Table 5. Effect of repeated daily administration of pantoprazole, omeprazole and lansoprazole on aminopyrine N-demethylation and 7-ethoxycoumarin O-deethylation in rat liver microsomes

Group	Dose (mg/kg/day)	Aminopyrine N-demethylase (nmol/min/mg protein)	Aminopyrine N-demethylase (nmol/min/g liver)	Aminopyrine N-demethylase (nmol/min/nmol P450)	7-Ethoxycoumarin O-deethylase (nmol/min/mg protein)	7-Ethoxycoumarin O-deethylase (nmol/min/g liver)	7-Ethoxycoumarin O-deethylase (nmol/min/nmol P450)
Treated	CMC 0.50%	6.31 ± 0.20	91.7 ± 8.2	9.51 ± 0.61	1.12 ± 0.08	16.3 ± 1.8	1.75 ± 0.05
	PAN 5	6.30 ± 0.18	97.2 ± 5.8	9.89 ± 0.66	1.01 ± 0.08	15.5 ± 0.7	1.58 ± 0.15
	PAN 50	7.57 ± 0.12*	113 ± 8.5	10.8 ± 0.29	1.04 ± 0.09	15.7 ± 2.5	1.48 ± 0.11
	PAN 300	8.24 ± 0.09*	126 ± 2.8*	10.0 ± 0.11	1.76 ± 0.10*	26.9 ± 2.1*	2.14 ± 0.12*
	OM 5	5.92 ± 0.29	82.1 ± 3.8	8.98 ± 0.22	0.82 ± 0.21	11.9 ± 3.7	1.26 ± 0.34
	OM 50	6.43 ± 0.85	101 ± 2.2	10.5 ± 0.74	1.42 ± 0.12	22.6 ± 1.4	2.36 ± 0.20*
	OM 300	7.38 ± 0.69	116 ± 7.2	7.61 ± 0.36*	2.96 ± 0.18*	46.9 ± 1.8*	3.07 ± 0.17*
	LAN 5	5.50 ± 0.16*	122 ± 6.0*	9.16 ± 0.35	0.90 ± 0.07	20.0 ± 1.8	1.49 ± 0.05*
	LAN 50	5.75 ± 0.18	126 ± 4.6*	8.20 ± 1.02	2.70 ± 0.12*	59.0 ± 2.6*	3.82 ± 0.29*
	LAN 300	6.51 ± 0.58	124 ± 6.0*	6.15 ± 0.46**	3.17 ± 0.23*	60.7 ± 2.6*	3.00 ± 0.16*
	MC 30	5.27 ± 0.56	85.5 ± 2.9	4.71 ± 0.25**	6.35 ± 0.68*	105 ± 13.7*	5.69 ± 0.35*
	PB 80	13.5 ± 0.41*	193 ± 4.5*	8.07 ± 0.22*	3.16 ± 0.21*	45.3 ± 3.7*	1.89 ± 0.11
Recovered	CMC 0.50%	6.12 ± 0.55	105 ± 5.5	5.77 ± 0.70	1.13 ± 0.09	19.5 ± 1.0	1.07 ± 0.12
	PAN 5	7.03 ± 0.67	94.3 ± 4.0	7.54 ± 0.31	1.20 ± 0.12	16.1 ± 0.6	1.29 ± 0.03
	PAN 50	6.82 ± 0.56	101 ± 9.6	7.86 ± 0.27*	1.21 ± 0.13	17.9 ± 1.8	1.39 ± 0.08
	PAN 300	7.66 ± 0.64	88.7 ± 9.2	8.38 ± 0.48*	2.19 ± 0.04*	33.8 ± 0.8*	1.31 ± 0.02
	OM 5	5.28 ± 0.24	100 ± 4.0	6.47 ± 0.37	0.94 ± 0.04	17.9 ± 0.9	1.16 ± 0.08
	OM 50	5.55 ± 0.68	105 ± 13.6	7.82 ± 1.56	1.08 ± 0.13	20.1 ± 2.6	1.53 ± 0.27
	OM 300	6.38 ± 0.11	99.5 ± 0.6	7.75 ± 0.18	1.02 ± 0.01*	16.0 ± 0.2*	1.24 ± 0.02
	LAN 5	5.46 ± 0.54	129 ± 10.1	9.15 ± 1.23	0.87 ± 0.06	20.6 ± 0.9	1.46 ± 0.16
	LAN 50	5.12 ± 0.53	113 ± 11.0	8.14 ± 0.88	0.96 ± 0.12	21.1 ± 2.6	1.53 ± 0.20
	LAN 300	5.13 ± 0.26	114 ± 10.4	8.33 ± 0.71	0.98 ± 0.05	21.5 ± 0.2	1.59 ± 0.12*
	MC 30	4.32 ± 0.62	85.1 ± 5.7	5.34 ± 0.47	2.52 ± 0.23*	50.4 ± 4.9*	3.17 ± 0.40*
	PB 80	6.36 ± 0.53	92.0 ± 3.2	7.77 ± 0.56	1.18 ± 0.04	17.3 ± 1.4	1.45 ± 0.08

Each value represents the mean ±S.E. for 3 rats. *, p<0.05, *, p<0.01, *, p<0.001.
PAN, pantoprazole; OM, omeprazole; LAN, lansoprazole; MC, 3-methylcholanthrene; PB, phenobarbital.

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Table 6. Effect of repeated daily administration of pantoprazole, omeprazole and lansoprazole on phenacetin O-deethylation, 7-ethoxyresorufin O-deethylation, 7-pentoxyresorufin depentylation and testosterone 6β-hydroxylation in rat liver microsomes

Group	Dose (mg/kg/day)	Phenacetin O-deethylase (pmol/min/mg protein)	Phenacetin O-deethylase (pmol/min/g liver)	Phenacetin O-deethylase (pmol/min/nmol P450)	7-Ethoxyresorufin O-deethylase (pmol/min/mg protein)	7-Ethoxyresorufin O-deethylase (pmol/min/g liver)	7-Ethoxyresorufin O-deethylase (pmol/min/nmol P450)
Treated	CMC 0.50%	0.73 ± 0.01	17.0 ± 0.7	1.19 ± 0.07	34.6 ± 10.4	0.48 ± 0.13	52.6 ± 14.8
	PAN 5	1.05 ± 0.14	16.0 ± 1.8	1.62 ± 0.16	37.8 ± 8.2	0.58 ± 0.11	58.5 ± 12.0
	PAN 50	1.02 ± 0.10	15.5 ± 2.7	1.46 ± 0.13	32.0 ± 6.9	0.49 ± 0.14	45.7 ± 9.5
	PAN 300	2.16 ± 0.30*	40.0 ± 6.3	2.82 ± 0.53	69.6 ± 10.3	1.06 ± 0.17*	84.8 ± 12.6
	OM 5	1.03 ± 0.07*	14.3 ± 0.5*	1.56 ± 0.06*	38.1 ± 5.0	0.52 ± 0.04	57.4 ± 5.3
	OM 50	1.09 ± 0.13	17.1 ± 0.6	1.80 ± 0.17*	62.5 ± 9.6	0.98 ± 0.10*	102 ± 5.9*
	OM 300	2.27 ± 0.21*	32.5 ± 6.3*	2.53 ± 0.17*	166 ± 21.5*	2.62 ± 0.31*	172 ± 21.5*
	LAN 5	0.75 ± 0.14	16.7 ± 3.4	1.23 ± 0.21	24.1 ± 1.8	0.53 ± 0.05	40.0 ± 2.3
	LAN 50	1.95 ± 0.12*	42.7 ± 2.3*	2.80 ± 0.38*	165 ± 10.4*	3.62 ± 0.25*	232 ± 10.6*
	LAN 300	1.82 ± 0.40	34.3 ± 6.0	1.71 ± 0.35	191 ± 14.0*	3.65 ± 0.17*	181 ± 9.5*
	MC 30	3.02 ± 0.35*	66.6 ± 7.4*	2.92 ± 0.27*	327 ± 28.2*	7.42 ± 0.54*	318 ± 24.1*
	PB 80	3.13 ± 0.58	98.0 ± 12.7*	1.91 ± 0.38	44.1 ± 4.8	1.40 ± 0.12*	27.0 ± 3.6

