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Oral Pharmacokinetics of KP511, a Prodrug of Hydromorphone, Relative to Hydromorphone in Human Volunteers

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Introduction

- Hydromorphone products are commonly prescribed for the management of pain and are available as immediate-release and extended-release products
- Hydromorphone is a potent μ-opioid receptor agonist and thus has a high susceptibility for abuse
- Surveillance data indicate that even among μ-opioid receptor agonists, hydromorphone is a particularly sought after drug of abuse, and non-oral routes of abuse (i.e., intranasal, intravenous) are commonly reported (Butler 2011)
- In experienced opioid users, intravenous hydromorphone produced a profile of pharmacological effects (e.g., subjective effects, onset of action, peak effects, and time course of effects) that was comparable to intravenous heroin (Brands 2004)
- There are currently no marketed hydromorphone products with abuse-deterrent label claims in accordance with the FDA Guidance Abuse-Deterrent Opioids — Evaluation and Labeling (FDA 2015)
- KP511 is a prodrug of hydromorphone being developed as an abuse-deterrent hydromorphone product for the treatment of moderate to severe pain
  - In a human pharmacokinetic study, KP511 administered intranasally showed markedly reduced bioavailability compared with intranasal hydromorphone HCl (data on file, KemPharm, Inc.)

Objective

- The objective of this proof-of-concept study was to assess the oral pharmacokinetics and dose-proportionality of KP511-derived hydromorphone compared with hydromorphone HCl in healthy volunteers

Methods

Study participants.

- Healthy adults, 18 to 55 years of age (inclusive), with a body mass index (BMI) between 18 and 32 kg/m^2 and a minimum weight of 59 kg (130 lbs.), and who have previously taken and tolerated opioids
- Female subjects were required to use an acceptable form of birth control
- The administration of concomitant medications other than ibuprofen during the study was prohibited except in a medical emergency

Study design.

- This was an open label, randomized, single dose, four-treatment, four-period, four-sequence crossover study that consisted of a screening period followed by four treatment periods that were each separated by a washout period
- Subjects underwent a 21-day screening and washout period prior to entering the open-label treatment phase of the study. Treatments were separated by a minimum 7-day washout period
- Twenty-four (24) eligible subjects were scheduled to receive separate, single oral doses of 4 mg, 8 mg and 16 mg of KP511 liquid, and 4 mg of hydromorphone HCl (Dilaudid® Oral Liquid, equimolar to 8 mg of KP511) according to a randomization schedule, under fasted conditions
- All eligible subjects also received naltrexone HCl (50 mg) tablets with each treatment to block opioid effects
- Safety assessments were performed at each study visit. Subjects were to return to the clinic 7 days +/- 2 days after Period 4 discharge for a follow-up visit

Pharmacokinetic Analyses.

- The primary objective of this study was to compare the rate and extent of absorption of a single dose (4 mg, 8 mg, or 16 mg) of KP511 to a single 4 mg dose (equimolar to 8 mg of KP511) of hydromorphone HCl
- Plasma pharmacokinetics were assessed after each dose of study medication. During each treatment period, blood samples were drawn at predose (0 hour, within 60 minutes prior to dosing), at 5 and 30 minutes postdose, and at 1, 1.25, 1.5, 1.75, 2, 3, 4, 6, 8, 10, 12, and 24 hours after dose administration

Safety Assessments.

- The Investigator evaluated safety using the following assessments: physical and oral cavity examinations, vital sign measurements, clinical laboratory evaluations, 12-lead ECGs, and reported or observed adverse events.

Statistical Analyses.

