Pharmacokinetics and Pharmacodynamics of Lysergic Acid Diethylamide Microdoses in Healthy Participants

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"Microdoses" of lysergic acid diethylamide (LSD) are used recreationally to enhance mood and cognition. Increasing interest has also been seen in developing LSD into a medication. Therefore, we performed a pharmacokinetic-pharmacodynamic study using very low doses of LSD. Single doses of LSD base (5, 10, and 20 µg) and placebo were administered in a double-blind, randomized, placebo-controlled crossover study in 23 healthy participants. Test days were separated by at least 5 days. Plasma levels of LSD and subjective effects were assessed up to 6 hours after administration. Pharmacokinetic parameters were determined using compartmental modeling. Concentration-subjective effect relationships were described using pharmacokinetic-pharmacodynamic modeling. Mean (95% confidence interval) maximal LSD concentrations were 151 pg/mL (127–181), 279 pg/mL (243–320), and 500 pg/mL (413–607) after 5, 10, and 20 µg LSD administration, respectively. Maximal concentrations were reached after 1.1 hours. The mean elimination half-life was 2.7 hours (1.5–6.2). The 5 µg dose of LSD elicited no significant acute subjective effects. The 10 µg dose of LSD significantly increased ratings of "under the influence" and "good drug effect" compared with placebo. These effects began an average of 1.1 hours after 10 µg LSD administration, peaked at 2.5 hours, and ended at 5.1 hours. The 20 µg dose of LSD significantly increased ratings of "under the influence," "good drug effects," and "bad drug effects." LSD concentrations dose-proportionally increased at doses as low as 5–20 µg and decreased with a half-life of 3 hours. The threshold dose of LSD base for psychotropic effects was 10 µg.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Microdosing of lysergic acid diethylamide (LSD) refers to the use of very small doses of LSD to enhance cognition and mood. Pharmacokinetic parameters for very low doses of LSD are lacking.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ The pharmacokinetics and pharmacokinetic-pharmacodynamic relationship of LSD doses of 5, 10, and 20 µg were investigated in a double-blind, randomized, placebo-controlled crossover study in healthy participants.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Participants began to perceive effects of LSD at a threshold dose of 10 µg. LSD had a half-life of 3 hours. Effects peaked at 1.5–2.5 hours and lasted 5 hours after LSD administration.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ The present pharmacokinetic and acute effects data will support the design of further studies that use low-dose LSD in healthy subjects and patients.

Lysergic acid diethylamide (LSD) is a well-known classic serotonergic psychedelic that is widely used for recreational purposes.[1] LSD is well-absorbed,[2,3] and maximal LSD concentrations are reached 1.5–2 hours after oral administration.[4] LSD is mainly metabolized to inactive O-H-LSD, which is renally eliminated.[3] The plasma half-life of LSD is 3–4 hours.[3,4] Increasing interest has been seen in using LSD for the treatment of various disorders, including depression and anxiety,[5] substance use,[6] and cluster headache,[7] among others.[8] LSD "microdosing" has recently become popular.[9,10] The practice of microdosing refers to the use of very low doses of LSD that are taken at 2-to-5-day intervals to improve cognitive function and mood.[11–13] However, little is known about the effects of very low doses of LSD. More data are needed to

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determine specific doses that do not produce subjective effects.[14] A few controlled studies have used defined very low doses of LSD. One recent phase I trial randomly assigned older subjects (mean age: 63 years) 5, 10, and 20 μg LSD tartrate or placebo.[15,16] Only limited pharmacokinetic data, however, were obtained, thus precluding definitions of all pharmacokinetic parameters and pharmacokinetic-dynamic modeling and plasma levels of LSD could not be determined after 5 μg LSD administration because of low sensitivity of the analytical assay. Another controlled study administered LSD tartrate at doses of 6.5, 13, and 26 μg and placebo in a crossover design in four laboratory sessions in 20 healthy young adults.[17] Dose-dependent acute drug effects of LSD were reported. The same authors then showed that the 13 μg LSD tartrate dose increased functional connectivity of the amygdala with frontal brain areas, despite producing only weak effects on mood in 20 young healthy subjects.[18] However, no pharmacokinetic data were obtained in these latter two studies. Therefore, the aim of the present study was to assess the pharmacokinetics and acute effects of LSD and pharmacokinetic-effect relationships at doses of 5, 10, and 20 μg LSD base and placebo in 23 healthy subjects using a sensitive analytical method. Notably, 13 μg LSD tartrate contains 10 μg of LSD base.

