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ORIGINAL RESEARCH ARTICLE

Pharmacokinetics and Pharmacodynamics of Lysergic Acid Diethylamide in Healthy Subjects

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Abstract

Background and Objective Lysergic acid diethylamide (LSD) is used recreationally and in clinical research. The aim of the present study was to characterize the pharmacokinetics and exposure–response relationship of oral LSD.
Methods We analyzed pharmacokinetic data from two published placebo-controlled, double-blind, cross-over studies using oral administration of LSD 100 and 200 µg in 24 and 16 subjects, respectively. The pharmacokinetics of the 100-µg dose is shown for the first time and data for the 200-µg dose were reanalyzed and included. Plasma concentrations of LSD, subjective effects, and vital signs were repeatedly assessed. Pharmacokinetic parameters were determined using compartmental modeling. Concentration-effect relationships were described using pharmacokinetic-pharmacodynamic modeling.
Results Geometric mean (95% confidence interval) maximum plasma concentration values of 1.3 (1.2–1.9) and 3.1 (2.6–4.0) ng/mL were reached 1.4 and 1.5 h after administration of 100 and 200 µg LSD, respectively. The plasma half-life was 2.6 h (2.2–3.4 h). The subjective effects lasted (mean ± standard deviation) 8.2 ± 2.1 and 11.6 ± 1.7 h for the 100- and 200-µg LSD doses, respectively. Subjective peak effects were reached 2.8 and 2.5 h after administration of LSD 100 and 200 µg, respectively. A close relationship was observed between the LSD concentration and subjective response within subjects, with moderate counterclockwise hysteresis. Half-maximal effective concentration values were in the range of 1 ng/mL. No correlations were found between plasma LSD concentrations and the effects of LSD across subjects at or near maximum plasma concentration and within dose groups.
Conclusions The present pharmacokinetic data are important for the evaluation of clinical study findings (e.g., functional magnetic resonance imaging studies) and the interpretation of LSD intoxication. Oral LSD presented dose-proportional pharmacokinetics and first-order elimination up to 12 h. The effects of LSD were related to changes in plasma concentrations over time, with no evidence of acute tolerance.
Trial registration: NCT02308969, NCT01878942.

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Key Points

The pharmacokinetics of lysergic acid diethylamide was dose proportional and the subjective effects were related to the time course of plasma concentrations within subjects, with no evidence of acute tolerance.

Between-subject differences in plasma concentrations of lysergic acid diethylamide did not predict the subjective response within a dose group and when plasma concentrations were above the half-maximal effective concentration of the response measures.

1 Introduction

Lysergic acid diethylamide (LSD) is the prototypical hallucinogen [1, 2]. Lysergic acid diethylamide has seen worldwide interest with regard to pharmacology, psychiatry, and society at large. Lysergic acid diethylamide continues to be used for recreational and personal purposes [3]. Additionally, considerable interest has been seen in its therapeutic potential [4–9], and experimental clinical research with LSD has recently been reinitiated [10–23]. However, basic pharmacokinetic information on LSD is largely missing. A small study in five male subjects reported a mean plasma elimination half-life of LSD of 175 min after intravenous administration (2 μg/kg) [24]. Another non-systematic study sampled blood after administration of LSD 160 μg in 13 subjects up to 2.5–5 h but because of sparse and short sampling could not derive pharmacokinetic parameters [25]. We recently reported the first pharmacokinetic data for orally administered LSD (200 μg) in 16 male and female subjects [23]. The concentrations of LSD were maximal after 1.5 h (median) and gradually declined to very low levels by 12 h, with an elimination half-life of 3.6 h [23].

Recent studies have reported the effects of LSD on various neuronal correlates of brain activation [12, 13, 16, 17]. However, plasma exposure and thus the actual presence of LSD in the body have not been documented in any of these studies to date. Unknown are the time point at which peak concentrations are reached and the actual or predicted concentrations of LSD at the time point at which pharmacodynamic outcomes were collected. Therefore, the primary goal of the present study was to describe the pharmacokinetics of a controlled administration of oral LSD by assessing the plasma concentration-time profile of two doses of LSD (100 and 200 μg). A second goal was to link the plasma concentration changes over time within subjects to the acute subjective and autonomic effects of LSD to derive half-maximal effective concentration (EC_{50}) values using standard pharmacokinetic-pharmacodynamic modeling.

Researchers have correlated subjective drug effects with brain functional magnetic resonance imaging (fMRI) data [12, 13, 16, 17]. This approach likely detects significant correlations for subjective effects that show large between-subject variance but not for subjective effects of the substance that are consistently present in all subjects. Plasma concentrations of LSD have not been determined in any of the published LSD fMRI studies to date; therefore, it is unclear how LSD exposure in the body is linked to subjective effects in these studies. Therefore, a further goal of the present study was to assess associations across subjects between plasma exposure to LSD and the pharmacodynamic effects at corresponding times.

The present study combined data from two similar clinical studies that tested 100- and 200-μg doses of LSD in 24 and 16 healthy subjects, respectively. The pharmacokinetic data and concentration–effect relationship of 100 μg LSD are presented. Similar data on 200 μg LSD have been previously reported [23]. In the present study, plasma concentrations after 200 μg LSD administration were newly measured using a more sensitive and specific analytical method. The results were included for comparisons with the 100-μg data and to newly evaluate dose/concentration–response effects. The subjective effects of LSD have been reported for both doses, but relationships to plasma exposure were not evaluated [21].

2 Methods

2.1 Study Design

We performed the pharmacokinetic data analysis on two similar previously performed studies [21–23] using double-blind, placebo-controlled, cross-over designs with two experimental test sessions (LSD and placebo) in a balanced order. Study 1 used a dose of LSD 100 μg and placebo in 24 subjects. Study 2 used LSD 200 μg and placebo in 16 subjects. The washout periods between sessions were at least 7 days. The studies were registered at ClinicalTrials.gov (NCT02308969, NCT01878942).

