Pharmacokinetics and Abuse Potential of Benzhydrocodone, a Novel Prodrug of Hydrocodone, After Intranasal Administration in Recreational Drug Users

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Background

Immediate-release opioids are commonly abused via alternative routes such as intranasal (IN) and intravenous administration. Benzhydrocodone HCl, a novel prodrug of hydrocodone, is developed to deter non-oral forms of abuse on a molecular level, rather than demonstrating formulation-based behavioral barriers to the opioid active pharmaceutical ingredient in a novel, immediate-release hydrocodone combination product (Apadaz™) as well as several opioid users.

Objectives

To compare the pharmacokinetics (PK) and abuse potential of benzhydrocodone hydrochloride with those of hydrocodone bitartrate (HB) following IN administration to non-dependent, recreational opioid users.

Methods

This was a randomized, double-blind, two-way crossover study.

Study Participants.

Subjects were eligible if they were experienced opioid users, male or female, 18 to 55 years of age, inclusive, who were not currently using to manage their pain.

Qualification Phases. Each of the study phases began with an in-clinic Qualification Phase designed to ensure that the subject was not currently using opioids or other substances available for abuse. The Qualification Phase in this study was 8 hours in duration. If the subject was positive for opioids, cannabinoids, benzodiazepines, or amphetamines, he or she was not eligible to move forward to the next phase.


• In Week 1, subjects were dosed twice the IN formulation of benzhydrocodone (BenzHyd) or HB.

• In Week 2, subjects were dosed twice the IN formulation of benzhydrocodone or HB.

• Study drug was dosed via IN administration. All subjects, whether eligible for antagonist exclusion, were excluded from all PK analyses due to blood sample mishandling.

• Subjects responded on a 100-point, bipolar visual analog scale (VAS) anchored at 0 by “strong disliking,” at 50 by “neither like nor dislike,” and at 100 by “strong liking.” For this rating, a 100-point, unipolar VAS was utilized, with a lower early and peak exposure with benzhydrocodone relative to HB.

• In addition to descriptive statistics, parameters including peak plasma hydrocodone concentration (Cmax) and area under the plasma concentration-time curve from time zero to the specified time point (AUC0–T) were estimated.

• A linear mixed-effect model was used to analyze the natural log-transformed PK parameters (log Cmax; log AUC0–24) and their ratio against the natural log-transformed PK parameters of HB (log Cmax; log AUC0–24), respectively.

• For each ratio, with a 95% confidence interval (CI), the log-transformed geometric least-squares mean values of benzhydrocodone relative to HB were calculated.

• Results

Study Participants. All subjects were enrolled.

• Cohort 1 (n = 22) excluded from all PK analyses due to blood sample mishandling.

• Cohort 2 (n = 26) continued to take study drug (safety population) and completed the study (Completers population).

• Subjects showed some degree of reduction, approximately 45% showed a ±30% reduction, approximately 25% showed a ±50% reduction.

Results

Pharmacodynamic Analyses. At 0.25, 0.5, 0.75, 1, 1.5, and 2 hours, and 4, 8, 12, and 24 hours post dose.

• Descriptive statistics were calculated for parameters including peak plasma hydrocodone concentration (Cmax) and area under the plasma concentration-time curve from time zero to the specified time point (AUC0–T).

• A linear mixed-effect model was used to analyze the natural log-transformed PK parameters (log Cmax; log AUC0–24) and their ratio against the natural log-transformed PK parameters of HB (log Cmax; log AUC0–24), respectively.

• For each ratio, with a 95% confidence interval (CI), the log-transformed geometric least-squares mean values of benzhydrocodone relative to HB were calculated.

• Drug Liking data mirrored the PK findings, benzhydrocodone may provide a deterrent to intranasal opioid abuse.

• Benzhydrocodone was more difficult to insufflate than HB.

• The findings suggest that the prodrug benzhydrocodone may provide a deterrent to intranasal opioid abuse.

Disclosures

Travis Mickle and Sven Guenther are employees of KemPharm, Inc. Kathryn Roupe, Jing Zhou and Daniel Dickerson have no conflicts of interest to disclose. Lynn Webster is an employee of KemPharm, Inc. and has received research grants and honoraria from a variety of companies.

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