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Time course of pharmacokinetic and hormonal effects of inhaled high-dose salvinorin A in humans

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Abstract

Salvinorin A is a kappa opioid agonist and the principal psychoactive constituent of the *Salvia divinorum* plant, which has been used for hallucinogenic effects. Previous research on salvinorin A pharmacokinetics likely underestimated plasma levels typically resulting from the doses administered due to inefficient vaporization and not collecting samples during peak drug effects. Six healthy adults inhaled a single high dose of vaporized salvinorin A (n=4, 21 mcg/kg; n=2, 18 mcg/kg). Participant- and monitor-rated effects were assessed every 2 min for 60 min post-inhalation. Blood samples were collected at 13 time points up to 90 min post-inhalation. Drug levels peaked at 2 min and then rapidly decreased. Drug levels were significantly, positively correlated with participant and monitor drug effect ratings. Significant elevations in prolactin were observed beginning 5 min post-inhalation and peaking at 15 min post-inhalation. Cortisol showed inconsistent increases across participants. Hormonal responses were not well correlated with drug levels. This is the first study to demonstrate a direct relationship between changes in plasma levels of salvinorin A and drug effects in humans. The results confirm the efficacy of an inhalation technique for salvinorin A.

Keywords

Salvia divinorum; salvinorin A; pharmacokinetics; prolactin; cortisol; endocrine

Introduction

The plant *Salvia divinorum* (a member of the mint family) has been used historically in shamanic practices of the Mazatec people of Oaxaca, Mexico for at least several hundred

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years (Ott, 1995; Valdés et al., 1983), although it was not botanically described until the 1960s (Epling and Jativa, 1962). Within the past 15 years *S. divinorum* has gained increased popularity as a psychoactive drug in non-traditional contexts (Perron et al., 2012; Wu et al., 2011). In non-traditional use, products containing *S. divinorum* leaves, sometimes infused with *S. divinorum* extract in order to increase drug effects, are typically smoked (Baggot et al., 2010; Gonzolez et al., 2006). Salvinorin A, the primary psychoactive compound in *S. divinorum*, is a kappa opioid agonist hallucinogen that is not active at the 5-HT2A receptor, the primary site of activity for classic hallucinogens such as LSD and psilocybin (Cunningham et al., 2011; Prisinzano, 2005; Roth et al., 2002). Although *S. divinorum* and salvinorin A have not been controlled at the federal level in the US, at the time of this writing at least 35 states within the US and 27 nations have enacted various levels of restriction for *S. divinorum* (Siebert, 2015).

Understanding the effects of salvinorin A, including its pharmacokinetic profile, in humans is important for understanding recreational use of *S. divinorum*. Laboratory research has not found evidence of persisting psychotic-type episodes resulting from salvinorin A (Addy, 2012; Johnson et al., 2011; MacLean et al., 2013; Ranganathan et al., 2012). Cases of persisting psychotic-type episodes have been reported in association with recreational use, although the causal role of *S. divinorum* remains unclear (Vandrey et al., 2013). In addition, the dissociative and perceptual effects resulting from salvinorin A (Addy, 2012; Johnson et al., 2011; MacLean et al., 2013; Ranganathan et al., 2012), could potentially result in dangerous behavior in an unsupervised environment. Therefore, studying the pharmacokinetic profile of salvinorin A may inform the understanding of potential adverse reactions observed in recreational *S. divinorum* use. Examining human salvinorin A effects is also important because salvinorin A or derivative compounds may serve as therapeutic agents for neurological (e.g., Alzheimer's disease), pain, mood, personality, gastrointestinal, and cocaine-use disorders (Cunningham et al., 2011; Kivell and Prisinzano, 2010; Mello and Negus, 2000; Morani et al., 2009; Sheffler and Roth, 2003; Tejeda et al., 2012). While a study of inhaled salvinorin A would primarily model inhaled recreational use of *S. divinorum*, its results may also have limited relevance for potential therapeutic applications. Regardless of whether potential therapeutic applications would deliver the drug via vaporization, examining the relation between plasma drug levels and resulting subjective effects in the vaporized route may inform the more general relation between plasma drug levels and subjective effects at play in potential therapeutic applications.