2.2 Participants

Forty healthy participants were recruited from the University of Basel campus via an online advertisement. Twenty-four subjects [12 men, 12 women; age 33 ± 11 years (mean ± standard deviation); range

25–60 years; body weight: 68 ± 8 kg, 55–85 kg) participated in Study 1 (100 µg), and 16 subjects (eight men, eight women; age 29 ± 6 years; range 25–51 years; body weight: 72 ± 12 kg, 52–98 kg) participated in Study 2 (200 µg). The inclusion and exclusion criteria were identical for both studies. The exclusion criteria were age <25 years or >65 years, pregnancy (urine pregnancy test at screening and before each test session), personal or family (first-degree relative) history of major psychiatric disorders (assessed by the semi-structured clinical interview for *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, Axis I disorders by the study physician and an additional interview by a trained psychiatrist), use of medications that may interfere with the study drug, chronic or acute physical illness (abnormal physical examination, electrocardiogram, or hematological and chemical blood analyses), tobacco smoking (more than ten cigarettes/day), lifetime prevalence of illicit drug use more than ten times (except for tetrahydrocannabinol), illicit drug use within the previous 2 months, and illicit drug use during the study. We performed urine drug tests at screening and before each test session, and no substances were detected during the study. The subjects were asked to abstain from excessive alcohol consumption between test sessions and particularly limit their use to one standard drink on the day before the test sessions. Additionally, the participants were not allowed to drink xanthine-containing liquids after midnight before the study day. The participants did not regularly use medications that could potentially interact with the study drug. No other medications aside from LSD were used during the study sessions. Eleven subjects had previously used a hallucinogen, including LSD (six participants), one to three times during their lives, and most of the subjects (29) were hallucinogen naive.

2.3 Study Procedures

Each study included a screening visit, a psychiatric interview, two 25-h experimental sessions, and an end-of-study visit. The experimental sessions were conducted in a quiet standard hospital patient room. The participants were resting in hospital beds except when going to the restroom. Only one research subject and one investigator were present during the experimental sessions. The participants could interact with the investigator, rest quietly, and/or listen to music via headphones, but no other entertainment was provided. LSD or placebo was administered at 9:00 A.M. A standardized lunch and dinner was served at 1:30 P.M. and 5.30 P.M., respectively. The subjects were never alone during the first 12 h after drug administration, and the investigator was in a room next to the subject for up to 24 h while the subject was asleep (mostly from 1:00 A.M. to 8:00 A.M.).

2.4 Study Drug

Lysergic acid diethylamide (*d*-lysergic acid diethylamide hydrate, high-performance liquid chromatography purity >99%; Lipomed AG, Arlesheim, Switzerland) was administered in a single oral dose of 100 or 200 µg as a capsule (Bichsel Laboratories, Interlaken, Switzerland). Both doses were within the range of doses that are taken for recreational purposes [1]. The 200-µg dose (the same capsules) was also used in LSD-assisted psychotherapy in patients [6], and intravenous doses of 75–100 µg have been used in fMRI studies in healthy subjects [13].

2.5 Measures

2.5.1 Blood Sampling

Blood was collected into lithium heparin tubes before and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, and 24 h after LSD administration. The 0.5-, 1.5-, and 2.5-h samples were not collected in Study 1 (100 µg). The blood samples were immediately centrifuged, and the plasma was rapidly stored at −20 °C and later at −80 °C until analysis within 12 months. Long-term stability has been shown for LSD when kept under refrigerated or frozen conditions [26, 27]. Samples were thawed for the first time for both analyses, this was also the case for study 2 (200 µg) because separate sets of samples were stored and used for the present [28] and previous [29] analyses.

2.5.2 Analysis of Lysergic Acid Diethylamide Concentrations

Lysergic acid diethylamide concentrations in plasma were determined using sensitive and validated liquid chromatography-tandem mass spectrometry methods as reported in detail elsewhere [28, 29]. The lower limit of quantification was 0.05 ng/mL in Study 1 (100 µg) [29] and 0.01 ng/mL in Study 2 (200 µg) [28].

2.5.3 Subjective Mood

Visual analog scales (VASs) were repeatedly used to assess subjective effects over time [21, 22]. The VASs included separate measures for "any drug effect," "good drug effect," and "bad drug effect" and were presented as 100-mm horizontal lines (0–100%) marked from "not at all" on the left to "extremely" on the right. The VASs were administered 1 h before and 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 16, and 24 h after drug administration. The 0.5- and 2.5-h ratings were not collected in Study 1 (100 µg).

2.5.4 Vital Signs

Blood pressure, heart rate, and body temperature were assessed repeatedly 1 h before and 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 24 h after drug administration. Diastolic and systolic blood pressure and heart rate were measured using an automatic oscillometric device (OMRON Healthcare Europe NA, Hoofddorp, Netherlands). The measurements were performed in duplicate at an interval of 1 min and after a resting time of at least 10 min. The averages were calculated for analysis. Core (tympanic) temperature was measured using a GENIUSTM 2 ear thermometer (Tyco Healthcare Group LP, Watertown, NY, USA). The 0.5- and 2.5-h measures were not collected in Study 1 (100 μg).

2.6 Pharmacokinetic Analyses and Pharmacokinetic-Pharmacodynamic Modeling

All of the analyses were performed using Phoenix WinNonlin 6.4 (Certara, Princeton, NJ, USA). Pharmacokinetic parameters were estimated using compartmental modeling. A one-compartment model was used with first-order input, first-order elimination, and no lag time. Initial estimates for apparent volume of distribution and λ were derived from non-compartmental analyses.

