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DISPOSITION OF IRINOTECAN AND ITS MAIN METABOLITES IN PLASMA, URINE, BILE AND FECES OF A CANCER PATIENT WITH A BILE DRAIN. W. J. Loos, PhD, F. A. de Jong, MSc, J. J. Kitzen, MD, J. Verweij, MD, PhD, P. de Bruijn, BSc, Erasmus MC - Daniel den Hoed Cancer Center, Rotterdam, The Netherlands.

BACKGROUND: Irinotecan (CPT-11) is metabolized by various enzymes, including CE, CYP3A and UGT1A. Here we report on the disposition of irinotecan and its metabolites in plasma, urine, bile and feces of a cancer patient with a bile drain.

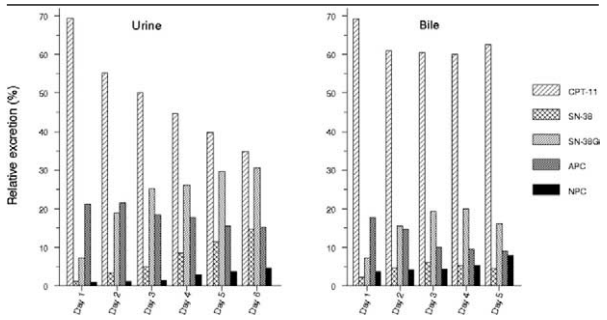
METHODS: Blood samples were collected up to 55 h after infusion, while bile, feces and urine were collected during 6 consecutive days.

RESULTS: The plasma CL of CPT-11 was 15.3 L/h, with relative metabolic conversions to SN-38, APC and NPC of 0.022, 0.40 and 0.016 respectively and a relative extent of glucuronidation of 6.9. Overall, 84% of the administered dose was recovered (see table). The relative contribution of CPT-11 to the excretion over the studied days in urine decreased, while those in bile was stable. The relative contribution of the metabolites to the excretion in bile and urine changes in time (see figure).

CONCLUSION: The PK of CPT-11 and metabolites in plasma are equivalent to historical data, with a relative slow CL of CPT-11 and relative high AUC of APC. The high percentage of the dose recovered in urine as compared to published data, the relative slow CL of CPT-11 and the preferential urinary excretion over biliary excretion of APC is most likely related to reduced transport by ABC transporters in the liver. Differential affinities of CPT-11 for substrate-binding active sites on CYP3A may contribute to the changed metabolic excretion profile of CPT-11 in time. Inhibition or decreased activity of CE, as well as sustained release from other compartments, also cannot be excluded.

Recovery of administered dose CPT-11

Excreta	CPT-11	SN-38	SN-38G	APC	NPC	Total
Urine	29.2%	0.9%	4.6%	9.3%	0.5%	44.5%
Bile	20.8%	0.9%	3.0%	5.2%	1.2%	31.0%
Feces	7.1%	0.5%	—	0.2%	0.1%	7.9%
All	57.3%	2.4%	7.6%	14.6%	1.7%	83.5%



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A STUDY TO EVALUATE THE PHARMACOKINETICS OF PAMOIC ACID FOLLOWING ORAL ADMINISTRATION AS HYDROXYZINE PAMOATE (VISTARIL®) IN HEALTHY MALE SUBJECTS. E. Lobo, PhD, M. Mitchell, MB, BS, MFPM, P. Kothare, PhD, J. Johnson, MS, R. Van Lier, PhD, J. Krull, PharmD, Eli Lilly & Company, Indianapolis, IN.

BACKGROUND: While several drugs are commercially available as the pamoate salts, information on the systemic exposure of pamoic acid (PA) from such drug products is not available in the literature. This study was conducted to determine the pharmacokinetics of PA from a marketed formulation, hydroxyzine pamoate.

METHODS: The study was conducted as open-label in 6 healthy Caucasian male subjects (25 to 37 years). Each subject received 100 mg hydroxyzine pamoate once on Day 1 and every 6 hours from Days 2 to 4 (9 oral doses). Blood samples were obtained on Days 1 and 4 at 0, 1, 2, 3, 4, 5, 6, 7, 8, 12, and 24 hr after the dose. PA concentrations were measured using a validated HPLC method with fluorescence detection and analyzed using non-compartmental method.

RESULTS: Plasma concentration-time profile of PA showed biphasic elimination. PA was rapidly absorbed with time to maximal concentration of 3 hr on Day 1 and 3.5 hr on Day 4. Mean apparent half-life on Days 1 and 4 were 5.7 and 7.0 hr, respectively. Upon multiple dosing, oral clearance ranged from 12 to 115 L/hr and oral volume of distribution ranged from 99 to 1200 L. Maximum average steady state concentrations of PA were 715 ng/mL.

CONCLUSIONS: PA is rapidly absorbed and eliminated from the systemic circulation on oral administration of hydroxyzine pamoate. The concentrations of PA reported in this study provide information on the systemic exposure of PA. Further studies are warranted to evaluate the pharmacokinetics of PA from other pamoate salts.

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EFFECT OF ASOPRISNIL ON THE PHARMACOKINETICS OF TRIAZOLAM AND ITS METABOLITE IN HEALTHY FEMALE SUBJECTS. R. D. Lee, PhD, D. Mulford, PhD, G. Witt, MS, K. Chwalisz, MD, PhD, TAP Pharmaceutical Products Inc., Lake Forest, IL.

BACKGROUND: Asoprisnil (J867) is a novel selective progesterone receptor modulator (SPRM) with partial or mixed agonist/antagonist effects depending on the biological action studied. The objective of this study was to evaluate the effect of asoprisnil on pharmacokinetics (PK) of triazolam, a CYP3A substrate, as the in vitro metabolism of asoprisnil to its active J912 metabolite involves CYP3A.

METHOD: In this open-label sequential drug-drug interaction study, 24 healthy postmenopausal subjects received a single 0.25 mg oral dose of triazolam on Day 1. On Days 2-15, subjects received a 25 mg oral dose of asoprisnil once daily, and on Day 15, subjects received an additional single 0.25 mg oral dose of triazolam. Serial blood samples were obtained on Days 1 and 15 over 24 hours to determine the PK of triazolam and its 1'-OH triazolam metabolite. Plasma concentrations of triazolam and 1'-OH triazolam were determined using a validated LC/MS/MS assay.

RESULTS: The 90% confidence intervals (CI) for the ratios of the central values of triazolam or 1'-OH triazolam C_{max} and AUC were contained within the *no effect* boundaries of 0.80-1.25 when triazolam was coadministered with asoprisnil. All treatments were safe and generally well tolerated.

	C_{max}		$AUC_{0-\infty}$	
	Ratio	90% CI	Ratio	90% CI
Triazolam	1.043	0.964-1.127	1.139	1.051-1.235
1'-OH Triazolam	0.953	0.856-1.061	1.050	0.941-1.173

CONCLUSION: Concomitant administration of 0.25 mg triazolam after multiple daily doses of 25 mg asoprisnil had *no effect* on the PK of triazolam and its metabolite in healthy subjects.