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RESEARCH ARTICLE

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Pharmacokinetics and subjective effects of 1P-LSD in humans after oral and intravenous administration

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Abstract

1-Propanoyl-lysergic acid diethylamide (1P-LSD) appeared as a non-controlled alternative to LSD a few years ago. Although evidence is beginning to emerge from in vitro and animal studies that 1P-LSD might serve as a prodrug for LSD, an equivalent evaluation in humans is unavailable. Controlled oral and intravenous self-administrations of 100 μg 1P-LSD hemitartrate are reported in two human volunteers followed by analyses of urine and serum samples using a fully validated LC–MS/MS method. Psychometric evaluations included assessment of selected subjective drug effects and administration of the Five-Dimensions of Altered States of Consciousness rating scale (5D-ASC). In serum and urine, oral administrations of 1P-LSD only led to the detection of LSD reflecting biphasic elimination with a terminal elimination half-life of approx. $t_{1/2}$ = 6.4 h. 1P-LSD could be detected for only up to 4.16 h in serum and 2.7 h in urine following intravenous administration, whereas LSD was detected in all serum samples (last sampling after approx. 24 h) and up to 80 h in urine. LSD showed first order elimination kinetics with an approx. $t_{1/2}$ = 5.7 h, whereas 1P-LSD showed a rapid decrease in concentration within the first hour followed by a slower decrease, most probably due to hydrolysis. The bioavailability of LSD after oral ingestion of 1P-LSD was close to 100%. The psychosensory effects of 1P-LSD and their time course were comparable to those seen after uptake of LSD in other studies which further supports the prodrug hypothesis. The 5D-ASC scores were higher after oral compared with intravenous administration of 1P-LSD.

KEYWORDS

5D-ASC score, psychedelics, pharmacodynamics, pharmacokinetics, VAS score

1 | INTRODUCTION

Lysergic acid diethylamide (LSD) soon became a widely used experimental drug after Albert Hofmann discovered its psychoactive effects in 1943. The ability to induce psychoactive effects at low doses (< 100 μg) and the finding that it interacted with the serotonergic system, triggered wide-ranging research into the neurotransmitter system at the time.[1] LSD induces a wide spectrum of psychotropic effects, including euphoria or dysphoria, hallucinatory phenomena, synesthesia, perceptual alterations, remembrance of significant life

Christina Grumann and Kerstin Henkel contributed equally to the manuscript

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events, mystical experiences, ego-dissolution, and cathartic experiences. Deep-reaching insightful experiences, but also anxiety-producing experiences were described by users.[2] LSD was also used in psychotherapy.[3] Nearly ten thousand scientific papers on experiments with LSD have been published since the 1950s (cf.[4]). In the mid-1960s, LSD became a major drug of abuse. Since the 1970s, its recreational use became more widespread internationally without loss of popularity ever since (cf.[5]).

Several analogs of LSD have been explored in scientific research[6–8] and in more recent years, a number of LSD derivatives have emerged on the market that did not appear to have any established history in the scientific literature. One of these LSD derived "designer drugs" is 1-propanoyl-LSD (1P-LSD) that was first reported to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) in 2015.[9] Anecdotal reports published on various Internet forums suggested 1P-LSD to show LSD-like effects but formal studies were not available. However, 1P-LSD was shown to display LSD-like effects in mice when using the head-twitch response (HTR) assay and it was confirmed that pretreatment with the selective 5-HT_{2A} antagonist M100,907 blocked the HTR.[10] The binding affinity of 1P-LSD to cloned human 5-HT_{1A} and 5-HT_{2A} receptors dropped 67- and 13-fold but increased by a factor of 3.5 at the human 5-HT_{2C} receptor when compared with LSD. Furthermore, when measuring 5-HT_{2A} receptor activation (G_q-mediated Ca^{2+} flux in HEK cells), it was revealed that 1P-LSD (and two other 1-acyl-LSD derivatives) only functioned as very weak partial agonists and antagonists, whereas no agonist activity was observed at 5-HT_{2B} and 5-HT_{2C} receptors.[11]

In vitro studies assessing the metabolic stability of 1P-LSD and other 1-acyl substituted lysergamides showed the formation of LSD[12] which suggested that 1P-LSD and other lysergamides acylated at the indole nitrogen atom might function as a prodrug. Consistent with this observation, the subcutaneous administration of 1P-LSD (0.1 or 0.3 mg/kg) to male Sprague–Dawley rats led to the detection of LSD and LSD metabolites when plasma samples were analyzed taken 15 min later which suggested the appearance of rapid hydrolysis in vivo.[11]

Although the pharmacokinetic (PK) and pharmacodynamic (PD) properties of LSD in humans have been thoroughly investigated,[2,13–16] data of this kind are still missing for 1P-LSD. Moreover, within the context of forensic toxicology, PK data will provide important information on casework. For example, in a recent intoxication case reportedly involving the ingestion of a 1P-LSD blotter, the implementation of urine and serum analyses only revealed the presence of LSD but without the detection of any 1P-LSD.[17] Thus, this case report provided support for the hypothesis that 1P-LSD might also act as a prodrug in humans. However, it also revealed a new challenge when attempting to differentiate between intake of 1P-LSD and LSD. In order to address this knowledge gap, a controlled self-administration study was conducted that involved one oral (p.o.) and one intravenous (i.v.) administration of 100 μg 1P-LSD hemitartrate to two human volunteers. The study included analyses of urine and serum samples and the determination of subjective effects in order to investigate PK and PD properties of the drug and to assess whether 1P-LSD was indeed a prodrug in humans.