The model fit was not relevantly improved by a two-compartment model based on visual inspection of the plots. The one-compartment model showed better Akaike information criterion values in all subjects than a two-compartment model. The pharmacokinetic model was first fitted and evaluated. The predicted concentrations were then used as inputs to the pharmacodynamic model, treating the pharmacokinetic parameters as fixed and using the classic pharmacokinetic/pharmacodynamic link model module in WinNonlin. The model uses a first-order equilibrium rate constant (k_{eo}) that related the observed pharmacodynamic effects of LSD to the estimated LSD concentrations at the effect site (Fig. S1) and accounts for the lag between the plasma- and effect-site concentration curves [30]. Initial estimates for k_{eo} values were obtained using semi-compartmental modeling by collapsing the hysteresis loop in the C_e vs. effect plots in WinNonlin. A sigmoid maximum effect (E_{max}) model (EC$_{50}$, E_{max}, γ) was selected for all pharmacodynamic effects. EC$_{50}$ and E_{max} estimates were taken from the pharmacokinetic-pharmacodynamic plots. Lower and upper limits for E$_{max}$ were set to 0 and 100%, respectively, for all the VAS scores. Upper limits for E_{max} for changes in heart rate, body temperature, and diastolic and systolic blood pressure were set to 100/min, 2 °C, 50 and 80 mm Hg, respectively. The sigmoidal E_{max} model best described the relationship between estimated effect-site concentrations and the effects of LSD compared with a simple E_{max} model (plot inspection and Akaike information criteria). Examples of diagnostic plots are shown in Figs. S8 and S9.

2.7 Statistical Analyses

The LSD-induced subjective and autonomic effects were determined as a difference from placebo in the same subject at the corresponding time point to control for circadian changes and placebo effects [22]. The pharmacodynamic effect changes after LSD administration for each time point were plotted over time (effect-time curves) and against the respective plasma concentrations of LSD and graphed as concentration-effect curves. The onset, time to maximum plasma concentration (T_{max}), offset, and effect duration were assessed for the model-predicted "any drug effect" VAS effect-time plots after LSD using a threshold of 10% of the maximal possible effect of 100% using Phoenix WinNonlin 6.4. Associations between concentrations and effects were assessed using Pearson correlations, and multiple regression analysis was used to exclude effects of sex and body weight (Statistica 12 software; StatSoft, Tulsa, OK, USA).

3 Results

3.1 Pharmacokinetics

The plasma concentration-time curves for the two LSD doses are shown in Fig. 1a. The pharmacokinetic parameters are shown in Table 1. In Study 1 (100 μg), LSD could be quantified up to 8, 10, 12, 16, and 24 h in 24, 23, 22, 9, and one subject, respectively. In Study 2 (200 μg), LSD could be quantified up to 16 h in all 16 subjects and up to

Fig. 1 Pharmacokinetics and pharmacodynamics of lysergic acid ▶ diethylamide (LSD). **a** LSD plasma concentration-time curves. The corresponding semi-log plot is shown in Fig. S3. LSD effect-time curves for Visual Analog Scale ratings (0–100%) of **b** "any drug effect," **d** "good drug effect," and **f** "bad drug effect." **c, e, g** In the LSD concentration-effect plots (hysteresis curves), the subjective effects of LSD showed moderate counterclockwise hysteresis, indicating a relatively short delay in the effect of LSD relative to the changes in plasma concentration over time. The plasma concentration-effect site equilibration half-lives were in the range of 21–48 min according to the pharmacokinetic-pharmacodynamic link model (Table 2). "Any drug effect" and "good drug effect" were robustly and markedly increased in all subjects and paralleled the changes in LSD concentration, whereas the mean "bad drug effect" increased only moderately after LSD owing to transient increases. "Bad drug effect" occurred mostly at the onset of the drug effect in some subjects but also later in time in others. The data are expressed as the mean ± standard error of the mean in 24 and 16 subjects after administration of 100 and 200 μg LSD, respectively. The time of sampling is noted next to each point. LSD was administered at $t = 0$
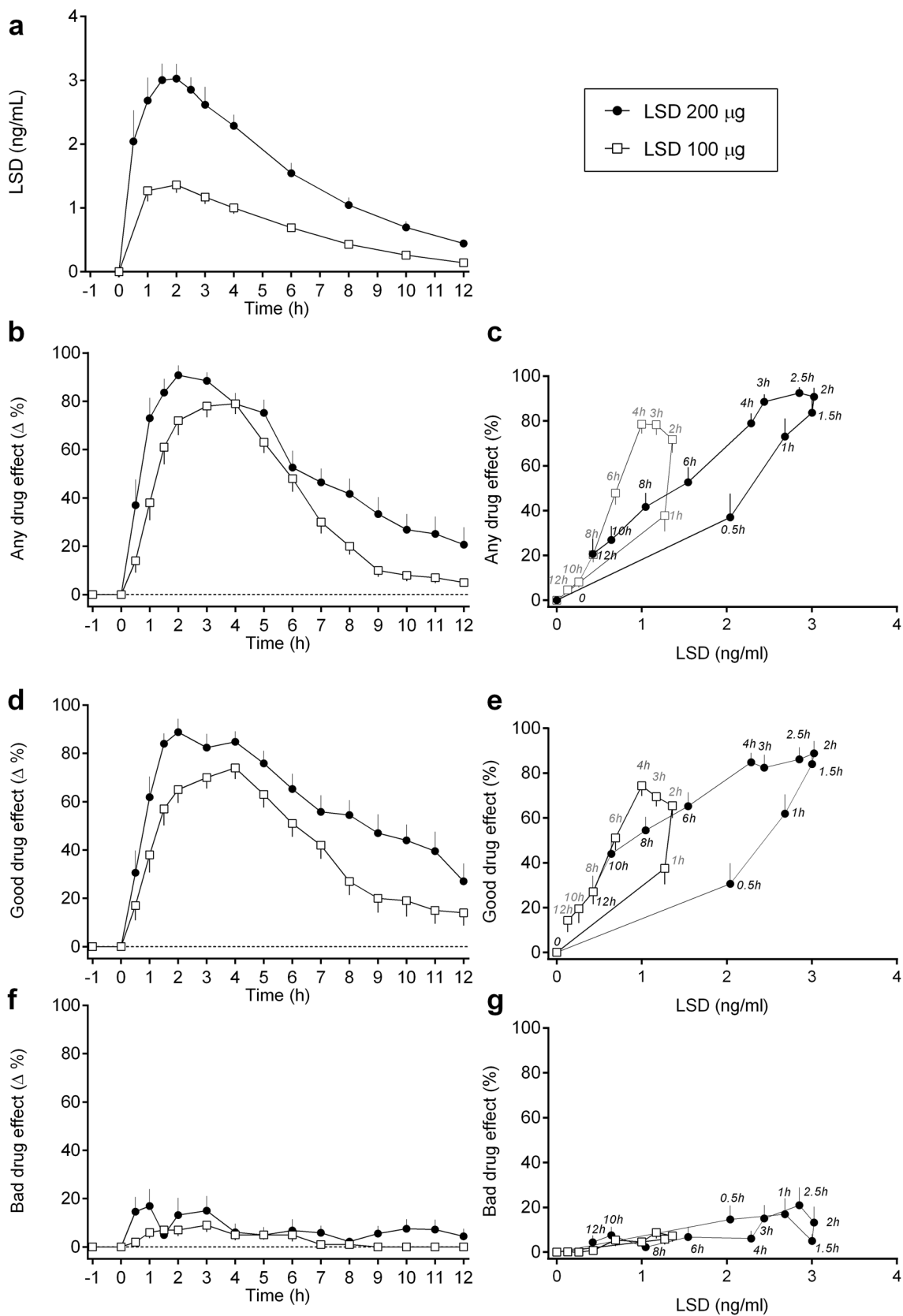
Table 1 Pharmacokinetic parameters for LSD based on compartmental modeling