Group	Dose (mg/kg/day)	7-Pentoxyresorufin O-depentylase (pmol/min/mg protein)	7-Pentoxyresorufin O-depentylase (nmol/min/g liver)	7-Pentoxyresorufin O-depentylase (pmol/min/nmol P450)	Testosterone 6β-hydroxylase (nmol/min/mg protein)	Testosterone 6β-hydroxylase (nmol/min/g liver)	Testosterone 6β-hydroxylase nmol/min/nmol P450)
Treated	CMC 0.50%	18.4 ± 6.8	0.26 ± 0.09	27.5 ± 9.7	0.092 ± 0.012	2.14 ± 0.28	0.148 ± 0.013
	PAN 5	23.8 ± 5.8	0.36 ± 0.08	36.8 ± 8.6	0.086 ± 0.007	1.32 ± 0.07*	0.135 ± 0.008
	PAN 50	22.5 ± 5.2	0.35 ± 0.10	32.1 ± 7.0	0.097 ± 0.003	1.45 ± 0.11	0.139 ± 0.005
	PAN 300	210 ± 31*	3.20 ± 0.46*	255 ± 37*	0.231 ± 0.007*	3.53 ± 0.22*	0.281 ± 0.009*
	OM 5	18.2 ± 2.2	0.25 ± 0.01	27.4 ± 2.5	0.116 ± 0.003*	1.62 ± 0.16	0.176 ± 0.010*
	OM 50	39.7 ± 4.7	0.63 ± 0.03*	65.0 ± 2.7*	0.097 ± 0.003	1.57 ± 0.20	0.166 ± 0.030*
	OM 300	125 ± 17*	1.96 ± 0.12*	129 ± 15*	0.266 ± 0.026*	4.11 ± 0.59*	0.297 ± 0.022*
	LAN 5	16.4 ± 1.2	0.36 ± 0.03	27.5 ± 2.6	0.085 ± 0.005	1.87 ± 0.13	0.140 ± 0.004
	LAN 50	27.2 ± 2.0	0.60 ± 0.05*	38.1 ± 1.4	0.110 ± 0.012	2.42 ± 0.27	0.154 ± 0.005*
	LAN 300	125 ± 28*	2.37 ± 0.43*	118 ± 25*	0.161 ± 0.014*	3.07 ± 0.16*	0.152 ± 0.012
	MC 30	16.2 ± 1.0	0.27 ± 0.04	14.7 ± 1.2	0.204 ± 0.031*	4.63 ± 0.65*	0.197 ± 0.026
	PB 80	436 ± 57*	14.2 ± 0.80*	198 ± 11*	0.676 ± 0.047*	21.5 ± 1.11*	0.410 ± 0.02*

Each value represents the mean ±S.E. for 3 rats. *, p<0.05, *, p<0.01, *, p<0.001.
PAN, pantoprazole; OM, omeprazole; LAN, lansoprazole; MC, 3-methylcholanthrene; PB, phenobarbital.

TABLE 7
Total P450 and specific P450 contents in hepatic microsomes from female rats treated with various drugs

Anti-P450	P-450 content (pmol P450/mg protein) U	PAN	OM	LAN	MC	PB
CYP1A1	42.7 ± 17.4	260 ± 38.7*	352 ± 17.4*	395 ± 11.5*	802 ± 19.6*	58.9 ± 24.0
CYP1A2	38.0 ± 5.8	136 ± 29.7*	149 ± 24.5*	240 ± 33.0*	375 ± 19.0*	63.7 ± 8.7
CYP2B1	28.0 ± 4.2	80.0 ± 1.9*	56.3 ± 5.4*	74.9 ± 2.4*	29.9 ± 5.2	416 ± 8.4*
CYP2B2	13.3 ± 2.7	68.1 ± 6.8*	41.0 ± 8.1*	31.7 ± 3.8*	15.4 ± 5.1	296 ± 6.7*
CYP2C6	107 ± 19.3	197 ± 17.3*	150 ± 21.1	212 ± 44.1	89.2 ± 25.0	377 ± 52.1*
CYP2E1	38.0 ± 6.4	37.4 ± 5.0	32.2 ± 4.0	32.2 ± 6.4	24.6 ± 4.3	51.5 ± 14.6
CYP3A2	50.1 ± 12.0	96.6 ± 4.7*	146 ± 10.2*	149 ± 28.0*	82.4 ± 17.5	506 ± 103*
CYP4A1	12.7 ± 0.7	13.2 ± 1.2	14.8 ± 1.5	23.4 ± 2.5*	15.3 ± 1.6	18.1 ± 1.4*
NADPH cyt.c	15.7 ± 4.7	36.6 ± 1.8*	28.9 ± 4.3	16.4 ± 3.8	17.7 ± 1.5	48.7 ± 5.8*
Total P450†	0.64 ± 0.06	0.82 ± 0.001	0.97 ± 0.046*	1.06 ± 0.025*	1.11 ± 0.078*	1.68 ± 0.097*

Female SD rats (7 weeks of age) were administered PAN (300 mg/kg/day), OM (300 mg/kg/day) and LAN (300 mg/kg/day) orally for 7 days. MC (30 mg/kg/day) and PB (80 mg/kg/day) intraperitoneally, for 3 days and 7 days, respectively. All were killed 24 hours after the last dose. Results are the mean ± S.E. of 3 rats. CYP, cytochrome P450; NADPH cyt.c, NADPH cytochrome c reductase. Significance of the increases in treated v.s. those in untreated controls (U): a, P<0.05, b, P<0.01, c, P<0.001.
† nmol P450/mg protein. Total cytochrome P450 was measured by

Effects of Pantoprazole (B8610-023) and B8401-026 (a Thiol Metabolite of Pantoprazole in Rats) on Selected Hepatic Drug Metabolizing Enzyme Activities Following oral Administration to Female Rats for 4-Weeks (GTR-31321).

Methods: Groups of female rats (n=8/group) were given oral (gavage) doses of vehicle (water), pantoprazole (300 mg/kg/day, pH 10.5), B8401-026 (50 mg/kg/day in 3% Methocel) or positive control (sodium phenobarbital, 75 mg/kg/day) for 4 weeks. At the end of study period, rats were killed and livers were removed and weighed. Various hepatic enzyme activities were monitored. P450-dependent mixed function oxidase activities were

assessed by determining the hepatic activities of 7-pentoxyresorufin-o-dealkylase (PROD), 7-ethoxyresorufin-o-deethylase (EROD), 7-ethoxycoumarin-o-deethylase (ECOD), and aniline 4-hydroxylase (A-4H) as well as by measuring concentration of cytochrome P-450. Activities of enzymes which catalyze the conjugation reactions such as UDP-glucuronyltranferase (UDPGT) and glutathione-s-transferase were also measured. Activities of cyanide insensitive palmitoyl-CoA oxidase (peroxisomal marker) were also measured.

Results: None of the tested compounds had liver peroxisome proliferating activity in rats as evident by lack of increase in palmitoyl-CoA oxidase activity. Both phenobarbital and pantoprazole significantly induced cytochrome P450-dependent mixed function oxidase activities. The most profound effect was seen in the induction of 7-pentoxyresorufin-o-dealkylase activities. Phenobarbital produced a 225-fold increase in PROD activity while pantoprazole produced 13-fold increase. PROD activity is related to CYP2B1/2 isoform of P-450. Pantoprazole acts as an inducer of specific isoforms of P-450 (CYP2B1/2), since it has no effect on the levels of cytochrome P-450. However, on molar basis, pantoprazole is about 0.025 times as potent as phenobarbital as an inducer of phase I (cytochrome P450-dependent mixed-function oxidase) activities in rats. Thiol metabolite had no significant effect on cytochrome P450-dependent mixed function oxidase activities. Pantoprazole, its thiol metabolite, and phenobarbital also significantly induced hepatic drug metabolizing enzyme activities which catalyzes the conjugation reaction (Phase II reaction: p-nitrophenol UDPGT and glutathione S-transferase activities), and pantoprazole potency was about 38-50% of that seen with phenobarbital on molar basis, while thiol metabolite (B8401-026) potency was similar to that seen with phenobarbital on molar basis.

