

C.6. Local Tolerance and Allergenic Studies

Sponsor Volumes: 1.49-1.54

Summary:

PPX was relatively free of locally irritating or allergenic effects. In rabbits, PPX caused mild ocular effects only after repeated treatment for 4 weeks, and mild irritation of abraded skin after repeated applications. PPX was considered a mild sensitizing agent in guinea pigs. PPX did not induce hemolysis in human blood.

Study Results:

- C.6.a. Rabbit Eye Irritation (single dose)- 0.1g PPX (formulation not specified) into one eye did not produce local ocular irritation.
- C.6.b. Rabbit Eye Irritation (multiple doses) - 0.05, 0.1, 0.25, and 0.5% PPX in 0.1 ml (8 times daily for 3 days) did not produce local ocular irritation (high dose of 0.5% = 0.5 mg/dose).
- C.6.c. Rabbit Eye Irritation (4-week study) - 0.00625, 0.05, and 0.5% in 50 µl applied 6 times daily to the conjunctival sac caused a mild to moderate increase in conjunctival secretion and mild reddening. The effect was not concentration-related.
- C.6.d. Dermal Irritation in Rabbits (single dose) - Topical application of 0.5g/0.5 ml PPX to shaved skin area did not produce irritation, erythema or edema.
- C.6.e. Dermal Irritation in Rabbits (multiple doses) - 0.1g/0.1 ml PPX was applied topically to a shaved intact or a shaved abraded skin area once daily for 5 days. No irritation occurred on the intact area. Mild irritation with erythema and eschar occurred on the abraded area.
- C.6.f. Dermal Irritation in Rabbits (4-week patch application) - Application of a patch containing 10.75 mg PPX free base for 4 weeks to shaved areas caused slight irritation. Irritation was also observed in placebo-treated animals, and thus may have resulted from mechanical trauma due to repeated patch removal and replacement.
- C.6.g. Paravenous Injectable Tolerability in Rats - 0.2 ml of an 0.1% PPX solution was injected medially and laterally to the jugular vein. Slight hemorrhages and edema in the area were observed between 1-24 hr after treatment.
- C.6.h. Acute Intravenous Tolerance in Rabbits - 0.2 ml of an 0.1% PPX solution was injected into the rabbit ear vein. Slight erythemas were observed in 3 of 4 animals, and bluish-red discoloration in 2 of 4 animals within the first few days of administration. Saline injection also caused 2 cases of erythemas.

- C.6.i. Acute Intra-arterial Local Tolerance in Rabbits - 0.5 ml of an 0.1% PPX solution was injected into the rabbit ear central artery. Slight erythemas were observed in 4 of 4 animals, and bluish-red discoloration in 3 of 4 animals. Similar effects were observed in saline-treated controls (2 of 4 cases of erythemas, 3 of 4 cases of discolorations).
- C.6.j. Skin Sensitization in Guinea Pigs - Animals were sensitized by six intradermal injections of 1% PPX free base (0.1 ml) into the dorsal skin. On days 8-10, 12.5 mg PPX was applied to the same area. On day 22, the animals were challenged by application of 12.5 mg PPX to an area of the left flank. A contact dermatitis response was noted in 5 of 20 animals. On day 36, animals were rechallenged with 6.25 mg PPX. Four of 20 animals had an allergic contact dermatitis, but only one of these animals had the reaction previously. Thus, PPX was considered a mild sensitizing reagent.
- C.6.k. Skin Sensitization in Guinea Pigs to Patch Exposure - Animals were sensitized to the PPX patch exposure (contains mg PPX free base) by either nine applications over 3 weeks or 15 applications over 5 weeks (6 hrs per application. Animals were challenged on day 29 and rechallenged on day 43. No allergic contact dermatitis and no primary skin irritations occurred.
- C.6.l. Test for Hemolytic Effect - An 0.1% solution of PPX (HCl) did not induce hemolysis in preparations of citrated human blood.

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D. PHARMACOKINETIC/ADME STUDIES

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1. Rats

- a. Biochemical investigations with [¹⁴C]-SND 919 CL2Y in rats (absorption, distribution, excretion, metabolism).
- b. Whole body autoradiographic studies with SND 919 CL2Y in rats.
- c. Studies on the placental transfer and on the crossing of the blood-brain barrier of [¹⁴C]-SND 919 CL2Y in the rat.
- d. Pramipexole: Steady-state concentrations in brain, liquor, and plasma of male rats after oral administration of 0.5 mg/kg (once per day) over 8 days.
- e. Excretion of [¹⁴C]-SND 919 CL2Y into rat milk after a single oral dose of 0.5 mg/kg.

2. Rabbit

- a. Pharmacokinetics and metabolism [of pramipexole] in the rabbit after intravenous and oral administration of a single dose of 1 mg/kg.

3. Monkeys

- a. Plasma concentrations and renal excretion in Rhesus monkeys after administration of three single intragastric doses (0.1, 0.5 and 1.0 mg/kg) and one intravenous dose (0.5 mg/kg).

4. Humans

- a. Pharmacokinetics and metabolism of [¹⁴C]-pramipexole after single intravenous and oral doses in healthy volunteers.
- b. A single dose tolerance and pharmacokinetic study of intravenous pramipexole in healthy male volunteers.

5. Multiple Species

- a. Balanced excretion studies and metabolic profile following oral administration of [¹⁴C]-SND 919 CL2Y to the mouse, rat, rabbit, dog, monkey and pig.
- b. Studies on the metabolism of pramipexole including experiments to detect a potential metabolic inversion at the optical active center of the molecule.

