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Research Article

Phase 1, First-in-Man Clinical Trial and Pharmacokinetics of Psilocin Mucate (L-130)

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Abstract

Psilocin mucate (L-130), a stabilized form of psilocin (US Patent 12,102,616), offers a potentially superior option for oral therapeutic formulations compared to psilocybin. A Phase 1, open-label, single-dose pharmacokinetic study was conducted in 10 healthy volunteers to assess the safety, bioavailability, and pharmacokinetic profile of psilocin mucate. The results demonstrated rapid absorption, highly reproducible inter-subject variability and 100% bioavailability. The compound was well-tolerated, with no hallucinogenic adverse events observed at 4 mg psilocin mucate - equivalent to 2 mg psilocin. Mild improvements in mood were reported for up to four weeks post-administration, suggesting a calming effect of the drug outlasting the acute pharmacological effects. These findings indicate that psilocin mucate is a safe and highly bioavailable candidate for further therapeutic development and may provide superiority over psilocybin.

Keywords: Psilocin; Psilocybin; Bioavailability; Pharmacokinetics; Psilocin mucate

Abbreviations

5HT: 5 Hydroxytryptamine; AUC: Area Under Curve; C_{max}: Maximum Plasma Concentration; Cl: Clearance; IV: Intravenous; MRT: Mean Residence Time; MMSE: Mini Mental State Examination; N: Number; T_{max}: Time to Peak Drug Concentration; VD: Volume of Distribution

Introduction

For decades, researchers have been intrigued by the potential of naturally occurring tryptamines as therapeutic agents for various mental disorders [1]. Interest in psilocybin as a therapeutic agent has grown, with clinical studies suggesting it may help treat conditions such as anxiety, post-traumatic stress disorder, addiction, treatment-resistant depression, chronic cluster headaches, and obsessive-compulsive disorder. *Psilocybe* mushrooms are particularly important because they contain two key tryptamines: psilocin (4-hydroxy-N, N-dimethyltryptamine) and psilocybin (4-phosphoryloxy-N, N-dimethyltryptamine). While these mushrooms contain small amounts of psilocin, they contain much higher concentrations of psilocybin. Although psilocybin is commonly touted as important for these effects, it actually serves as a prodrug for the active component, psilocin. Despite this, psilocin has been largely overlooked by researchers due to its instability and tendency to degrade quickly. Psilocybin serves as a stable pro-drug for psilocin, with its conversion facilitated by the enzyme alkaline phosphatase. This enzyme removes the phosphate group from psilocybin, producing psilocin, the compound responsible for the pharmacological effects.

Psilocin is structurally similar to serotonin, a neurotransmitter involved in regulating diverse functions which include mood, cognition, learning, memory, sleep, appetite and vomiting. The similarity in chemical structure to serotonin makes psilocin an agonist at serotonin receptors, with strong affinity for the serotonin 2A receptor (5-HT2AR). At high concentration, psilocin produces psychedelic and euphoric effects. However, at low to moderate concentration it appears to have potential applications in the treatment of several neurological disorders as noted above with little or no psychedelic effect.

A recent publication reports that the pharmacokinetics and metabolism of psilocybin are highly variable [2]. Despite this variability, and the apparent effects of food and erratic elimination rates, psilocybin researchers often overlook its oral bioavailability, which is approximately 50%. When psilocybin is taken orally, psilocin reaches its maximum concentration in the blood after about two hours. The elimination rate of psilocin can vary significantly with half-lives ranging from about one hour for intravenous (IV) administration to nearly four hours after oral administration of psilocybin. Brown, et al. [3] suggest that the slower absorption and variable elimination rates may be due to the reversible glucuronidation of psilocin. However, they recommend further investigation to confirm this theory. We propose that the issue may be related to either a slow conversion to the active metabolite in the gut or the retention of psilocin in the gastrointestinal tract (GI), where it may bind to serotonin receptors prevalent there, contributing to its reduced bioavailability. This slow transit through the GI tract may also contribute to noted side effects seen in most studies including nausea. The variable bioavailability of psilocybin renders it problematic as an Active Pharmaceutical Ingredient (API) for pharmaceutical development, especially at low concentrations [4].

