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PHARMACOKINETICS AND DOPAMINE D_2 AND SEROTONIN 5-HT_{2A} RECEPTOR OCCUPANCY OF PALIPERIDONE IN HEALTHY SUBJECTS: TWO OPEN-LABEL, SINGLE-DOSE STUDIES. P. Karlsson, MD, PhD, E. Dencker, S. Nyberg, E. Mannaert, S. Boom, K. Talluri, S. Rossenu, B. Eriksson, M. Eerdekens, L. Farde, Karolinska Institutet, Johnson & Johnson Pharmaceutical Research & Development, Janssen-Cilag AB, Stockholm, Sweden.

OBJECTIVES: Assess pharmacokinetics, dopamine D_2 and serotonin 5-HT_{2A} receptor occupancy of paliperidone immediate-release 1mg (paliperidone IR; Study 1) and paliperidone extended-release tablets 6mg (paliperidone ER; Study 2).

METHODS: Blood samples were collected pre-dose and ≤24h (Study 1) and ≤48h (Study 2). Striatal D_2 receptor binding was measured using PET and ^{11}C-raclopride pre-dose and post-dose at 2.5h (Study 1) and at 22h and 46h (predicted C_{max}; Study 2). Frontal cortex 5-HT_{2A} receptor occupancy (Study 1) was assessed using [^{11}C]M100,907 ≥1 week pre-dose and 4.5h post-dose (C_{max}). The apparent dissociation constant (K_D^{app}=plasma concentration at which 50% of target receptor is occupied) was estimated using an E_{max} model.

RESULTS: Formulation differences were reflected in t_{max} and C_{max}. Paliperidone ER 6mg corresponds to median D_2 occupancy of 64% at 22h post-dose. Using the K_D^{app}, plasma concentrations corresponding to 70-80% D_2 occupancy were estimated: 15-25ng/mL (Study 1); 10-17ng/mL (Study 2). Using pooled data from both studies the *in vivo* K_D^{app} is estimated to be 4.9ng/mL.

CONCLUSION: Paliperidone occupies central D_2 and 5HT_{2A} receptors. D_2 receptor occupancy with paliperidone ER suggests 6mg will be an effective dose in the treatment of schizophrenia.

Measure	Paliperidone IR 1mg*. Study 1 (n=3)	Paliperidone ER 6mg*. Study 2 (n=4)
Median C_{max} (ng/mL) (range)	6.02 (5.34-6.14)	11.3 (7.73-16.5)
Median t_{max} (h) (range)	4.2 (4.1-8.1)	24.1 (23.1-29.0)
Median % D_2 receptor occupancy (range)	48 (35-51) [2.5h post-dose]	64 (56-79) [22h post-dose]; 53 (40-62) [46h post-dose]
Calculated K_D^{app} for D_2-receptor occupancy (ng/mL)	6.4	4.4
Median % 5-HT_{2A}-receptor occupancy (range)	65 (65-71) [4.5h post-dose]	Not measured
Corresponding plasma concentration range (mg/mL)	5.1-6.0 [4.0h post-dose]	Not measured

*Initial studies have shown that paliperidone ER has a bioavailability of approximately 33% of that of paliperidone IR.

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DISTINCT ABSORPTION CHARACTERISTICS OF FIVE ORAL FORMULATIONS OF VALPROIC ACID. S. Dutta, PhD, R. C. Reed, PharmD, Abbott Laboratories, Abbott Park, IL.

AIM: Model the distinct pharmacokinetic (PK) profiles of 5 oral formulations of valproic acid (VPA) that are commonly used for treatment of epilepsy & bipolar disorder, & for migraine prophylaxis.

METHODS: Plasma VPA concentration-time profiles, following single oral dose administration of 5 VPA formulations under fasting conditions, from 4 PK studies in healthy subjects (N=10-15) were compared: VPA syrup & capsule, divalproex sodium sprinkles capsule, delayed-release (DR) tablet & extended-release (ER) tablet. Mammillary compartmental disposition models (CM) coupled with either 1st- or 0-order, or multiphasic absorption models, were fit to the observed data using WINNONLIN.

RESULTS: The optimal models & mean absorption parameters were: (1) syrup: 2CM, k0=1 g/h; (2) capsule: 1CM, ka=1.7 1/h; (3) sprinkles capsule: 1CM, ka=0.99 1/h, Tlag=0.89 h; (4) DR tablet: 1CM, ka=0.79 1/h, Tlag=1.4 h; & (5) ER tablet: 1CM, multiphasic absorption characterized by a peak rate of 0.12 mg/h/mg-dose that occurs immediately after dosing followed by a constant rate of 0.027 mg/h/mg-dose over 22 h. Mean CL/F & V/F values were consistent across formulations & ranged over 0.52-0.65 L/h & 9.9-11 L, respectively.

CONCLUSIONS: The 5 VPA formulations demonstrated distinct absorption characteristics. The rate of absorption may be rank-ordered as VPA syrup > VPA capsule > divalproex sprinkles capsule ≅ divalproex-DR tablet > divalproex-ER tablet. ER is the only formulation exhibiting true sustained-release characteristics.

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POPULATION PHARMACOKINETICS OF ALVIMOPAN & ITS METABOLITE IN HEALTHY VOLUNTEERS & IN POST-OPERATIVE ILEUS PATIENTS. V. D. Schmith, PhD, D. Fisher, MD, J. F. Foss, MD, P Less Than Company, Glaxo Smith Kline, Adolor Corporation, RTP, NC.

AIM: To characterize the population pharmacokinetics (PK) of alvimopan (ALV) & its metabolite (MET) in post-operative ileus patients (POI) & healthy volunteers (HV) after oral dosing with ALV.

METHODS: Data from 9 HV studies (n=256) & 2 well-controlled Phase III studies in POI (n=464) were combined to characterize the PK of ALV & MET using NONMEM. ALV PK was described by a two compartment model with oral absorption & a lag time. MET PK was described by a one-compartment model with a catenary chain & lag time. Because MET is formed in stool by gut microflora, the input function for MET is the dose (and not plasma concentrations) of ALV. The effects of covariates on ALV & MET PK were evaluated.

RESULTS & CONCLUSIONS: The PK of ALV & MET were not related to weight, body mass index, gender, or renal function. Food resulted in a decrease in the rate & extent of absorption of ALV. Concentrations were 87% & 40% higher in POI than in HV for ALV & MET, respectively. ALV PK was related to age, but this effect was not clinically important because ALV concentrations were only ~35% higher in a >70 yr old than in a <30 yr old. ALV PK was not affected by race. Compared to Caucasians, MET concentrations were 43% lower in black subjects & 82% lower in Hispanics following ALV administration. ALV PK was not affected by concomitant administration of acid blockers or antibiotics. MET concentrations were 49% lower in patients receiving acid blockers & 81% lower in subjects receiving preoperative antibiotics.