2 | MATERIALS AND METHODS

2.1 | Chemicals and reagents

Boric acid (H_3BO_3, for molecular biology, 99.8%) was obtained from AppliChem (Darmstadt, Germany), whereas potassium chloride (KCl ≥ 99.5%, p.a.), formic acid (HCOOH, > 98%, p.a.), and propan-2-ol (Rotisolv®, ≥ 99.95%, LC–MS grade) were obtained from Carl Roth (Karlsruhe, Germany). 1-Chlorobutane (C_4H_9Cl, LiChrosolv®, for liquid chromatography) and sodium carbonate (Na_2CO_3, anhydrous, for analysis) were purchased from Merck (Darmstadt, Germany). Methanol (MeOH, Chromasolv™, LC–MS, ≥ 99.9%) was obtained from Honeywell Riedel-de Haën (Seelze, Germany), and deionized water (H_2O) was prepared in-house using a Medica® Pro single high flow purification system from ELGA LabWater (Celle, Germany). Ammonium formate (10 M, 99.995%) and acetonitrile (ACN, HPLC-Super gradient grade) were obtained from Sigma Aldrich (Steinheim, Germany) and VWR International (Fontenay-sous-Bois, France), respectively. Hydrochloric acid (HCl, 3.7%) and sodium hydroxide solution (NaOH, 1%) were part of an enzyme kit (Schlüter-Enzym-Kit) obtained from Schlüter Biologie (Neudorf, Germany). 1P-LSD hemitartrate (2:1) was provided by Synex Synthetics BV (Maastricht, the Netherlands) (> 98%; residual LSD content < 1‰) and LSD was purchased from LGC Standards (Wesel, Germany). The internal standard (IS) LSD-D_3 was obtained from Cerilliant (Round Rock, TX, USA). Drug free urine and serum specimens were collected from volunteers for calibration purposes.

2.2 | Solutions

The borate buffer solution (pH 9) was prepared by adding 370 mL of solution 1 (consisting of 106 g Na_2CO_3 dissolved in 1.0 L deionized water) to 630 mL of solution 2 (consisting of 61.8 g H_3BO_3 and 74.6 g KCl in 1.0 L deionized water). If necessary, the pH was adjusted by further adding solution 1. Mobile phase A consisted of deionized water with 1% ACN, 0.1% formic acid, and 2 mM ammonium formate. Mobile phase B consisted of 0.1% formic acid and 2 mM ammonium formate in ACN. Stock (10 μg/mL) and working solutions (50 ng/mL and 5 ng/mL) of 1P-LSD hemitartrate and LSD were prepared in ACN (concentrations refer to the base form). The internal standard (IS) solution contained LSD-D_3 at a concentration of 500 ng/mL in ACN. A separate solution of 1P-LSD hemitartrate in EtOH with a concentration of 1.0 mg/mL was prepared for the controlled self-administration study (here, the concentration refers to 1P-LSD hemitartrate). The diluted HCl solution was prepared by dilution of the 3.7% HCl solution in two steps: 4 mL of the 3.7% HCl solution was mixed with 10 mL deionized water and 5 mL of this solution was further diluted with 1 mL of deionized water (resulting pH: approx. 1).

The diluted NaOH solution was obtained by addition of four drops of the 1% NaOH solution to 10 mL of deionized water (resulting pH: approx. 8).

2.3 | Sample preparation and method validation

Sample preparation and analysis were performed using a fully validated method described elsewhere.[17] The sample preparation consisted of a liquid–liquid extraction with 1-chlorobutane. The limit of detection (LOD) and the lower limit of quantification (LLOQ) in serum and urine were 0.005 ng/mL for 1P-LSD and 0.015 ng/mL for LSD.

2.4 | Instrumentation

The LC–MS/MS system and MRM parameters were employed according to the procedure published previously.[17] In brief, a Nexera LC (Shimadzu, Duisburg, Germany) was coupled to a QTRAP® 5500 mass spectrometer (Sciex, Darmstadt, Germany) using positive electrospray ionization. Chromatographic separation was achieved on a biphenyl column (100 × 2.1 mm, 2.6 μm particle size, Phenomenex, Aschaffenburg, Germany) with a corresponding guard column (SecurityGuard™ ULTRA Cartridges UHPLC Biphenyl for 2.1 mm i.d. columns, Phenomenex, Aschaffenburg, Germany). Starting with 10% mobile phase B (total flow rate: 0.3 mL/min), the gradient was increased to 30% mobile phase B within 3 min. Mobile phase B was further increased to 50% after 4 min and 75% after 6 min. Within 0.5 min mobile phase B was increased to 95% and held at this percentage for 1 min. For column re-equilibration, the starting conditions were restored within 0.5 min and kept for 7 min. Propan-2-ol was added post-column for signal enhancement (0.1 mL/min).

2.5 | Pharmacokinetic analysis

MS Excel 2010 (Microsoft Corporation, Redmond, WA, USA) was used to gather pharmacokinetic (PK) data from the measured serum concentrations. c_{max} and t_{max} were obtained directly from the observed data. After semi-logarithmic transformation of the serum concentration data the elimination rate k_e was estimated by log-linear regression using at least six data points. The terminal half-life was calculated using the equation $t_{1/2} = \ln(2)/k_e$. The area under the concentration–time curve (AUC) was estimated using the linear trapezoidal method in the respective time range without further extrapolation. The bioavailability was determined by division of the AUC after oral administration and the AUC after i.v. administration ($F = AUC_{po}/AUC_{iv}$).