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This paper introduces psilocin mucate (L-130), a novel stabilized salt of psilocin formed from a weak base and a weak acid, which is potentially more suitable for oral therapeutic formulations than its pro-drug, psilocybin. Unlike psilocybin, it does not require enzymatic conversion and is readily dissociated back to the free acid (mucic acid) and the free base (psilocin) in the aqueous environment of the GI tract which is then absorbed rapidly and reproducibly. Toxicology studies in rodent models indicate that psilocin mucate is safe at concentrations much higher than those needed for its therapeutic effects (in preparation for publication). Psilocin mucate was also evaluated in a Phase 1 "First-in-Man" trial with healthy volunteers and is reported herein. This paper presents the safety, bioavailability, and pharmacokinetic parameters of psilocin mucate. L-130 may provide the promise of a new chemical entity that can be administered at doses below those having psychedelic side effects, allowing at home therapeutic use to treat several unmet medical needs such as chronic cluster headache, general anxiety and other disorders where tryptamines have shown effectiveness [5,6].

Materials and Methods

First-in-Man clinical trial of psilocin mucate

A phase one, open-label, single-treatment, single-dose, single-period, safety and pharmacokinetic study in 10 healthy subjects under fasting conditions was performed. During the study 13 blood samples each of 8 ml, were withdrawn in K3 EDTA blood tubes Under Sodium Light at pre-dosing (-1.00) and at 0.25, 0.50, 0.75, 1.00, 1.50, 2.00, 3.00, 5.00, 8.00, 12.00, 16.00 and 24.00 hours after dosing.

Number of subjects screened and selected

For this study, 23 subjects were screened, 10 subjects did not meet inclusion criteria, 1 subject dropped out, 12 subjects were enrolled into the study, 10 subjects received study medication, and 2 subjects were kept as alternates in case there were further dropouts.

Subjects screening chart (Chart 1)

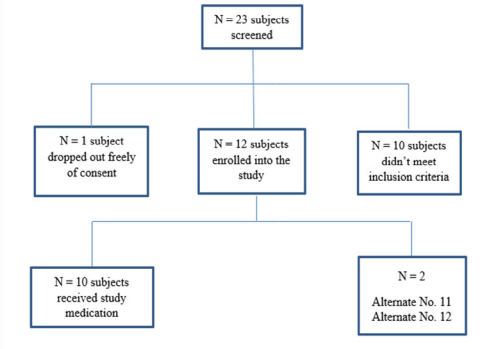

Chart 1: Subjects Screening Chart

Inclusion criteria

Of the 23 healthy subjects recruited and screened, 10 failed to meet the inclusion criteria and were rejected. The inclusion criteria were: Subjects were males between 21 and 50 years of age with a body-mass index of 18.5 to 30.0 kg/m^2, a minimum of 50 kg weight, and non-smokers or individuals who had stopped smoking 24 hours prior to dosing. Table 1 provides the procedures used to evaluate each subject and timing for when the evaluation was conducted.

Treatment and procedures

Following the screening procedure outlined in Table 1, 10 subjects were chosen to enroll in the trial and were admitted to the clinical site the day before the study initiation. During the study period, each subject was checked for vital signs, drugs of abuse, alcohol consumption and queried for adverse events. Following the admission of the subjects to the clinical site and completion of the study, they were released with the understanding that they would be participating in two additional follow up phone discussions: one at 14 days and the final one at 28 days. These follow-up discussions included an assessment of the persistence of any residual effects of the study medication including adverse effects, if any.

Table 1: Each subject was evaluated according to the following table.

Procedure	Screening	Study Period	Follow up
Consent document	X		
Medical history	X		
Physical examination	X		X
Concurrent medications	X	X	X
Demography	X		
Vital signs	X	X	X
Mini Mental State Examination (MMSE)		X	
Clinical chemistry	X		X
Virology	X		
Hematology	X		X
Urine analysis	X		X
ECG Examination	X		X
Testing drugs of abuse	X	X	
Alcohol consumption test	X	X	
Product administration		X	
Adverse events		X	X
Blood collection for drug assay		X	

The investigational test product was a hard gelatin capsule containing 4 mg of L-130 (psilocin mucate), equivalent to 2 mg of psilocin. A single capsule was administered orally to each subject with 240 mL of water after an overnight fast of at least 10 hours. Dosing occurred in the morning to each subject. The subjects stayed in the treatment center for a period of 12-18 hours before dosing, and 24 hours after dosing.

Safety, tolerability and plasma psilocin concentrations were assessed and were the primary objectives of this study. Pharmacokinetic parameters were calculated following blood sampling. Each subject had 8 milliliters of blood drawn at the following intervals: -1 hour and at 0.25, 0.50, 0.75, 1.00, 1.50, 2.00, 3.00, 5.00, 8.00, 12.00, 16.00 and 24.00 hours after dosing. The actual time of blood collection was recorded and considered in the pharmacokinetic analysis.

