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EFFECT OF ORLISTAT ON THE PHARMACOKINETIC OF RIMONABANT. S. Turpault, S. Woolfrey, G. F. Lockwood, R. Bishai, D. Bonnet, J. Newton, sanofi-aventis, Malvern, PA.

BACKGROUND: Rimonabant is the first selective CB1 blocker developed for the management of multiple cardiometabolic risk factors in overweight/obese patients.

AIMS: To assess the effect of repeated doses of orlistat on the pharmacokinetics (PK) of rimonabant.

METHODS: This was a two-treatment, single-sequence, crossover study in 13 healthy males. Subjects received 20 mg of rimonabant on Day 1 of Period 1 and Day 4 of Period 2 and 120 mg 3 times daily of orlistat from Days 1 to 6 in Period 2. Blood samples were collected up to 336 hours after rimonabant dose in each period. Plasma was analyzed for rimonabant with a validated LC-MS/MS method. Non-compartmental PK parameters were calculated.

RESULTS: Mean (SD) and ratio of the geometric means (90% confidence interval, CI) for rimonabant PK parameters are as follows:

Parameter	Rimonabant alone (N=13)	Rimonabant + orlistat (N=12)	Ratio (90%CI)
C_{max}(ng/mL)	211 (95)	129 (50)	0.720 (0.550, 0.941)
AUC_{last}(ng.h/mL)	2990 (1160)	3300 (1500)	1.069 (0.954, 1.199)
AUC(ng.h/mL)	3520 (1400)	3230 (1290)	1.025 (0.926, 1.136)

The 90% CI for AUC_{last} and AUC were within the bioequivalence limits of 0.80 to 1.25. There was a slight reduction in rimonabant C_{max} when administered with orlistat.

CONCLUSIONS: Orlistat had no appreciable effect on the PK of rimonabant at a clinically relevant dose.

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NXY-059, A NOVEL NEUROPROTECTANT, HAS NO EFFECT ON PHARMACOKINETICS OF A SINGLE DOSE OF DIGOXIN IN HEALTHY SUBJECTS. G. Huledal, D. Nilsson, M. Kågedal, I. Reinholdsson, Y. Cheng, H. Svensson, O. Borgå, AstraZeneca R&D, Borga PK Consulting, Södertälje, Sweden.

BACKGROUND: NXY-059 is a novel, free-radical trapping neuroprotectant that reduces infarct size and preserves brain function in animal models of acute ischemic stroke (AIS). In an initial Phase III study (SAINT I) NXY-059 has shown efficacy in AIS by reducing functional disability. Cardiac disease requiring digoxin treatment is commonly observed in AIS patients. Since both digoxin and NXY-059 are eliminated primarily by renal excretion, and digoxin has a narrow therapeutic window, this study aimed to determine whether NXY-059 affects the pharmacokinetics (PK) of digoxin.

METHODS: In this open, randomized, cross-over, two-period study 22 healthy subjects received NXY-059 / placebo as a 60-h iv infusion with a wash-out of 2 weeks. The infusion produced NXY-059 plasma levels similar to those achieved in clinical trials. 0.5 mg oral digoxin was given at 2 h. Blood and urine were collected for 60 h for digoxin assay by LC-MS-MS (limit of quantification 0.10 ng/mL).

RESULTS: The ratio of the geometric mean (90% confidence interval) between the treatment and placebo was 0.91 (0.83 to 0.99) for the digoxin area under the concentration-time curve and 1.15 (1.05 to 1.25) for the digoxin renal clearance. These confidence intervals were within the predefined range of 0.80 to 1.25 for no relevant interaction. No safety concerns were raised.

CONCLUSIONS: NXY-059 had no effect on the PK of a single dose of digoxin.

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INHIBITORY POTENCY OF CLARITHROMYCIN TOWARDS CYP3AS. V. Michaud, MSc, R. Massé, PhD, J. Turgeon, PhD, Université de Montréal, MDS Pharma Services, Montréal, PQ, Canada.

BACKGROUND/AIMS: Drug-drug interactions observed in patients and involving clarithromycin are mostly explained through inhibition of CYP3As. The objective of our study was to characterize further the inhibitory potency of clarithromycin against CYP3As.

METHODS: *In vitro* inhibition studies were conducted with human liver microsomes (HLM) and microsomes from baculovirus-expressed human recombinant CYP3A4 (rCYP3A4) or CYP3A5 (rCYP3A5), with or without CYP b5. Experiments were initiated by a preincubation period (0-60min) of clarithromycin (0-70μM) followed by incubation of domperidone (200 or 300μM) or midazolam (25, 50 or 300μM) for 45 or 20 min, respectively. Formation rate of domperidone major hydroxylated metabolite (M3) or 1- and 4OH-midazolam were monitored by HPLC with fluorescence and UV detection, respectively.

RESULTS: Clarithromycin at concentrations as high as 70μM caused very limited inhibition of domperidone and midazolam in HLM. Percent inhibitions from clarithromycin 70μM were as follows:

Enzyme Sources	M3-domperidone	1OH-midazolam	4OH-midazolam
HLM	10%	27%	5%
rCYP3A4	61%	12%	25%
rCYP3A4+CYPb5	9%	0%	0%
rCYP3A5	45%	27%	3%
rCYP3A5+CYPb5	18%	15%	5%

CONCLUSIONS: Our results suggest that CYP3As play a minor role in *in vivo* interactions involving clarithromycin. CYP b5 appears to be a major determinant of rCYP3A activity. We propose that the underlying mechanism of drug-drug interaction with clarithromycin should be revisited.

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ASCENDING SINGLE DOSE STUDY OF THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF ROTIGAPTIDE (ZP123) ADMINISTERED INTRAVENOUSLY TO HEALTHY SUBJECTS. C. Udata, PhD, M. Micalizzi, RN, MS, A. Katz, MD, Q. M. Giorgio, MD, X. Meng, PhD, Wyeth, Collegeville, PA.

BACKGROUND/AIMS: To assess the safety, tolerability and pharmacokinetics of single ascending doses of rotigaptide, a first-in-class cardiomyocyte gap junction modifier, in healthy subjects.

METHODS: In a randomized, double-blind, placebo-controlled, sequential-group study, ascending single doses of rotigaptide or placebo were administered to 79 men as a 24-hour IV infusion of 0.03 to 30 mg or as a bolus of 2 or 3 mg. Safety was determined from reported adverse events (AEs), physical exams, vital signs, laboratory tests, and 12-lead ECGs. Plasma and urine samples were analyzed for rotigaptide using LC/MS/MS method and rotigaptide pharmacokinetics was characterized.

RESULTS: The most common AEs were asymptomatic orthostatic increase in pulse (n=28) and decrease in blood pressure (n=4), and local irritation, rash, and/or blistering at the electrode site (n=23). All were considered by the investigator as mild or moderate and probably not related to test article. There were no dose-related trends in AEs or laboratory tests. Rotigaptide disposition was characterized by low Cl (133 mL/min) and low V_{SS} (21.4 L) and the terminal disposition $t_{1/2}$ was 2.7 h. AUC increased in a dose-proportional manner. Approximately 61-84% excreted unchanged in urine and no metabolites were apparent in plasma.

CONCLUSION: Rotigaptide appeared to be safe and well-tolerated at the doses tested in healthy subjects. Rotigaptide showed predictable and linear pharmacokinetics and renal excretion was the primary route of elimination.