Effects on Hepatic Enzymes
(Expressed as a Fraction of Control Values)

Parameters	Phenobarbital (75 mg/kg/day = 295 µmole/kg/day)	Pantoprazole (300 mg/kg/day = 694 µmole/kg/day)	B8401-026 (50 mg/kg/day = 231 µmole/kg/day)
Microsomal Protein	1.4	1.1	0.9
PROD	225.5	13.3	0.9
EROD	7.8	2.6	1.3
ECOD	7.3	2.7	1.5
A-4H	3.7	1.2	0.7
Cytochrome P450	2.9	1.1	0.8
UDPGT	2.0	2.7	1.7
Glutathione-s-transferase	2.1	1.9	1.7
Palmitoyl-CoA Oxidase	1.2	1.1	0.9

Effects of Selected Hepatic Drug-Metabolizing Enzyme Activities After Oral Administration to Female Rats for 4 Weeks Followed by a 4 Week Recovery (GTR-31304).

In female SD rats, pantoprazole (200 mg/ kg/day for 4 weeks) induced significant increases in 7-pentoxyresorufin O-dealkylase, p-nitrophenol UDP-glucuronyltransferase and glutathione S-transferase activities (340%, 130% and 70% respectively). Activities of above mentioned enzymes returned to base-line after 4 weeks of recovery period. In this study, pantoprazole had no significant effect on T_3, T_4 and TSH levels (even though p-nitrophenol UDPGT activity was induced). It is quite possible that an induction of T_4 UDPGT activity alone may not change thyroid homeostasis, and increase rate of biliary excretion of conjugated T_4 may be compensated by a corresponding increase in the rate of absorption of deconjugated T_4 through the gut (De Sandro et al., Biochemical Pharmacology 43:1563, 1992).

Rat: Metabolism Characteristics and Metabolites

Biotransformation of ^{14}C-Pantoprazole in Selected Organs of the Rat (GTR-31302).

Methods: Metabolites of pantoprazole were identified in liver, kidneys, and lungs from male Sprague Dawley rats following intravenous administration of [Pyridylmethyl-^{14}C]-pantoprazole at 5 mg/kg. Five rats per time point were sacrificed at 0.083, 0.5, 1, 2, 4, 8, 24, and 48 hr after dosing. At each time point, blood was collected and plasma and red blood cells were isolated. Organs and tissues were collected as follows: adrenal glands, brain, fat, gastrointestinal tract (divided into stomach, small intestine, large intestine, and gut contents), heart, kidneys, lacrimal glands, lungs, liver, muscle (thigh), pancreas, salivary glands (submandibular, sublingual, parotid), spleen, skin, testes, thymus, and thyroid. The liver, lung, and kidney samples at 0.083, 0.5, 1, 2, 4, 8, and 24 hr were pooled at each time point and lyophilized after determination of total radioactivity. Lyophilized products were extracted and separated by

Results: Metabolites in liver, kidney, and lungs were identified over the first 24 hr after dosing. Percentages shown are % of the total dose. Metabolites, M64 and M75, of unknown structures, were observed at varying levels in the liver, lung, and kidneys, but were not found in the plasma, urine, or feces of rats.

1. Liver: Eleven radioactive peaks were identified in the liver. Major metabolites observed at 5 min, which declined over the 24 hr study period were the demethylated sulfide derivative of pantoprazole (B8710-042) at 1.88 to 0.02%, the sulfide derivative (B8510-028) at 2.28 to 0.01%, a metabolite of unknown structure (M80) at 2.55 to 0.01%, and another metabolite of unknown structure (M64) at 1.88 to 0.01%. Over the first 24 hr, unchanged pantoprazole declined from 0.67% to 0.01%.

2. Kidney: Unchanged pantoprazole was observed over the first 2 hr after dosing (0.44% to 0.1%). An unknown metabolite (M64) was observed at 0.59% at 5 min and declined to 0.03% at 4 hr. With the decline of pantoprazole and M64, there was concomitant appearance of B8710-042 (0.08% at 5 min to 0.30% at 0.5 and 1 hr), B8510-028 (0.10% at 5 min to 0.16% at 1 hr), the sulfone, B8610-014, (0.02% at 5 min to 0.09% at 1 hr), an unknown metabolite (M10) (0.02% at 5 min to 0.10% at 1 hr), and another unknown metabolite (M75) (0.02% at 5 min to 0.04 at 1 hr). Metabolite levels declined after 1 hr.

3. Lungs: Unchanged pantoprazole accounted for the majority of radioactivity observed in the lung declining from 0.43% at 5 min to 0.02% at 2 hr. An unknown metabolite (M64) also declined from 0.16% at 0.5 hr to 0.02% at 2 hr. B8610-014 remained relatively constant at 0.04 to 0.08% over the first 4 hr.

Metabolic Fate of ^{14}C-Pantoprazole [Labelled at 2-position of Benzimidazole Ring] in Rats After an Oral Dose of 5 or 500 mg/kg (GTR-31317).

Methods: Intact as well as bile-duct cannulated rats of both sexes were given single oral (gavage) dose of ^{14}C-pantoprazole (5 or 500 mg/kg). Urine, feces and bile samples were collected at various time intervals. The time intervals for urine collection were 0-8, 8-24 and then every 24 hour intervals through 96 hours. Feces were collected every 24 hr for up to 96 hours. Bile samples were collected from bile cannulated rats over (0.5 hr pre-dose), 0-2, 2-4, 4-6, 6-8 and 8-24 hr after drug administration. Plasma samples were collected at 1, 4 and 8 hours after drug administration. In the above experiment 3 rats/sex/time point were used. Total radioactivity and metabolic profile were determined by _____ methods.

Results: Irrespective of the dose, about 60% and 40% of administered radioactivity were excreted in urine and feces, respectively, over 0-96 hr after drug administration, and most of the excretion occurred during 0-24 hr period. In bile duct cannulated rats (both sexes), about 40-44% of the administered radioactivity (low dose or high dose) was excreted in the bile over 0-24 hr after drug administration. The 0-24 hr urinary excretion of 21-42% in bile cannulated rats was much less than that seen in intact rats (see above), which indicates enterohepatic recycling. In intact rats over 0-72 hr, about 32% and 40% of the administered radioactivity were eliminated in feces after low and high doses, respectively.

Percent of Radioactivity Excreted in Urine and Feces (n=3)

	Low Dose		High Dose	
Duration (hr)	Urine	Feces	Urine	Feces
Male				
0-24	51.2 ± 1.7	24.8 ± 3.0	42.9 ± 11.3	6.7 ± 9.7
0-96	60.8 ± 1.4	32.8 ± 1.5	59.5 ± 3.2	40.6 ± 2.5
Female				
0-24	59.6 ± 2.7	24.3 ± 7.6	42.7 ± 3.8	6.2 ± 5.7
0-96'	64.5 ± 4.4	30.8 ± 3.5	62.3 ± 5.4	40.4 ± 6.5

Percent of Radioactivity Excreted in Bile Duct Cannulated Rats Over 0-2; hr Post Dose (n=3)				
Dose Level	Sex (M/F)	Urine	Feces	Bile
Low Dose	M	42.3 ± 27.9	7.9 ± 7.0	43.4 ± 24.0
	F	30.0 ± 3.5	21.4 ± 2.7	44.1 ± 2.3
High Dose	M	20.8 ± 8.6	13.8 ± 6.0	43.3 ± 11.5
	F	22.4 ± 5.8	10.1 ± 5.5	40.1 ± 10.0

Pantoprazole was extensively metabolized in rats generating — metabolites.