D.1. Rat Pharmacokinetics

D.1.a. Biochemical investigations with [¹⁴C]-SND 919 CL2Y in rats (absorption, distribution, excretion, metabolism).

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Upjohn TR 7256-94-035

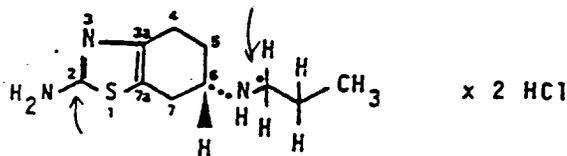
Sponsor Volume: 1.56

Summary:

Radiolabeled PPX was administered to Wistar rats at doses of 0.25 mg/kg i.v. or mg/kg, p.o. Plasma levels and excretion balances were determined. PPX was absorbed rapidly and nearly completely following oral administration. Elimination of radiolabel is relatively slow, and not complete by hr. The parent compound is eliminated primarily by renal excretion, whereas the fecally excreted portion is primarily polar metabolites of biliary origin. Plasma protein binding was relatively low in rat and other species (dog, pig, monkey, man).

Methods:

Substance administered: [¹⁴C]-pramipexole labeled at the 2-position of the thiazole ring, or C1 of the propyl group



* = ¹⁴C labelling

(Active substance carrying the ¹⁴C label in the 2 position of the thiazole ring was used in some preliminary experiments.)

Dosing Regimen:

Study	Dose (mg/kg)	Route of Administration	No. of Animals N	Batch No.*
Exhalation of ¹⁴ CO ₂	0.24	IV	2	1
"	0.6	IV	3	2
"	0.5	IV	2	3
Blood levels	0.4	Oral	10	1
Plasma levels	2.5	IV	5	-
Excretion	0.25	IV	11	1
Excrétion	0.01	Oral	4	1
"	0.1	Oral	4	
"	1.4	Oral	4	
"	10.8	Oral	4	
"	79.1	Oral	4	
Excretion (bile)	0.28	IV	4	3

Parameters measured: exhalation, excretion balance (urine, feces), blood levels, plasma protein binding (different species), biliary excretion, metabolite profiles (urine, feces)

Results:

Exhalation study: With the propyl-C radiolabelled material, 4.6% of an i.v. dose was exhaled as CO₂ during 0-24 hrs postdose. With the thiazole ring-labeled material, less than 1% was eliminated by this route. Thus, the ring-labeled material was used for subsequent studies.

Excretion balance: Average elimination (% dose) during 0-96 hr collection:

		<u>Urine</u>	<u>Feces</u>
intravenous	0.25 mg/kg	52.9	36.5
oral	0.01 "	51.9	28.7
	0.1 "	64.8	38.3
	1.4 "	48.2	41.2
	10.8 "	52.1	29.3
	79.1 "	43.6	25.8

No effect of dose or sex

Biliary Excretion: % of iv dose in 0-24 hr (ca. equivalent to fecal excretion).

PK parameters:

Blood [¹⁴C]-Activity after Oral dosing (0.4 mg/kg)

		AUC (ng.ml/hr)	MRT (hr)	Cl (ml/min)
Single dose	Male	469	9.8	3.9
	Female	581	19.0	3.4
After 3 doses	Male	537	16.0	3.4
	Female	577	14.6	3.5

Parent Compound after IV dosing (2.5 mg/kg)

	AUC (ng.ml/hr)	MRT (hr)	Cl (ml/min)	t _{1/2} (α) (min)	t _{1/2} (β) (hr)	Vd (l)
2m/3f	840	1.5	13	4.0	1.2	1.2

Plasma Protein Binding: Relatively low (%) in all species tested (rat, dog, pig, monkey, man)

Metabolite Profiles:

- Urine: 0-24 hr collection.
Chromatographic profiles are similar irrespective of route, dose and sex.
Parent accounts for % of radioactivity; metabolites are %.
- Bile: 0-6 or 0-12 hr collection.
Parent accounts for $\leq 5\%$ of radioactivity.
9-11 metabolites are present; % are polar.
- Feces: 0-24 hr collection.
Parent accounts for $\leq 5\%$ of radioactivity.
% polar metabolites.

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D.1.b. Whole body autoradiographic studies with SND 919 CL2Y in rats.

Document #(s): BI Document U86-0727
Upjohn TR 7256-95-018

Sponsor Volume: 1.59

Summary:

After i.v. administration of 1.3 mg/kg [¹⁴C]-pramipexole, radioactivity was rapidly distributed. Aside from the gut, the highest tissue concentrations were found in the lacrimal, salivary, and adrenal glands, kidney, pancreas, bone, liver and lung. The significant levels of radioactivity in the small intestine after i.v. administration is indicative of biliary excretion of PPX or its metabolites. Brain levels of radioactivity peaked at 2 hrs, and were detectable up to 6 hrs. At 24 hrs, radioactivity was still detected in liver, kidney, and adrenals.

Two hrs after p.o. administration of 1.3 mg/kg, a similar pattern of distribution was observed, although levels of radioactivity were lower. At 24 hrs, radioactivity was still present in the lacrimal, salivary, adrenal glands, kidney, and liver.

Methods:

Substance administered: [¹⁴C]-pramipexole labeled at the of the propyl group; Batch I, 7400 MBq/g (200 μCi/mg)

Dosages/Routes: 1.3 mg/kg (ca. 1.57 MBq/animal) administered i.v. (tail vein) or p.o.

Animals: Male Chbb:THOM Wistar rats, 150-170 g.