- The primary statistical comparison of interest was performed for hydromorphone pharmacokinetic parameters (C_{max}, AUC_{last}, AUC_{inf}, and partial AUCs) using an analysis of variance model (ANOVA) on the ln-transformed data with sequence, treatment, and period as the fixed effects and subject within sequence as a random effect
- The reference treatment was the 4 mg hydromorphone HCl dose. The C_{max} and the AUC parameters for the 4 mg and 16 mg doses of KP511 were normalized to the 8 mg of KP511 dose (equimolar to 4 mg hydromorphone HCl) before statistical comparison. Least squares geometric mean (LSGM) ratios and associated 90% confidence intervals (CIs) were calculated
- Bioequivalence was concluded if the 90% CIs for the LSGM ratio of KP511, 8 mg and hydromorphone HCl, 4 mg fell within the acceptable range of 80%-125%
- To assess dose proportionality, the pharmacokinetic parameters AUC_{last}, AUC_{inf}, and C_{max} after KP511 administration were compared across each dose level using a power analysis
- Differences in hydromorphone T_{max} values across treatments were analyzed using nonparametric analysis (Wilcoxon Signed Rank Test)

Results

Study participants.

- A total of 24 subjects participated in the study; 23 completed at least two periods of the study and 21 completed all four treatment periods. One subject withdrew consent prior to the second dosing period and therefore was excluded from PK analyses.
- Mean (SD) age was 35.6 (9.0) years, mean (SD) weight was 76.2 (10.8) kg, and 62.5% were males. Mean BMI (SD) at screening was 26.71 (2.67) kg/m^2.

Pharmacokinetic Findings.

- Plasma concentrations of intact KP511 were below the limit of quantitation in all subjects
- **Figure 1** shows that for hydromorphone HCl and all doses of KP511, plasma hydromorphone concentrations increased rapidly and peaked at approximately 30 min, and were below the limit of quantitation in most subjects at the end of the sampling period.
- Pharmacokinetic parameters for all treatments are shown in **Table 1**.

Figure 1. Mean Plasma Hydromorphone Concentration-Time Data after Single Oral Doses of 4 mg KP511 API, 8 mg KP511 API, 16 mg KP511 API, and 4 mg Hydromorphone HCl from A) 0-24 hours and B) 0-4 hrs

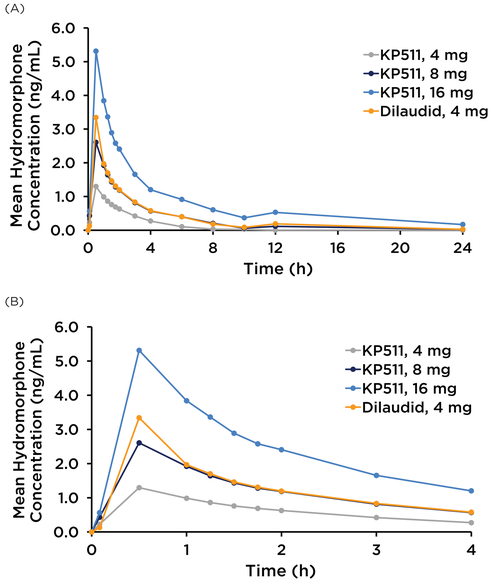


Table 1. Pharmacokinetic Parameters

Parameter	4 mg KP511	8 mg KP511	16 mg KP511	4 mg HM HCl
C_{max} (ng/mL), mean (SD)	1.41 (0.46)	2.70 (1.05)	5.50 (1.84)	3.41 (1.31)
T_{max} (h), median (range)	0.50 (0.50 – 1.25)	0.50 (0.50 – 1.25)	0.50 (0.50 – 1.25)	0.50 (0.50 – 1.00)
$T_{1/2}$ (h), mean (SD)	2.56 (1.34)	3.32 (1.41)	5.47 (2.21)	3.38 (1.90)
AUC_{last} (h*ng/mL), mean (SD)	2.88 (1.63)	7.39 (4.09)	18.19 (6.87)	8.16 (4.03)
AUC_{inf} (h*ng/mL), mean (SD)	4.09 (2.15)	8.19 (3.34)	21.95 (10.06)	10.03 (5.31)