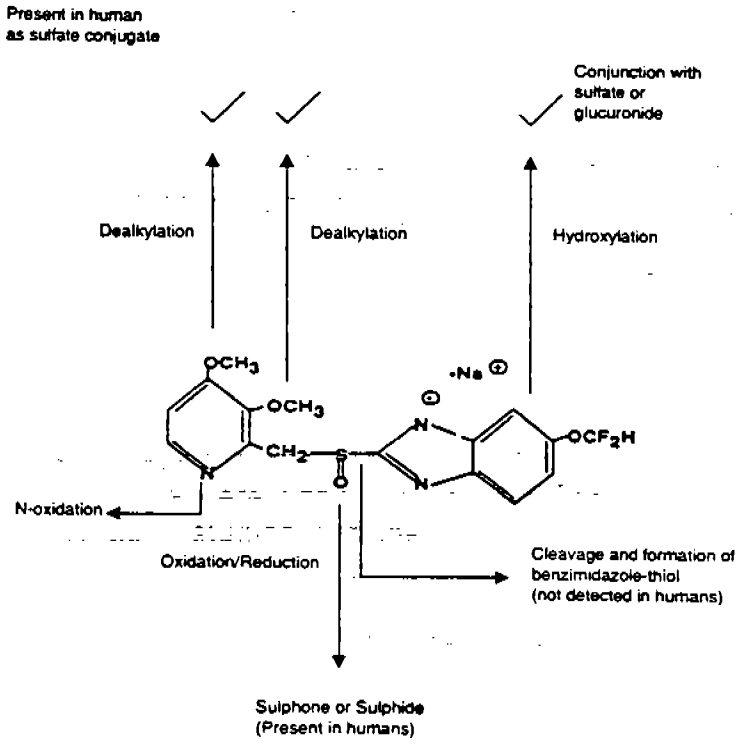
Urinary Metabolites: Greater than 95% of urinary radioactivity was excreted within the first 48 hr after dosing. Twenty-four metabolites of ^{14}C-pantoprazole were detected and structural data was acquired for 21 of these compounds. Most products were relatively minor, each accounting for < 5% of the administered dose. Primary routes of biotransformation for metabolites observed in urine were hydroxylation of the benzimidazole ring and demethylation of either of the two methoxy groups on the pyridyl ring. Subsequent conjugation with sulfation or glucuronidation occurred. The number of metabolites detected was further increased by simultaneous oxidation or reduction of the sulfoxide group to either the sulfone or sulfide oxidation states. Hydroxylated metabolites were all conjugated and included: RU12, RU15-21, and RU34. Metabolites conjugated with glucuronide were RU12, RU16, RU17, and RU19. Metabolites conjugated with sulfate were RU15, RU18, RU20, RU21, and RU34. ^{14}C-pantoprazole was susceptible to cleavage, through a minor route, yielding metabolites that had lost the benzimidazole ring and the radiolabel (these metabolites were not quantified).

Plasma Metabolites: Unchanged pantoprazole and its sulfone metabolite (RP24) were the major circulating drug-related compounds at 500 mg/kg. Unchanged pantoprazole and RU28, the sulfate conjugate of the 3-demethylated sulfide of pantoprazole were the major circulating metabolites at 5 mg/kg. RP20 (sulfated hydroxylated pantoprazole) and RP21 (sulfated hydroxylated sulfide of pantoprazole) were the only hydoxylated metabolites observed in the plasma. Six sulfated metabolites were observed in the plasma, which included RP6, RP20, RP21, RP23, RP26, and RP28. No glucuronide conjugates were found in the plasma. Cleavage of pantoprazole was detected with the formation of RP29 (the benzimidazole methyl-sulfoxide) and RP30 (the benzimidazole methyl-sulfone) and corresponding non-radiolabeled metabolites (RP42 and RP43).

Fecal Metabolites: Fecal elimination of pantoprazole and its metabolites constituted 30-40% of the administered oral dose. No conjugates were detected in the feces and all metabolites found had been reduced to the sulfide oxidation state. Major drug-related compounds found in the feces included unchanged pantoprazole and RF25 (the hydroxylated benzimidazole sulfide of pantoprazole), which comprised approximately 16% of the administered oral dose. RF (4-demethylated RP25) was found at 8% of the administered dose. At 5 mg/kg, a major metabolite was RF33, which constituted 9% of the dose and not been structurally identified.

Bile Metabolites: In bile duct-cannulated rats, approximately 40-44% of the administered dose was eliminated in the bile during the first 24 hr. Eighteen metabolites were identified and 16 were structurally identified. Nine metabolites were hydroxylated on the benzimidazole ring, which included: RB-12, RB15-17, RB19-21, RB38, and RB41. Fifteen of the metabolites were conjugated with glucuronide or sulfate. Glucuronide conjugates included RB5, RB12, RB16, RB17, RB19, RB36, and RB39-41. Sulfate conjugates included RB6, RB15, RB20, RB21, and RB38. There was one acetyl cysteine conjugate, RB9.

Routes of pantoprazole metabolism in rats and dogs.



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The Metabolism of ^{14}C-Pantoprazole in the Rat After a Single Administration (GTR-31202).

Methods: The metabolism of pantoprazole was studied quantitatively by ——— in plasma, urine and feces from male rats (n=5-6) following single I.V. administration of ^{14}C-pantoprazole (5 mg/kg) or after oral administration of ^{14}C-pantoprazole (5, 50 or 500 mg/kg).

Results: Following I.V. administration (5 mg/kg), parent compound and sulfone (B8610-14/ 97167) and two other polar component were present in plasma. After oral dosing, parent compound, sulfone (96167), sulfide (96166) and unidentified polar metabolites were present. According to sponsor, 96165 (thiol) was detected in plasma following oral dose of pantoprazole at 5 mg/kg. However, such data was not submitted. No parent compound was detected in the urine and feces. Urine samples up to 24 hr after dosing, consisted of 8 drug-related compounds when examined by ———; however, the

majority of radioactivity was found at the origin, suggesting the presence of polar compounds. No unchanged drug or sulfide were found. Only traces of benzimidazolethiol were found. Identified compounds included the desmethylhydoxylated sulfide (B8710-42) found as the conjugate or the hydroxysulfate (B8710-47). Treatment of urine samples collected after intravenous administration with β-glucuronidase indicated the presence of several compounds (i.e., M8, M12, B8710-42, B8710-47, and M-17) conjugated with glucuronide. Treatment of urine samples collected after oral administration with β-glucuronidase indicated the presence of glucuronides and sulfates (M12 and B8710-47). In fecal extracts, 8 metabolites were detected after drug administration. Main metabolites were the desmethylhydoxylated sulfide, sulfide, hydroxysulfide, M12 (unidentified), and polar compound(s).

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Metabolism of [^{14}C-Pyridyl] Pantoprazole in Rats After a Single Oral or I.V. Dose (5 mg/kg) (GTR-31325).

Methods: Male rats were given a single oral or I.V. dose of ^{14}C-pantoprazole (5 mg/kg). Blood samples were collected by cardiac puncture at 5 min, 30 min, 1, 2, 4, 8 and 24 hours after drug administration. Five rats per time point were used. Urine samples were collected during 0-4 hr and 4-10 hr after drug administration. Fecal samples were also collected over 0-24 hr and 24-48 hr after drug administration. Parent drug and its metabolites were identified by ——————— methods.

Results: Results were similar after oral and I.V. administration of the drug. In plasma, as a function of time, pantoprazole levels decreased along with a simultaneous increase in the sulfone derivative. Apart from polar peak (and M5) two additional minor metabolites (M64 and M65) were identified, which were not seen when pantoprazole labeled at 2-position of benzimidazole ring was used in other studies, suggesting the cleavage of the parent drug molecule. M64 was also seen in urine sample. Desmethylhydroxylated sulfide (B8710-42) and hydroxysulfide (B8710-47) free as well as conjugated metabolites were also seen in urine and feces. In addition sulfide metabolite was also detected in feces. Irrespective of route of administration no parent drug was seen in urine or feces.

Percent of Dose (Radioactive Bands) Excreted in Urine and Feces During 0-24 hr.				
	Urine		Feces	
Metabolites	I.V.	P.O.	I.V.	P.O.
Polar metabolites	14.8	7.4	8.1	7.3
M5	1.3	4.3	--	--
M10	8.7	--	4.9	3.3
BB710-42	4.3	3.9	10.0	7.7
M33	3.0	1.2	--	--
BB710-47	5.9	5.0	6.1	9.2
M64	3.2	1.7	--	--
Sulfide	1.6	0.6	4.9	5.5

The Metabolism of 14C-Pantoprazole in Rat and Dog (GTR-31201).