Studies of intraperitoneally injected salvinoirin A in rats, and intravenously injected salvinorin A in rhesus monkeys, have provided basic pharmacokinetic data (Schmidt et al. 2005; Teksin et al., 2009). However, cross-species differences and differences between routes of administration may limit the implications of these findings for the pharmacokinetics of inhaled salvinorin A in humans. One previous study assessed the pharmacokinetic profile of salvinorin A in humans (Ranganathan et al., 2012). That study showed increases in salvinorin A, prolactin, and cortisol resulting from inhaled administration of the drug. However, there are several issues that remain unexamined. First the previous study did not examine the relation between individual salvinorin A pharmacokinetic and psychoactive effects. Second, Ranganathan and colleagues examined plasma levels of salvinorin A at only 3 timepoints post-inhalation (15, 20, and 30 min.), with

the first assessment occurring substantially after the time at which peak participant-rated effects were observed in our research (2 min. post-inhalation) (Johnson et al., 2011; MacLean et al., 2013), suggesting that pharmacokinetic analysis of peak drug effects was missed. Third, Ranganathan and colleagues used a commercial vaporizer to deliver a maximum dose (12 mg) that was approximately eight to twelve time higher than the maximum doses administered in studies that used a glass pipe to vaporize salvinorin A (Johnson et al., 2011; MacLean et al., 2013; Maqueda et al., in press), and a study that had participants smoke *S. divinorum* leaves infused with additional salvinorin A (Addy, 2012; Addy et al., 2015). Substantial differences with the previously reported pharmacokinetic study regarding dose and delivery system warrant a pharmacokinetic analysis of our study.

In the present study, we examined the time course of salvinorin A plasma levels after inhalation of a high dose, delivered via a relatively efficient vaporization system. Blood was drawn at relatively frequent post-inhalation timepoints in order to accurately describe plasma levels surrounding the relatively rapid peak drug effects of salvinorin A. This frequent sampling allowed us to analyze the correspondence between drug levels and subjective effects throughout the drug time course. In addition, we examined levels of prolactin and cortisol, which are both sensitive to kappa agonist administration (Ur et al., 1997). In order to address one aspect of the efficiency of the delivery system, residual salvinorin A from the glass pipe was assayed for each session.

Methods

Participants

Participants were 6 individuals who participated in a previous study assessing the effects of inhaled salvinorin A in the laboratory (Johnson et al., 2011; MacLean et al., 2013). The sample size was judged sufficient for examining pharmacokinetic data because robust significant subject-rated effects were observed with fewer participants (Johnson et al., 2011). Participants had taken part in up to 20 previous sessions (16 salvinorin A doses in ascending order and 4 intermixed placebo sessions under blind conditions) that did not involve collecting blood samples. Two individuals (1 female, 1 male) whose subjective and cognitive data were included in our previous sample of 8 participants (MacLean et al., 2013) did not participate in the final salvinorin A administration session, which was the only session involving blood draws. In the case of the male, the participant decided not to participate in the blood draw session upon considering several subjectively intense sessions previously in the study. In the case of the female, the investigators decided not to continue her onto the blood draw session due to excessive spontaneous arm movements in previous sessions, which may have interfered with the blood draws.

For the 6 participants reported here, mean age was 25 years (range: 21–35). They reported using *S. divinorum* on a mean of 11 previous occasions (range: 1–40), with their reported first use at a mean age of 21 years (range: 16–31). They reported using classic hallucinogens on a mean of 32 previous occasions (range: 5–111). Study staff who were present during drug administration had established rapport with participants during previous preparatory sessions and lower dose and placebo sessions as described previously (Johnson et al., 2011).

Procedure

Each participant inhaled a single high dose of vaporized salvinorin A. The dose administered was the highest tolerated dose of salvinorin A in previous sessions. For four participants this dose was 21.0 mcg/kg, which was the maximal dose in the dose run-up. For the other two this dose was 18.0 mcg/kg because they replied “yes” to a question asking them if they would refuse to receive the same or higher doses at the conclusion of a 19.5 mcg/kg session. As described previously (MacLean et al., 2013) subjective drug strength and monitor-rated effects (drug strength, distance from usual daily reality, unresponsiveness, psychological distress, paranoia, anxiety/fear, motor activity, joy/peace and physical distress) and physiology measures (systolic and diastolic blood pressure, heart rate) were assessed every 2 min for 60 min after inhalation. Blood samples were collected at 13 time points (baseline, 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 60, 90) and cold centrifuged to obtain plasma. Plasma samples were purified by solid phase extraction and analyzed in triplicate via liquid chromatography-tandem mass spectrometry (LC-MS/MS) using a +5 mass analogue of salvinorin A as internal standard (Caspers et al., 2013). Analyses of prolactin and cortisol were performed with ELISA kits (Calbiotech, Spring Value, CA) and were run in triplicate. The average of these three assays was used in analyses. Residual salvinorin A in the glass pipe was determined for each session. Specifically, dichloromethane (1mL in 3 separate washes) was used to wash the inner surfaces of the glass pipe. The combined 3 ml of resulting solution was then dried under a stream of nitrogen. Three separate samples from the resulting residue were dissolved into mobile phase and subjected to LC-MS/MS for analysis.