Dose	N		k_{01} (1/h)	λ (1/h)	V_d (L)	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC_∞ (ng·h/mL)	CL/F (L/h)
100 µg	24	Geometric mean (95% CI)	1.4 (1.2–4.1)	0.27 (0.24–0.31)	46 (35–76)	1.3 (1.2–1.9)	1.4 (1.3–2.1)	2.6 (2.4–3.0)	8.1 (7.5–11.1)	12.3 (7.8–24)
		Range	0.31–9.9	0.17–0.50	24–270	0.3–3.7	0.4–3.2	1.4–4.2	1–19	5.2–103
200 µg	16	Geometric mean (95% CI)	1.2 (0.68–4.6)	0.27 (0.22–0.35)	37 (32–46)	3.1 (2.6–4.0)	1.5 (1.3–2.4)	2.6 (2.2–3.4)	20.3 (17.3–26.2)	9.9 (8.3–12.8)
		Range	0.27–10	0.12–0.59	18–66	1.9–7.1	0.4–3.8	1.2–5.6	11–39	5.1–18.5

AUC_∞ area under the plasma concentration-time curve from time zero to infinity, C_{max} estimated maximum plasma concentration, $t_{1/2}$ estimated plasma elimination half-life, t_{max} estimated time to reach C_{max}, k_{01} first-order absorption coefficient, λ first order elimination coefficient, V_d volume of distribution

24 h in 15 subjects (Fig. S2). Mean maximum plasma concentration (C_{max}) and area under the concentration-time curve values were approximately twice as high for the 200-µg dose compared with the 100-µg dose. Dose-normalized C_{max} and area under the concentration-time curve values were not statistically different between the dose groups and the T_{max} and plasma half-lives were also similar, consistent with dose-proportional pharmacokinetics (Table 1). Consistent with the fit of the one-compartment model, inspection of the semi-logarithmic concentration-time curves showed linear elimination kinetics for both doses (Fig. S3) up to 12 h as previously reported for the 200-µg dose [23]. The individual-observed and model-predicted LSD concentrations are shown in Fig. S2. Plasma concentrations varied considerably between subjects, especially at the lower 100-µg dose (Table 1; Fig. S2).

3.2 Pharmacodynamics

Lysergic acid diethylamide produced robust increases in "any drug effect" (Fig. 1b, Fig. S4) and "good drug effect" (Fig. 1d, Fig. S5). Transient "bad drug effect" was reported in some subjects, resulting in a moderate increase in mean group ratings (Fig. 1f, Fig. S6). The corresponding subjective peak effects have previously been reported and were shown to be dose dependent [21]. "Any drug effect," "good drug effect," and "bad drug effect" ratings for each subject are shown in Figs. S4–6, respectively. After administration of the 100-µg dose of LSD, the times of onset and offset of the subjective response, assessed by the "any drug effect" VAS, were (mean ± standard deviation) 0.8 ± 0.4 h (range 0.1–1.7 h) and 9.0 ± 2.0 h (range 6.1–14.5 h), respectively. The mean effect duration was 8.2 ± 2.1 h (range 5–14 h). The time to peak drug effect was 2.8 ± 0.8 h (range 1.2–4.6 h). After administration of the 200-µg dose of LSD, the times of onset and offset of the subjective response were 0.4 ± 0.3 h (range 0.04–1.2 h) and 11.6 ± 4.2 h (range 7.0–19.5 h), respectively. The mean effect duration was 11.2 ± 4.2 h (range 6.4–19.3 h). The time to the subjective peak response was

2.5 ± 1.2 h (range 0.8–4.4 h). LSD increased diastolic and systolic blood pressure, heart rate, and body temperature compared with placebo to similar extents for both doses (Fig. 2). The corresponding peak effect data and dose-response statistics have been previously reported [21].