To test for instability under acidic or basic conditions in the gastrointestinal tract, 1P-LSD was treated either with diluted HCl (pH approx. 1) or diluted NaOH (pH approx. 8) for 2 hours at 37°C in an oven (final concentration in the samples: 2 μg/mL). Therefore, 2 μL of the ethanolic 1P-LSD solution (1 mg/mL) was added to 1 mL of diluted HCl solution or 1 mL of diluted NaOH solution. One mL of deionized water with 2 μL of ethanolic 1P-LSD solution (1 mg/mL) was used as reference. Both tested conditions as well as the reference were conducted in triplicates. After 2 hours of storage at 37°C, 10 μL of each sample was diluted with 990 μL of mobile phase A and B (99/1, v/v) and analyzed as described above.

2.6 | Pharmacodynamics: Quality and course of subjective effects

2.6.1 | Subjective drug effects

Visual analog scales (VAS) are a well-established tool that facilitate the assessment of subjective features that occur during acute phases of intoxication similar to those reported in studies involving hallucinogens such as LSD.[18] In the present study, three measures were assessed using visual analog scales (VAS): "any drug effect", "good drug effect", and "bad drug effect". Items were presented to each subject at 30 min intervals for 14 h (oral administration, session 1) or 12 h (i.v. administration, session 2) to monitor the time course of subjective drug effects.

2.6.2 | Five-dimensions of altered states of consciousness (5D-ASC)

The 5D-ASC questionnaire is an instrument designed to record psychometric scales developed at the Psychiatric University Clinic in Zürich (Switzerland). It was validated across a broad range of studies and has become a standard tool for measuring changes in waking consciousness induced by hallucinogenic drugs.[19] The 5D-ASC involves 94 items that consist of statements in one sentence that are rated on a VAS with two poles ("not more than usual" and "much more than usual"). The 5D-ASC was administered no longer than 2 h after the effects had ceased. At that time, both subjects were able to understand and answer the items presented without problems. The common subscales/dimensions of the 5D-ASC are described as follows.

Oceanic boundlessness (OB)

This scale assesses changes in the experience of the self and body, the relation to the environment, alterations in time experience, and mood changes directed towards elevation and sublimity. The state implies a positively experienced ego dissolution with euphoria. The separation between the self and the external world becomes tenuous and sometimes nonexistent. Core items for OB included: "It seemed to me that my environment and I were one" and "I felt very happy and content for no outward reason".

Anxious ego dissolution (AED)

This scale describes an unpleasant experience with diminished self-control characterized by ego-disintegration or ego-fragmentation accompanied by great distress and anxiety. Thought processes are

altered, sometimes occupied with threatening themes (e.g. loss of control) or interfered by disruptions of thinking. Time may be experienced as painfully slow. Core items for AED included: "It seemed as though there was an invisible wall between me and my surroundings" and "I was afraid to lose control over myself".

Visionary restructuralization (VR)

Typical aspects of altered states of consciousness are visionary-hallucinatory phenomena. They can be divided in three different categories: elementary, amorphous "primitive" optical phenomena, organized scenic hallucinatory phenomena, and changed meaning of objects perceived in the environment. Hypnagogic imagery and synesthesia belong to this category. Core items for VR included: "I saw light or flashes of light in total darkness or with closed eyes" and "Things around me had a new, strange meaning to me".

Vigilance reduction (VIR)

Items of this scale characterize reduced alertness and clouded consciousness, typically accompanied by reduced cognitive performance and self-control. Core items for VIR included: "I was in a doze" and "My perception was clouded".

Auditory alterations (AA)

This dimension measures acoustic hallucinatory phenomena, e.g. hearing clicks or amorphous low noise, music or voices (possibly commenting on the subjects thinking or behavior). Core items for AA included: "I heard diffuse noises without being able to identify the source" and "I heard my own thoughts as if I was speaking".

2.7 | Controlled self-administration study

Two healthy, Caucasian males (age: 46 and 56 years, weight: both 74 kg) participated in the controlled self-administration study consisting of two experimental sessions. The environment of the sessions was non-clinical in a "living-room atmosphere". Experiments were started 2 hours after a light breakfast. Both subjects had prior experience with LSD-like compounds in the past (no consumption in the 3 months before the study). Sleep during pre-experimental nights was more than 6 hours. In session 1, a single oral dose of 100 μg of 1P-LSD hemitartrate (2:1), equivalent to 71.2 μg LSD base assuming complete hydrolysis, was administered (gelatin capsules containing pieces of wafer soaked with 100 μL of an ethanolic 1 mg/mL 1P-LSD hemitartrate solution). Session 2 took place after a washout phase of 11 months and included the i.v. administration of the same total amount of 1P-LSD. Here, 10 mL of normal saline were mixed with 100 μL of an ethanolic 1 mg/mL 1P-LSD hemitartrate solution and administered intravenously. A venous access was placed in both the right and the left arm of each subject (one for the administration of the 1P-LSD solution and the other for taking blood samples).