Determination of hallucinogenic effect and prolonged effect on mood were conducted by a psychiatrist who monitored each subject. At 2 hours post-dosing, then again one and four weeks after subjects were released, an evaluation utilizing Mini Mental State Examination (MMSE) was performed to screen for cognitive impairment.

Analytical method

The analyses for psilocin in human plasma samples were performed using liquid-liquid extraction technique with tandem mass spectrometry method and LC-MS/MS detection. Psilocin chromatography was carried out using Phenomenex Gemini 5 µm C18 110A (150 × 4.6 mm) and mobile phase consisted of (70: 30) (V: V) (MEOH: 0.002M Ammonium Acetate with 0.1% FA), at flow rate

0.5 ml/min.

The calibration range was linear over the range (0.058 - 76.8) ng/ml. The LLOQ was set to 0.058 ng/ml for psilocin, which is the lowest concentration of the standard curve that fulfilled the acceptance criteria. The inter-day (overall) precision expressed as CV (%) values for psilocin at the four quality control samples and the inter-day accuracy was 97, 97, 98 and 98 respectively. Alternative bioanalytical methods (4,5,6) were considered but were not used in favor of developing a more responsive assay.

Independent Ethics Committee (IEC) / Institutional Review Board (IRB)

The study was conducted in accordance with the international ethical guidelines for clinical studies in humans set out in the declaration of Helsinki, as well as with the latest guidelines on Good Clinical Practice and Good Laboratory Practice. The study protocol was approved by both the Independent Ethics Committee and the Institutional Review Board.

Quality assurance

The study was conducted in compliance with Good Clinical Practice (GCP), Good Laboratory Practice (GLP) and the applicable regulatory requirements. Quality audits and inspections were conducted by the study site Quality Department and an independent 3rd party audit team. Quality assurance personnel had access to all raw data, medical records, CRFs and all other relevant documentation. The Quality Assurance personnel and audit teams reviewed the study protocol, inspected facilities, equipment, procedures and methods to ensure compliance with GCP and GLP requirements.

Clinical Trial Results

Safety evaluation and Adverse Events (AEs)

All 10 subjects were included in the safety evaluation. Safety parameters evaluated were adverse events, laboratory examination, physical examination, ECG examination and vital signs.

Evaluations of safety occurred at the same time intervals as blood draws noted above. Subjects were queried by the professional medical staff and were urged to report any adverse events. In addition, voluntary reporting of adverse events at any time during the study was encouraged and data collected and reported.

Nausea and, dizziness in one subject and increased leucocytes in urine of another subject were adverse events that occurred in this study. No serious adverse event occurred in this study. Table 2 lists the AEs reported. All AEs resolved without any treatment. Increase in leucocytes in urine did not reproduce upon re-analysis. The vital signs did not show clinically significant changes. Based on this study, the 2 mg psilocin dose, administered as psilocin mucate (4 mg) capsules were found to be safe. No safety concerns were identified in this Phase 1 first-in-man clinical trial.

Pharmacological observations

Mini Mental State Examinations were performed for each subject 2 hours after dosing. The test was administered by a trained psychiatrist. In every case, scores were reported above 25 which is normal per the standardized Mini-Mental State Examination (MMSE) scoring with no negative effect observed on cognitive functions. Subjects had a follow up interview and evaluation 7 days post-dosing. Only 8 subjects responded to the follow-up and of those 63% reported persistently improved mood and mental state. At the second follow-up after 4 weeks, only 7 subjects responded and of those 43% indicated an improvement in mood and mental state.

The tolerance to 2 mg psilocin dose, administered as psilocin mucate, (4 mg), was good with no observed impact on cognition and surprising improvement in self-reported mood up to 4 weeks after drug administration. No hallucinogenic effect was observed in any of the subjects at the dose administered.

Pharmacokinetic evaluation of psilocin

Pharmacokinetic parameters of psilocin obtained from a single dose of 4 mg of psilocin mucate (equivalent to 2 mg of psilocin) in this study are provided in Tables 3 and 4, Figure 1.