Data Analysis

For each participant, we calculated Pearson’s correlations between each hormonal assay (prolactin, and cortisol) and subjective and monitor ratings of drug effects, using only the 7 time points when both blood and ratings were collected (baseline, 2, 4, 10, 20, 30 and 60 min post-inhalation). Correlations were also conducted for each participant between salvinorin A and prolactin levels, between salvinorin A and cortisol levels, and between prolactin and cortisol levels. Correlations between drug and hormones used the 7 common timepoints indicated above, while correlations among hormones used 13 common timepoints. Because a delayed hormonal response (relative to drug levels) might obscure a relationship between drug and hormonal levels, the same pairs of correlations were also conducted at the group level using peak values (i.e., single maximal value across the time course for each participant) for drug and hormonal levels.

Repeated measures regression (SAS PROC MIXED, AR(1) covariance structure) was used to model the relationship between salvinorin A plasma level and participant and monitor ratings of drug effects from baseline to 60 min post-administration. As with the correlations, this analysis only used the 7 timepoints common to both blood draws and drug strength ratings. Statistical significance was defined as $p < .05$.

The percent of the intended dose that remained as residual salvinorin A in the glass pipe was calculated using the salvinorin A residual mass for each participant (i.e., mean of the triplicate LC-MS/MS assays) and the prepared absolute salvinorin A dose for each participant (i.e., taking bodyweight into account).

Results

Samples were collected and assayed for salvinorin A level at all timepoints. For prolactin and cortisol, sample volumes were insufficient to obtain results for two timepoints for 1 participant (at the 1 and 10 min timepoints). Coefficients of variation (CV) for plasma samples (in triplicate) and standards (in duplicate) were < 10%. The upper panel of Fig. 1 shows mean salvinorin A levels at all blood collection time points (up to 90 min post-inhalation). In order to show individual variability contributing to mean levels, the lower panel shows individual participant salvinorin A levels at each time point up to 30 min post-inhalation. The upper panel shows that mean peak salvinorin A levels occurred at 2 min post-inhalation, followed by rapid reductions and then more gradual reductions until the final time point at 90 min post-infusion, at which time salvinorin A levels were close to baseline (zero). Although these trends were generally observed at the individual participant level (lower panel), notable variations occurred, with peak effects occurring as early at 1 min to as late as 4 min post-inhalation.

To illustrate the relationship between drug blood levels and subjective drug strength, each panel of Fig. 2 shows an individual participant's salvinorin A plasma levels and subjective drug strength. Ratings of drug strength were closely associated with plasma levels. The median Pearson correlation between plasma levels and drug strength across individuals was r = .93 (range: .88–.99; all significant).

Repeated measures regression showed that salvinorin A level significantly increased participant ($F(1,35) = 74.08$, $p < .0001$) and monitor ($F(1,35) = 29.14$, $p < .0001$) ratings of drug strength, and monitor ratings of distance from usual daily reality ($F(1,35) = 15.41$, $p < .001$), unresponsiveness ($F(1,35) = 19.82$, $p < .0001$), psychological distress ($F(1,35) = 21.26$, $p < .0001$) and paranoia ($F(1,35) = 11.87$, $p = .002$). The effect of salvinorin A level was not significant for the remaining monitor ratings (anxiety/fear, motor activity, joy/peace and physical distress). The effect of salvinorin A level was also not significant for physiology measures (systolic and diastolic blood pressure, heart rate). Results remained unchanged after controlling for lifetime use of hallucinogens and lifetime use of *S. divinorum*.