METHODS

Study design

The present study used a double-blind, placebo-controlled, crossover design with four experimental 6-hour test sessions to investigate responses to placebo, 5 μg LSD, 10 μg LSD, and 20 μg LSD base. Twenty-four subjects were randomly assigned to 24 possible treatment sequences, counterbalancing all treatments. The washout periods between sessions were at least 5 days. The study was registered at the Dutch Clinical Trial register (no. NTR7102; www.trialregister.nl). Additional data from this study are published elsewhere.[19]

Participants

Participants were recruited from the University of Maastricht campus via advertisement, via social media, and by word of mouth. Only healthy participants who were between 18 and 40 years old, who had a body mass index between 18 and 28 kg/m^2, and who had at least one previous experience with a hallucinogen were included in the study. The exclusion criteria were the following: pregnancy (urine pregnancy test at screening and before each test session) or lactation, a personal history of drug addiction, current or a history of psychiatric disorders or family (first-degree relative) history of major psychiatric disorders, previous experience of serious side effects to psychedelic drugs (anxiety or panic attacks), chronic or acute physical illness (based on abnormal physical exam, electrocardiogram, or hematological and chemical blood analyses or hypertension > 140/90 mmHg), tobacco smoking (> 20 cigarettes/day), excessive drinking (> 20 alcoholic consumptions per week), illicit drug use within the last 3 months, and illicit drug use during the last 7 days prior to the study or during the study. A urine drug test and alcohol breath test were performed at screening and before each test session. No illicit substances were detected during the study. The participants were not allowed to drink alcohol or xanthine-containing liquids after midnight before the study day. Previously used hallucinogens included LSD (n = 12), psilocybin (n = 19), methylenedioxymethamphetamine (MDMA)/ecstasy (n = 15), *N*,*N*-dimethyltryptamine (n = 1), ketamine (n = 1), "2C drugs" (n = 3), and salvia (n = 1).

Study procedures

The study included a screening visit and four experimental sessions (test days). Experimental sessions began at 9:00 AM. An indwelling intravenous catheter was placed in an antecubital vein for blood sampling. A single oral dose of LSD or placebo was administered at 10:00 AM. Autonomic and subjective drug effects were assessed repeatedly throughout the session. Test sessions ended at 4:00 PM. For the analysis of LSD concentrations in plasma, blood samples were collected in lithium heparin tubes before and 0.5, 1, 1.5, 2, 3, 4, and 6 hours after drug administration. Timepoints were selected based on existing pharmacokinetic data on LSD.[4] Blood samples were centrifuged, and plasma was frozen at − 20°C until analysis.

Study drugs

LSD (D-lysergic acid diethylamide base, high-performance liquid chromatography purity > 99%; Lipomed AG, Arlesheim, Switzerland) was manufactured as an oral solution in units that contained 25 μg LSD in 1 mL of 96% ethanol.[4] Stability of the formulation for longer than the study period was documented as described elsewhere.[4] One microgram of LSD base that was used in the present study corresponded to approximately 1.23–1.33 μg of LSD tartrate (depending on the salt form and amount of crystal water), which is the form of LSD that is more likely to be used when acquired illegally (i.e., in blotter form) or was used in two recent studies that used very low doses.[15–17] However, absorption of LSD base likely takes place orally, while LSD base derived from LSD tartrate is likely absorbed when reaching the basic environment of the small intestine. To prepare doses of 5, 10, and 20 μg, 0.2, 0.4, and 0.8 mL of LSD solution, respectively, solution was diluted with ethanol (96% volume) to a final volume of 1 mL. Placebo consisted of 1 mL of ethanol (96% volume) only.

Measures

Analysis of LSD concentrations. Plasma LSD levels were analyzed by ultra-high-performance liquid chromatography tandem mass spectrometry as previously described in detail.[4] Pharmacokinetic samples with an LSD concentration below 5 pg/mL were reanalyzed by a different extraction procedure. Briefly, 150 μL aliquots of plasma were extracted with 450 μL of methanol. The samples were rigorously mixed and subsequently centrifuged. The supernatant was evaporated under a constant stream of nitrogen and resuspended in 200 μL of mobile phase A and B (10:90, volume/volume). The lower limit of quantification of 2.5 pg/mL was reached using this extraction method.

Subjective effects. Visual analog scales (VASs) were repeatedly used to assess subjective effects over time.[20–23] The VASs included separate measures for "under the influence" (any drug effect), "good drug effect," and "bad drug effect," and were presented as 10 cm horizontal lines (0–10), marked from "not at all" on the left to "extremely" on the right. These VASs have been shown to be sensitive and reliable measures of the effects of LSD and other psychoactive substances and suitable for pharmacokinetic-pharmacodynamic (PK-PD) analyses.[3,4,22,24–26] The VASs were administered before and 0.5, 1, 1.5, 2, 3, 4, and 6 hours after LSD administration and immediately after blood sampling to provide matched measures of LSD concentrations and effects for the PK-PD modeling.

Pharmacokinetic analyses and PK-PD modeling

A noncompartmental analysis was performed prior to compartmental modeling. Peak plasma concentration (C_{max}) and time to C_{max} were obtained directly from the observed data. The terminal elimination rate constant (λ_z) was estimated by log-linear regression after semilogarithmic transformation of the data using at least three data points of the terminal

linear phase of the concentration-time curve. The area under the concentration-time curve (AUC) from 0–6 hours after dosing (AUC_6) was calculated using the linear up log down method. The AUC to infinity (AUC_∞) was determined by extrapolation of the AUC_6 using λ_z.