Sacrifice times: i.v.: 10 min, 2, 4, 6, 24 hr
p.o.: 30 min, 2, 4, 6, 24 hr

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Tissue Preparation: Animals were sacrificed, frozen and sectioned for autoradiography by standard techniques. Autoradiogram exposure time was 7 days. Tissue uptake of radioactivity was determined with a microscope photometer; field sections were 100 μm in diameter. Intensities of light penetration, which decrease with uptake of radioactivity, was scored on a scale of 0-7.

Results:

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The following table summarizes the experimental results.

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Tab. 1: Photometric analysis of the whole body autoradiograms after i.v. and p.o. administration of SMD 919 Cl. 2 Y
 0 = maximum transmission = no radioactivity
 7 = minimum transmission = maximum radioactivity

Organ	i.v.					p.o.				
	30'	2 h	4 h	6 h	24 h	30'	2 h	4 h	6 h	24 h
Pancreas	6	4	2	0	0	2	2	0	0	0
Blood	2	1	1	0	0	1	0-1	0	0	0
Brown nuchal fat	4	2	1	0	0	1	2	0	0	0
Contents of large intestine	0	1	7	upto 7	upto 7	0	2	7	upto 7	upto 7
Mucosa of large intestine	4	2	-	0	0	1	0	0	0	0
Contents of small intestine	upto 7	7	upto 7	upto 6	0	upto 7	7	upto 7	upto 7	upto 6
Mucosa of small intestine	5-5	3	3	0	0	0	0	0	0	0
Fat	1	0	0	0	0	0	0	0	0	0
Brain	3	4	3	1-2	0	0-1	2	1	0-1	0
Urine	7	6	2	1	0	4	4	2	0	0
Skin	3	2	2	1	0	1	2	1	0	0
Heart	4	2	1	0	0	1	1	0	0	0
Testes	2	3	2	2	0	0	2	0	0	0
Bone	5	4	-	0	0	1	-	0	0	0
Liver	5	4-5	5	3	2	3	4	3	3	2
Lung	5	2	1	0	0	1	2	0	0	0
Gastric contents	upto 7	7	7	upto 6	0	7	7	7	7	upto 6
Gastric mucosa	4-7	2	2	2	0	-	0	1	2	0
Spleen	5	4	2	1	0	1	3	0	0	0
Muscle	4-5	2	1	0	0	1	2	0	0	0
Adrenal medulla	7	4	3	1	1	2	3	1	1	0-1
Kidney	6	4	3	1-2	1	2	3	2	1	1
Rib	5	3	1	0	0	1	3	0	0	0
Spinal marrow	3	3	1	0	0	0-1	2	1	0	0
Thyroid	2	1	1	0	0	0-1	2	1	0	0
Salivary glands	6-7	5-6	3-4	2	0	3	4-5	3	2	1
Thymus	4	3	2	0	0	1	3	0	0	0
Lacrimal gland	5	4	3	2	0	2	5	2	1	1
Vertebra	5	4	1	0	0	1	3	0	0	0
Dental germ	-	3	1	0	0	1	2	0	0	0
Intervertebral disks	3	1	0	0	0	0	1	0	0	0

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D.1.c. Studies on the placental transfer and on the crossing of the blood-brain barrier of [¹⁴C]-SND 919 CL2Y in the rat.

Document #(s): BI Document U94-0359
Upjohn TR 7256-94-103

Sponsor Volume: 1.59

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Summary:

[¹⁴C]-PPX (1.0 mg/kg) was administered to pregnant Wistar rats by the i.v. or oral routes, and its capacity to penetrate the blood:brain barrier or blood:placental barrier was determined. By either route, PPX and/or its metabolites rapidly crossed both the blood:placental and blood:brain barriers. Concentrations of label tended to be higher in the placenta than in maternal blood or in the fetus. Highest fetal tissue concentrations of radiolabel were detected in the liver. In both dams and fetuses, brain levels are higher than plasma levels for up to 6 hrs postdose.

Methods:

Substance administered: [¹⁴C]-pramipexole labeled at the 2-position of the thiazole ring; Batch 7, 7800 MBq/g (210 μCi/mg). Cold substance was Batch II.

Dosages/Routes: 1.0 mg/kg (ca. 1.57 MBq/animal) administered i.v. (tail vein) or p.o.

Animals: 44 pregnant Chbb:THOM Wistar rats

Design: Radioactivity distribution was assessed by tissue analysis with liquid scintillation spectroscopy, and by whole body autoradiography (WBAR). In the tissue analysis studies, animals (n=2 per condition) were administered drug by i.v. or p.o. routes on day 14 or 19 of gestation and sacrificed at for time points (i.v.: 1, 3, 6 or 24 hr; p.o.: 30 min, 3, 6 or 24 hr). For the WBAR study, rats (n=1) were sacrificed at 10 min, 6 or 24 hrs after i.v., and 1, 6 or 24 hrs after p.o. treatments on day 14 or 19 of gestation.

Analysis: WBAR studies were conducted according to standard procedures. Tissue analyses were conducted on the following tissues:

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14th day of pregnancy:	blood	-	dam
	plasma	-	dam
	heart	-	dam
	liver	-	dam
	muscle	-	dam
	brain	-	dam
	uterus		
	placenta		(3-4 placentas were pooled as one sample and measured)

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	amniotic fluid		
	fetus		(4 fetuses were measured individually per animal)
19th day of pregnancy:	blood	-	dam
	plasma	-	dam
	heart	-	dam
	liver	-	dam
	muscle	-	dam
	brain	-	dam
	uterus		
	placenta		(4 placentas were measured individually per animal)

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	amniotic fluid		
	fetus		(4 fetuses were measured individually per animal)
	blood	-	fetus
	liver	-	fetus (livers of 3-4 fetuses)
	fetal tissue		(muscle and bones of the hind limbs)
	fetal brain		

Results:

WBAR Studies:

After intravenous treatment, radioactivity distributed rapidly, and crossed the placental barrier within 10 min. Label was detected in the fetus up to 6 hr postdose. Levels appeared to be higher in the placenta than in the fetus. Low levels were detectable within the placenta and fetus at 24 hrs.