Fig. 3 shows the effects of salvinorin A administration on plasma prolactin. The upper panel shows mean prolactin levels, and the lower panel shows prolactin levels in individual participants. Mean peak effects occurred at 15 min post-inhalation and gradually decreased through 90 min. However, individual participant data show a plateau of peak prolactin levels from 10 to 30 min post-inhalation for some individuals. Fig. 4 shows the effects of salvinorin A administration on plasma cortisol. The upper panel shows mean cortisol levels, and the lower panel shows cortisol levels in individual participants. The mean cortisol time course resembled that of prolactin. However, there was substantial individual variability with little evidence of a cortisol response observed in some participants. There were no significant correlations between cortisol or prolactin levels and drug-effect ratings within individual participants. No individual participant correlations between hormone levels and physiological measures were significant with the exception of 1 positive correlation between pulse and cortisol, and 1 negative correlation between systolic blood pressure and prolactin.

Salvinorin A levels were not significantly correlated with either cortisol or prolactin levels within any individual participant. Levels of prolactin and cortisol were positively correlated within each participant across the 13 timepoints (1 participant with 11 timepoints due to missing data) (Pearson r range: .36 to.92; significant for 4 of 6 participants). In correlations at the group level, no significant relation was detected between salvinorin A and prolactin levels ($p = .82$), between salvinorin A and cortisol levels ($p = .15$), or between prolactin and cortisol levels ($p = .68$).

Coefficients of variation for the triplicates of residual salvinorin A assays for each participant were <4%. The mean mass of salvinorin A residue in the glass pipe across participants was 57.1 mcg (SD= 24.3 mcg), representing a mean of 4.21% (SD=2.25%) of the prepared absolute dose.

Discussion

This study is unique in that it examined the time course (including frequent, early timepoints) of salvinorin A plasma levels after salvinorin A inhalation, delivered via a relatively efficient vaporization system. The present study resulted in novel information relevant to three domains: drug delivery, time course of drug levels, and time course and magnitude of hormonal effects.

Drug delivery

The present study showed substantially higher salvinorin A plasma levels compared to the previous study of inhaled salvinorin A pharmacokinetics (Ranganathan et al., 2012). The previous study found a mean salvinorin A level of approximately 0.9 to 1.0 ng/ml resulting from 8 and 12 mg salvinorin A (with little difference between those two doses). In contrast, in the present study, at doses ~8 times lower (18.0 and 21.0 mcg/kg, which equate to ~1.26 and 1.47 mg for a 70 kg bodyweight person), resulted in a mean of 18.8 ng/ml at peak effects. These data suggest the present study used a substantially more efficient delivery method. Differences in efficiency could involve multiple factors including temperature and air flow topography. Moreover, the analysis showing only a small percentage of residual salvinorin A in the glass pipe highlights the efficiency of the delivery system.

Time course of salvinorin A blood levels

The present study found strong correspondence between salvinorin A levels and ratings of drug strength throughout the time course. Unlike the previous study of salvinorin A pharmacokinetics (Ranganathan et al., 2012), this study was able to demonstrate this relationship due to more frequent drug effect rating assessments and blood draws. The present results indicate that subjective effects of salvinorin A are a direct function of concurrent plasma levels of the drug. This finding is consistent with a study of intravenous salvinorin A in rhesus monkeys reporting overt sedation-like behavior effects generally overlapping with the period of detected plasma levels of salvinorin A (e.g., within ~15 min. post-injection) (Schmidt et al. 2005).

Time course and magnitude of hormonal response

Similar to Ranganathan et al. (2012), the present study showed increases in prolactin and, less consistently, cortisol following salvinorin A administration. Due to infrequent sampling, the previous study did not have the ability to determine how closely hormone levels and salvinorin A levels were related in time. By showing rapid increases in salvinorin A levels that match the rapid subjective effects of the drug, the present study had the potential to demonstrate a strong correspondence between drug and hormone levels. However, the present study showed that prolactin and cortisol responses to salvinorin A administration followed a more delayed and prolonged time course than the drug itself.