Pharmacokinetic parameters were estimated using compartmental modeling in Phoenix WinNonlin 6.4 (Certara, Princeton, NJ). A one-compartment model was applied with first-order input, first-order elimination, and no lag time as previously used to assess the pharmacokinetics of high doses of LSD.[4] Initial estimates for apparent volume of distribution and λ were derived from noncompartmental analyses. The model fit was not improved by a two-compartment model based on visual inspection of the plots and resulted in smaller Akaike information criterion values. The pharmacokinetic model was first fitted and evaluated. The predicted concentrations were then used as an input to the pharmacodynamic model by treating the pharmacokinetic parameters as fixed and using the classic PK/PD link model module in WinNonlin. Thus, the goal was to model the PD parameters using the PK parameters and the observed PD values. The model used a first-order equilibrium rate constant that related the observed pharmacodynamic effects of LSD to the estimated LSD concentrations at the effect site and accounted for the lag between the plasma and effect site concentration curves.[22,27] A sigmoid maximum effect (E_{max}) model (EC_{50}, E_{max}, γ) was selected for all pharmacodynamic effects. Half-maximal effects (EC_{50}) and E_{max} estimates were taken from the PK-PD plots.[4] Lower and upper limits for E_{max} were set to 0 and 10, respectively, for all of the VAS scores. The sigmoidal E_{max} model best described the relationship between estimated effect-site concentrations and LSD effects compared with a simple E_{max} model (plot inspection (**Figure S1**) and Akaike information criteria).

Statistical analyses

The VAS score data were analyzed using repeated-measures analysis of variance, with drug dose as the within-subjects factor (four levels), followed by Tukey *post hoc* comparisons. Scores measured repeatedly over time are expressed as peak (E_{max} and/or minimum effect (E_{min})) values prior to the analysis of variance (Statistica 12 software; StatSoft, Tulsa, OK). The criterion for significance was $P < 0.05$. The time to onset, time to C_{max}, time to offset, and effect duration were assessed for the model-predicted VAS "under the influence" ratings over time plots using a threshold of 25% of the maximum individual response to LSD using Phoenix WinNonlin 6.4.

RESULTS

Study sample

The final study sample included 23 participants (12 males and 11 females) who completed the study. The participants were (mean ± SD) 23 ± 3 years old (range: 19–29 years) with a mean body weight of 70 ± 10 kg (range: 55–87 kg).

Pharmacokinetics

Plasma concentrations of LSD were determined for the 5, 10, and 20 µg LSD doses in 13, 18, and 15 participants, respectively, for whom all blood samples per session could be collected for valid determination of the pharmacokinetic parameters. LSD could be quantified in all samples. The mean predicted and observed LSD concentrations are shown in **Figure 1a**. Individual predicted