A similar pattern of distribution was observed at 6 and 24 hrs after oral administration.

Isolated Tissue Analyses:

Intravenous studies: Levels of radioactivity appeared to be higher in the placenta than in the fetus on both day 14 and day 19. Maternal blood and liver concentrations were higher than in corresponding fetal tissues. Within the fetus, highest concentrations of radiolabel were detected in liver. Low levels of radioactivity were present in amniotic fluid. Up to six hrs postdose, brain concentrations of radiolabel were higher than blood concentrations in both the dams and fetuses. The calculated half-life of tissue elimination in fetuses is slightly longer than in the dams.

Spectroscopic radioactivity determinations in isolated tissues are summarized in the Tables D.1.c.1-4.

Table ●: Comparison of the concentration values (ng equivalent/g blood or D.1.c.1 ng equivalents/g organ) in the blood of the dams, in the placentas and in the total fetus after i.v. administration of [¹⁴C]-SND 919 CL 2 Y (days 14 and 19 of pregnancy, mean values each of 2 animals)

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measuring time	day 14			day 19		
	blood dam	placenta	fetus	blood dam	placenta	fetus
10 min	326.16	623.36	406.82	430.20	707.70	287.70
3 h	114.88	255.81	102.99	147.43	433.09	179.64
6 h	74.29	106.37	80.92	81.27	138.92	69.43
24 h	37.71	35.52	23.71	40.28	52.97	29.16

Table ●: Comparison of the concentration values (ng equivalents/g blood) in D.1.c.2. the maternal blood and in the fetal blood after i.v. administration of [¹⁴C]-SND 919 CL 2 Y (day 19 of pregnancy, mean values each of 2 animals)

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measuring time	day 19		
	blood dam	blood fetus	ratio blood dam : blood fetus
10 min	430.20	184.76	2.3 : 1
3 h	147.43	103.84	1.4 : 1
6 h	81.27	49.87	1.6 : 1
24 h	40.28	34.37	1.2 : 1

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D.I.C.3 Table 12: Comparison of the concentration values (ng equivalents/g organ) in the livers of the dams and the livers of the fetuses and quotient of the concentrations in the livers and concentration in the blood after i.v. administration of [¹⁴C]-SND 919 CL 2 Y (day 19 of pregnancy, mean values each of 2 animals)

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measuring time	liver dam	liver fetus	<u>liver dam</u> blood dam	<u>liver fetus</u> blood fetus
10 min	3477.98	448.29	8.1	2.4
3 h	1481.78	278.85	10.1	2.7
6 h	787.19	105.39	9.7	2.1
24 h	380.99	62.33	9.4	2.4

D.I.C.4 Table 13: Ratios of the radioactivity concentrations in the brains and the blood of dams and fetuses after i.v. administration of [¹⁴C]-SND 919 CL 2 Y

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	time			
	0.166 h	3 h	6 h	24 h
day 14 of pregnancy				
<u>brain dam</u> blood dam	1.5	4.5	2.7	0.8
day 19 of pregnancy				
<u>brain dam</u> blood dam	1.5	2.9	3.1	1.1
<u>brain fetus</u> blood fetus	1.6	1.9	1.9	1.0

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Oral studies: As with the i.v. route, maternal blood and liver concentrations are higher than in corresponding fetal tissues, and the fetal liver contains higher concentrations than other fetal tissues. Also, higher brain levels relative to blood levels of radioactivity were detected in both dams and fetuses.

Data from the oral administration studies are summarized in Tables D.1.c.5-8:

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D.1.c.5. Table 10: Comparison of the concentration values (ng equivalent/g blood or ng equivalents/g organ) in the blood of the dams, in the placentas and in the total fetus after oral administration of [¹⁴C]-SND 919 CL 2 Y (days 14 and 19 of pregnancy, mean values each of 2 animals)

measuring time	day 14			day 19		
	blood dam	placenta	fetus	blood dam	placenta	fetus
1 h	139.58	229.15	145.79	131.39	255.65	114.61
3 h	91.82	192.68	102.81	166.69	354.22	201.78
6 h	98.46	147.70	65.94	148.69	274.94	146.78
24 h	37.91	54.71	33.17	39.61	64.29	38.43

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D.1.c.6. Table 11: Comparison of the concentration values (ng equivalents/g blood) in the blood of the dams and in the blood of the fetuses after oral administration of [¹⁴C]-SND 919 CL 2 Y (day 19 of pregnancy, mean values each of 2 animals)

measuring time	day 19		
	blood dam	blood fetus	ratio blood dam : blood fetus
1 h	131.39	69.33	1.8 : 1
3 h	166.69	114.66	1.4 : 1
6 h	148.69	111.65	1.3 : 1
24 h	39.61	44.49	1 : 1

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Table 2: Comparison of the concentration values (ng equivalents/g organ) in the livers of the dams and in the fetal livers, and the quotients of the concentrations in the livers and the concentrations in the blood after oral administration of [¹⁴C]-SND 919 CL 2 Y (day 19 of pregnancy, mean values each of 2 animals)

D.l.c.7.

measuring time	liver dam	liver fetus	<u>liver dam</u> blood dam	<u>liver fetus</u> blood fetus
1 h	1773.72	183.52	13.5	2.6
3 h	1648.20	280.52	9.5	2.4
6 h	1305.84	197.75	8.8	1.7
24 h	369.57	74.05	9.3	1.6

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Table 3: Ratios of the radioactivity concentrations in the brains and the blood of dams and fetuses after oral administration of [¹⁴C]-SND 919 CL 2 Y

D.l.c.8

	time			
	1 h	3 h	6 h	24 h
day 14 of pregnancy				
<u>brain dam</u> blood dam	1.8	3.3	2.4	1.7
day 19 of pregnancy				
<u>brain dam</u> blood dam	1.8	3.5	2.9	1.5
<u>brain fetus</u> blood fetus	2	1.6	1.1	0.9

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D.1.d. Pramipexole: Steady-state concentrations in brain, liquor, and plasma of male rats after oral administration of 0.5 mg/kg (once per day) over 8 days.