3.3 Pharmacokinetic-Pharmacodynamic Modeling

Figures 1 and 2 show the subjective, cardiovascular, and thermogenic effects of LSD plotted against the plasma concentration over time. A close relationship was found between LSD concentrations and LSD effects over time. Counterclockwise hysteresis was observed during the assumed drug distribution phase (<2 h), especially for body temperature (Fig. 2h). Model-predicted effects of LSD on the VASs for "any drug effect," "good drug effect," and "bad drug effect" are illustrated for each subject in Figs. S4–6, respectively. Table 2 shows the predicted concentrations of LSD at the effect site that produced half-maximal effects (EC_{50} values). Mean EC_{50}

Fig. 2 Pharmacokinetics and autonomic effects in response to ▶ lysergic acid diethylamide (LSD). The figure shows LSD effect-time curves for **a** diastolic blood pressure, **c** systolic blood pressure, **e** heart rate, and **g** changes in body temperature and corresponding **b, d, f, h** LSD concentration-effect plots (hysteresis curves). The cardiovascular stimulant effects of LSD at the higher 200-µg dose showed only little counterclockwise hysteresis, indicating a short delay in the effect of LSD relative to the changes in plasma concentration over time and thus a close relationship between LSD concentration and changes in cardiovascular effects over time within subjects. The plasma concentration-effect site equilibration half-lives were in the range of 13–34 min according to the pharmacokinetic-pharmacodynamic link model (Table 2). In contrast, marked counterclockwise hysteresis was observed in the LSD concentration-body temperature change plot, indicating that the LSD-induced changes in body temperature manifested themselves slowly and with a mean plasma concentration-effect site equilibration half-life of 136 min for the 200-µg dose (Table 2). The data are expressed as the mean ± standard error of the meant in 24 and 16 subjects after administration of LSD 100 and 200 µg, respectively. The pharmacodynamic values are the mean ± standard error of the mean differences from placebo at each time point. The time of sampling is noted next to each point. LSD was administered at $t = 0$
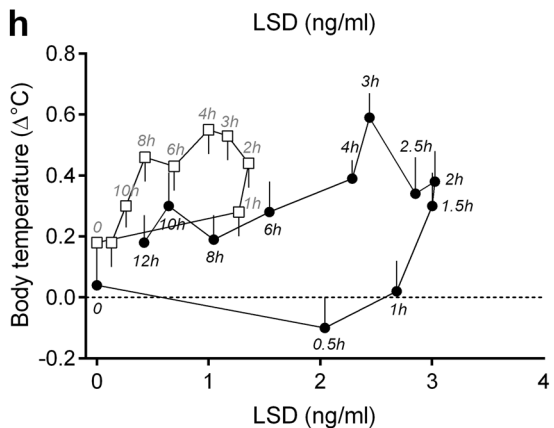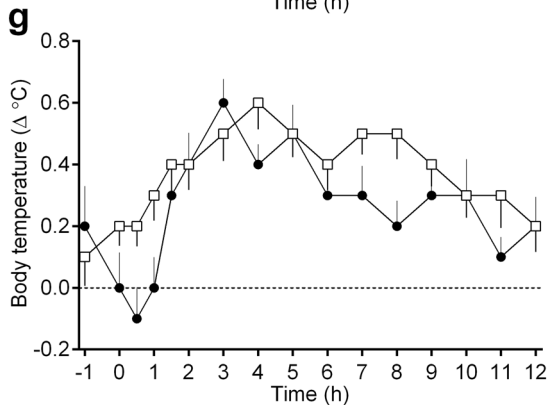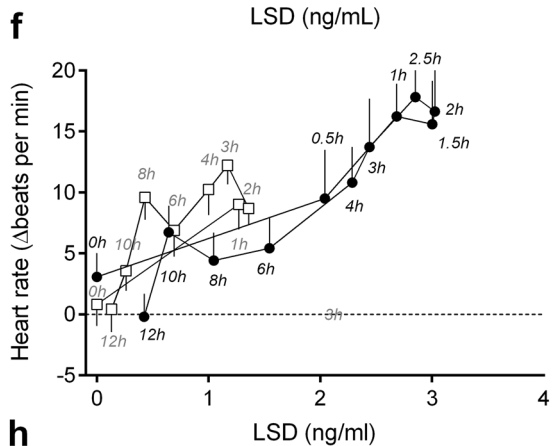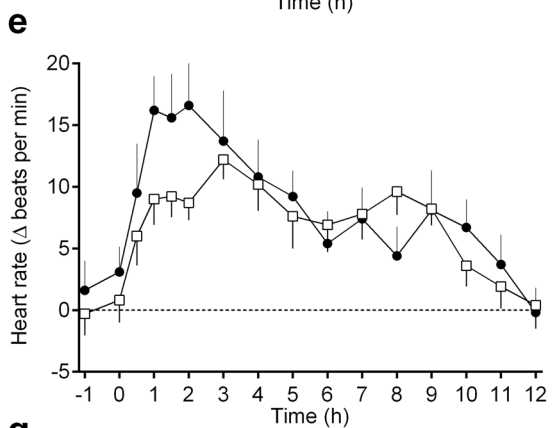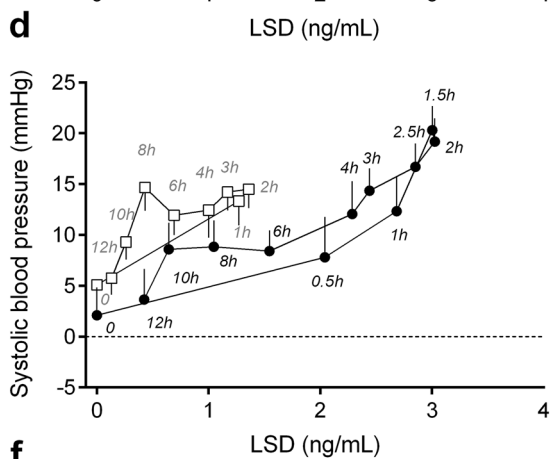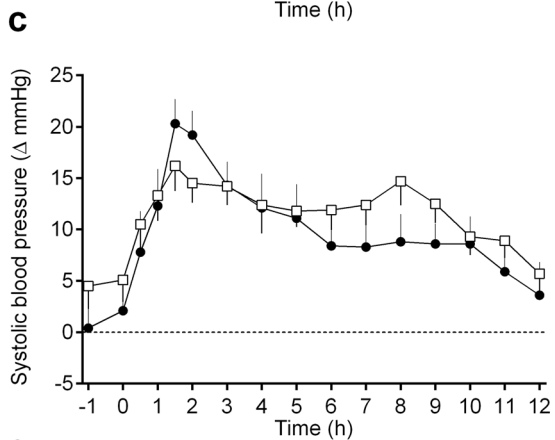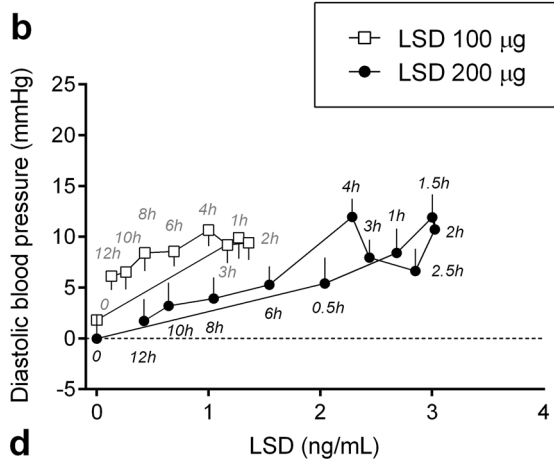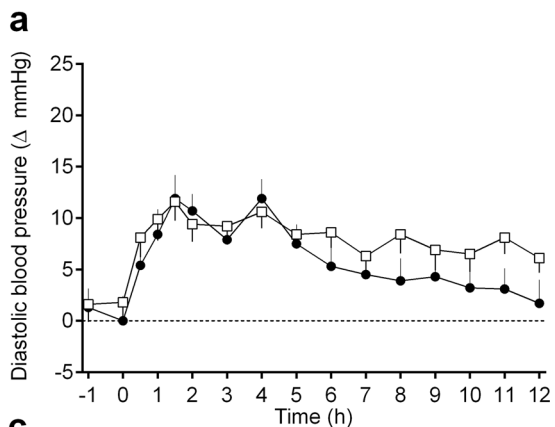
Table 2 Pharmacodynamic parameter estimates (PK-PD link model)