Methods: The metabolism of ^{14}C-pantoprazole was examined in male Sprague Dawley and Wistar rats following intravenous administration of 5 mg/kg or in male beagle dogs following either intravenous or oral administration of 10 mg/kg. Radiolabel was located at the C-2 position of the benzimidazole ring. Urine and fecal samples were collected from male Sprague Dawley rats. Blood for determination of plasma metabolites was collected from male Wistar rats by cardiac puncture. Metabolites in plasma, urine, and feces were identified by

Results: Radiolabeled metabolites identified in plasma and fecal extracts from dogs and rats were similar.

1. Metabolism in Dogs:

Plasma: Pantoprazole and its metabolites were characterized at 1, 2, and 4 hr after intravenous or oral administration. The two major component identified in plasma were unchanged pantoprazole and the sulfone (—— 97167).

Feces: Fecal elimination is main route of excretion in dogs. Fecal extracts up to 72 hr after drug administration consisted primarily of 2 or 3 components identified as the sulfide (—— 97166, peak 1), hydxoysulfide (peak 2), and desmethylsulfide (peak 1). No unchanged pantoprazole was found.

[ ]

Urine: Following intravenous or oral administration, 10-12 drug-related peaks were evident in radiochromatograms. No unchanged pantoprazole was found. Metabolites that were identified consisted primarily of glucuronide conjugates.

2. Metabolites in Rats:

Plasma: At 5 min after dosing, the major components were pantoprazole and the sulfone metabolite (—— 97167). By 1 hr after dosing, the major component was —— 97167 as levels of unchanged drug had significantly declined. Another unidentified component was also present.

Urine: Urinary elimination is the primary route of excretion in rats. With samples up to 24 hr after dosing, 10-12 drug-related peaks were observed. No unchanged pantoprazole was observed. Compounds identified included the N-acetyl cysteine conjugate of the benzimidazole function of pantoprazole and products of desmethylation and N-oxidation.

Feces: Fecal extracts from 0-24 hr after dosing, were found to contain 5 to 7 drug-related peaks. No unchanged pantoprazole was found. The major metabolite was desmethylsulfide, which was also observed in dogs. Another component was hydroxysulfide, which was also observed in dogs. Two other components included desmethylated sulfide (or desmethyl —— 96022) and a N-oxide sulfone.

Metabolic Fate of ^{14}C-Pantoprazole [Labelled at 2-Position of Benzimidazole Ring] in Dogs After an Oral Dose of 10 or 100 mg/kg (GTR-31316).

Methods: Beagle dogs (n=3/sex/dose) were given a single oral (gavage) dose of ^{14}C-pantoprazole (labeled at 2-position of the benzimidazole ring, 10 mg/kg). When dogs were given 100 mg/kg of ^{14}C -pantoprazole then emesis occurred in all dogs within 3 hr of the dose, therefore, high dose study was terminated. Urine samples were collected at 0-8, 8-24 hour, and then every 24 hour intervals through 96 hr. Feces were collected every 24 hr for up to 96 hours. Blood samples were collected from the cephalic vein at 1, 3, and 6 hours after drug administration. Total radioactivity and metabolic profile were determined by —

Results: In males, about 22% and 56% of the administered dose were excreted in urine and feces, respectively. In females, about 39% and 50% of the administered dose were excreted in urine and feces, respectively. Most of urinary excretion occurred during the first 24 hr after drug administration and most of the fecal excretion took place during 0-48 hours after drug administration. ^{14}C-pantoprazole was metabolized to >24 products in dogs. Metabolites identified in the plasma, urine, and feces demonstrated that metabolism occurred through oxidation (hydroxylation and/or demethylation) and conjugative pathways (sulfation and glucuronidation). Hydroxylation was restricted to benzimidazole ring. Demethylation occurred primarily at the 4-position on the pyridyl ring. In plasma, unchanged drug and its sulfone metabolite (DP24) were the major circulating species, and concentrations of parent drug decreased with time along with concomitantly increase of DP24 levels. At 6 hr, DP27 (benzimidazole thiourea metabolite) was the second most abundant circulating metabolite (9-22% of the dose). About 20 urinary radiometabolites were detected and structures of 11 were characterized. Most of the metabolites accounted for <5% of the administered dose. In urine, the levels of parent drug was minimal (about 0.1-0.4% of the dose). In feces, no conjugated metabolites were seen. The major metabolite in the feces was the 4-demethylated sulfide metabolite (DF7), which constituted 12% of the oral dose. Unchanged parent drug and the 6-hydroxylated (benzimidazole) sulfide metabolite (DF25) constituted 10% of the oral dose. The fecal metabolites that were identified, had been reduced to the sulfide oxidation state. There were no significant qualitative differences in the biotransformation of ^{14}C-pantoprazole between male and female dogs.

Excretion

Mouse

Excretion of Radioactivity in Mice After Oral Administration of ^{14}C-Pantoprazole [Labelled at 2-Position of Benzimidazole Ring] (GTR-31315).

Methods: Male and female NMRI mice (2-4 mice/sex/group) were given a single oral (gavage) dose of ^{14}C-pantoprazole at 5, 25 or 125 mg/kg. Urine and feces samples were collected over periods of 24 hr for up to 96 hours after drug administration. Total radioactivity in each sample was measured by

Results: Urinary excretion from 0-96 hr at doses of 5, 25 and 125 mg/kg was approximately 34%, 30% and 34% of the administered radioactivity, respectively. Fecal excretion from 0-96 hr at doses of 5, 25 and 125 mg/kg was approximately 54%, 41% and 38% of the administered dose, respectively. Most of the excretion (urinary and fecal) occurred during the 0-24 hour period after the drug administration. No sex differences were evident with respect to excretion pattern. However, at the high dose (125 mg/kg), fecal excretion was significantly lower than that seen at the other two dose levels.

Rat

Pharmacokinetic Investigation of Pantoprazole in the Rat: ^{14}C-Kinetics in Blood and Balance Excretion After Oral Dosing (GTR-31196).

Methods: Pharmacokinetics and excretion of ^{14}C-pantoprazole were examined in male Sprague Dawley rats following oral administration of 5, 50, or 500 mg/kg. Radiolabel was located at the C-2 position of the benzimidazole ring. There were 5-6 male rats per dose. Blood for determination of plasma radioactivity was collected at time points ranging from 0.25 to 168 hr after dosing. Urine and feces were collected separately in intervals from 0 to 168 hr after dosing. At 168 hr after dosing, animals were sacrificed and organs were collected as follows: brain, thymus, spleen, adrenal glands, heart, lungs, kidneys, liver, stomach, and skin. Erythrocytes were isolated from blood at 168 hr after dosing. Samples were processed and radioactivity contents were measured by ———

Results: C_{max} values for plasma radioactivity increased in a manner proportional to ascending dose. However, AUC values for total radioactivity increased with ascending dose, but increases were greater than proportional to dose. Half-life values were prolonged to > 215 hr due to association of radioactivity with red blood cells. Radioactivity was primarily excreted in the feces (53-59%) with lesser amounts in the urine (39-46%). For doses of 5 and 50 mg/kg, 88-95% of the radioactive was excreted in the first 24 hr; however, for 500 mg/kg, 95% of the radioactive was excreted in the first 48 hr. At 168 hr after dosing, significant levels of radioactivity were still associated with the skin/hair shafts and erythrocytes.

Pharmacokinetics parameters for plasma radioactivity in rats that received ^{14}C-pantoprazole by the oral route at doses of 5, 50, and 500 mg/kg.

Dose, mg/kg	C_{max}, mg/L	$AUC_{0-\infty}$, mg*hr/L	T_{max}, hr	T½, hr
5	2.65	139.5	———	221
50	35.1	2634	———	215
500	297	55867	———	256

Percentage of total radioactivity excreted in the urine and feces from 0-168 hr by rats that received ^{14}C-pantoprazole by the oral route at doses of 5, 50, and 500 mg/kg.