To gather PK data of 1P-LSD, blood samples were taken regularly from subject A and B for up to 150 h and 26 h (session 1), respectively, and for up to 24 h in session 2. The blood samples were immediately centrifuged for 15 min at 2879 × g and the serum was transferred into sodium fluoride containing glass tubes (approx. 10 mg sodium fluoride per mL serum) to prevent hydrolysis of 1P-LSD.[17] Urine samples were collected from subject A for 14 (session 1) and 10 days (session 2). Urine samples from subject B were solely taken on the day of administration. Urine concentrations were normalized to creatinine and are given in ng/mg (1 ng/mg is equivalent to 1 ng/mL in a urine sample with 100 mg/dL creatinine). Serum and urine samples were stored overnight at 5°C and subsequently stored at −20°C until analysis.

3 | RESULTS AND DISCUSSION

3.1 | Pharmacokinetic analysis

After p.o. ingestion of 100 μg 1P-LSD hemitartrate (session 1), only LSD but no 1P-LSD was detected in serum and urine samples. LSD serum and urine concentration–time curves are shown in Figures 1 and 2, respectively. LSD urine concentrations were normalized to urinary creatinine concentrations. The creatinine concentration ranged from 28 to 230 mg/dL. The highest serum concentration of LSD was observed after approximately 2 hours in both subjects (c_{max} (subject A) = 3.7 ng/mL and c_{max} (subject B) = 2.3 ng/mL). LSD could be detected for up to 49 h in subject A and for at least 25 h in subject B (= last sampling). In urine, LSD was detected for up to 69 h

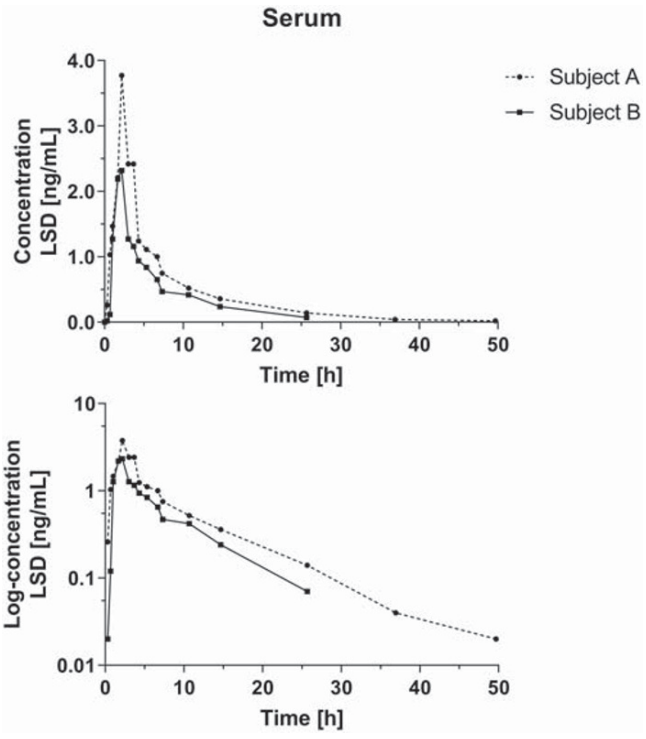

FIGURE 1 LSD concentration–time curves in serum after p.o. administration of 100 μg 1P-LSD hemitartrate

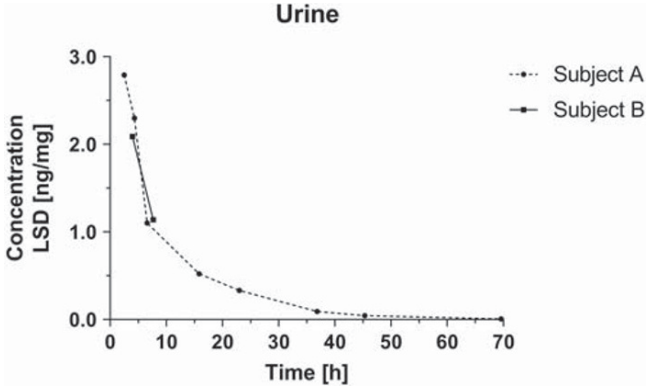

FIGURE 2 LSD concentration–time curves in urine after p.o. administration of 100 μg 1P-LSD hemitartrate. LSD urine concentrations were normalized to urinary creatinine concentrations

passage (pH = 1–2) following oral ingestion and that hydrolysis mainly occurs either at neutral/weakly basic pH conditions found in the duodenum/jejunum or during the first liver passage.

Interestingly, the results from session 2 showed that i.v. administration resulted in the rapid formation of LSD, a process that might be explained by serum esterase activity in combination with liver metabolism. A fast decrease in concentration was observed in the first hour (roughly estimated $t_{1/2}$(1 h) = 0.19 and 0.21 h for subject A and B, respectively) followed by a slower decrease in concentration in the following hours. The small AUC values after i.v. administration (subject A: $AUC_{0.15\rightarrow 2.75\ h}$ = 0.2 ng•h/mL, subject B: $AUC_{0.15\rightarrow 4.16\ h}$ = 0.4 ng•h/mL) were consistent with 1P-LSD being a prodrug of LSD not only after p.o. administration, where no 1P-LSD was detected in serum at all. This also implied that the pharmacological effects of 1P-LSD are primarily reflecting the presence of LSD.