Effect	Dose	EC_{50} (ng/mL)	E_{max} (%)	γ	k_{eo} (1/h)	$T_{1/2}k_{eo}$ (min)
Any drug effect	100 µg	0.75 ± 0.4	95 ± 9	4.2 ± 1.2	1.8 ± 1.3	35 ± 23
	200 µg	1.2 ± 0.7	97 ± 5	3.4 ± 1.5	3.4 ± 1.7	21 ± 17
Good drug effect	100 µg	0.71 ± 0.5	89 ± 15	3.9 ± 1.5	2.0 ± 1.6	39 ± 37
	200 µg	0.94 ± 0.5	93 ± 9	3.2 ± 1.6	2.4 ± 1.8	32 ± 29
Bad drug effect	100 µg	1.5 ± 1.1	32 ± 37	4.7 ± 2.3	2.7 ± 2.2	42 ± 37
	200 µg	2.5 ± 1.6	34 ± 35	3.2 ± 2.1	2.8 ± 2.0	48 ± 66
Heart rate increase	100 µg	0.67 ± 0.5	22 ± 25	3.7 ± 2.0	2.5 ± 1.9	46 ± 52
	200 µg	1.9 ± 1.2	33 ± 28	2.7 ± 1.8	4.0 ± 2.0	13 ± 8
Body temperature increase	100 µg	0.75 ± 0.4	1.1 ± 0.6	2.2 ± 1.8	1.5 ± 1.6	107 ± 121
	200 µg	1.8 ± 1.1	1.0 ± 0.6	3.6 ± 2.0	1.7 ± 1.9	136 ± 155
Diastolic blood pressure increase	100 µg	0.9 ± 0.6	23 ± 14	2.0 ± 1.6	2.6 ± 1.9	53 ± 70
	200 µg	1.6 ± 0.9	18 ± 11	3.5 ± 1.6	3.4 ± 1.9	31 ± 42
Systolic blood pressure increase	100 µg	0.8 ± 0.5	30 ± 17	1.9 ± 1.6	2.6 ± 1.7	51 ± 78
	200 µg	1.9 ± 1.4	30 ± 17	2.9 ± 1.9	3.2 ± 1.9	34 ± 41

Values are means ± standard deviations. $T_{1/2}k_{eo} = \ln2/k_{eo}$, calculated for each individual value

EC_{50} maximal effect predicted by the PK-PD link model, $EC50$ predicted drug concentration at effect site producing a half-maximal effect, γ sigmoid shape parameter, k_{eo} first-order rate constant for the equilibration process between plasma concentration and effect site (PK-PD model link parameter), $t_{1/2}k_{eo}$ (min) plasma-effect-site equilibration half-life

values were in the range of 0.67–2.5 ng/mL and lower for "good drug effect" than for "bad drug effect" (Table 2). "Any drug effect" and "good drug effect" could be modeled in all of the subjects, whereas no "bad drug effect" (ratings <5% at any time point) was reported in eight (33%) and five (31%) subjects after 100 and 200 µg, respectively. Thus, the EC_{50} and k_{eo} values could not be determined in these subjects. Similarly, vital signs did not change sufficiently in a few subjects (one to three/outcome) to determine these values.

The predicted C_{max} of LSD did not correlate with the predicted maximal response on the "any drug effect" VAS when analyzed across subjects and separately for the two dose groups ($R_p = 0.38$, $p = 0.08$, and $R_p = 0$, $p = 0.9$, for the 100- and 200-µg doses, respectively). There was a significant correlation in the pooled sample ($R_p = 0.38$, $p < 0.05$, $n = 40$, Fig. S7). The predicted area under the concentration-time curve of LSD did not correlate with the predicted area under the concentration-time curve for "any drug effect", a measure of the overall pharmacodynamic response ($R_p = 0$, $p = 0.9$, and $R_p = 0.27$, $p = 0.4$, respectively). Additionally, there were generally no correlations between plasma LSD concentrations and different pharmacodynamic effects for matched time points across subjects within dose groups (Table 3). A few correlations were significant at the beginning (1 h) and end (8 and 12 h) of the LSD effect. However, no significant associations were found between plasma concentrations and effects during the peak response to LSD (3–6 h). Multiple regression analysis, including LSD concentration, body weight, and sex, revealed no associations between the

effects of LSD and any of these possible predictors. Thus, the plasma concentrations of LSD did not predict the effects of LSD during the time it produced robust and similar effects in all of the subjects (i.e., little between-subject variability). In contrast, a close relationship was found over time within subjects, as shown in the pharmacokinetic-pharmacodynamic analysis (Figs. 1, 2).