Document #(s): BI Document U94-0378
Upjohn TR 7256-95-031

Sponsor Volume: 1.60

Summary:

This study was conducted to determine the steady-state pharmacokinetics of PPX in rats following once daily oral administration of 0.5 mg/kg/day for 8 days. Highest levels of PPX were observed in brain tissue, and occur at later time points than in the plasma or CSF. The half-life of PPX in the three compartments was similar.

Methods:

Dosing Regimen: Oral administration of 0.5 mg/kg PPX (Batch II) once daily for 8 days.

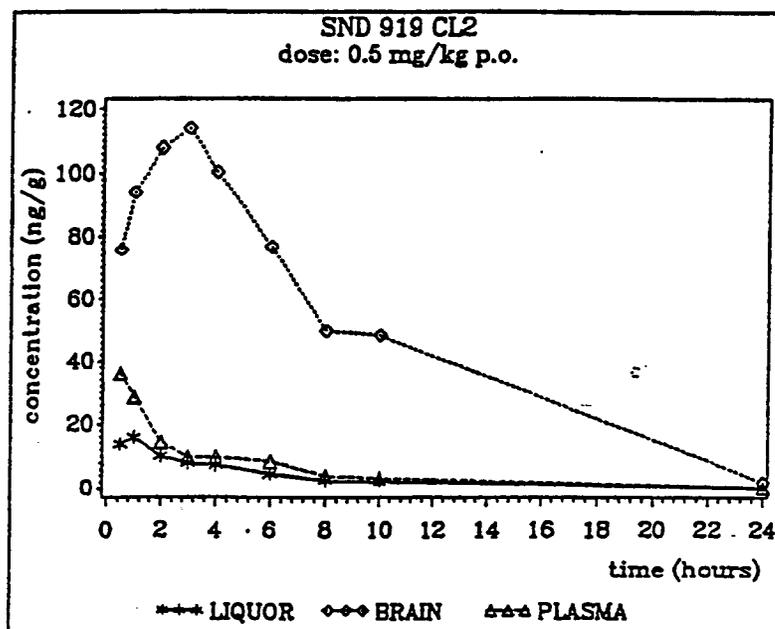
Animals: 35 male Chbb:THOM rats (32 drug, 3 controls), 7g.

Sample collection: Rats (n=3-4/time point) were anesthetized for collection of brain "liquor", then sacrificed for collection of brain and plasma samples.

Pramipexole measurements: by after suitable sample preparation.

Results:

The time-course profiles and kinetic parameters for pramipexole in various matrices were as follows:



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Tab. D.l.d.1

Kinetic steady state parameters of pramipexole in rats after a multiple oral administration of 0.5 mg/kg (calculated from geometric means of concentrations in Table 5)

parameter	dimension	brain	liquor	plasma
AUC (0-∞)	ng/ml · h	1131.00	79.24	129.57
AUC ratio (plasma=1)		8.7	0.6	1
half-life	hours	3.29	3.33	3.18
log-lin. regression. *)	hours	6-24	4-10	4-24
MRT _{ss}	hours	6.49	4.87	4.68
peak concentration	ng/ml	113.82	15.89	36.20
time to reach peak	hours	3	1	0.5

*) within the time period given the concentration data were used for the estimation of the terminal half-life ($t_{1/2}$)

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D.1.e. Excretion of [¹⁴C]-SND 919 CL2 into rat milk after a single oral dose of 0.5 mg/kg.

Document #(s): BI Document U88-0097
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Sponsor Volume: 1.56

Summary:

This study determined the excretion of [¹⁴C]-PPX and/or its metabolites into rat milk following oral administration of 0.5 mg/kg. Greater levels of radioactivity were detected in milk than in plasma, and the rates of elimination from the two compartments were relatively similar. Most of the radioactivity appeared to be metabolites of pramipexole.

Methods:

Test article: 0.5 mg/kg, p.o. (μCi/rat)[¹⁴C]-pramipexole labeled at the 2-position of the thiazole ring (Batch 14; 7800 KBq/mg = 210.8 μCi/mg)

Animals: Six nursing female rats (Chbb:THOM, weight g) with pups (days old).

Procedure: Pups were weaned 4 hrs before first milking. Samples were collected at 1, 4 and 8 hrs after drug administration (n=2/time point). Lactation was stimulated in the mothers by oxytocin, and milk collected using a vacuum pup (under anesthesia). After milking, blood was collected by exsanguination and a portion was processed to plasma. Radioactivity in the milk, blood, and plasma samples was determined by A fraction of each sample was also chromatographed for determination of metabolites.

Results:

Levels of radioactivity in the milk were times higher than in plasma. The milk:plasma concentration ratio did not change over time suggesting relatively equivalent rates of elimination from the two compartments (Fig. D.1.e.1).