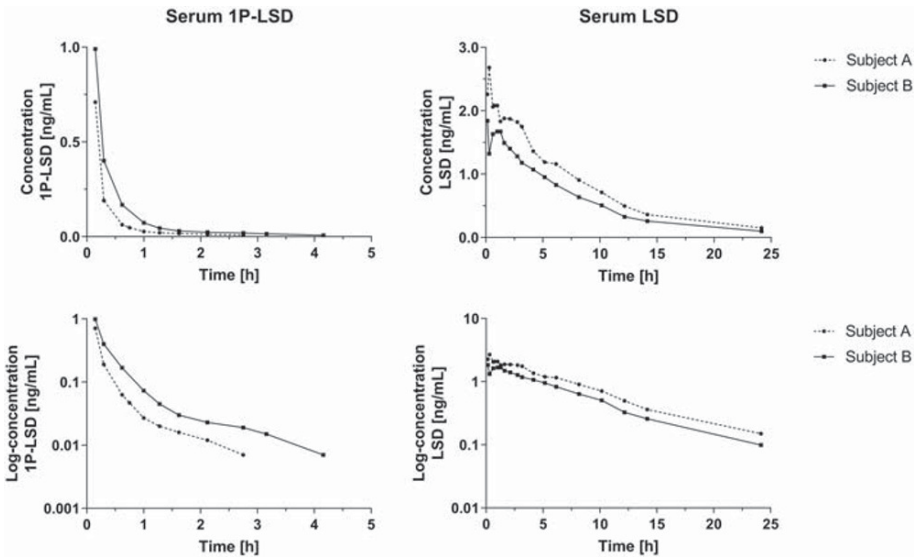

FIGURE 3 1P-LSD and LSD concentration–time curves in serum after i.v. administration of 100 μg 1P-LSD hemitartrate

in subject A. Only two urine samples were collected from subject B, and both were positive for LSD (2.0 ng/mg LSD after 4 h and 1.1 ng/mg LSD after 7.7 h).

In session 2 (i.v. administration, see Figure 3), LSD was found in all serum samples (last sampling after 24.16 h), whereas 1P-LSD was detected in serum for up to 2.75 h (subject A) und 4.16 h (subject B). In urine (Figure 4), LSD was detected in subject A for up to 80 h, whereas 1P-LSD was only detected in the first sample after 2.7 h (0.032 ng/mg). Subject B donated only a single urine sample (taken 2.9 h after i.v. administration) that tested positive for LSD (3.7 ng/mg) as well as 1P-LSD (0.073 ng/mg). Similar to observations reported previously from in vitro studies and administrations to rats,[11,12] these measurements confirmed for the first time that 1P-LSD also acts as a precursor of LSD in humans following p.o. administration and that it is rapidly hydrolyzed to LSD. The stability of 1P-LSD under acidic and basic conditions at 37°C also showed that it is rapidly hydrolyzed to LSD under basic conditions (pH approx. 8) but that it was stable under acidic conditions. Therefore it can be assumed that 1P-LSD remains intact during stomach

Results from the analysis of the PK data for the hydrolysis product LSD from both sessions are shown in Table 1. Although PK/PD data for 1P-LSD in humans are unavailable, Holze et al.[16] recently

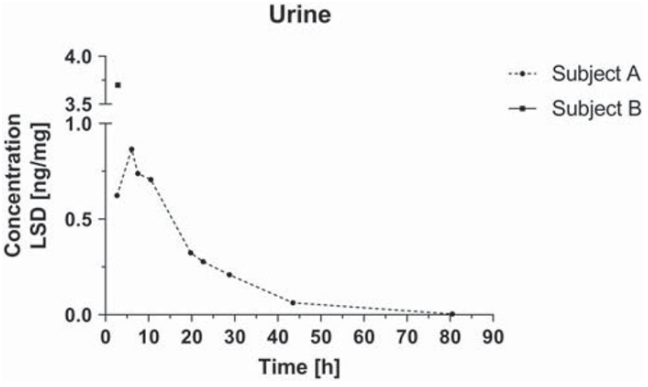

FIGURE 4 LSD concentration–time curve in urine after i.v. administration of 100 μg 1P-LSD hemitartrate. LSD urine concentrations were normalized to urinary creatinine concentrations

TABLE 1 Pharmacokinetic parameters for LSD after p.o. and i.v. administration of 1P-LSD

		c_{max} [ng/mL]	t_{max} [h]	$t_{1/2}$ [h]	AUC [ng•h/mL]
Oral	Subject A	3.7	2.2	6.8*	18.6
	Subject B	2.3	2.2	6.0*	12.3
i.v.	Subject A	2.6	0.30	5.8	18.4
	Subject B	1.8	0.15	5.5	13.4

c_{max}, maximum LSD serum concentration; t_{max}, time to reach c_{max}; $t_{1/2}$, half-life; AUC, area under the curve (estimated from t = 0 h to t = 25.7 h and t = 24.2 h for p.o. and i.v. administration, respectively).
*Terminal half-life values calculated from serum concentrations beyond 4.3 h.