Route	5 mg/kg	50 mg/kg	150 mg/kg
Urine	54	59	53
Feces	39	41	46
Total	93	99	99

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Pharmacokinetic Investigation of Pantoprazole in the Rat: ^{14}C-Kinetics in Blood and Balance Excretion After Multiple Oral Administration (GTR-31196).

Methods: Pharmacokinetics and excretion of pantoprazole were examined in male Sprague Dawley rats following oral administration of 5 or 500 mg/kg/day for 8 days. On days 1 and 8 rats received ^{14}C-pantoprazole. Radiolabel was located at the C-2 position of the benzimidazole ring. On days 2-7, rats received unlabeled drug. There were 4 male rats per dose. On days 1 and 8, blood for determination of plasma radioactivity was collected at time points ranging from 0.25 to 72 hr after dosing. On days 1 and 8, urine and feces were collected separately in intervals from 0 to 72 hr after dosing. Samples were processed and radioactivity contents were measured by ———

Results: C_{max} values for plasma radioactivity increased in a manner proportional to ascending dose. C_{max} values on day 8 were approximately two-fold greater than those observed on day 1. AUC values on days 1 and 8 for plasma radioactivity increased with ascending dose, but increases were greater than proportional to dose. AUC values on days 1 and 8 were relatively similar. Half-life values were prolonged to > 67 hr on days 1 and 8 due to association of radioactivity with red blood cells. For a dose of 5 mg/kg/day on days 1 or 8, excretion of radioactivity in the urine and feces were approximately equal. For a dose of 500 mg/kg/day on day 1, excretion of radioactivity in the urine was greater than that observed in the feces; however, on day 8, excretion of radioactivity in the urine and feces were approximately equal. The sponsor attributed differences in excretion for rats at 500 mg/kg/day on days 1 and 8 to acclimatization to metabolic cages rather than enzyme induction or changes in metabolism.

Pharmacokinetics parameters for plasma radioactivity on days 1 and 8 in rats that received ^{14}C-pantoprazole by the oral route at doses of 5 or 500 mg/kg.

Dose, mg/kg/day	AUC, mg*hr/L		C_{max}, mg/L		T_{max}, hr		T½, hr	
	Day 1	Day 8	Day 1	Day 8	Day 1	Day 8	Day 1	Day 8
5	102.7	80.65	2.3	4.5	—	—	173	67
500	18363	17969	172	309	—	—	89	91

Percentage of total radioactivity excreted in the urine and feces on days 1 and 8 from 0-72 hr after dosing by rats that received ^{14}C-pantoprazole by the oral route at doses of 5 or 500 mg/kg.

Route	5 mg/kg/day		50 mg/kg/day	
	Day 1	Day 8	Day 1	Day 8
Urine	50	44	69	48
Feces	46	57	26	47
Total	95	100	96	94

([^{14}C-Pyridyl)-Pantoprazole in the Rat: Balance, Excretion, and Pharmacokinetic Study Following Oral and Intravenous Administration (GTR-31310).

Methods: Male rats (n=6) were given a single oral (gavage) or I.V. dose of 5 mg/kg of radiolabelled pantoprazole (^{14}C at the pyridyl moiety of the molecule). Blood samples were collected from tail vein at pre-dose, 5 (only after I.V. dose), 15, 30 min, 1, 2, 4, 6, 8, 10, 24, 48, 56, 72, 96, 120, 144 and 168 hours after drug administration. Urine samples were collected over the periods of 0-2, 2-4, 4-6, 6-8, 8-10, 10-24, 24-32, 32-48, 48-56, 56-72, 72-96, 96-120, 120-144 and 144-168 hours after drug administration. Feces were collected every 24 hr for up to 168 hours after drug administration. In all samples, total radioactivity was measured by ———— Levels of unchanged drug and its sulfone derivative were also monitored as a function of time (0.08, 0.5, 1, 2, 4, 8 and 24 hr) in rats plasma.

Results: About 53% and 46% of the administered radioactivity were excreted in urine and feces respectively during 0-168 hr after I.V. administration of the drug. After oral administration of the drug about 33% and 59% of the administered radioactivity was excreted in urine and feces respectively. Irrespective of route of administration, most of the excretion (urine and feces) occurred during 0-24 hr after drug administration (92.5% post I.V. and 86.50% post oral). After oral dose, about 59% of the radioactivity was absorbed (T_{max} = ————). The T½ beta for radioactivity from plasma were 32.2 hr and 24.9 hr for I.V. and oral doses, respectively. In plasma, levels of unchanged drug declined as a function of time while levels of sulfone increased concomitantly.

Pharmacokinetics of ^{14}C-Pantoprazole (radioactivity) in Rats Plasma Single Dose (5 mg/kg)[1]

Parameters	I.V.	Oral
$t_{1/2}$ alpha (hr)	2.3	2.9
$t_{1/2}$ beta (hr)	32.2	24.9
T_{max} (hr)	--	————
Cl_{plasma} (L/h/kg)	0.124	--
AUC_{0-inf} (mg.hr/2)	39.07	23.07
Bioavailability (%)	--	59

1 = results are mean of 6 rats, no SD was provided by the sponsor

Pharmacokinetic Investigation of Pantoprazole in the Rat: ^{14}C-Kinetics in Blood and Balance Excretion Profile After Intravenous Dosing (GTR-31218).

Methods: Pharmacokinetics and excretion of ^{14}C-pantoprazole were examined in male Sprague Dawley rats following intravenous administration of 5 mg/kg. Radiolabel was located at the C-2 position of the benzimidazole ring. There were 6 male rats per dose. Blood for determination of plasma radioactivity was collected at time points ranging from 0.08 to 168 hr after dosing. Urine and feces were collected separately in intervals from 0 to 168 hr after dosing. At 168 hr after dosing, animals were sacrificed and organs were collected as follows: brain, lungs, heart, liver, spleen, kidneys, adrenal glands, thyroid gland, skin/hair shafts, erythrocytes, gastrointestinal tract, (stomach, small and large intestine). Samples were processed and radioactivity contents were measured by ————

Results: Pharmacokinetic parameters for plasma radioactivity were as follows: $AUC_{0-\infty}$ = 433.8 mg*hr/L; V_d = 4.516 L/kg; Cl = 0.011 L/hr/kg; and T½ = 268.9 hr. The volume of distribution exceeded blood volume (0.054 L/kg) suggesting extensive distribution of radioactivity into tissues. Clearance was significantly lower than hepatic (1.914 L/hr/kg) or renal (1.28 L/hr/kg) plasma flow. The prolonged half-life was due to the association of radioactivity with erythrocytes. Elimination of radioactivity into the urine (62.4%) was the primary route of excretion as compared to feces (36.9%). At 168 hr after dosing, significant levels of radioactivity were still associated with erythrocytes and the skin/hair shafts.

Biliary Excretion and Metabolism of [^{14}C-Benzimidazole]-Pantoprazole in Rats (GTR-31328).

Methods: Bile cannulated male rats (6=group) were given a single intravenous or intraduodenal dose of ^{14}C-pantoprazole (labeled at 2-position of benzimidazole ring, 5 mg/kg). Bile samples were collected at 30 min intervals up to 8 hr after drug administration. Total radioactivity in each sample was measured by ——— If possible unchanged drug and metabolites were also identified by ———

Results: Within 8 hr after drug administration, about 65% and 46% of the administered dose were excreted in the bile following intravenous or intraduodenal doses, respectively. Drug was rapidly metabolized and no parent drug was seen in the bile. The data also indicates that there was an incomplete absorption of the drug via intraduodenal route. It should also be noted that no benzimidazole-thiol metabolite was seen in the bile.

Dog

^{14}C-Pantoprazole Balance Excretion and Pharmacokinetic Study in the Male Beagle Dog Following Oral and Intravenous Administration at Target Dose Level of 10 mg/kg (GTR-31191).