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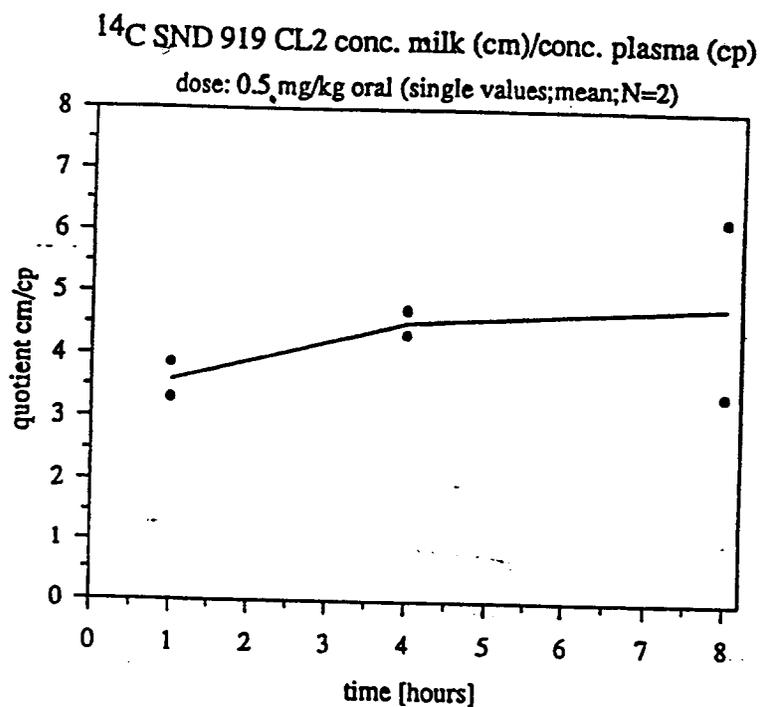


Figure 1: Distribution of radioactivity between milk and plasma in albino rats after oral administration of 0.5 mg/kg [^{14}C]SND 919 CL₂ (• individual values).

indicated that the primary radioactive peak in the plasma extracts is pramipexole. In contrast, very little pramipexole was present in rat milk extracts. The in milk extracts was an apparently lipophilic metabolite. Several smaller polar metabolites were also evident

D.2 Rabbit Pharmacokinetics

D.2.a. Pramipexole: Pharmacokinetics and metabolism in the rabbit after intravenous and oral administration of a single dose of 1 mg/kg.

Document #(s): BI Document U94-0340
Upjohn TR 7256-94-102

Sponsor Volume: 1.56

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Summary:

Plasma concentration and balanced excretion determinations of parent compound and radiolabel were made in rabbits following the intravenous or oral administration of 1 mg/kg [¹⁴C]-PPX. Absorption after oral administration was rather slow (T_{max} = ca. 6 hrs), but relatively high (F = 68.7). The radiolabel was slowly excreted in urine and feces as indicated by long mean residence times. The degree of metabolism of PPX is more extensive in rabbits than in other species on both a qualitative and quantitative basis.

Methods:

Drug Lot: Batch II (non-radioactive material) used to prepare Batch 7 of [¹⁴C]-PPX labeled in the 2-position of the thiazole ring (7.8 MBq/mg).

Dosages: 1 mg/kg/day (prepared in distilled water)

Route of Administration: oral (gavage) or intravenous

Species/Number: 4 female Himalayan rabbits

Mean initial weights/age: ca. 2.8 kg

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Parameters measured:

Plasma concs -	pramipexole and [¹⁴ C]-activity
Excretion -	urine (pramipexole and [¹⁴ C]-activity) and feces ([¹⁴ C]-activity) from hrs
Metabolic profile -	and hr urine analyzed by with radiochemical detection

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Results:

Plasma concentrations:

PK parameters for 1 mg/kg pramipexole (i.v. or p.o.) in rabbits

	AUC (ng.ml/hr)	Cmax (ng/ml)	MRT (hr)	Cl (ml/min)	Vd (l)	t _{1/2} (hr)	Tmax (hr)	F (%)
i.v.	1243	486.2	8.6	32.2	16.6	12.1		
p.o.	990	64.1	12.0			11.0	6	68.7

* Peak concentration of [¹⁴C]-activity after oral dose was 282.8 ng/ml, 4.4-fold higher than parent compound, indicating a high degree of biotransformation.

Excretion Balance (0-192 hrs):

	% Dose (Radioactivity)		
	urine	feces	total
i.v.	74.3	14.7	89.0
p.o.	74.4	14.6	89.0

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Metabolic Profiles:

In addition to the parent compound, 7-9 metabolites are present in urine after 24-48 hrs. None were identified in this study, but one appears to be rabbit specific.

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D.3 Monkey Pharmacokinetics

D.3.a. SND 919 CL 2 Y: Plasma concentrations and Renal Excretion in Rhesus Monkeys after administration of three single intragastric doses (0.1, 0.5 and 1.0 mg/kg) and one intravenous dose (0.5 mg/kg).

Document #(s): BI Document U92-0337
Upjohn TR 7256-94-042

Sponsor Volume: 1.59

Summary:

Plasma and urine concentrations of PPX in rhesus monkeys were determined after oral (0.1, 0.5 and 1.0 mg/kg) and intravenous (0.5 mg/kg) administrations. PPX was readily absorbed from the gut, had a high bioavailability (%), and demonstrated linear kinetics. T_{max} was approximately 2 hrs, and the half-life of elimination from plasma was 3 hr. The plasma concentration:time profile suggested enterohepatic circulation of PPX. The renal clearance of PPX was 4.3 ml/min.kg, and the degree of biotransformation is moderate (p.o.: 35-42%, iv: 48%; based on amount detected as unchanged in urine).