reported on a controlled LSD administration study in humans that served as a reference for comparison in the present study. The analysis method used in this study (LLOQ: 0.015 ng/mL) was slightly more sensitive than the method employed by Holze et al. (0.025 ng/mL).[16] In the present study (session 1, p.o.), the rate of elimination changed after approximately 4 hours post ingestion (Figure 1), therefore suggesting a biphasic elimination with two elimination half-life values ($t_{1/2}$(4.3 h) = 1.5 and 1.7 h, $t_{1/2}$(terminal) = 6.8 and 6 h for subject A and B, respectively). Holze et al.[16] reported a mono-phasic elimination with half-life values between 2.4 h and 7.3 h (geometric mean 3.6 h) in 27 subjects after ingestion of a 100 μg dose of LSD base (oral administration of an ethanolic solution). However, it has to be taken into account that in the present case (ingestion of a prodrug) the elimination parameters of LSD in the first hours are dependent on the concurrent process of LSD formation until the hydrolysis of 1P-LSD is fully completed. It seemed therefore most reasonable to compare the half-life values of Holze et al. with the terminal half-life values presented here (assuming the complete hydrolysis of 1P-LSD after approx. 4 h), which lay in the upper area of the range reported by Holze et al.[16] The time of maximum concentration (t_{max}) reported in the study of Holze et al. (geometric mean 1.7 h, range 1.0–3.4 h) was also comparable to our study (2.2 h). The AUC was estimated from *t* = 0 to *t* = 25.7 h (18.6 ng•h/mL for subject A, 12.3 ng•h/mL for subject B) and was in accordance with the range reported by Holze et al. (geometric mean 13 ng•h/mL, range 7.1–28 ng•h/mL for AUC from zero to infinity).[16]

After semi-logarithmic transformation of the LSD serum concentrations following i.v. administration of 1P-LSD (session 2, Figure 3), it was found that the data showed linear elimination kinetics consistent with a mono-phasic elimination and elimination half-life values of 5.8 h and 5.5 h for subject A and B, respectively. The AUC was comparable with p.o. administration, resulting in a calculated bioavailability of LSD of 100% and 92% for subject A and B, respectively. In contrast to Dolder et al.[20] who estimated the bioavailability of LSD at 71%, the data obtained in the present study suggest that the bioavailability of LSD was almost complete following hydrolysis of 1P-LSD. It is noteworthy that the bioavailability data reported by Dolder et al. were based on a comparison of their own results (p.o. administration of LSD) with those from another study reported by Aghajanian and Bing conducted in 1964 (i.v. administration of LSD[21]) which might therefore be less reliable.

Usually, 1P-LSD is sold in the form of blotters, and sublingual administration is thought to be the most common form of ingestion. Sublingual administration is considered to result mainly in parenteral uptake of 1P-LSD via mucosa and therefore circumvents the first-pass effect. However, a concurrent p.o. ingestion of 1P-LSD might occur via swallowing oral fluid. The presented p.o. and i.v. administration study was conducted to obtain the first PK data for 1P-LSD and might therefore not fully represent this scenario. But even if sublingual administration is considered as a combination of p.o. and parenteral uptake, it can be expected that 1P-LSD is only detectable for a few hours at very low concentrations (pg/mL range) in serum and urine following sublingual administration.

The findings obtained in this study are consistent with the intoxication case reported previously that involved ingestion of 1P-LSD blotters where only LSD but not 1P-LSD could be detected in serum and urine samples of the patient.[17] The detection of unique 1P-LSD metabolites would allow for an unambiguous distinction between the uptake of 1P-LSD and LSD or other LSD derivatives, but further metabolites were not investigated in the aforementioned intoxication case. Recently, Wagmann et al. investigated the metabolism of nine LSD derivatives including 1P-LSD via in vitro incubations with pooled human liver S9 fractions[12] and identified eight metabolites of 1P-LSD. However, six of them were found in the incubations of LSD as well and another one could also evolve from 1-propanoyl-*N*-ethyl-nor-lysergic acid diethylamide (1P-ETH-LAD), so that only one potentially unique 1P-LSD metabolite remained (*N*-deethyl 1P-LSD). Wagmann et al.[12] attempted to confirm the results of their in vitro study by administration of 0.01 mg/kg doses of 1P-LSD to rats (gastric intubation), but neither 1P-LSD nor the postulated metabolites were detectable in rat urine, possibly due to the low sensitivity of the applied screening methods and/or due to insufficient dosing. The urine samples obtained from the self-administrations presented here were subsequently reanalyzed, but no signal was recorded for the MRM transitions representing *N*-deethyl-1P-LSD. However, *N*-deethyl 1P-LSD (among other metabolites) was detected in rat plasma samples collected 15 min after subcutaneous administration of 0.03 mg/kg as part of a follow-up study.[11] Further studies are needed to confirm the presence of unique 1P-LSD metabolites in humans and it is anticipated that highly sensitive analysis methods would be required for this purpose, especially if urinalysis is considered.

3.2 | Pharmacodynamics: Quality and course of subjective effects

3.2.1 | General observations

The subjects did not report any anxiety or any grave discomfort. No complications were seen and no after effects were experienced from the experiments (observation period > 1 year). In general, the psychosensory drug effects and the course of clinical effects after p.o. administration (Figure 5) followed a pattern similar to that known for LSD[2] with an onset at around 30 to 40 min, a plateau during the 1 to 4 h period and a come-down period after 5 to 6 h with the effects gradually disappearing after 7 to 10 h. This course of action roughly correlated with the course of 1P-LSD/LSD serum levels as measured.

When 40 to 180 μg LSD is administered intravenously, it takes about 15 to 25 min until the onset of effects begin to be noticeable with a peak occurring after approximately 1 hour (similar to p.o. administration).[22] The duration of effects after i.v. administration of LSD was reported to be 9 to 10 h[22] comparable to the p.o. route. The observations made in the present study seemed to be consistent with this general profile. The unexpectedly slow onset after LSD or 1P-LSD i.v. administration might be related to a slowed passage of LSD into the central nervous system. This is a remarkable phenomenon given that the similarly acting hallucinogens *N*,*N*-dimethyltryptamine (DMT)[23] and psilocybin[24] show an immediate onset following i.v. administration.