Conclusion

This study provides important information regarding the pharmacokinetics of a relatively novel drug used for its hallucinogenic effects. It confirmed that a relatively efficient vaporization method resulted in substantially higher drug plasma levels compared to a previous study of salvinorin A pharmacokinetics (Ranganathan et al., 2012). Moreover, this study showed strong correlations between salvinorin A blood levels and drug strength ratings across the time course of drug effects, suggesting that subjective effects are a product of concurrent blood levels. This study also showed that salvinorin A generally increased prolactin, although it followed a more delayed and prolonged time course than the drug itself. Cortisol showed inconsistent increases across participants. Because smoking and vaporization both involve inhalation, the results of this study may be relevant to the recent use of *S. divinorum* in non-traditional contexts.

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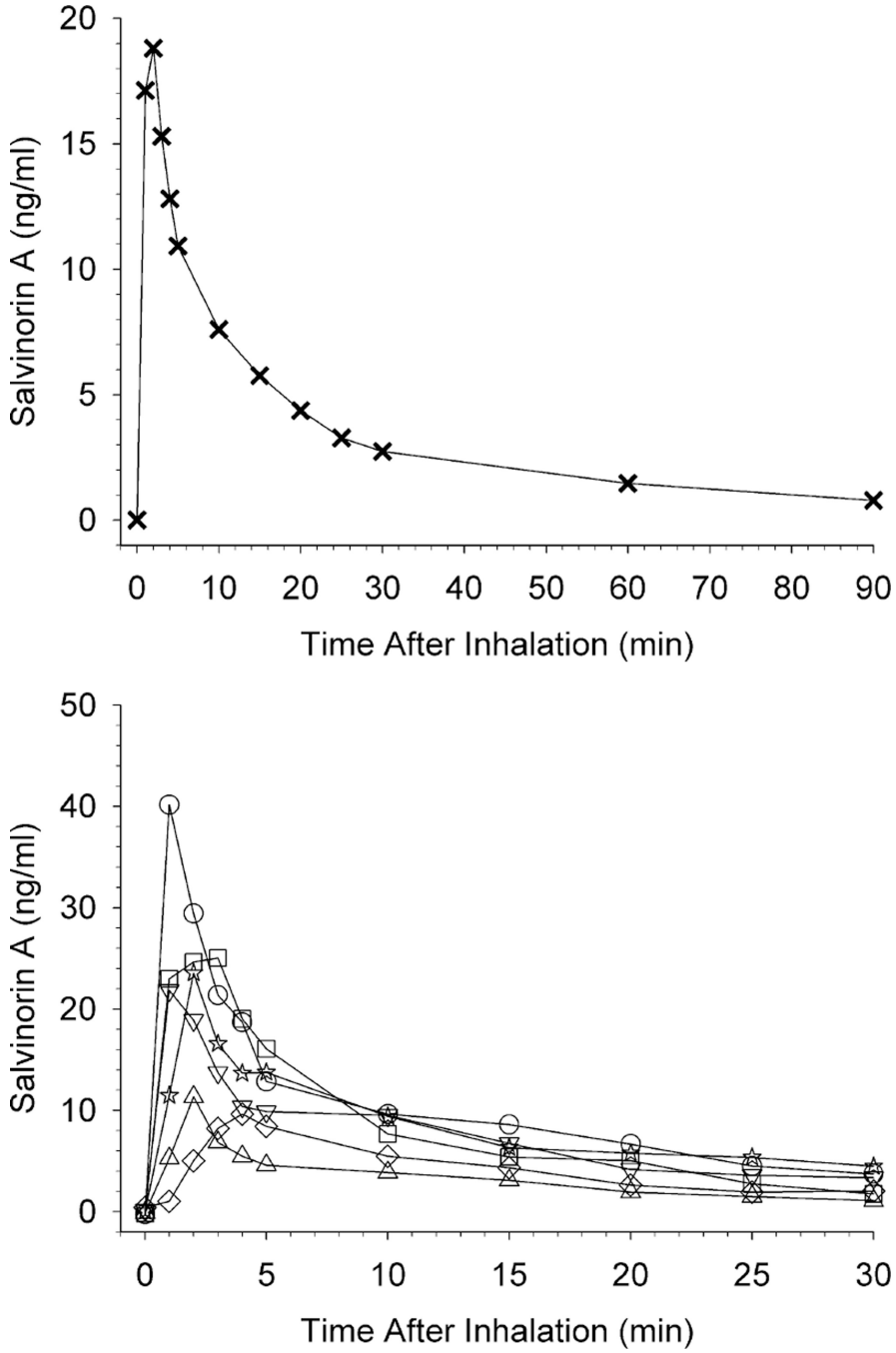

Fig. 1.