4 Discussion

The present study describes the pharmacokinetics and concentration–effect relationship after oral administration of LSD 100 µg. Additionally, the previously reported pharmacokinetics and concentration–effect relationship for the 200-µg dose of LSD [23] were reanalyzed and included for comparison with the 100-µg dose. Compartmental modeling predicted geometric mean peak plasma concentrations of 1.3 ng/mL, 1.4 h after administration of the 100-µg dose. Mean C_{max} values of 3.1 ng/mL were reached after 1.5 h after administration of the 200-µg dose. The predicted mean half-lives of LSD were 2.6 h after both doses. The plasma half-life in the present study was comparable to the value of 2.9 h after intravenous administration of 2 µg/kg of LSD [24] but shorter than the 3.6-h value previously determined using non-compartmental analysis [23]. Additionally, the plasma concentrations after administration of the 200-µg dose in the present study were lower than those that were previously published in the same research subjects [23]. This can be explained by the different analytical methods and modeling approach that were

Table 3 Correlations between plasma levels of LSD and its pharmacodynamic effects at the corresponding time points after administration

Effect			1 h	2 h	3 h	4 h	6 h	8 h	10 h	12 h
Any subjective drug effect	100 µg	N = 24	0.17	0.13	−0.02	−0.04	−0.18	0.09	0.01	−0.03
	200 µg	N = 16	0.21	0.17	0.1	0.13	0.2	0.16	0.33	0.42
	Both	N = 40	**0.36**	**0.35**	0.19	0.04	0.06	**0.41**	**0.46**	**0.49**
Good drug effect	100 µg	N = 24	**0.6**	0.3	0.23	0.15	−0.13	−0.2	−0.03	0.04
	200 µg	N = 16	0	−0.23	0.32	0.27	0.28	**0.55**	0.39	0.17
	Both	N = 40	**0.39**	**0.34**	**0.36**	0.31	0.24	**0.42**	**0.35**	0.23
Bad drug effect	100 µg	N = 24	0.06	−0.11	−0.23	−0.1	−0.08	−0.03	0	−0.15
	200 µg	N = 16	0.34	−0.32	−0.27	0.07	0.2	0.35	−0.26	−0.16
	Both	N = 40	**0.36**	−0.16	0	0	0.1	0.29	0.05	0.07
Heart rate increase	100 µg	N = 24	**0.41**	0.3	0.4	0.27	0.1	0.26	−0.4	0.027
	200 µg	N = 16	0.3	0.21	0.3	−0.06	−0.08	0.19	−0.16	**−0.52**
	Both	N = 40	**0.44**	**0.41**	**0.33**	0.08	−0.05	−0.02	0.03	−0.2
Body temperature increase	100 µg	N = 24	0.12	−0.27	0.14	0.07	0.18	−0.06	−0.2	**0.41**
	200 µg	N = 16	0.09	−0.11	**0.54**	−0.1	−0.02	0.37	0.15	−0.19
	Both	N = 40	−0.08	−0.18	0.25	−0.15	−0.09	−0.12	0.02	0.06
Diastolic blood pressure increase	100 µg	N = 24	0.16	−0.09	0.14	0.04	0.17	0.15	0.28	0.13
	200 µg	N = 16	−0.53	−0.22	0.2	−0.13	0.09	0.27	0.09	0.47
	Both	N = 40	−0.2	−0.03	0.07	0.03	−0.06	−0.01	0.01	0.07
Systolic blood pressure increase	100 µg	N = 24	0.1	0.05	0.06	0	0.2	0.23	0.29	0.21
	200 µg	N = 16	−0.03	−0.4	−0.1	0.25	0	**0.54**	−0.02	0.19
	Both	N = 40	0	0.07	0.03	0.07	−0.07	0.11	0.05	0.08

Data are Pearson correlation coefficients between the LSD concentration in plasma and the corresponding time-matched effect of LSD. Bold values indicate significant associations ($p < 0.05$)

used in the present study, which predicts lower C_{max} values than the observed values. Overall, we observed linear dose and elimination kinetics of LSD up to 12 h after drug administration.

The present data on the plasma concentration-time curves of LSD are important because many experimental and therapeutic studies are currently being conducted or have been published without this detailed information on the presence of LSD in the human body. Specifically, the effects of LSD on emotion processing after 100 and 200 µg have been reported [23], but no pharmacokinetic data were reported. Additionally, fMRI data were obtained in Study 1 (100 µg) in Basel and in an additional study in Zurich ($n = 22$) that did not perform blood sampling. Doses of 100 µg were used in both studies. Thus, the present study provides estimates of LSD concentrations in plasma over time for these studies and the observed and predicted time courses of the subjective and autonomic effects of LSD. The 200-µg dose preparation of LSD has been used in patients [5, 6], and the present phase I study provides the pharmacokinetic data for these phase II studies.

In contrast, no data are currently available on the plasma concentrations of LSD after intravenous administration of 75 µg of LSD base in saline [11], despite the publication of extensive pharmacodynamic data using this preparation

and route of administration [10–19]. The intravenous 75-µg dose of LSD produced comparably strong alterations in consciousness to the 100-µg dose in the present study [10, 31]. Additionally, the time-concentration curve for the 75-µg intravenous preparation remains unknown. Specifically, an intravenous bolus dose of LSD would be expected to result in peak effects shortly after administration. Indeed, early studies reported that intravenous administration of LSD tartrate salt at a higher dose (2 µg/kg of base) produced a rapid onset within seconds to minutes and peak effects that occurred approximately 30 min after administration [24, 32–34].

