

symptoms. Safety, tolerability, and pharmacokinetics (PK) of montelukast oral granules were evaluated in children 1–3 months of age.

METHODS: *Design*—Period I: 1-day, open-label; Periods II & III: randomized, double-blind, placebo-controlled. *Setting*—Health clinics in Chile, Colombia, and United States. *Participants*—Twelve children 1–3 months of age with active bronchiolitis or a history of bronchiolitis and asthma-like symptoms. *Intervention*—All patients received montelukast 4-mg oral granules in Period I. Patients were randomized to receive montelukast 4-mg oral granules or placebo in Period II (6 days) and montelukast 8-mg oral granules or placebo in Period III (7 days).

Sparse blood samples for PK analysis were collected from all patients at intervals up to 24 h after the first dose (Period I). Single-dose population estimates of area under the concentration-time curve [AUC_{pop}] and other population PK parameters were determined. The 95% confidence interval (CI) for the AUC_{pop} ratio of this population/historical data from children 3–24 months of age was estimated. Safety and tolerability were evaluated in all periods.

RESULTS: The AUC_{pop} estimate (4-mg dose) in patients 1–3 months of age was 13195.7 ngohr/mL. The AUC_{pop} ratio (95% CI) in patients 1–3 months old/patients 3–24 months old was 3.62 (2.26, 5.80). The population estimate of C_{max} was 1234.6 ng/mL, ~2.1-fold higher than that in patients 3–24 months of age.

Six patients reported a total of 10 clinical adverse experiences (AEs). None was considered serious or drug related. No serious laboratory AEs were reported. No patients discontinued due to an AE.

CONCLUSIONS: Multiple 4-mg or 8-mg doses of montelukast oral granules were generally well tolerated. The plasma concentration-time profile of a single dose of montelukast 4-mg oral granules in children 1–3 months of age was greater than that in patients 3–24 months of age, as measured by population PK estimates.

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EFFECT OF FOOD ON ABSORPTION OF ZIPRASIDONE. S. H. Preskorn, MD, I. Lombardo, MD, J. Alderman, PhD, K. Wilner, PhD, J. Miceli, PhD, Clinical Research Institute, Pfizer, Wichita, KS.

BACKGROUND: Food produces an increase in the bioavailability of orally administered ziprasidone. Therefore, the label recommends administration with food.¹ We describe pharmacokinetic studies conducted to further quantify the food effect under various conditions.

METHODS: In the first study, absorption of ziprasidone was investigated in an open-label, nonrandomized, 6-way crossover study in 8 healthy male subjects. Subjects received oral ziprasidone 20, 40, and 80 mg single doses in a fasting state (8-hour fast) or immediately following consumption of an FDA standard meal (ie, a high-fat breakfast). The second study tested the impact of dietary fat content on ziprasidone absorption in an open-label, randomized, 3-way crossover study in 14 healthy subjects. Subjects received ziprasidone 40 mg using a steady state regimen under 3 conditions: in the fasting state, with an FDA standard meal (60% fat content), and with a lower-fat meal (30% fat content).

RESULTS: The AUC_{0-inf} was greater in the fed state than in the fasting state at each dose tested (20 mg, +48%; 40 mg, +87%; 80 mg, +101%). The increases in AUC_{0-inf} and C_{max} with dose were nonlinear in the fasting state but linear in the fed state. Nonlinearity was attributed to dose-limiting absorption at the higher doses under fasting conditions. Decreasing the fat content from 60% to 30% in test meals (using the 40 mg dose) had a modest impact on ziprasidone absorption. Compared with the fasting state, there was a 100% increase in AUC for the high-fat meal and an 80% increase for the lower-fat meal. Less variability of AUC and C_{max} values was observed in the fed state, suggesting more consistent absorption when taken with food.

CONCLUSION: The results are attributed to enhance ziprasidone solubilization secondary to food consumption resulting in greater intestinal absorption, more consistent systemic exposure, reduced pharmacokinetic variability and more linear pharmacokinetics.

For these reasons, co-administration of ziprasidone with food should enhance symptom control and patient tolerability.

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THE EFFECT OF MK-0524 (DP RECEPTOR ANTAGONIST) ON THE PHARMACOKINETICS AND PHARMACODYNAMICS WARFARIN. J. I. Schwartz, M. A. Stroh, F. Liu, A. M. Gipson, L. Wenning, K. C. Lasseter, J. A. Wagner, Merck Research Laboratories, Clinical Pharmacology Associates, Rahway, NJ.

BACKGROUND: MK-0524 is a DP (prostaglandin D₂) receptor antagonist that is currently in development to reduce the symptoms of niacin-induced flushing. This study was conducted in order to evaluate MK-0524 on the pharmacokinetics and pharmacodynamics of warfarin.

METHODS: Twelve healthy male and female subjects completed this randomized, open-label, multiple-dose, 2-period study in a Phase I clinic. In Treatment A, MK-0524 was administered Days—5 to Day 7 with a single 30 mg warfarin dose on Day 1; Treatment B was a 30 mg warfarin on Day 1. Blood was collected at predose warfarin through 168 for R(+)- and S(-) enantiomers of warfarin and PT/INR. There was a 14-day interval between warfarin doses.

RESULTS: Compared to placebo, MK-0524 had no clinically meaningful effect on warfarin pharmacokinetics including T_{max} and apparent terminal half-life or changes in INR and the results of primary parameters are presented in the table:

Parameter	Comparison [MK-0524 with Warfarin] vs. [Warfarin Alone]	p-value
Pharmacokinetics (Warfarin)		
S(-) Warfarin		
$AUC_{0-\infty}$	1.04 (0.98, 1.09)	0.278
C_{max}	1.11 (0.99, 1.24)	0.141
R(+) Warfarin		
$AUC_{0-\infty}$	1.02 (0.96, 1.09)	0.539
C_{max}	1.13 (1.02, 1.26)	0.050
Pharmacodynamics (INR)		
INR $AUC_{0-168hr}$	1.02 (0.99, 1.05)	0.336
INR _{max}	1.04 (0.98, 1.10)	0.305

†Least-squares geometric mean ratio with 90% confidence interval for S(-) and R(+) warfarin $AUC_{0-\infty}$ and C_{max} , and INR $AUC_{0-168hr}$ and INR_{max}.

Six mild, transient clinical adverse experiences occurred in 4 subjects and were deemed possibly related to study drug.

CONCLUSIONS: The results suggest that MK-0524 treatment is unlikely to have clinically meaningful effects on warfarin therapy. Co-administration of multiple daily doses of 40 mg MK-0524 with a single dose of 30 mg warfarin was generally well tolerated in all subjects.

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EFFECT OF THE HIV PROTEASE INHIBITOR TMC114, COADMINISTERED WITH LOW-DOSE RITONAVIR, ON THE PHARMACOKINETICS OF DIGOXIN IN HEALTHY VOLUNTEERS. V. J. Sekar, PhD, M. El Malt, E. De Pape, R. Mack, M. De Pauw, T. Vangeneugden, E. Lefebvre, R. Hoetelmans, Tibotec Inc, Tibotec BVBA, Yardley, PA.

BACKGROUND: TMC114 (darunavir) is a new HIV protease inhibitor with in-vitro activity against wild-type HIV virus and multidrug-resistant strains. TMC114 is coadministered with low-dose ritonavir (TMC114/r). This study examined the pharmacokinetic (PK) interaction between the cardiac glycoside digoxin and TMC114/r in 17 HIV-negative healthy volunteers.