The upper panel shows mean salvinorin A levels at all blood collection time points. The lower panel shows individual participant salvinorin A levels at each time point up to 30 min post-inhalation; individual participants are designated by different symbols. In both panels, the pre-inhalation assessment timepoint is shown at 0 min.

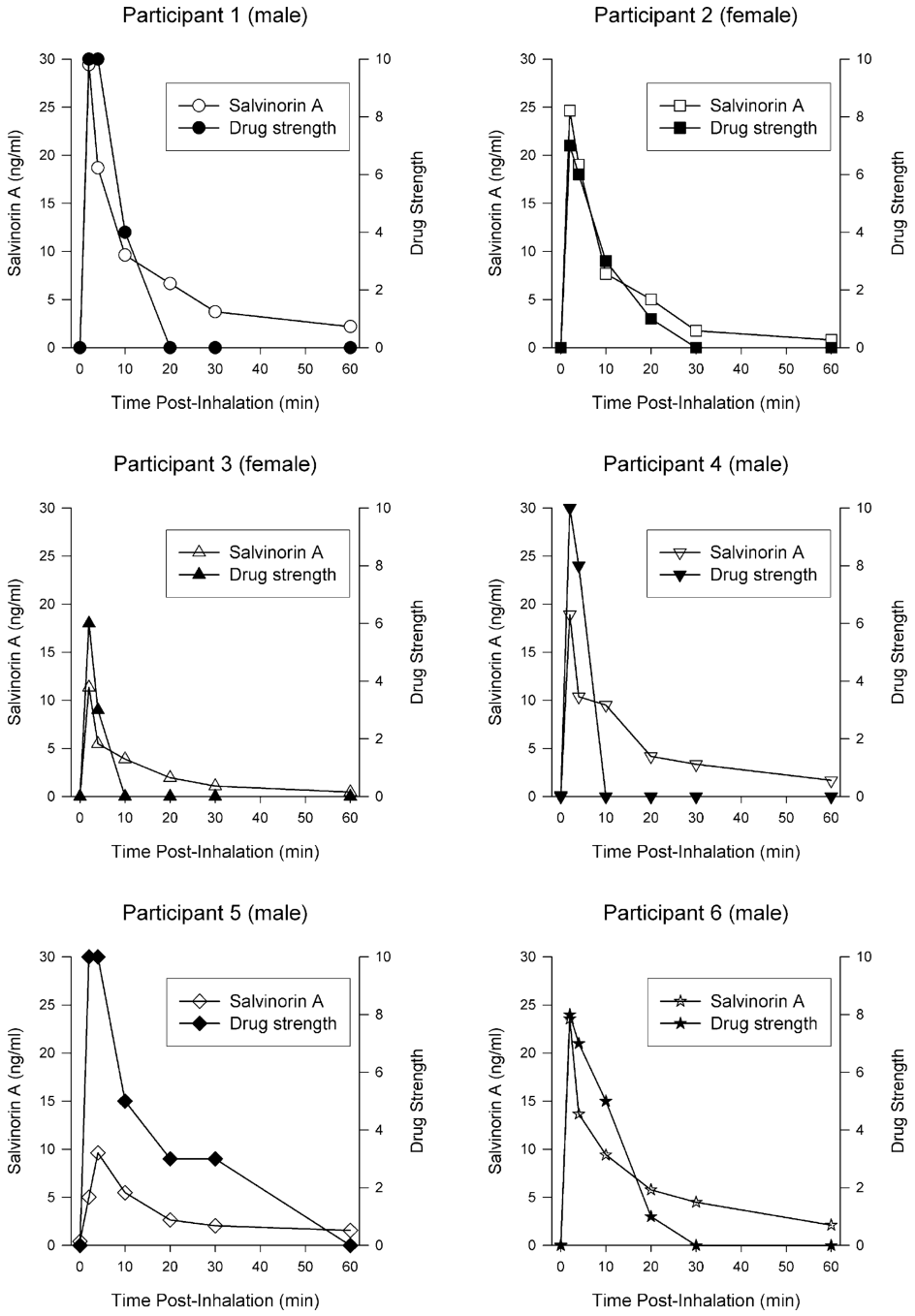

Fig. 2.