In the more recent studies that used the 75-µg dose administered as the base, subjective drug effects reportedly began within 5–15 min and peaked 45–90 min after intravenous dosing, although further details were not reported [13, 19]. Other hallucinogens with mechanisms of action that are similar to those of LSD (e.g., serotonin 5-HT$_{2A}$ receptor stimulation [35]), such as dimetyl-tryptamine or psilocybin, also produced subjective and autonomic effects almost instantaneously and peak effects within 2–5 min after intravenous administration [36–38]. In the present study, the mean effect onset and peak were 48 and 170 min, respectively, after oral administration of LSD 100 µg. Thus, the effect began and peaked an average

of 30 and 100 min later, respectively, after oral administration compared with intravenous administration of an equivalent dose [13, 19]. Magnetic resonance imaging scanning correctly started at approximately 70 and 150 min in the studies that used intravenous [13] and oral (unpublished data from Study 1, 100 µg) routes of LSD administration, respectively, coinciding with the maximal response to LSD. Nevertheless, the plasma concentrations of LSD and associated time-matched subjective responses after intravenous LSD administration should also be determined to better evaluate the considerable research data that have been generated with this formulation.

After intravenous administration, a drug is rapidly diluted and distributed within the blood. Peak plasma concentrations are typically reached rapidly, and elimination begins immediately. Using the model parameters λ and k_{eo} from the present study, the T_{max} for "any drug effect" after intravenous administration can be predicted to occur at approximately 70 and 50 min for the 100- and 200-µg doses and are thus similar to the recently observed times to peak effects [13, 19]. In our model, the relatively long T_{max} of the effect of LSD is represented by the lag that is attributable to distribution of the drug from plasma to the hypothetical effect compartment. The cause for this lag is unclear. Additional studies are needed to determine whether LSD is distributed slowly because it is present only in small concentrations or slowly penetrates the blood–brain barrier or whether there is a lag in the response mechanism.

The present study showed that LSD produced robust and high subjective "any drug effect" and "good drug effect" in almost all of the subjects. The estimates of the corresponding EC_{50} values were in the range of 0.71–1.2 ng/mL and lower than the mean LSD C_{max} values (1.3 and 3.1 ng/mL for the 100- and 200-µg doses, respectively) observed in the present study. "Bad drug effects" were moderate and not present in every subject. Consistent with this finding, the EC_{50} values were higher than those for "good drug effect" and "any drug effect" (1.5–2.5 ng/mL). As previously reported, the subjective effects were dose dependent, whereas the autonomic effects were comparable at both doses [21]. When analyzed within subjects using pharmacokinetic-pharmacodynamic modeling, a close relationship was found between plasma concentrations of LSD and the effects of LSD, with moderate counterclockwise hysteresis. Counterclockwise hysteresis typically reflects the time lag that is caused by drug distribution to the effect site and the response time associated with the mechanism of action. The present study showed that the subjective and autonomic effects establish themselves relatively slowly. On average, the subjective "any drug effect" peak was reached 2.8 and 2.5 h after administration of the 100- and 200-µg doses, respectively, and 1.1 and 0.6 h after the respective peak LSD concentrations were reached. The lag times were

comparable for the increases in heart rate and blood pressure but longer for the thermogenic response. No clockwise hysteresis was found for any of the pharmacodynamic outcome measures, and thus no evidence was found of acute tolerance as described for other psychoactive substances, such as methylenedioxymethamphetamine [39] or cocaine [40], or for repeated administration of LSD [41]. Thus, as long as relevant concentrations of LSD were present in plasma, subjective and autonomic effects were observed. The mean durations of the subjective effects of LSD was 8 and 11 h after administration of the 100- and 200-µg doses, respectively, and the difference corresponded to the plasma half-life of LSD.

The present analyses typically found no correlations between LSD concentrations and the effects of LSD across subjects within dose groups, likely because of the relatively high concentrations of LSD and generally consistently high subjective response ratings in most subjects. If relatively high and similar doses of LSD are used that result in plasma concentrations above the EC_{50} of a particular response measures, then responses do not vary across subjects because responses are close to maximal. This would typically also be the case with measures with a maximal effect limit such as VAS ratings and some physiological effects such as pupil size [42]. In fact, responses to LSD or other drugs in a standardized experimental setting may vary only if the response is not induced consistently in all subjects (e.g., at the beginning and end of the response) because of individual differences in drug absorption/distribution and elimination. Correlations of plasma concentrations with the subjective and cardiovascular effects of LSD or 3,4-methylenedioxymethamphetamine [42] across subjects are only weak during the peak response. This finding needs to be considered when interpreting associations between subjective responses and other measures, such as fMRI parameters. fMRI findings may reflect the variance in LSD plasma concentrations. The likelihood of detecting correlations within a dose group increases for effects that are not robustly induced in all subjects.

The present study has limitations. First, the two doses of LSD were evaluated in two separate studies in different participants and not within subjects. Second, the plasma samples were analyzed in different laboratories. Nonetheless, the pharmacokinetic data were consistent across the two studies and laboratories.

5 Conclusion

We gathered pharmacokinetic data for oral LSD that are essential for interpreting the findings of clinical studies and LSD intoxication. LSD had dose-proportional pharmacokinetics and first-order elimination up to 12 h. A close

plasma concentration–effect relationship was found within subjects over time, with moderate counterclockwise hysteresis because of a short lag of the response. Generally, no association was found between plasma LSD concentrations and its robust effects when analyzed across different subjects and within a dose group. This has implications for studies that interrelate different effects of LSD.

Compliance with Ethical Standards

Conflict of interest Patrick C. Dolder, Yasmin Schmid, Andrea E. Steuer, Thomas Kraemer, Katharina M. Rentsch, Felix Hammann, and Matthias E. Liechti declare no conflicts of interest.

Ethics approval and consent to participate The studies were conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee. The administration of LSD to healthy subjects was authorized by the Swiss Federal Office for Public Health, Bern, Switzerland. All of the subjects provided written consent before participating in either of the studies, and they were paid for their participation.

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