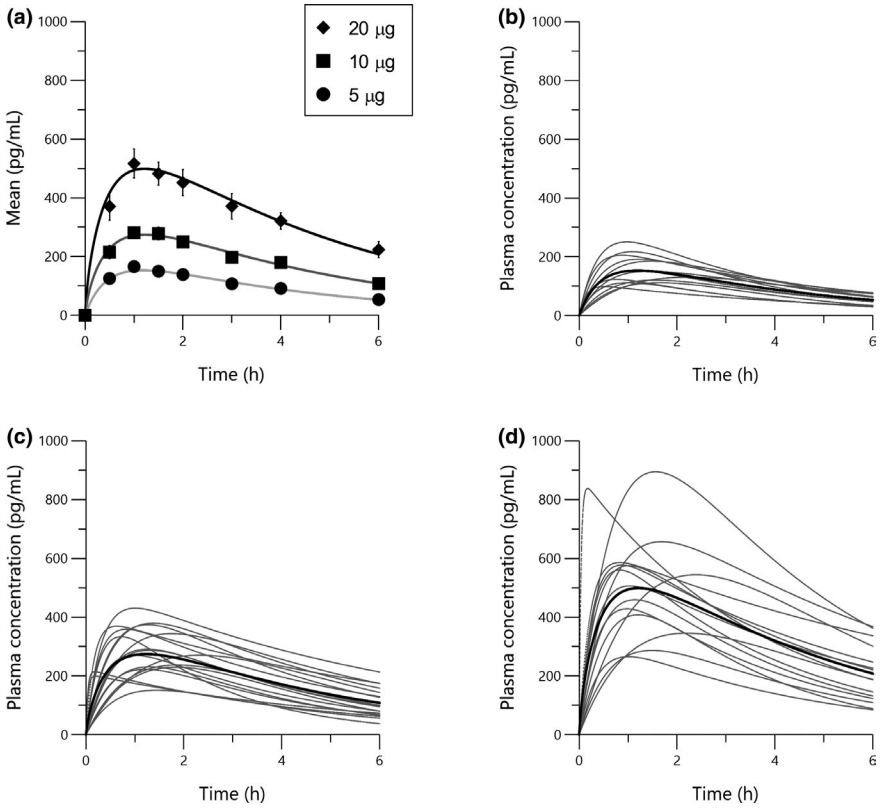

Figure 1 Pharmacokinetics of three very low doses of LSD, 5, 10, and 20 µg, in 13, 18, and 15 subjects, respectively. (**a**) Plasma LSD concentration-time curves representing the mean of the individual pharmacokinetic model predictions. The observed data are expressed as symbols and the mean ± SEM. Dose-linear increases in LSD concentrations were observed. (**b–d**) Predicted individual plasma LSD concentration-time curves shown separately for each subject and the mean marked in bold and illustrating the between-subject variability of LSD concentrations after the administration of (**b**) 5 µg, (**c**) 10 µg, and (**d**) 20 µg LSD. LSD was administered at $t = 0$ hour. h, hours; LSD, lysergic acid diethylamide.

concentrations after the administration of 5, 10, and 20 μg LSD are shown in **Figure 1b–d**, respectively and **Figures S4–S6**. **Figure 1b–d** also illustrate between-subjects variance in the concentrations of LSD for each dose. Coefficients of variation for C_{max} values (**Table 1**) were 30.3%, 28.1%, and 36% for the 5, 10, and 20 μg LSD doses, indicating overall moderate variance and greater variance at the highest dose. The corresponding pharmacokinetic parameters based on compartmental and noncompartmental analyses are shown in **Table 1** and **Table S1**, respectively. LSD concentrations increased proportionally with increasing doses. Elimination occurred according to first-order kinetics. Elimination half-lives were 2.5, 2.7, and 2.9 hours for the 5, 10, and 20 μg doses, respectively, as defined using compartmental analysis (**Table 1**).

Subjective effects

The PK-PD model-predicted subjective effect-time curves for VAS ratings of "under the influence," "good drug effect," and "bad drug effect" are shown in **Figures 2–4**, respectively. Individual predicted effect-time curves for each dose are shown in **Figures 2b,c**, **3b,c** and **4b,c**, respectively and **Figures S5–S13**.

The 5 μg dose of LSD produced no significant acute subjective effects compared with placebo (**Table S2**). The 10 μg dose of LSD significantly increased VAS ratings of "under the influence" and "good drug effect" (both $P < 0.05$, **Table S2**). Time to onset, time to offset, and effect duration of the subjective response were assessed by the VAS "under the influence" as a measure of the overall response to LSD for each dose (**Table 2**). For example, at the 10 μg dose of LSD, subjective effects began an average of 1.1 hours after administration, peaked at 2.5 hours, and ended at 5.1 hours, resulting in an effect duration of 4.0 hours (**Table 2**). The 20 μg dose of LSD significantly increased VAS ratings of "under the influence" ($P < 0.001$), "good drug effect" ($P < 0.001$), and "bad drug effect" ($P < 0.001$) (**Table S2**).

PK-PD modeling parameters are shown in **Table S3**. The predicted concentrations of LSD that produced half-maximal effects (EC_{50} values) were lower for good drug effects (mean ± SD = 0.86 ± 0.7 for 10 μg) compared with bad drug effects (1.6 ± 0.8 for 10 μg; **Table S3**).

DISCUSSION

The present study comprehensively described the pharmacokinetics of low doses of LSD for the first time. Using a sensitive analytical method, full concentration-time curves could be established for the very low single dose of 5 μg LSD base. LSD administration at very low to low doses resulted in dose-proportional changes in plasma LSD concentrations. We also documented first-order elimination kinetics of LSD, confirming past studies that used high doses.[4,22] The average plasma elimination half-lives of LSD were 2.5, 2.7, and 2.9 hours according to the compartmental analysis and 3.0., 3.3, and 3.6 hours according to the noncompartmental analysis for the 5, 10, and 20 μg doses, respectively, and where the noncompartmental analysis may provide a better estimate of the terminal elimination half-life. These half-lives were consistent with the administration of high doses of LSD in four previous pharmacokinetic

Table 1 Pharmacokinetic parameters for different very small doses of LSD based on compartmental modeling