Each panel shows individual participant salvinorin A plasma levels (left axis) and subjective rating of drug strength (right axis) for all time points in which both measures were assessed. Individual participants are designated by the same symbols shown in Fig 1. The pre-inhalation assessment timepoint is shown at 0 min.

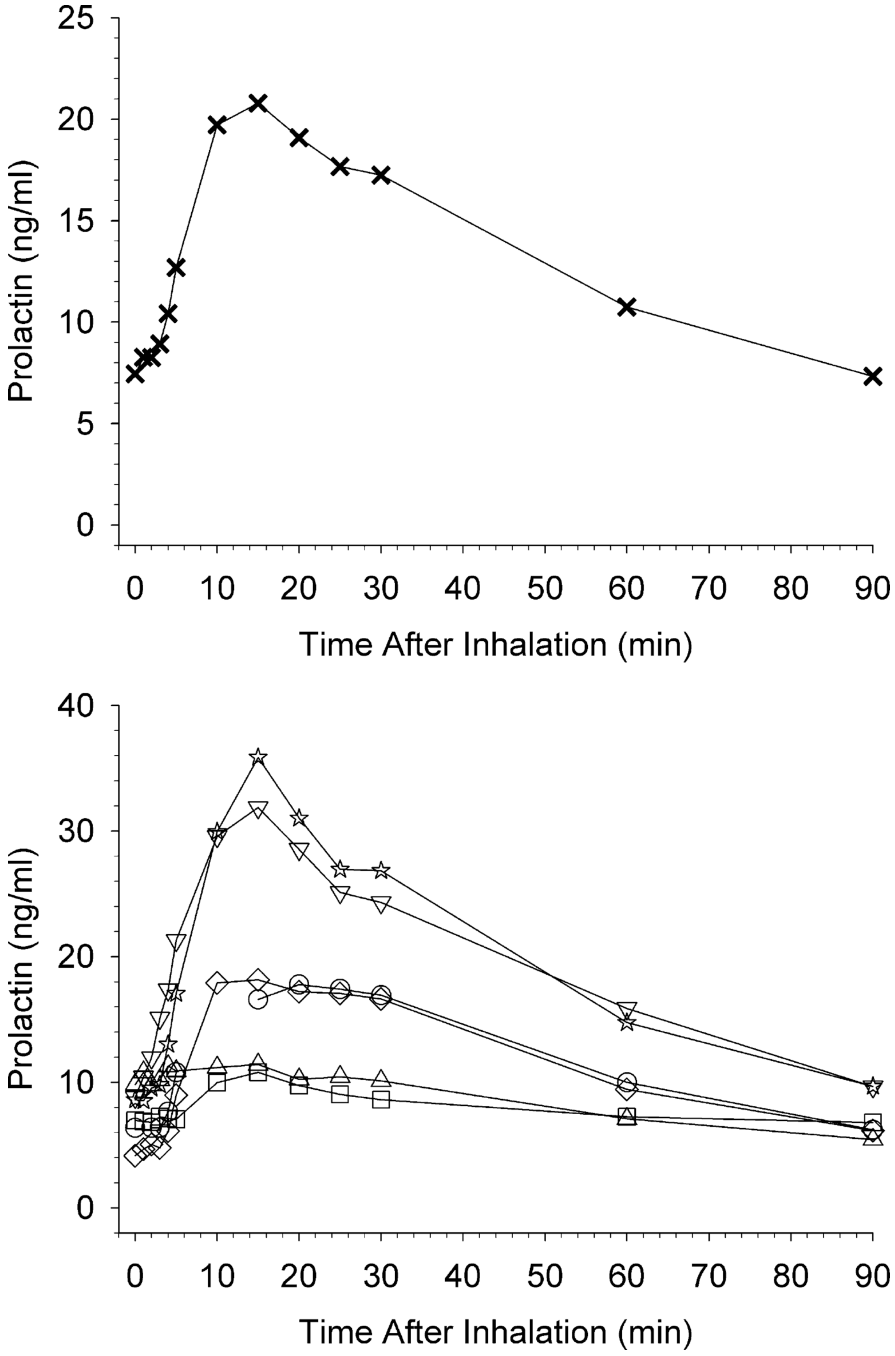

Fig. 3.

The upper panel shows mean prolactin levels at all blood collection time points. The lower panel shows individual participant prolactin levels at each time point up to 30 min post-inhalation; individual participants are designated by the same symbols shown in Fig 1; unconnected data points indicate a missing timepoint. In both panels, the pre-inhalation assessment time-point is shown at 0 min.

