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LACK OF EFFECT OF ORLISTAT ON THE PHARMACOKINETICS AND PHARMACODYNAMICS OF PRAVASTATIN. C. Oo, PharmD, PhD, B. Akbari,* PharmD, S. Lee,* PhD, G. Nichols,* MD, & C. Hellmann,* BS, Medical Affairs, Roche Lab, Inc, Nutley, NJ.

24 male subjects with cholesterol levels of 200-300 mg/dL completed a randomized, double-blind, placebo-controlled, 2-way cross-over study. Subjects received either pravastatin (PS) 40 mg QPM and orlistat (OS) 120 mg TID (PS+OS), or PS 40 mg QPM and placebo TID (PS+PL) after meals for 6 days, with a 9-day washout. Blood samples were obtained before and after evening doses on days 3-5 (1 h) and on day 6 (0, 0.5, 1, 1.5, 2, 3, 4, 6, 8 & 12 h). PS plasma levels did not accumulate from days 3 to 6. Mean half-life of PS for both regimens was 2±1 h. For regimen PS+OS vs PS+PL, differences in mean $AUC_{0\rightarrow 12h}$ (59.7±23.6 vs 57.4±24.3 ng·h/mL; p=0.35) and C_{max} (32.3±15.9 vs 29.8±15.9 ng/mL; p=0.33) were 4% and 9%, respectively. 90% C.I. for the ratio of means for AUC and C_{max} were 95-119% and 92-136%, which fall within 80-125% for AUC and 70-143% for C_{max}. Comparing regimen PS+OS vs PS+PL, % decrease in total cholesterol (24 vs 23%) and LDL-cholesterol (35 vs 34%) from baselines were equivalent. 90% C.I. for the ratio of means of total and LDL cholesterols were 94-118% and 87-111%, respectively. No significant adverse events were reported. The results indicate that OS does not affect the pharmacokinetics or pharmacodynamics of PS after 6 days of concomitant treatment.

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THE PHARMACOKINETIC PROFILE OF THEOPHYLLINE IS NOT SIGNIFICANTLY ALTERED BY REPAGLINIDE CO-ADMINISTRATION. M.S. Thomsen, PhD,*[1] V. Hatorp, MSc,[1] M. Seiberling, MD, PhD,*[2] Copenhagen, Denmark,[1] Freiburg, Germany.[2]

This single-center, open-label cross-over study investigated the potential pharmacokinetic interaction between theophylline (THEO) and repaglinide (REP), a prandial glucose regulator (PGR) and the first of a new class of oral antidiabetic agents for Type 2 diabetes. Subjects (14 healthy non-smoking males; 27.6±5.7 years) were allocated to a 2-period treatment sequence (5 days each) of either THEO administered alone, followed by REP co-administered with THEO (n=7), or the reverse (n=7). THEO (300 mg) was orally administered every 12 h on days 1-4, and once on day 5. REP (2mg) was administered preprandially, t.i.d. on days 1-4 and once on day 5. Results are presented below. Co-administration was well tolerated and did not affect the safety profile of THEO. Thus, REP does not alter THEO pharmacokinetics at steady state in healthy male subjects at the dose range studied.

	THEO	THEO/REP	ratio %	Δ	95% CI
AUC (μg/ml·h)	160	152	94.7	-	85.4, 105
$C_{ss,max}$ (μg/ml)	8.84	8.00	90.4	-	82.5, 99.1
$C_{ss,min}$ (μg/ml)	6.35	6.17	97.1	-	83.8, 112.5
t_{max} (min)	290	265	-	-24	-72.5, 24.2
$t_{½}$ (h)	7.2	7.1	-	-0.04	-0.65, 0.55

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DISPOSITION OF ONE DOSE OF ^{14}C-REPAGLINIDE DURING NON-LABELED REPAGLINIDE MULTIPLE DOSING. V. Hatorp, MSc,[1] P.N.M. Van Heiningen, PhD, RPh,*[2] J.J. Van Lier, MD,*[2] N.C. Van de Merbel, PhD,*[2] K.K. Nielsen, PhD,*[1] K.T. Hansen, PhD,*[1] J.H.G. Jonkman, PhD, FCP, RPh,*[2] Novo Nordisk A/S,[1] Denmark, Pharma Bio-Research Int B.V.,[2] The Netherlands.

Repaglinide (REP) is a new short-acting prandial glucose regulator (PGR), developed for the treatment of Type 2 diabetes. To assess the disposition of ^{14}C in whole blood, plasma, urine and feces, 6 healthy male volunteers were administered REP (2 mg), preprandially q.i.d. for 13 days in tablet form, except on the morning of day 7, when an oral solution of ^{14}C-REP (49.7 μCi; 2 mg) was administered. T_{max} for ^{14}C-REP (M_0) indicated rapid absorption (0.5 h). M_0, the major compound recovered in plasma (61%), was cleared from the circulation 3 to 5 h post-dosing. No measurable radioactivity was observed in plasma, 36 h after dosing. The mean plasma:whole blood radioactivity ratio was 1.62. Within 96 hours after dosing, ^{14}C-recovery in feces and urine was 90% and 8%, respectively. Almost no M_0 was excreted via urine whilst only a small amount of M_0 (2% of fecal ^{14}C) was excreted via the feces. In urine, the major metabolites recovered included the aromatic amine (M_1 <2% of administered dose) and dicarboxylic acid (M_2 <2% of administered dose). In feces the major metabolite was M_2 (66% of administered dose). In conclusion, M_0 pharmacokinetics show that REP 2 mg has rapid absorption and metabolic clearance, low distribution into red blood cells and almost no excretion via urine.

PIII-44

REPAGLINIDE PHARMACOKINETICS IN HEALTHY & CHRONIC LIVER DISEASE SUBJECTS. V. Hatorp, MSc, G. Haug-Pihale, MD, PhD,* Novo Nordisk A/S, Denmark, Apex Research, Germany.

Repaglinide (REP) is a prandial glucose regulator (PGR) with a unique physiological insulin release profile. This single center, single-dose, open-label study, compared the pharmacokinetics of REP in healthy subjects (n=12, 53.2±5.6 years) with those in subjects (n=12, 52.9±7.3 years) with chronic liver disease (CLD). Following a 10 h overnight fast, subjects received a single REP 4 mg dose. Subjects with CLD had significantly higher and more prolonged serum levels of both total and unbound REP: AUC, P<0.01; Cmax, P<0.01 compared with the healthy subjects. For CLD subjects AUC was correlated (r=-0.7) with caffeine clearance (P=0.017). $t_{½}$ was in the range 0.6-14.7 h for the CLD group. Protein binding of REP was similar for both subject groups (97%). There were no serious adverse events or withdrawals during the trial. In both groups, 24 hypoglycemic events were reported by 10 subjects. In conclusion, higher and more prolonged REP serum concentrations in CLD subjects did not result in an increased incidence of hypoglycemic episodes compared to healthy subjects.

	AUC (ng/ml·h)	C_{max} (ng/ml)	MRT (h)	t_{max} (h)
CLD (SD)	368.9 (233.4)	105.4 (31.6)	5.9 (4.4)	0.8 (0.5)
Healthy (SD)	91.6 (67.0)	46.7 (24.3)	1.2 (0.4)	0.8 (0.5)