	Dose (μg)		*N*	K_{01} (1/hour)	λ_z (1/hour)	V_z/F (L)	C_{max} (pg/mL)	t_{max} (hour)	$t_{1/2}$ (hour)	AUC_∞ (pg·h/mL)	CL/F (L/h)
LSD	5	Geometric mean (95% CI)	13	1.9 (1.3–2.9)	0.27 (0.23–0.32)	23 (19–28)	151 (127–181)	1.1 (0.91–1.4)	2.5 (2.2–1.4)	800 (658–968)	6.3 (5.2–7.6)
		Range		0.45–7.1	0.18–0.45	14–46	99–250	0.52–2.2	1.5–3.9	513–1,217	4.1–9.7
	10	Geometric mean (95% CI)	18	2.3 (1.4–4.0)	0.26 (0.21–0.30)	25 (21–30)	279 (243–320)	1.0 (0.71–1.4)	2.7 (2.3–3.2)	1,544 (1,273–1,872)	6.5 (5.3–7.9)
		Range		0.43–27	0.14–0.47	14–48	152–431	0.18–2.3	1.5–4.8	849–3,332	3.0–12
	20	Geometric mean (95% CI)	15	2.2 (1.3–3.7)	0.24 (0.20–0.29)	29 (23–36)	500 (413–607)	1.1 (0.77–1.5)	2.9 (2.4–3.5)	2,912 (2,271–3,734)	6.9 (5.4–8.8)
		Range		0.41–27	0.11–0.43	13–59	266–894	0.17–2.4	1.6–6.2	1,373–5,742	3.5–15

AUC_∞, area under the plasma concentration-time curve from time zero to infinity; CL/F apparent total clearance; C_{max}, estimated maximum plasma concentration; LSD, lysergic acid diethylamide; $t_{1/2}$, estimated plasma elimination half-life; t_{max}, estimated time to reach C_{max}; V_z/F, volume of distribution during terminal phase; k_{01}, first-order absorption koefficient; λ_z, first order elimination coefficient.

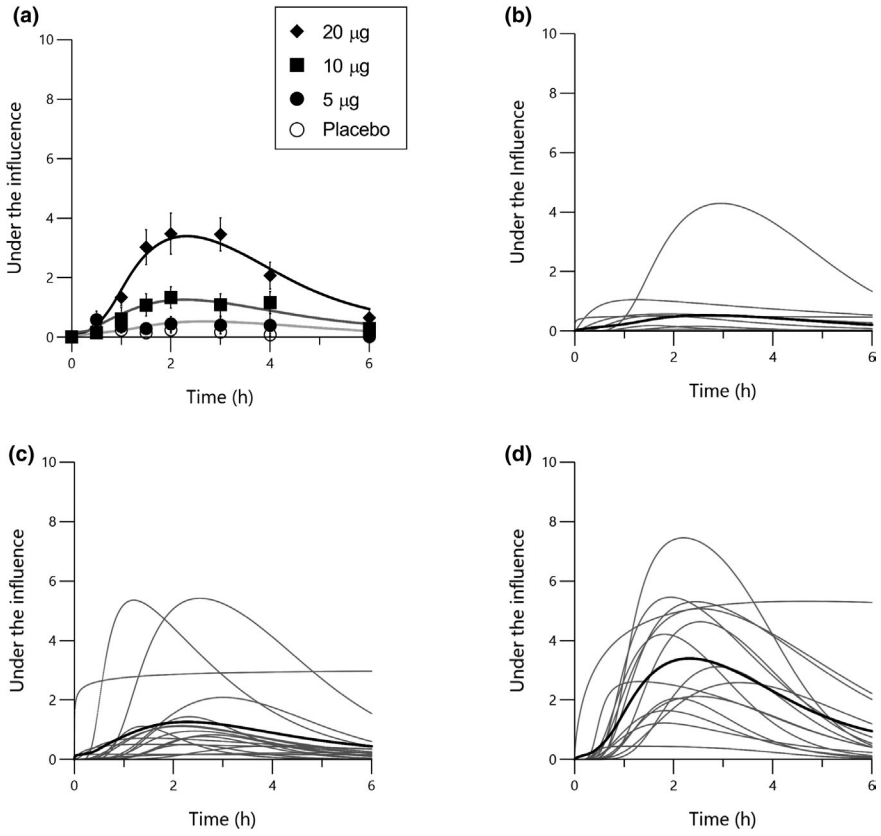

Figure 2 Subjective effects of LSD and placebo over time based on visual analog scale (VAS) ratings from 0–10 for "under the influence" for the 5, 10, and 20 µg LSD doses. (**a**) Effect-time curves represent the mean of the individual pharmacokinetic model predictions. The observed data are expressed as symbols and the mean ± SEM. (**b–d**) Individual LSD effect-time curves for (**b**) 5 µg, (**c**) 10 µg, and (**d**) 20 µg. Predicted individual effect-time curves are shown separately for each subject, and the mean is marked in bold to illustrate the between-subject variability of LSD effects after the administration of (**b**) 5 µg, (**c**) 10 µg, and (**d**) 20 µg LSD. LSD was administered at *t* = 0 hour. The corresponding maximal effect values are shown in **Table S2**. h, hours; LSD, lysergic acid diethylamide.

