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Formulation Design Considerations and Pharmacokinetics Assessments of Bupropion Drug Products

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PURPOSE

Bupropion HCl is a drug which has been formulated as several drug products indicated for major depressive disorder, smoking cessation, and seasonal affective disorder. Bupropion HCl is extensively metabolized to form 3 primary active metabolites; hydroxybupropion, threohydrobupropion, and erythrohydrobupropion. The goal of this study is to evaluate whether different formulation release mechanisms (immediate release, sustained release, and extended release formulations) alters bupropion absorption and/or metabolism *in vivo*; and to estimate *in vivo* release and absorption rate with modified release (MR) products.

METHODS

Clinical Recruitment:

Healthy volunteers (n=14) were recruited for a 6-phase randomized cross-over pharmacokinetics study. The study was posted on ClinicalTrials.gov with the registry number of NCT02078180. Both the informed consent and study protocol was approved by the Food & Drug Administration Institutional Review Board / Research Involving Human Subjects Committee (RIHSC #13-087D) and the University of Michigan Institutional Review Board (HUM00081894).

Study Design

Prior to baseline, each participant fasted for at least 10 hours pre-dosing and 4 hours post-dosing. No water was given one hour pre-dosing or post-dosing, with the exception of 240 mL of water which was taken with each pill. For each phase, participant was given a single dose of an immediate release (75 or 100 mg), sustained release (100 or 150 mg), or extended release (150 or 300 mg) bupropion product. A minimum of a 10 day washout period occurred in between each phase. For sample collection, blood was drawn at 0, 0.5, 1, 2, 3, 4, 6, 8, (12 hours for extended release), 24, 48, 72, and 96 hours.

LC-MS/MS analysis

The LC-MS/MS analysis was conducted using an Agilent 1200 HPLC system coupled to an API 3200 mass spectrometer. Quantitative analysis was accomplished on a Supelco C18 (150 x 4.6 mm I.D., 5 µm). The mobile phases were 0.04% formic acid in purified water (A) and methanol (B). An isocratic gradient was held constant at 35% and the flow rate was set at 0.8 mL/min for 17 minutes. The analytical data were processed by Analyst software.

METHODS

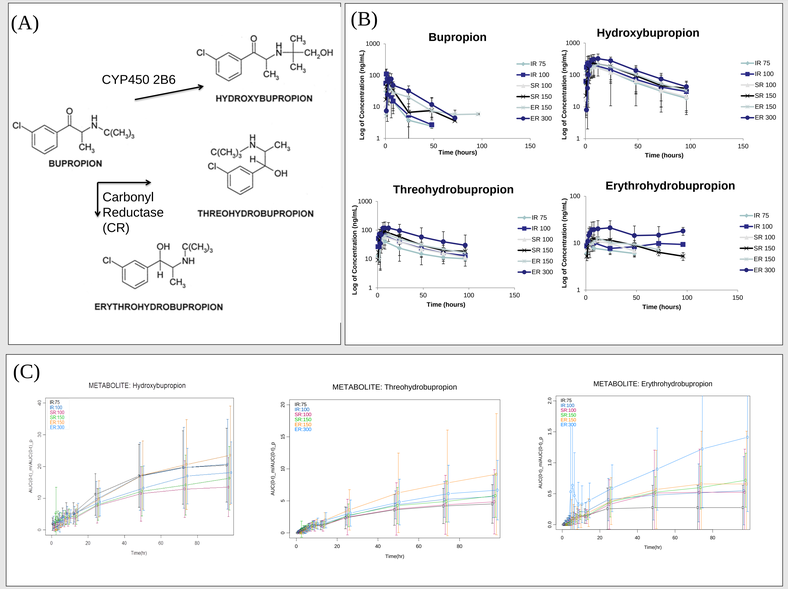
Data Analysis

Data analysis was performed using Phoenix WinNonlin (version), a Non-Compartmental Analysis to estimate the clearance (CL) and volume of distribution (Vd) based on plasma concentration data. The Weibull function (a) was used to predict the absorption rate using Non-linear Mixed Effect Modeling (NONMEM) 7.3.0. using ADVAN 6. We estimated alpha, beta, CL, and Vd using the mean plasma concentration for each formulation. The equation shows the Weibull distribution (a) were t= times, beta=shaping parameter, and alpha=scaling parameter; where Ka represents the absorption applying the Weilbull. Amount of Drug Appeared (ADA) is calculated using the Weibull accumulative distribution function (b).

(a) $$Ka = \frac{beta}{alpha} * \left(\frac{t}{alpha}\right)^{(beta-1)} * EXP\left(-\frac{t}{alpha}\right)^{beta}$$

(b) $$ADA = 1 - e^{-(\frac{time}{alpha})\wedge Beta}$$

Results

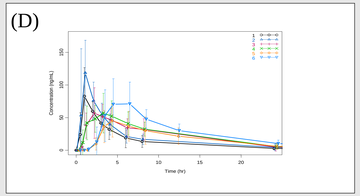


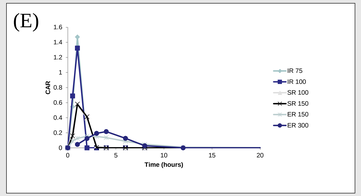
(A) Bupropion is metabolized by CYP2B6 and Carbonyl Reductase to form hydroxybupropion and threo/ erythrohydrobupropion respectively. These metabolites are thought to exhibit potency.

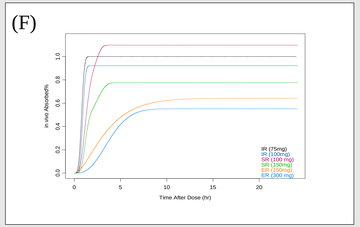
(B)Plasma Concentration vs Time profiles for bupropion and major metabolites.

(C) There were no differences in AUC(m)/ AUC(p) for the 3 major metabolites of bupropion amongst all formulations.

RESULTS







(D) The mean Plasma Concentration vs Time is represented for bupropion.

(E) Weibull type absorption was applied to the various formulations.

(F) ADA is shown for each formulation and normalized by the relative bioavailability.

CONCLUSIONS

1. Plasma samples were successfully analyzed by LC-MS/MS.
2. We saw no significant difference in AUC(m)/ AUC (p) for the 3 major metabolites, indicating that metabolism was not causing this decrease.
3. When applying Weibull type absorption, we were able to characterized different release profiles. The data suggest that release beyond 10 hours will have minimal/ no absorption. This phenomena needs to be further validated.

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