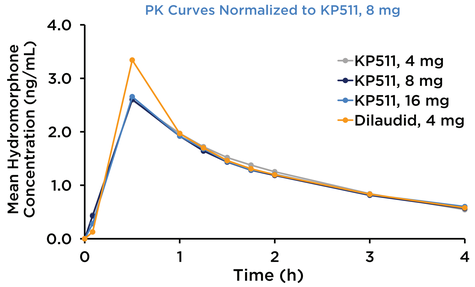
- **Table 2** shows systemic exposure analyses for the primary comparison, 8 mg KP511 API vs. 4 mg hydromorphone HCl (equimolar doses)
- The equivalent doses, 8 mg of KP511 and 4 mg of hydromorphone HCl, were bioequivalent with regard to overall hydromorphone exposure (AUC_{last} and AUC_{inf}).
- Peak hydromorphone exposure (C_{max}) was approximately 19% lower for 8 mg of KP511 compared to 4 mg of hydromorphone HCl

Table 2. Statistical Analysis of the Natural Log-Transformed Systemic Exposure Parameters of Hydromorphone Comparing 8 mg KP511 API to 4 mg Hydromorphone HCl

Dependent variable	Geometric mean		Ratio (%)	90% CI	
	Test	Reference	(Test/Ref)	Lower	Upper
ln (C_{max})	2.5349	3.1302	80.98	71.63	91.56
ln (AUC_{last})	6.5368	7.1124	91.91	83.14	101.60
ln (AUC_{inf})	7.5592	8.0174	94.28	83.70	106.21

- **Figure 2** shows PK curves for all treatments normalized to 8 mg of KP511
- Similar to 8 mg of KP511, reductions of approximately 15% and 17%, in dose-adjusted peak hydromorphone exposure (C_{max}) were observed for the 4 mg and 16 mg doses of KP511, respectively, relative to 4 mg of hydromorphone HCl
- With respect to dose-proportionality, the slope for ln (C_{max}) was close to 1 (0.9772) and the 90% confidence intervals included 1, indicating that C_{max} increased proportionally with an increase in KP511 dose
- The slopes for ln(AUC_{last}) and ln(AUC_{inf}) were greater than 1 (1.3745 and 1.1586, respectively) and the 90% confidence intervals did not bracket 1 (1.2994 – 1.4495 and 1.0560 – 1.2613, respectively), indicating that over the dose range of 4 mg to 16 mg KP511, AUC_{last} and AUC_{inf} increased in a slightly greater than proportional manner with increases in dose

Figure 2. Mean Plasma Hydromorphone Concentration-Time Data (0-4 hrs) after Single Oral Doses of 4 mg KP511 API, 8 mg KP511 API, 16 mg KP511 API, and 4 mg Hydromorphone HCl, Normalized to KP511, 8 mg



Safety.

- AEs were typical of oral opioid therapy
- The most commonly reported AEs were nausea and headache
- Nausea was reported by 2-4 (9.1%-17.4%) subjects in each treatment group
- Headache was reported by 1-2 (4.3%-8.3%) subjects in each treatment group
- No clinically significant abnormalities in vital signs, ECGs, or physical exams were observed

Conclusions

- The lack of systemic exposure to the prodrug KP511 indicates that KP511 effectively released active hydromorphone into systemic circulation after oral administration
- KP511, 8 mg was bioequivalent to hydromorphone HCl, 4 mg with respect to overall hydromorphone exposure, while peak plasma concentrations were approximately 19% lower
- KP511 produced dose-proportional increases in peak hydromorphone plasma concentrations over the 4 mg – 16 mg dose range

References

1. Butler, S.F., R. A. Black, T. A. Cassidy, T. M. Dailey and S. H. Budman (2011). "Abuse risks and routes of administration of different prescription opioid compounds and formulations." Harm Reduct J 8: 29.

2. Brands, B., D. Marsh and U. Busto (2004). "Comparison of heroin and hydromorphone in opioid users." Clinical Pharmacology & Therapeutics 75(2): P3.

3. Food and Drug Administration (2015). FDA Center for Drug Evaluation and Research (CDER). Guidance: Abuse-Deterrent Opioids — Evaluation and Labeling.

Disclosures

Rene Braeckman, Travis Mickle and Sven Guenther are employees of KemPharm, Inc. Kathryn Roupe, Michael Nutt and Cynthia Zamora are employees of Worldwide Clinical Trials.

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