studies.[4,22,28] Importantly, the longer terminal half-life of 8.9 hours that was described in one preliminary study[3] could not be confirmed by any of the aforementioned studies, including the present study. The relatively short half-life of LSD of approximately 3 hours indicates that LSD does not accumulate in the body with repeated administration (e.g., during "microdosing" when small doses of LSD are used repeatedly), even when used at 24-hour intervals. Additionally, the plasma concentration-time curve of LSD is consistent with its within-subject effect-time curve as documented with the PK-PD modeling in this study for low doses, thus confirming the results with high doses.[4,22] The subjective effects of LSD relatively closely mirror LSD concentrations in healthy subjects. Psychotropic effects of LSD are generally present as long as LSD is present in the body. Accordingly, no acute tolerance occurs as with other psychoactive substances, such as MDMA, in which the drug is present in plasma in high concentrations for several hours beyond its acute psychoactive effects.[29] LSD concentrations and its effects are closely linked within subjects as evidenced by the good PK-PD model fit. Greater variance in the effects of LSD is observed between individuals. However, the variance in plasma concentrations between subjects at a given dose was surprisingly small in the present study, indicated by the coefficients of variation for the C_{max} values of 30–36%. Similar low variability in plasma has previously been reported with the same formulation of LSD base when used at high doses.[4] In contrast, higher variation was seen with older and less stable formulations that were used in older studies[3,22] and would be expected with non-controlled recreational products. This observation indicates that more consistent exposure to the drug is produced with the novel formulation of LSD used in the present and some recent studies,[4] which may then likely result in more consistent and predictable effects compared with past and less well-characterized pharmaceutical preparations. Using pharmaceutical formulations of LSD with confirmed content and stability and documenting consistent pharmacokinetic characteristics will be important for LSD research and the further development of LSD as a pharmaceutical product. We suggest that researchers use LSD formulations with known pharmacokinetic characteristics or obtain such data during their studies when using novel preparations to validate the doses that are used and allow reliable comparisons with other studies as discussed and suggested previously.[4,14,17]

Limited preliminary pharmacokinetic data on low-dose LSD tartrate administration have previously been published in older healthy volunteers (mean age: 63 years).[15] However, the use of an analytical

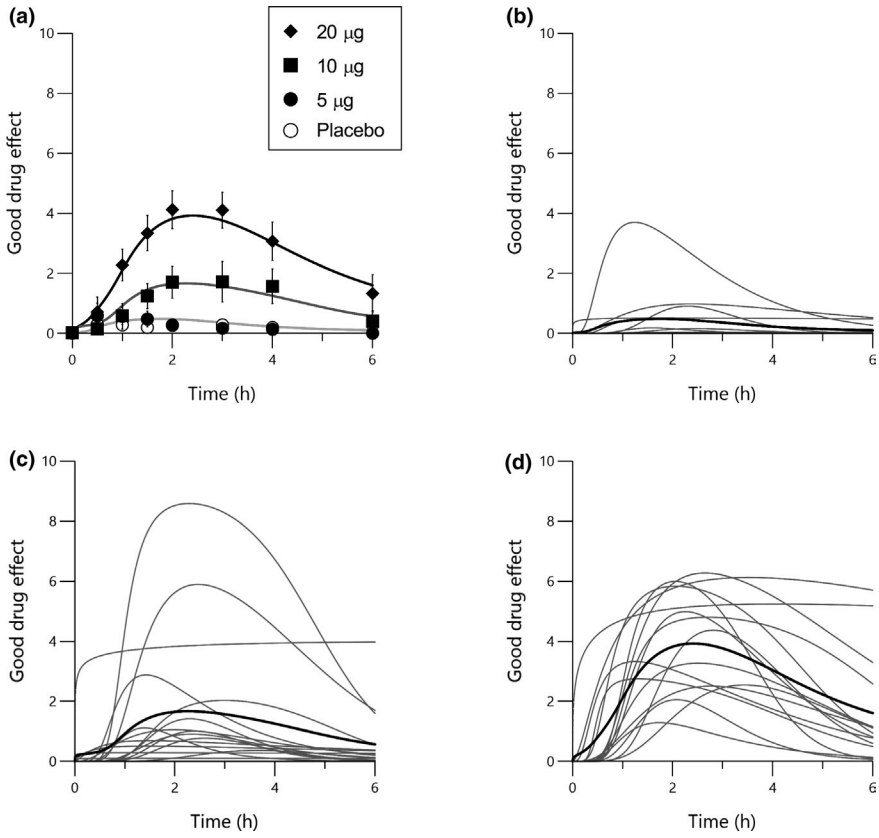

Figure 3 Subjective effects of LSD and placebo over time based on visual analog scale (VAS) ratings from 0–10 for "good drug effect" for the 5, 10, and 20 µg LSD doses. (**a**) Effect-time curves represent the mean of the individual pharmacokinetic model predictions. The observed data are expressed as symbols and the mean ± SEM. (**b–d**) Individual LSD effect-time curves for (**b**) 5 µg, (**c**) 10 µg, and (**d**) 20 µg. Predicted individual effect-time curves are shown separately for each subject, and the mean is marked in bold to illustrate the between-subject variability of LSD effects after the administration of (**b**) 5 µg, (**c**) 10 µg, and (**d**) 20 µg LSD. LSD was administered at $t = 0$ h. The corresponding maximal effect values are shown in **Table S2**. h, hours; LSD, lysergic acid diethylamide.

method with a lower limit of quantification of 200 pg/mL in that previous study compared with 2.5 pg/mL in the present study did not allow for the sensitive and valid quantification of very low LSD concentrations. We also took eight blood samples within the first critical 6 hours after LSD administration compared with five samples in the previous study. Altogether, only the sensitive analytical method and more frequent sampling allowed valid determinations of pharmacokinetic parameters of very low doses of LSD in the present study. Nevertheless, the present data and previously published C_{max} and AUC values for 10 and 20 µg LSD base equivalent doses are comparable.[15] Additionally, pharmacokinetic data for the 5 µg LSD base dose and half-lives are presented here for the first time.

