated gradually over ~15 min. This salvinorin A dose is known to be behaviorally active by the subcutaneous route in this species (Butelman et al., 2004). Overall, the elimination $t_{1/2}$ was found to be 56.6 ± 24.8 min for the four subjects. Interestingly, there appears to be gender differences in the distribution and elimination of salvinorin A. In the male subjects, the $t_{1/2}$ for distribution was rapid, the $t_{1/2}$ for elimination was 37.9 ± 5.6 min, and the AUC was 572 ± 133 ng min/ml. For the two female subjects, the $t_{1/2}$ for distribution was slower 0.95 ± 0.20 min, the $t_{1/2}$ for elimination was 80.0 ± 13.1 min, and the AUC was 1087 ± 46 ng min/ml. The above results indicate that the effects of salvinorin A may be different in male and female subjects.

Sex differences have been seen previously in the antinociceptive effects of opioids in rats and rhesus monkeys (Negus et al., 2002, 2004). In addition, gender differences in the analgesic effects of mixed μ/κ-opioids such as pentazocine or butorphanol have been detected in humans under some, but not all situations (Fillingim et al., 2004; Gear et al., 1996). Sexually dimorphic effects of more selective synthetic κ-agonists have also been detected in rodents and nonhuman primates (Craft, 2003; Negus and Mello, 1999). The direction and robustness of such sex differences in κ-opioid pharmacology exhibit a complex pattern between species and experimental (or clinical) situations. Different genetic or neuroendocrine mechanisms may potentially underlie such sex differences (Mogil et al., 2003; Negus and Mello, 1999).

At present, there are few studies into the toxicity of salvinorin A or its metabolites (Mowry et al., 2003). Previous ex vivo work in nonhuman primates demonstrated that salvinorin B was a major metabolite of salvinorin A in plasma (Schmidt et al., 2005). Data from these in vivo experiments show that plasma levels of salvinorin B were below the limit of detection (50–1000 ng/ml for a 0.5 ml sample) over the course of the studies. Salvinorin B does not, however, appear to be accumulating as seen in ex vivo experiments of salvinorin A in plasma incubation in blood (Schmidt et al., 2005). It is quite likely that salvinorin B is either cleared rapidly by other routes or that it may be accumulating in tissues and other organs. Furthermore, a recent report in human volunteers indicates that only a small portion of salvinorin A is excreted unchanged in urine (Pichini et al., 2005).

Salvinorin A-containing products (e.g., *Salvia divinorum* leaves, with or without concentrated extract) are self-administered in humans either by smoking, or less commonly, by buccal absorption. In the few studies available, the duration of action of salvinorin A is thought to be brief (Siebert, 1994), consistent with its short half-life in the present studies. The present initial study focused on bolus i.v. administration to tightly control the administered dose of compound, rather than on the aforementioned smoked or buccal routes. It is known that other smoked drugs, such as nicotine in tobacco, also result in rapid increases in blood levels for the drug of interest, somewhat similar to an i.v. bolus (see Mendelson et al. (2003), for recent findings).

In conclusion, this paper describes for the first time the pharmacokinetics of salvinorin A in nonhuman primates. Intravenous injection of 0.032 mg/kg of salvinorin A produced rapid behavioral effects, as observed with synthetic κ-agonists, which cause sedation-like effects in human and nonhuman primates (Dykstra et al., 1987; Pfeiffer et al., 1986). Pilot studies indicate that these effects dissipated on a time course roughly equivalent to the degradation of salvinorin A in vivo. The same dose of salvinorin A, administered by the subcutaneous route, produced κ-agonist-like discriminative effects in rhesus monkeys (Butelman et al., 2004). The half-life of salvinorin A in rhesus monkeys was highly variable over the subjects tested (especially in its rapid distribution phase) and there appears to be a gender difference. Overall, the present findings could be of utility to researchers further probing the pharmacological effects of this potent, naturally occurring hallucinogen in vivo.

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