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BAZEDOXIFENE ACETATE METABOLIC DISPOSITION IN HEALTHY, POSTMENOPAUSAL WOMEN. A. Chandrasekaran, PhD, J. Ermer, MS, W. McKeand, MS, H. Lee, PhD, W. DeMaio, PhD, A. Kotake, PhD, P. Sullivan, BS, G. Orczyk, MD, PhD, J. Scatina, Wyeth Research, Collegeville, PA.

Bazedoxifene (BZA) is a selective estrogen receptor modulator being developed for the prevention and treatment of postmenopausal osteoporosis. The objective of this study was to characterize the metabolic disposition of [^{14}C]bazedoxifene in postmenopausal women.

A single oral dose of 20 mg (200 μCi) of [^{14}C]bazedoxifene acetate was administered in a capsule to six healthy, postmenopausal women. Following dosing, blood, urine and feces were collected for up to 10 days. Aliquots of plasma, blood, urine and fecal homogenates were analyzed for radioactivity concentrations. Metabolite profiles in plasma and feces were determined by HPLC, and the structures of the metabolites were confirmed by LC/MS.

The single 20-mg oral dose of [^{14}C]bazedoxifene was safe and well tolerated. The major route of excretion of radioactivity (84.7%) was the feces. Excretion in urine represented a minor route (0.81%). Blood/plasma ratios of radioactivity were below 0.55 at all time points calculated, which indicated no preferential binding of radioactivity to whole blood constituents. Glucuronidation was the major metabolic pathway. Little or no P450 mediated metabolism was evident. The majority of the circulating radioactivity was constituted by metabolites, with BZA-5-glucuronide predominant (40 to 95%). BZA-4'-glucuronide was a minor metabolite (1 to 20%). BZA represented between 1 to 13% of the radioactivity in most plasma samples. BZA was the major radioactive component in feces, representing unabsorbed drug and glucuronides that were hydrolyzed by gut bacterial enzymes.

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THE SINGLE-DOSE PHARMACOKINETICS OF CLOPIDOGREL IN HEALTHY ADULT VOLUNTEERS. J. Grenier, MSc, S. Ciric, BPharm, J. Curry, BA, G. Morelli, MD, A. Arseneault, M. Tanguay, BPharm, PhD, MDS Pharma Services, Montreal, Canada.

Objective: The pharmacokinetics (PK) of the antiplatelet drug clopidogrel have not yet been characterized, as PK data is available only for its inactive carboxylic acid metabolite (SR26334). The objective of this study was to determine the PK of clopidogrel using a new analytical method.

Study Design: Six healthy adult males were enrolled in an open-label, 2-way, single-dose study. On two occasions, after an overnight fasting, subjects received a single-dose of 75 mg clopidogrel bisulfate. Blood samples were collected up to 24 hours following dosing. Plasma samples were analyzed using a new LC/MS/MS method that was developed with a range of quantitation of 0.05-25 ng/mL for clopidogrel.

Results: The following pharmacokinetic parameters (mean±SD) were obtained for clopidogrel and SR26334.

	AUCt (ng·h/mL)	Cmax (ng/mL)	tmax (h)	t½ (hour)
Clopidogrel	50 ± 23	20 ± 7	1.0 ± 0.4	8.8 ± 4.3
SR26334	9000 ± 2500	4100 ± 1700	0.8 ± 0.4	14 ± 5

Discussion/Conclusion: Clopidogrel is rapidly absorbed with peak concentrations occurring at 1h after dosing. The plasma concentrations of clopidogrel are approximately 200 fold lower than its metabolite. The early tmax of SR26334 suggest pre-systemic formation of the metabolite (e.g. in the gut wall). The apparent elimination half-life of clopidogrel is shorter than that of SR26334 with an average of 9h.

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THE SINGLE-DOSE PHARMACOKINETICS OF PERGOLIDE IN HEALTHY ADULT VOLUNTEERS. J. Grenier, MSc, N. Cardillo Marricco, MSc, G. Morelli, MD, L. Letarte, R. Farmen, PhD, M. Tanguay, BPharm, PhD, MDS Pharma Services, Genanda, Montreal, Canada.

Purpose: The pharmacokinetics (PK) of pergolide, a synthetic ergot derivative, have not yet been well characterized due to very low plasma concentrations. The objective of this study was to determine the PK of pergolide using a more sensitive assay.

Study Design: 9 healthy adult males were enrolled in an open-label, parallel, single-dose study. Subject received 1 of the following 3 doses: 0.15 mg, 0.25 mg or 0.50 mg of pergolide mesylate. Metoclopramide was used as an antiemetic prophylactic and was started 2 days prior to pergolide dosing. Blood samples were collected up to 24 hours post-dose. A LC/MS/MS method was used (range of 5-500 pg/mL).

Results: The following PK parameters (mean±SD) were obtained for pergolide in plasma

Dose (mg)	AUCt (pg·h/mL)	AUCinf (pg·h/mL)	Cmax (pg/mL)	tmax (hour)	t½ (hour)
0.15	245±120	295±135	38±5	2.8±1.4	4.7±2.7
0.25	400±200	460±210	56±26	2.7±0.8	3.9±0.5
0.50	760±150	850±180	95±23	2.5±0.9	8.0±4.5

The sulfone and sulfoxide metabolites were also analyzed for one subject (dose 0.15mg). The sulfone concentrations were undetectable but Cmax and AUCt of the sulfoxide were 27 and 12 times higher than those observed for pergolide, respectively. Simulations were performed using multiple dosing strategies to predict the steady-state plasma concentrations.

Conclusion: For the first time, the single dose PK of pergolide could be well characterized. The rate and extent of pergolide bioavailability appears to increase proportionally with the dose.

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DOMPERIDONE AS A SUBSTRATE MARKER DRUG FOR CYP3A4 AND CYP3A5. V. Michaud, BPharm, C. Simard, PhD, N. Morin, MSc, J. Turgeon, PhD, Université de Montréal, Vanderbilt University, Montreal, Canada.

Recent studies from our laboratories have indicated that dopamine D2 receptor antagonist domperidone is mainly metabolized by the CYP3As family. The objective of our study was to characterize further the cytochrome P450 isozymes involved in the metabolism of domperidone and to determine whether this agent could be used as a marker substrate to differentiate between CYP3A4 and CYP3A5 activities. *In vitro* incubations were conducted with microsomes from baculovirus transfected cells (Supersomes) expressing high levels of either CYP3A4 or CYP3A5. Domperidone (1-300 μM) was incubated for 45 minutes with these enzymatic sources in the presence of a NADPH regenerating system. Formation rate of domperidone major hydroxylated metabolite (M3) was monitored by HPLC with fluorescence detection. Km for the formation of M3 was 5 μM with CYP3A4 but 150 μM with CYP3A5. Incubations were also made at low (5 μM; Km for CYP3A4) and high (200 μM) domperidone concentrations using human liver microsomes from different donors (n=15). Using this strategy, we estimated that content of CYP3A4 varied from 20-40% in these preparations; thus CYP3A5 appears to be the major CYP3A isoform in human liver. Inhibition studies with clarithromycin, ketoconazole and monoclonal antibodies also suggest the prevalence of CYP3A5 over CYP3A4. In conclusion, we propose that domperidone can be used in vitro as a substrate marker to differentiate between CYP3A4 and CYP3A5 activities in various enzymatic preparations.