3.2.2 | Subjective drug effects

The time course of subjective drug effects as monitored by VAS are shown in Figure 5 and it can be seen that the subjective effects peaked after 2 to 3 h post administration followed by a gradual decline. In total, the subjective effects were found to last between 8 to 10 h. 1P-LSD produced pronounced increases in drug effect ratings. Peak effects for "any drug effects" and "good drug effect" reached 90% of the maximal possible score. 1P-LSD induced only

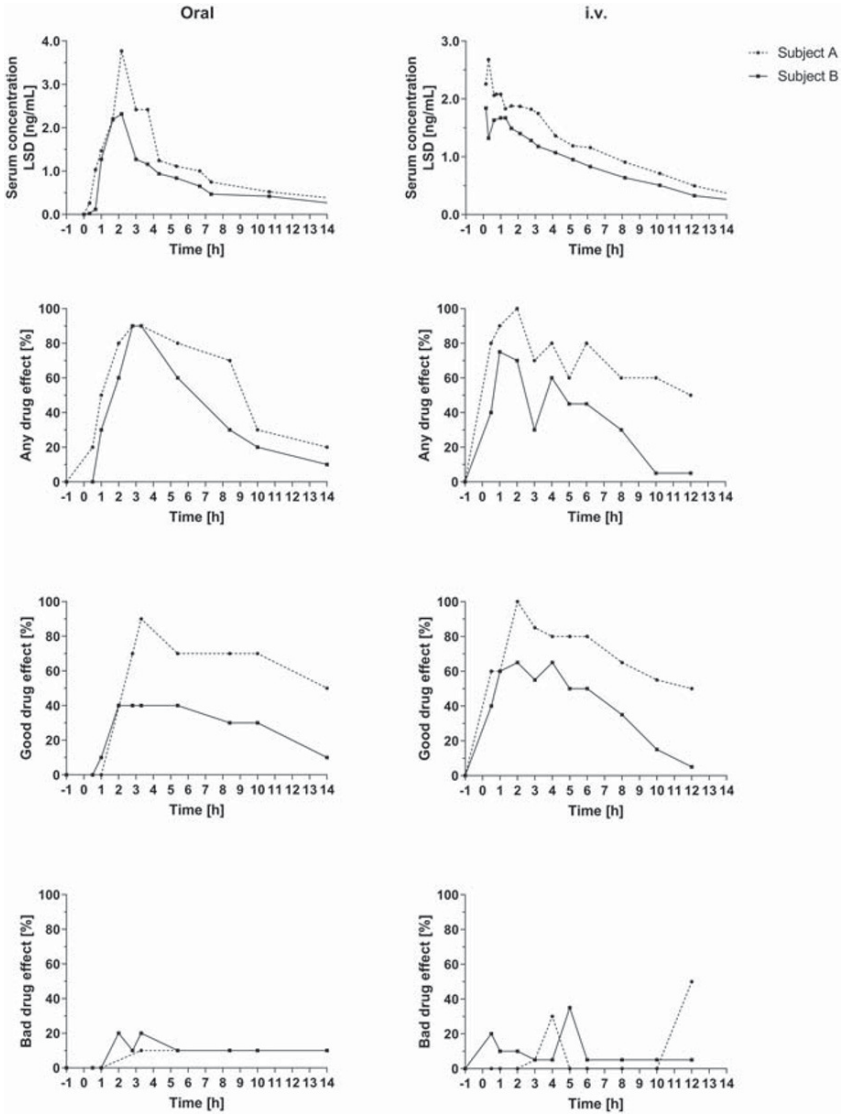

FIGURE 5 Time course of selected subjective drug effects ("Any drug effect", "Good drug effect" and "Bad drug effect")

very small increases in "bad drug effect" scores. The course of clinical effects and subjective intensity as rated on the VAS were comparable to the results reported by Schmid et al.[18] although a lower dose was applied in the present experiment (100 μg 1P-LSD hemitartrate vs. 200 μg LSD). It has to be noted that the full spectrum of LSD's psychosensory effects is already produced by a dose of 100 μg.[2,25] The difference to a dose of 200 μg is mainly quantitative, and the instrument used is not designed to detect quantitative differences.

Regarding subjective drug effects, it appeared that 1P-LSD produced slightly higher scores and a somewhat shorter duration when administered intravenously. However, this did not apply to all subscales (Figure 5). Subject A reported stronger subjective effects (or rated them higher), but in general the subjective drug effects measured during the four trials were remarkably similar. These results suggest that the mode of administration did not make a major difference with respect to the clinical course of effects, which corresponds to a few reported studies involving an i.v. administration of LSD.[21,22,26] In these studies, similar effects were found for i.v. and p.o. administrations. This is remarkably different to the i.v. administration of the closely related LSD-like hallucinogens psilocybin[24] and DMT.[23] With these two substances, effects after i.v. administration were felt immediately and with much higher intensity compared with oral administration.

3.2.3 | 5D-ASC scores

In both sessions, the two subjects reported a positive psychological state that followed a more or less uniform fashion as expressed in high OB scores (Figure 6). Scores that expressed the levels of anxiety (AED scale) were low and both subjects reported visual alterations. However, subject A did not experience any visual phenomena (VR) during the i.v. trial and virtually no acoustic alterations were experienced (AA scale). The VIR score was comparable to states induced by LSD-like compounds. The numerical scores were consistently higher with the p.o. dose compared with the i.v. dose except for the AED scores (Figure 6) that remained equally low.