In addition to being the first comprehensive description of the pharmacokinetics of LSD, we confirmed the results of a previous study of the subjective effects of 5–20 µg LSD microdoses. Specifically, the 5 µg dose of LSD base in the present study had no significant acute subjective effects in healthy young subjects, confirming the absence of relevant effects of an equivalent 6.5 µg dose of LSD tartrate.[17] The 10 µg dose of LSD base that was used in the present study induced subjective feelings of "under the influence" and "good drug effects," consistent with the increase in "feel good" at the drug peak effect that was seen with 13 µg LSD tartrate.[17] Interestingly, although having negligible subjective effects, 13 µg LSD tartrate (equivalent to 10 µg LSD base) has been shown to alter brain connectivity in the limbic system.[18] These data indicate that healthy subjects begin to subjectively perceive effects of LSD at a threshold dose of 10 µg LSD base. Thus, doses < 10 µg LSD base could be considered subperceptual and would qualify as "microdoses."[14] Doses of 10 µg LSD base could also likely be used safely in future studies that use multiple dosing and/or administration in patients when aiming at producing no acute perceptual effects.

The higher 20 µg dose of LSD base that was used in the present study and the equivalent 26 µg dose of LSD tartrate that was used previously[17] both induced weak but clearly significant subjective effects compared with placebo under double-blind controlled conditions.[17] These data indicate small but measurable psychedelic-like effects at a 20 µg LSD base equivalent.[17] Thus, 20 µg LSD base could be considered a very low to low psychedelic dose. Doses of 5–10 µg LSD appear to be without relevant subjective effects. However, requiring further investigation is how well the subjective effects of 10–25 µg doses are tolerated by participants in studies with less close monitoring after drug administration compared with the present study. The present study indicates that relevant alterations of the mind can be induced by 20 µg LSD in some study participants. Additionally,