Methods: The pharmacokinetics and excretion of radioactivity were examined in 4 male beagle dogs following oral or intravenous administration of ^{14}C-pantoprazole at a dose of 10 mg/kg. Radiolabel was located at the C-2 position of the benzimidazole ring. There was a 3-month period between intravenous and oral phases of the study. Blood samples were collected at time points up to 168 hr after dosing. Urine and feces were collected separately at intervals up to 168 hr after dosing. Samples were processed and radioactivity levels were determined by —— Plasma samples were assayed simultaneously for pantoprazole and its sulfone (—— 97167, B8610-14) by ———

Results: Following oral or intravenous administration of ^{14}C-pantoprazole to male beagle dogs, radioactivity was primarily eliminated in the feces (53.6-65.0%) as compared to the urine (28.9-53.6%). The mean bioavailability of pantoprazole following oral administration was 49%. Pharmacokinetic parameters for plasma radioactivity were not provided.

Percent of total radioactivity excreted into urine and feces from 0-168 hr after dosing by male beagle dogs that received ^{14}C-pantoprazole by the oral or intravenous route at 10 mg/kg.

Route	Oral	Intravenous
Urine	28.9	35.0
Feces	65.0	53.6
Total	94.2	89.8

Pharmacokinetic parameters for plasma pantoprazole and its sulfone metabolite following intravenous or oral administration of pantoprazole to male beagle dogs at a dose of 10 mg/kg.

Route	$AUC_{0-\infty}$ µmol*hr/L		C_{max}, µmol/L		T_{max}, hr		T½, hr		Bioavail, %
	Panto	Sulfone	Panto	Sulfone	Panto	Sulfone	Panto	Sulfone	Panto
IV	86.73	101.5	69	11	[redacted]		0.63	5.7	-
Oral	46.45	74.975	26	8	[redacted]		0.83	4.3	49

Monkey

Pantoprazole : (^{14}C)-B8610-023: A Study of Absorption, Distribution, and Excretion Following Oral and Intravenous Administration to the Cynomolgus Monkey (GTR-31549).

Methods: The absorption, distribution, and excretion of pantoprazole were examined in cynomolgus monkeys. Four (2 male and 2 female) captive-bred cynomolgus monkeys (Macaca fascicularis) were used for these studies. For oral and intravenous administration studies, ^{14}C-pantoprazole was administered at dose of 5 mg/kg. For oral administration studies, 5 mL of a 0.1 M sodium bicarbonate was administered by oral gavage at 2 min prior to dosing and at 10, 20, and 30 min after dosing in order to maintain a high gastric pH to protect acid labile pantoprazole from premature degradation. For excretion studies, monkeys were transferred to metabolism cages. Urine samples were collected as follows: 0-12 hr, 12-24 hr, and 24 hr intervals from 24-168 hr post-dosing. Feces were collected in 24-hr intervals from 0-168 hr post-dosing. Cage debris and cage washings were pooled separately for each animal over the 168-hr collection period. Radioactivity in urine, cage washings, feces, cage debris, and tissue swabs was determined by [redacted] At the end of the collection period, animals were swabbed to collect any radioactivity associated with body surfaces.

Results: Following oral or intravenous administration of pantoprazole, the principal route of elimination was renal excretion. Following oral administration, renal and fecal elimination were > 90% complete by 48 and 72 hr after dosing, respectively. Following intravenous administration, renal and fecal elimination were > 90% complete by 24 and 48 hr after dosing, respectively. Excretion of radioactivity was similar between male and female monkeys.

Excretion of radioactivity in cynomolgus monkeys following a single oral or intravenous administration of ^{14}C-Pantoprazole at a dose of 5 mg/kg.

Excreta	Percent of Administered Dose			
	Oral Administration		Intravenous Administration	
	Male	Female	Male	Female
Urine	42.47	40.36	32.58	35.58
Feces	15.28	17.28	12.47	18.66
Cagewash	14.53	12.57	23.79	18.31
Cage Debris	3.645	5.306	2.303	1.414
Final Cagewash	0.715	0.920	2.104	1.521
Body Wash	1.181	0.700	1.016	2.261
Total	77.82	77.14	74.26	77.74

The absorption, distribution, metabolism, and excretion of pantoprazole were examined in mice, rats, dogs, and monkeys. Pharmacokinetic studies in mice, rats, dogs, and cynomolgus monkeys that received pantoprazole (radiolabeled in the benzimidazole ring or adjacent to the pyridyl ring for several studies) by the intravenous or oral route found that plasma C_{max} and AUC values for total radioactivity and/or the parent drug increased with increasing dose, although, generally not in a dose-proportional manner. C_{max} and AUC values for unchanged drug in mice, rats, dogs, and monkeys encompassed values observed in healthy human volunteers that received pantoprazole at a therapeutic dose of 40 mg/kg (equivalent to 0.8 mg/kg for a 50 kg person). Plasma AUC values for unchanged drug following a single oral administration of pantoprazole were as follows: $B6C3F_1$ mice that received doses from 25 to 150 mg/kg were observed with values ranging from ——— μg*hr/mL; Sprague Dawley rats that received doses from 5 to 1200 mg/kg were observed with values ranging from ——— μg*hr/mL; Fischer rats that received doses from 5 to 50 mg/kg were observed with values ranging from ——— μg*hr/mL, beagle dogs were that received doses of 7.5 to 100 mg/kg were observed with values ranging from ——— μg*hr/mL, and cynomolgus monkeys that received a dose of 5 mg/kg were observed with a value of 0.46 μg*hr/mL. Plasma AUC values for unchanged drug in healthy human male volunteers, who received a therapeutic dose of pantoprazole at 40 mg/day by the oral route ranged from ——— μg*hr/mL. Plasma AUC values for the parent compound were found to represent a small fraction of the total radioactivity suggesting extensive metabolism. Pantoprazole appeared to undergo extensive first pass metabolism and rapid elimination and bioavailability values displayed high variability. Bioavailability of total radioactivity and parent drug following oral administration of pantoprazole to rats at 5 mg/kg were 66 and 31%, respectively. Bioavailability of parent drug in dogs following an oral dose of 60 mg/kg was 44%. Bioavailability of total radioactivity and parent drug following oral administration of 5 mg/kg pantoprazole to cynomolgus monkeys were 51.77 and 3.5%, respectively. The half-lives of the parent compound in most species were generally < 1 hr. For studies with pantoprazole in healthy human male volunteers, bioavailability of an oral therapeutic dose at 40 mg/day ranged from ——— For humans, little acid degradation of the drug occurred in the stomach and there was a low hepatic first-pass effect. The half-life of pantoprazole following oral or intravenous administration to human volunteers was approximately 1 hr. Non-linear toxicokinetics of pantoprazole may be due to reduced absorption at higher dose levels (i.e., dissolution rate limited absorption) or increased first-pass metabolism of pantoprazole. Pantoprazole [(±)-PAN] is a chiral sulfoxide. Following