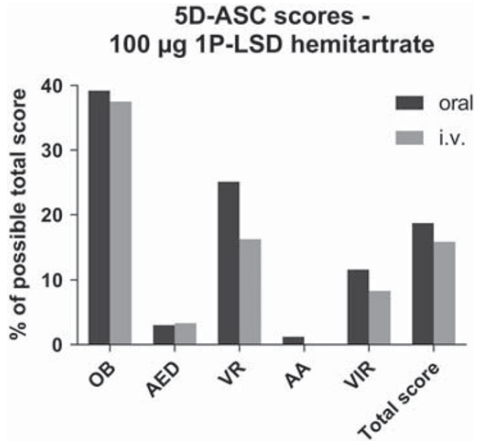

FIGURE 6 5D-ASC scores after administration of 100 μg 1P-LSD hemitartrate (p.o. vs. i.v.; mean of the two participants)

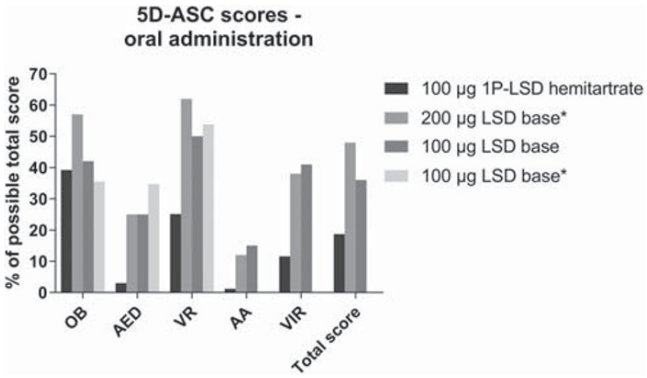

FIGURE 7 5D-ASC scores after p.o. administration of 100 μg 1P-LSD hemitartrate (mean of the two participants), 100 μg LSD[27,28] base (n = 24[27] and n = 28[28]) and 200 μg LSD base (n = 16).[18] The referenced studies showed great interindividual variances for the scores (not shown in this figure). The study of Preller et al.[27] did not report the scores for AA and VIR, and therefore, the total score was also omitted. *Actual dose was lower than stated in the reference, see also[16]

The results obtained for OB scores in the present study were in agreement with those reported after p.o. administration of 100 to 200 μg LSD[18,27,28] (Figure 7). However, the other parameters (AED, VR, AA, VIR) were rated with markedly lower scores (Figure 7).

Figure 8 compares the 5D-ASC scores of session 2 (i.v.) with the study of Carhart-Harris et al.[26] using an LSD dose in the same range. The OB scores were essentially the same in both studies. As mentioned above, subject A reported no visual effects during the i.v. session which might explain why the mean VR score was lower than the score reported by Carhart-Harris et al.[26] The AED score was much lower for both subjects in the present study, which might be due to the more agreeable environmental conditions ("living-room-like" atmosphere vs. complex neuroimaging environment).

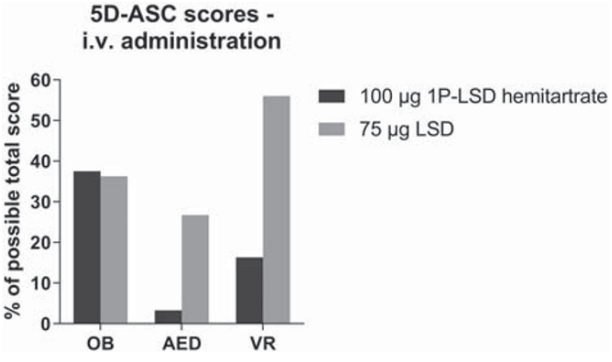

FIGURE 8 5D-ASC scores after i.v. administration of 100 μg 1P-LSD hemitartrate (mean of the two participants) and 75 μg LSD (AA and VIR omitted due to missing data in the reference)[26]

4 | CONCLUSIONS

1P-LSD is rapidly hydrolyzed to LSD after oral as well as i.v. administration which confirms for the first time that 1P-LSD can be considered a prodrug of LSD in humans. Unexpectedly, the bioavailability of the hydrolysis product LSD after oral ingestion of 1P-LSD was close to 100%. Although the prototypical hallucinogen LSD has been studied for decades, to our surprise no valid oral bioavailability data have been published for this drug. Based on our data an oral bioavailability of LSD very close to 100% seems plausible. 1P-LSD can be found in serum and urine samples only after i.v. administration and for a very short time (approx. 4 h) before it is completely converted to LSD. Therefore, the results of this study show that it is not possible to reliably distinguish between the oral uptake of LSD and 1P-LSD until unique metabolites can be detected by sufficiently sensitive analytical methods. This has to be kept in mind when interpreting LSD findings in urine and serum, particularly against the background that – in contrast to 1P-LSD – LSD is a controlled substance across the globe. Qualitative and quantitative effects were similar after i.v. and p.o. application and comparable to recreational LSD. The unexpectedly slow onset of effects after i.v. 1P-LSD administration appears to reflect a slowed passage of LSD into the central nervous system compared with other serotonergic hallucinogens such as DMT and psilocin. The absence of "bad drug effects" in this experiment can be regarded as a consequence of the setting rather than a characteristic of 1P-LSD.

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