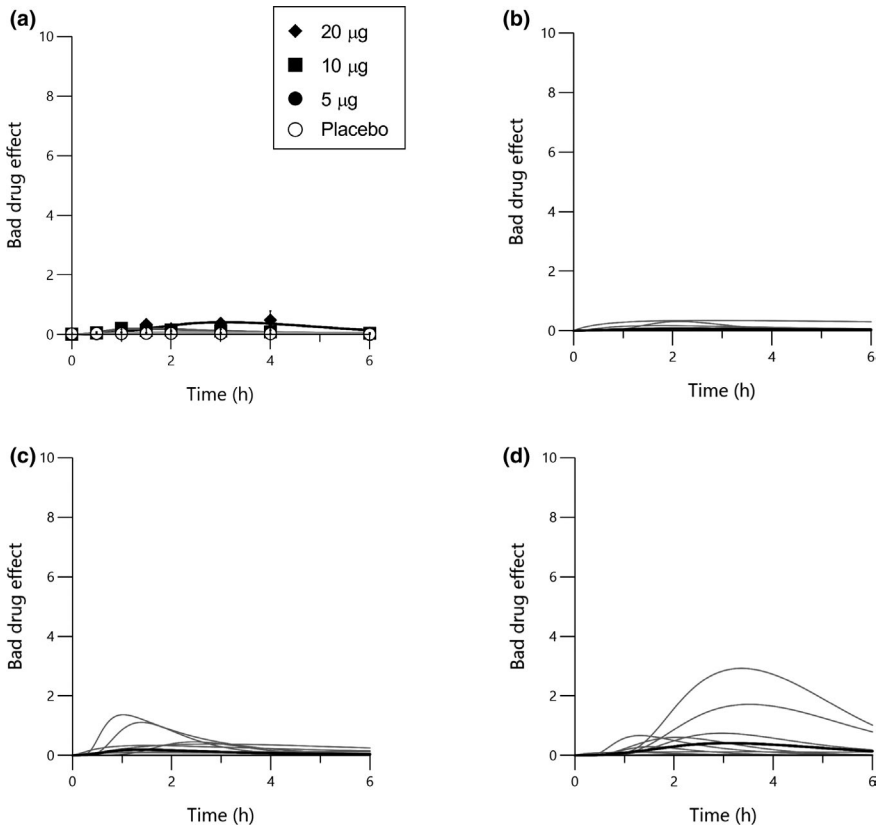

Figure 4 Subjective effects of LSD and placebo over time based on visual analog scale (VAS) ratings from 0–10 for "bad drug effect" for the 5, 10, and 20 µg LSD doses. (**a**) Effect-time curves represent the mean of the individual pharmacokinetic model predictions. The observed data are expressed as symbols and the mean ± SEM. (**b–d**) Individual LSD effect-time curves for (**b**) 5 µg, (**c**) 10 µg, and (**d**) 20 µg. Predicted individual effect-time curves are shown separately for each subject, and the mean is marked in bold to illustrate the between-subject variability of LSD effects after the administration of (**b**) 5 µg, (**c**) 10 µg, and (**d**) 20 µg LSD. LSD was administered at $t = 0$ hour. The corresponding maximal effects and statistics are shown in **Table S2**. h, hours; LSD, lysergic acid diethylamide.

the participants in the present study were healthy, and such responses may differ in clinical patients.

In the present study, we found that the subjective effects of 5–20 µg LSD base began an average of ~ 1 hour after administration, peak at 1.5–2.5 hours, and lasted 5 hours. Most of the subjects reported no subjective response to the 5 µg LSD base dose. The PK-PD modeling yielded lower EC_{50} values for "under the influence" and "good drug effect" compared with "bad drug effects," thus confirming previous studies that used 100 and 200 µg LSD[4,22] and indicating that bad drug effects are associated with higher LSD concentrations.

The present study has several strengths. Three different doses of LSD were used within subjects and compared with placebo under double-blind conditions in a controlled laboratory setting. Additionally, we used a very sensitive and validated analytical method.[4] The study included several assessments of the acute pharmacodynamics of LSD, which allowed the PK-PD modeling of different aspects of the acute subjective response to LSD. The present study also has important

Table 2 Characteristics of the subjective response ("under the influence") to different small doses of LSD

	5 µg LSD	10 µg LSD	20 µg LSD
Time to onset (hour)	0.71 ± 0.58 (0.25–1.6)[a]	1.1 ± 0.52 (0.35–2.3)[b]	0.85 ± 0.41 (0.10–1.7)
Time to offset (hour)	5.4 ± 0.57 (4.6–5.9)[a]	5.1 ± 0.94 (2.9–6.0)[b]	5.2 ± 0.62 (4.2–6.0)
Effect duration (hour)	4.7 ± 0.96 (3.7–5.6)[a]	4.0 ± 0.97 (2.3–5.6)[b]	4.3 ± 0.57 (3.2–5.0)
Time to maximal effect (hour)	1.5 ± 1.2 (0–3.7)	2.5 ± 1.6 (0–6)	2.3 ± 0.84 (1.2–4.6)
Maximal effect	0.57 ± 1.2 (0–4.3)	1.4 ± 1.6 (0–5.4)	3.6 ± 2.0 (0.44–7.5)
Area under effect-time curve	2.2 ± 4.1 (0–15)	4.9 ± 5.9 (0–19)	12 ± 8 (1.7–29)

Parameters are for the VAS "under the influence" as predicted by the pharmacokinetic-pharmacodynamic link model. The threshold to determine times to onset was set individually at 25% of the individual maximal response. Values are mean ± SD (range).
LSD, lysergic acid diethylamide; VAS, visual analog scale.
[a] For four subjects. Ratings of other subjects were too low to define onset and offset. [b] For 13 subjects. Ratings of other subjects were too low to define onset and offset.

limitations. The primary focus of the clinical trial was on psychological measures. Plasma samples could not be obtained from all 23 participants or for all doses because of technical problems. Therefore, the pharmacokinetic analyses included different total numbers of subjects for each dose and partly different subjects. Therefore, confirmative pharmacokinetic studies are needed with more comprehensive blood sampling. Furthermore, the present study used a standardized formulation with an exactly known content of LSD base, while recreational users use noncontrolled products containing mainly LSD tartrate. Thus, the present data may not reflect the PK of LSD when used recreationally.

In summary, we newly described the pharmacokinetics of three very low doses of LSD base in healthy subjects, provided PK-PD modeling data, and confirmed the previously reported dose-linear subjective effects of LSD.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

M.E.L. is a consultant for Mind Medicine, Inc., which had no role in funding or conduct of the present study. All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

F.H. and M.E.L. wrote the manuscript. F.H., M.E.L., N.R.P.W.H., P.C.D., A.F., J.G.R., and K.P.C.K. designed the research. N.R.P.W.H., N.L.M., E.L.T., P.C.D., and U.D. performed the research. F.H. and M.E.L. analyzed the data.

ETHICAL APPROVAL

The study was conducted in accordance with the Declaration of Helsinki and approved by the Medical Ethics Committee of the Academic Hospital of Maastricht and Maastricht University. The use of LSD in humans was authorized by the Dutch Drug Enforcement Administration.

INFORMED CONSENT

All of the subjects provided written consent before participating in the study and were paid for their participation.

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