Bioavailability of psilocin (F Value)

Hasler, et al. [7] reported pharmacokinetic results for psilocybin when dosed Intravenously (IV) and orally. He reported that a 1 mg IV dose of psilocybin, equal to 0.718 mg of psilocin had an AUC0-infinity of 240 ng.min/ml. Converting Hasler's units to ng.h/ml and correcting for body weight (70 kg), one can use the IV pharmacokinetics to compare with those obtained from the 2 mg oral dose of psilocin. Using the equation: F = (AUC p.o/Dose p.o)/ (AUC iv/Dose iv)*100, the F value (or bioavailability) appears to be 107%. The value above 100% may imply a possible incomplete conversion of psilocybin to psilocin when dosed intravenously, but strongly indicates that psilocin, dosed as the mucic acid salt, is nearly 100% bioavailable.

Discussion

Psilocin mucate (L-130) was demonstrated to be safe in 10 healthy volunteers at a dose of 2 mg psilocin equivalent or 4 mg of the salt form. Nausea, dizziness, and increased leucocytes in urine were minor adverse events observed in this study and resolved without treatment. No serious adverse events occurred.

No hallucinogenic events were reported by the participants or observed by the attending staff, suggesting absence of psychedelic effects at this dose. Subjects were evaluated using the MMSE test to assess their mental acuity and memory during the trial with no reported impact from the study drug. However, the psychiatrist administering the test noted that all but one subject exhibited an anxiolytic response to the study drug, reporting a calming sensation two hours after being dosed. Improved mood was reported by 63% of the subjects one week after being dosed, while 43% reported mild improvement in mood four weeks after being dosed.

The bioavailability and pharmacokinetics of L-130 indicated rapid uptake of the drug with T_{max} occurring at 0.75 hours post-dosing. C_{max} was reported at 3.593 ng/ml, AUC (infinity) at 11.337 ng·hr/ml, and $t_{1/2}$ at 3.11 hours. The overall bioavailability (F) calculated using published data for the intravenous dosing of psilocybin (converted to psilocin) was 107%. Data appeared highly reproducible between subjects.

Although psilocin exerts effects by engaging several serotonin receptors, stimulation of 5-HT2ARs is regarded as the crucial mechanism for psilocin's brain effects. Using information from a previous human positron emission tomography study [8], which measured the relation between plasma psilocin concentration and occupancy at brain 5-HT2ARs, it is possible to estimate 5-HT2AR occupancy from plasma psilocin level. We can calculate that C_{max} (3.593 ng/ml) is associated with 5-HT2AR occupancy of approximately 50%. Thus, although hallucinogenic effects are absent at a 4 mg dose of L-130, there is substantial 5-HT2AR occupancy. Overall, this suggests

Table 2: Observed or reported adverse events for L-130 Phase 1 Safety Assessment.

Subject No.	AE Start-End Time	Related to Study Drug	Severity	Action Taken	Outcome
Study Period					
	Dizziness				
6	Start on 6/21 at 08:51 End on 6/21 at 09:53	Related	Mild	Vital Signs Measured	Recovered
	Nausea				
6	Start on 6/21 at 08:54 End on 6/21 at 10:00	Related	Mild	Vital Signs Measured	Recovered
Follow UP					
	Increase in Leucocytes in Urine				
3	Start on 6/22 at 08:10 End on 6/25 at 11:00	Not Related	Mild	Lab Test Was Repeated	Recovered

Table 3: Pharmacokinetic parameters from a single dose of 4 mg psilocin mucate equivalent to 2 mg of psilocin.

PK parameters	Arithmetic Mean	Geometric Mean	Minimum	Median	Maximum
C_{max} (ng/ml)	3.812	3.66	2.534	3.593	6.246
$AUC_{0 \rightarrow last}$ (ng.hr/mL)	11.501	11.189	7.63	10.815	15.732
$AUC_{0 \rightarrow inf}$ (ng.hr/mL)	11.939	11.617	7.825	11.337	16.088
T_{max} (hr)	0.93	0.88	0.5	0.75	1.5
$t_{1/2}$ (hr)	3.6	3.37	2.05	3.11	7.52
Residual area (%)	3.685	3.527	2.21	3.457	6.503
Λz (1/h)	0.2175	0.2058	0.0922	0.2229	0.3388

Table 4: Additional Pharmacokinetic Parameters from a single dose of 4 mg psilocin mucate equivalent to 2 mg of psilocin.