Methods:

Dosages: intragastric: (i.g.) 0.1, 0.5, 1.0 mg/kg PPX (Batch II, in water)
intravenous: 0.5 mg/kg (in saline)

Subjects: 4 rhesus monkeys (2M, 2F)
Average weights: M = 6.8 kg, F = 6.4 kg

Parameters measured:

Plasma concs -
Urine concs -

exhalation, excretion balance (urine, feces), blood levels, plasma protein binding (different species), biliary excretion, metabolite profiles (urine, feces).

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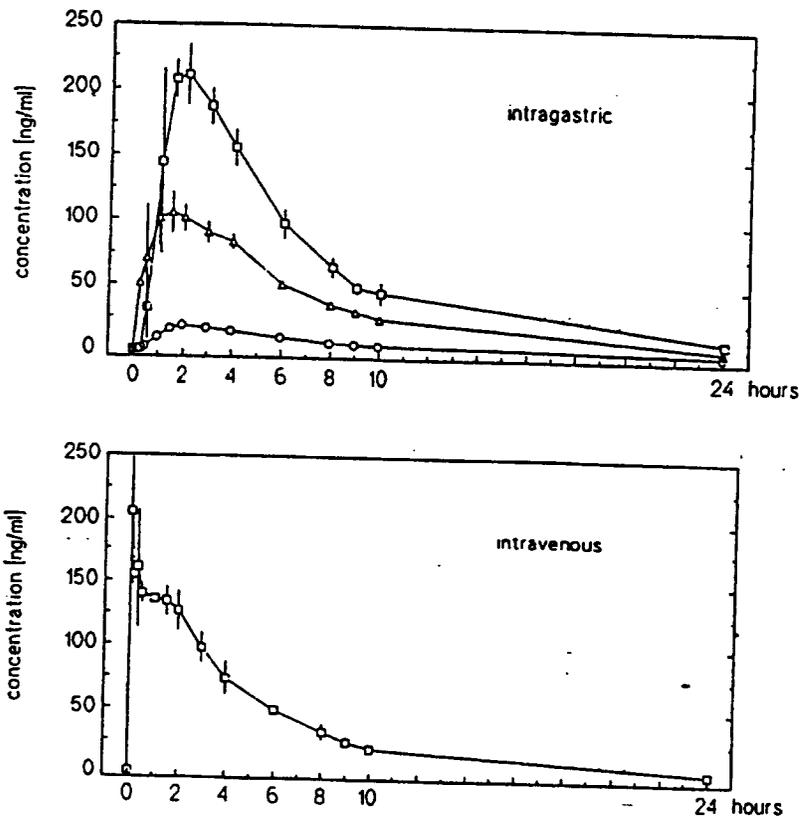
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Results:

Single Dose Pharmacokinetic Parameters in Rhesus Monkeys:

	AUC (ng.ml/hr)	Cmax (ng/ml)	Tmax (hr)	MRT (hr)	Cl (ml/min)	Vd(l)	t _{1/2λ} (hr)	F (%)
					(ml/min/kg)	(l/kg)		
0.1 i.g.	141.9	19.0	1.9	6.2			3.7	79.2
0.5 i.g.	832.9	106.3	1.6	6.0			3.6	93.0
1.0 i.g.	1519.9	218.6	2.0	6.2			3.3	84.6
1.0 i.v.	886.6			4.8	61.5	17.6	3.0	
					9.4	2.7		

Increases in AUC were approximately dose proportional. The t_{1/2} calculation was based on data from 3 hrs postdose, i.g., or 4 hrs postdose, i.v. Elimination kinetics were not uniformly monotonic. A small secondary maxima was evident in the plasma concentration:time profile following i.v. administration suggesting enterohepatic recirculation (Fig. D.3.a).



D.3.a.
 Fig. 3. Mean plasma concentrations of pramipexole [ng/ml] ± SD in the rhesus monkey after single dose
 intragastric: 0.1 (○—○), 0.5 (△—△), 1.0 (□—□) mg/kg
 intravenous: 0.5 mg/kg

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Renal Excretion:

Cumulative Renal Excretion as Percent Dose

Renal Clearance

	0-24 hr	0-96 hr	ml/min
0.1 mg/kg, i.g.	30.8	34.9	24.6
0.5 " , i.g.	37.6	42.0	25.2
1.0 " , i.g.	37.1	41.7	27.0
0.5 " , i.v.	44.1	47.8	24.5

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D.4 Human Pharmacokinetics (provided for comparisons to animal pharmacokinetics)

D.4.a. Pharmacokinetics and metabolism of [¹⁴C]-pramipexole after single intravenous and oral doses in healthy volunteers.

Document #(s): BI Document U92-0018
Upjohn TR 7215-94-014

Sponsor Volume: 1.57

Summary:

The single dose pharmacokinetics of orally (0.304 mg) and intravenously (0.099 mg) administered [¹⁴C]-PPX were determined by monitoring levels of radiolabel and parent compound over 24 hrs in healthy volunteers. Following oral administration, PPX was quantitatively absorbed from the GI tract (F = ca. 90%), and peak plasma concentrations were achieved in approximately 1 hr. Elimination from the plasma was rather slow ($t_{1/2\gamma} = 12.8$ hrs). Renal excretion is the primary route of elimination (ca. 90%; $Cl_{ren} = 409$ ml/min), and the major fraction is unchanged parent compound. Plasma protein binding was low (14.1%). The only clinical change were slight decreases in systolic pressure and pulse rate.

Methods:

Drug Lot: Batch VI (non-radioactive)
Radioactive Batch 6 (labeled in the 2-position of thiazole ring)

Subjects: Oral/IV cross-over design with 6 subjects. Washout period of 5 weeks between administrations.