oral or intravenous administration of (+)-PAN to rats, there was significant chiral interconversion to form (-)-PAN; however, no interconversion was found following administration of (-)-PAN. Pantoprazole binding with rat and human serum protein exceeded 95%. Binding with dog serum protein was lower at 80-90%. ——— studies with rats that received pantoprazole, with ^{14}C-label located at the C-2 position of the benzimidazole ring, by the oral or intravenous route, found that radioactivity was widely distributed following administration and peak concentrations of radioactivity were generally found in all tissue at 1 hr after dosing. Plasma concentrations declined over time; however, radioactivity levels in whole blood remained relatively constant from 24 to 96 hr after dosing due to association of radiolabeled material with red blood cells. The liver and kidney appeared to be excretory organs. In ——— studies, using pantoprazole with ^{14}C-label adjacent to the pyridyl ring, results were similar; however, binding with erythrocytes was not evident due to loss of the radiolabel. This experiment indicated that the benzimidazole moiety and not the pyridyl ring of pantoprazole was responsible for binding to cellular component(s) of red blood cells. Studies using pregnant female rat that received ^{14}C-pantoprazole indicated that drug or its metabolites crossed the placenta and fetal retention of radioactivity increased as the pregnancy progressed. Studies using lactating female rats that received ^{14}C-pantoprazole, found radioactivity in milk collected from suckling neonates. Proton pump inhibitors, such as pantoprazole, undergo extensive metabolism by cytochrome P450 as well as induce the activities of specific isozymes and inhibit the metabolism of other substrates (i.e., drugs). Using human liver microsomes fractions, it was found that pantoprazole was mainly metabolized by CYP2C19 and CYP3A4 isozymes of cytochrome P450, but very little metabolism was carried out by CYP2D6 isozyme. Other studies suggested that P450 isozymes, 2D6 and 2C9-10, also appeared to play roles in biotransformation. For female rats treated with pantoprazole, hepatic content of cytochrome P450, cytochrome b5, and NADPH-cytochrome C reductase were increased and induction of P450 isozyme activities was determined to be of the phenobarbital-type; although, it was 0.025 times as potent as phenobarbital on a molar basis. Pantoprazole acted as a specific inducer of isoforms, CYP2B1 and CYP2B2. No evidence of liver peroxisomal proliferation activity was evident. The thiol metabolite of pantoprazole had no effect on phase I (P450-dependent mixed-function oxidase) activities in rats; however, the thiol metabolite as well as pantoprazole significantly induced hepatic drug metabolizing enzyme activities which catalyze conjugation reactions (Phase II reactions: UDPGT- and glutathione S-transferase activities). The potency of pantoprazole with regard to phase II reactions was ≤ 50% of phenobarbital on molar basis, while potency of the thiol was equivalent to phenobarbital. For female rats treated with pantoprazole at 200 mg/kg/day for 4-weeks, there were no significant changes in T_3, T_4 and TSH levels even though UDPGT activity was induced. For mice, urinary and fecal excretion accounted for 30-34% and 38-50% of the elimination of drug-related compounds. For rats, about 60% and 40% of administered radioactivity were excreted in urine and feces, respectively. For dogs, 22-39% and 50-56% of the administered oral dose were excreted in urine and feces, respectively. For cynomolgus monkeys, the principal route of elimination was renal excretion. Following oral or intravenous administration of drug to human volunteers, urinary excretion accounted for ≤ 90% of drug-related compounds, while fecal excretion accounted for ≤ 18%. For bile duct-cannulated rats, about 40-44% of the administered radioactivity was excreted in the bile. The total number of drug-related compounds detected in rats and dogs were 31 and >24, respectively. Unchanged parent drug and the sulfone metabolite

— 97167) were the major circulating drug-related compounds detected in plasma for rats and dogs. The thiol metabolite — 97165), associated with pulmonary toxicity was also detected in rat and dog plasma at low levels. The number of urinary radiometabolites detected in rats and dogs were 24 and 10-20, respectively, with each metabolite generally accounting for <5% of the administered dose. The primary routes of biotransformation for metabolites observed in urine for rats and dogs were hydroxylation of the benzimidazole ring and demethylation of either of the two methoxy groups on the pyridyl ring. Subsequent conjugation with sulfation or glucuronidation occurred. The number of metabolites detected was further increased by simultaneous oxidation or reduction of the sulfoxide group to either the sulfone or sulfide oxidation states. Feces collected from rats were found to contain no conjugated metabolites, as expected, and all metabolites had been reduced to the sulfide oxidation state. The main identified metabolites in the feces were the desmethylhydoxylated sulfide, sulfide, and hydroxysulfide. Fecal elimination was the main route of excretion in dogs, and major components in fecal extracts were identified as the sulfide — 97166), hydroxysulfide, and desmethylsulfide. For rats, 18 metabolites were detected in the bile. Metabolites of pantoprazole undergo enterohepatic recycling. Four major metabolites of pantoprazole have been identified in human plasma. Three of these compounds designated as M1, M2, and M3 are sulfate conjugates of pantoprazole at the 4-position of the pyridine ring, which has been metabolically O-demethylated. M2 is a sulfoxide similarly to pantoprazole, whereas for M1 and M3, the sulfoxide group has been oxidized or reduced to the corresponding sulfone or sulfide, respectively. M2 is the predominant metabolite observed in the plasma. A minimum of 10 urinary radiometabolites were observed in humans, which accounted for 46-67% of the administered dose. Unchanged pantoprazole was not observed. Based upon metabolites observed in the urine, the major pathway of pantoprazole metabolism was p-O-desmethylation on the pyridine ring moiety followed by sulfation or glucuronidation. Both reduction to the sulfide and oxidation to the corresponding sulfone were also observed with and without subsequent conjugation. Two major metabolites were observed in fecal extracts. Metabolism of pantoprazole in healthy human male volunteers appears to occur through many of the same pathways observed in rats and dogs.

Plasma pharmacokinetic parameters of pantoprazole in $B6C3F_1$ mice, Sprague Dawley rats, Fischer rats, Beagle dogs, and Cynomolgus monkeys following oral or intravenous administration of drug. Results from male and female animals were averaged together.

Species and Route	Dose, mg/kg/day	AUC, μg*hr/mL	C_{max} μg/mL	T_{max}, hr	T½, hr	CL, L/hr/kg	Vd L/kg
$B6C3F_1$ Mouse-PO	25	35.35	15.25	0.25	-	-	-
	150	114.5	61.3	0.375	8.15	-	-
SD rat-PO	50	36.5	26.033	0.33	0.8	-	-
	300	91.7	62.394	0.25	2.2	-	-
	600	380.9	77.422	0.29	5.2	-	-
	1200	519.3	112.222	0.25	6.7	-	-
SD rat-IV	5	10.72	12.308	extrapolated value	0.47		
Fischer rat-PO	5	1.165	1.64	0.25	0.385	-	-
	15	4.995	4.505	0.25	0.86	-	-
	50	24.525	15.445	0.25	0.96	-	-
Dog-PO	40	3.22	2.12	1.0	0.78	-	-
	160	41.30	22.54	0.50	0.64	-	-
Dog-IV	60	10.63	-	-	0.43	0.554	0.322
Monkey-PO	5	0.46	0.56	0.63	0.48	-	-
Monkey-IV	5	6.88	-	-	0.30	0.737	0.316

Pharmacokinetic parameters of pantoprazole in healthy human male volunteers following oral or intravenous administration of drug.

Route and Dose, mg	Number of Daily Doses	Pantoprazole		Bioavailability, %
		AUC, μg*hr/mL	C_{max}, μg/mL	
IV-40 mg	1	5.42	5.53[A]	-
Oral-40 mg	1	2.562	1.197	47.3
Oral-40 mg (R)	1	2.752	1.390	50.8
Oral-40 mg	1	4.10	2.37	75.6
Oral-40 mg	7	4.92	2.52	90.8

A. Plasma concentration at 15 min after intravenous administration.

TOXICOLOGY:

For toxicology studies, doses were expressed in terms of the free acid except for acute toxicity studies, where doses were expressed in terms of the sodium salt.

Acute Toxicity of Pantoprazole in the Mouse, Rat, and Dog.

Testing Laboratories: Byk Gulden
Konstanz, Germany

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Report Number, Study Start and Completion Dates, and Drug Batch:

Report Number	Animals	Study Started	Study Completed	Drug Batch
GTR-31633	Male NMRI mice	January 1990	March 12, 1990	489065
GTR-31634	Male NMRI mice	January 1990	March 12, 1990	489065
GTR-31635	Female Sprague Dawley Rats	June 1987	April 13, 1992	K23/144
GTR-31636	Female NMRI mice	June 1987	June 15, 1992	K23/144
GTR-31637	Female NMRI mice	June 1987	April 15, 1992	K23/144
GTR-31638	Female Sprague Dawley rats	June 1987	March 31, 1992	K23/144
GTR-31639	Male and Female Sprague Dawley rats	August 1989	January 13, 1990	589085
GTR-31640	Male and Female Sprague Dawley rats	August 1989	January 31, 1990	589085
GTR-32136	Male Sprague Dawley rats	August 1995	May 14, 1996	294160[A] 513150
GTR-31650	Male Sprague Dawley rats	January 1995	August 29, 1995	033927[B] 349235
GTR-31642	Male and Female Beagle Dogs	July 1989	January 30, 1990	589085
GTR-31643	Male and Female Beagle Dogs	July 1989	January 30, 1990	589085

A. Batch No. 294160 = old batch and Batch No. 513150 = new batch
B. Batch No. 033927 = stressed storage batch and Batch No. 349235 = cold storage batch.