Subject No	MRT last (hr)	MRT inf (hr)	VD (L)	Cl (L/hr)
1	3.72	4.49	777178.89	132215.3
2	3.28	3.86	494684.72	124722.1
3	3.14	3.57	718982.57	200480.5
4	3.18	3.69	794247.26	205417.7
5	3.75	4.23	786459.89	171426.4
6	2.84	4.4	1970686.2	181697
7	3.48	4.1	1182015.3	214084.5
8	3.32	4.11	1012065.5	158924.8
9	3.62	3.99	545636.48	124320.1
10	2.89	3.19	754418.19	255589.1
Number of Subjects (N)	10	10	10	10
Arithmetic Mean	3.32	3.963	903637.5	176887.7
SD	0.32	0.397	424434.69	43210
CV (%)	9.64	10.02	46.97	24.43
Geometric Mean	3.31	3.944	836406.75	172156
Minimum	2.84	3.19	494684.72	124320.1
Median	3.3	4.045	781819.39	176561.7
Maximum	3.75	4.49	1970686.2	255589.1

L: Liter; hr: Hour; VD: Volume of Distribution; Cl: Clearance; MRT: Mean Residence Time

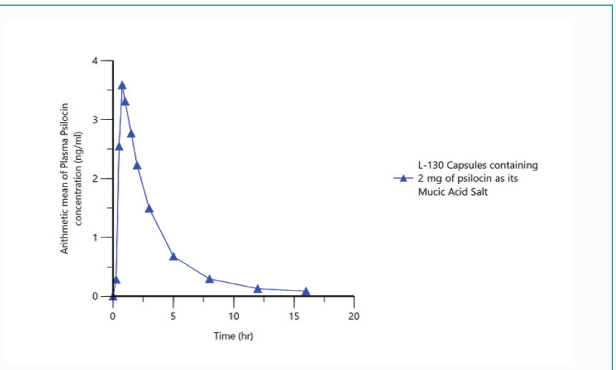

Figure 1: Graphical representation of the arithmetic mean of the plasma concentration in ng/ml versus time for psilocin delivered as psilocin mucate.

a plasma level sweet spot with a high degree of 5-HT2AR stimulation but no or few psychedelic effects.

Psilocin mucate (L-130) appears to be safe for use in expanded clinical trials. No hallucinogenic effects were observed at the given dose of 2 mg psilocin. We believe that the data presented herein indicates that psilocin mucate may be a superior pharmaceutical ingredient when compared to psilocybin. Additional research is needed to more comprehensively characterize psychoactive effects observed in this study at low doses of psilocin mucate. Further analysis of the pharmacokinetics and especially the apparent high reproducibility between subjects must also be verified, but if valid, it strongly suggests psilocin mucate should replace psilocybin and could reduce the size and cost of clinical studies in a wide range of applications. This coupled with a lack of hallucinogenic effects at lower doses than required for psilocybin may translate to an overall superiority and a reduced need for clinical monitoring during dosing.

Clinical and regulatory implications

For psilocybin, dosing must consider the conversion efficiency and variability as well as the potential sequestration by gut serotonin receptors and a food effect [2]. Additionally for psilocybin, higher oral doses may be needed to ensure sufficient psilocin reaches systemic circulation for therapeutic effects but may result in adverse events, such as hallucinations or "bad" trips. However, for psilocin mucate (L-130), direct administration ensures immediate and predictable bioavailability and extensive distribution, allowing for more precise control of therapeutic levels. In applications where psilocybin is used, focus must always be on actual psilocin levels after absorption which are highly variable. Hence, consideration must be given to challenges associated with inconsistent plasma concentrations. Given this variability and interaction with gut serotonin receptors when psilocybin is ingested and the impact of transit time, there may be variations in its absorption, side effects and the resulting variable concentration would have to be carefully monitored to maintain therapeutic efficacy and avoid potential serious side effects. In most cases, the use of psilocybin as is currently being investigated, would occur under supervision of a health care practitioner. Perhaps with the lower doses of L-130, the medication could be self-administered, thereby avoiding the need for practitioner supervision.

Conclusion

This study shows that psilocin mucate (L-130) is a highly

bioavailable, safe drug candidate and appears to be 100% bioavailable when compared to prior pharmacokinetic studies of its pro-drug psilocybin. No hallucinogenic effects were seen in any of the 10 healthy subjects, at 4 mg dose level, possibly indicating that psilocin mucate may be dosed at this or slightly higher level without psychedelic events. This may allow a therapeutic dose that is non-hallucinogenic, taken daily for the treatment of neurological or psychiatric disorders.

Additional studies are being conducted to assess the maximum non-hallucinogenic dose that can be administered without professional oversight, optimizing dosing frequency and designing the formulations for a specific therapeutic target.

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