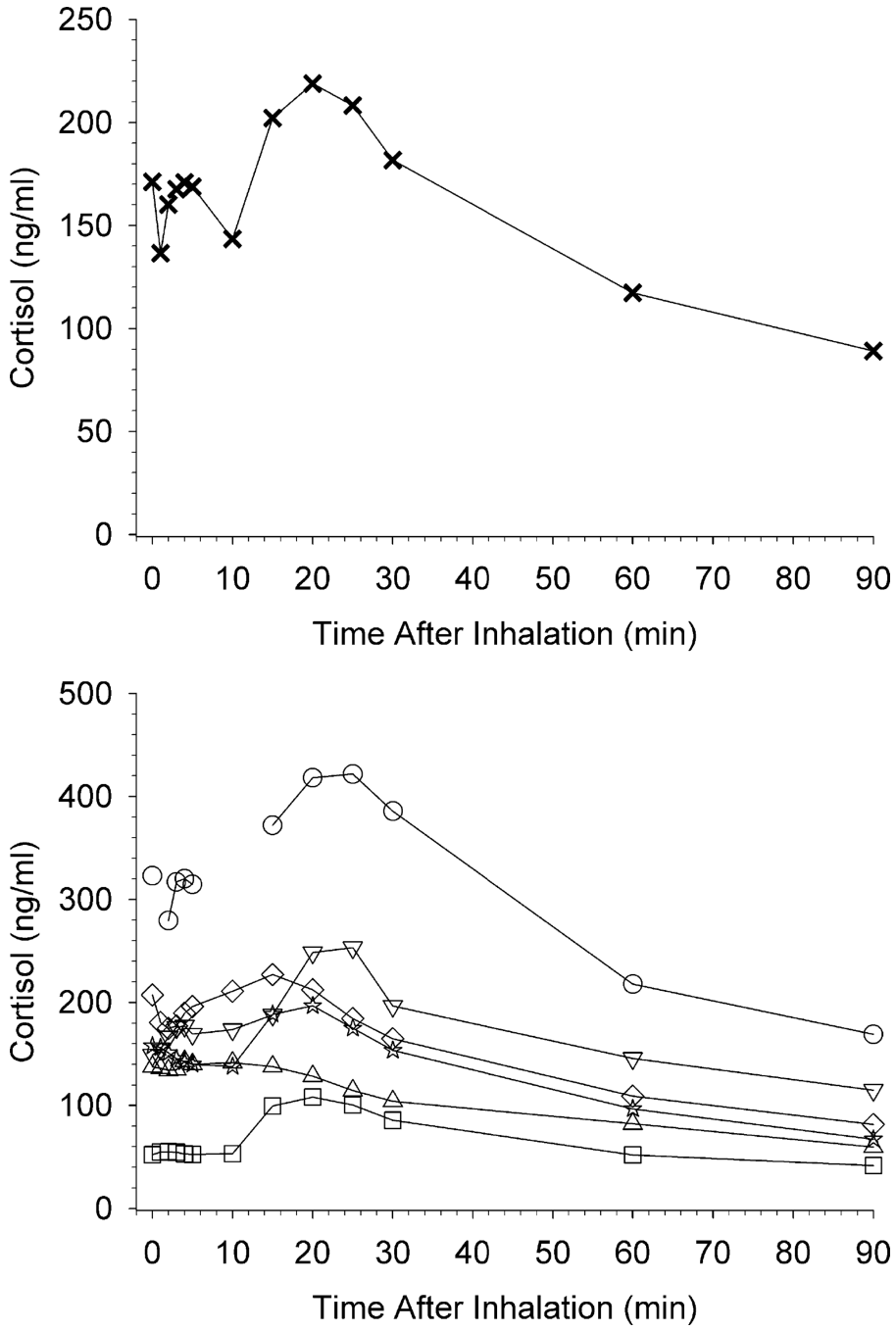

Fig. 4.

The upper panel shows mean cortisol levels at all blood collection time points. The lower panel shows individual participant cortisol levels at each time point up to 30 min post-inhalation; individual participants are designated by the same symbols shown in Fig 1; unconnected data points indicate a missing time-point. In both panels, the pre-inhalation assessment timepoint is shown at 0 min.