Doses: 0.099 mg [¹⁴C]-pramipexole, i.v. (0.812 MBq), or
0.304 mg [¹⁴C]-pramipexole, p.o. (2.15 MBq)

Parameters measured:

Plasma concs	-	pramipexole and [¹⁴ C]-activity over 24 hrs
Ce/Cp	-	erythrocyte/plasma distribution
Excretion balance	-	or hrs
Plasma protein binding	-	
Metabolic profile	-	and hr urine analyzed by with radiochemical detection

Results:

Human PK parameters for PPX (0.099 mg, i.v., or 0.304 mg, p.o.):

(PK data for the parent compound, pramipexole, were analyzed using both a 3-compartment open model and a moment analysis, but [14C]-activity data were analyzed only by moment analysis. PK parameters for the parent compound were similar by both methods. In order to compare the PK parameters for parent compound and [14C]-activity, the values obtained by moment analysis are presented, except where indicated*).

	AUC (ng.ml/hr)	Cmax (ng/ml)	MRT (hr)	Cl (ml/min)	Vd (l)	t _{1/2λ} (hr)	Tmax (hr)	F (%)
PPX (iv)	3.64		16.1	506.2	451	12.6		
[¹⁴ C] (iv)	4.75		18.8	355.6	395	14.4		
PPX (p.o.)	10.43	0.85*	17.0			12.1	1.0	93.3
[¹⁴ C] (p.o.)	15.84	0.91*	24.8			17.6	1.0	108.6

PPX was still present in plasma at 24 hrs.
F calculations based on AUCs corrected for dose:

$$(AUC_{po})(0.99/3.04)/AUC_{iv}$$

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Absorption/Bioavailability:

Absorption of [14C]-activity and bioavailability of PPX were determined by two methods:

- normalization of AUCs (as described under PK parameters Table), and
- renal excretion

$$\frac{\text{renal excretion } (^{14}\text{C, oral})}{\text{renal excretion } (^{14}\text{C, iv})} \times 100$$

By either method, the absorption of radioactivity and bioavailability of PPX were essentially quantitative:

	AUC method	renal excretion method
[¹⁴ C] absorption	108.6	98.3
PPX bioavailability	93.3	95.6

Erythrocyte/Plasma Distribution:

Most values were in the range of 1.3-2.6, indicating slight enrichment of [¹⁴C] activity in erythrocytes.

Excretion:

		% Dose		
		urine	feces	total
[¹⁴ C] (0-96 hr)	i.v.	89.1	2.0	91.1
	p.o.	87.6	1.6	89.2
Pramipexole (0-24 hr)	i.v.	61.8	nd	
	p.o.	56.3	nd	
Pramipexole (0-inf)	i.v.	81.5	nd	
	p.o.	77.9	nd	

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Small amounts of radioactivity were excreted later than 120 hrs.
Mean renal clearance of PPX was 409 ml/min (exceeds GFR).

Plasma Protein Binding: (Assessed at two concentrations of PPX) **APPEARS THIS WAY ON ORIGINAL**

[PPX]	% Bound (Range)
2.5 ng/ml	
5.0 "	

Metabolism pattern:

In NOT PPX (of urines collected after dosing, very little of the radioactivity was % of dose; .% of dose).

Vital Signs:

Small decreases in systolic blood pressure and heart rate were evident between 1-8 hrs after dosing by either route. No clear changes in ECG, diastolic blood pressure, or laboratory values were observed.

D.4.b. A single dose tolerance and pharmacokinetic study of intravenous pramipexole in healthy male volunteers.

Document #(s): BI Document U92-0018
Upjohn TR 7217-94-014

Sponsor Volume: 1.58

Summary:

This study was primarily a dose tolerance study with limited pharmacokinetic evaluations. PPX (μg) was administered by intravenous infusion and plasma levels were determined over 24 hrs; levels were below the LOD by 24 hrs. Increases in AUC were slightly greater than dose proportional. Cardiovascular changes were increases in pulse rate after doses of 200 and 300 μg , and decreases in diastolic blood pressure after 300 μg . Orthostasis occurred in 1/5 patients after 200 μg , and 2/4 patients after 300 μg . No other drug-related effects on ECG or laboratory parameters were observed.

Methods:

Drug Lot: Batch 802203

Subjects: Healthy, adult male volunteers; three groups of eight subjects.

Group A: 10 and 50 μg

Group B: 25 and 100 μg

Group C: 50, 200 and 300 μg (50 μg administered as a pretest)

Five subjects per dose received active drug, three received placebo.

Drug administered as an i.v. infusion over 20 min.

Washout period was 6 days.

Parameters measured:

Plasma concs -

Laboratory - hematology, clinical chemistry, urinalysis

Vitals - blood pressure, ECG, etc.

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Results:

Pharmacokinetics:

The pharmacokinetic data were not subjected to rigorous analysis.

Dose (μg)	AUC (ng.ml/hr)	$C_{20\text{min}}$ (ng/ml)	$t_{1/2}$ (hr)
50	1.01	0.40	
100	2.06	0.64	4.8
200	4.94	1.89	7.9
300	7.35	2.26	6.6

Increases in AUC were generally dose proportional, although slightly nonlinear (slope > 1). Plasma PPX levels were below LOD at 24 hrs. The $t_{1/2}$ calculation was based on plasma levels determinations between hrs

Clinical Determinations:

Increases in pulse rate lasting up to 4 hrs occurred following doses of 200 and 300 μg . A decrease in diastolic blood pressure was noted 40 min after 300 μg infusion. Orthostasis occurred in 1/5 patients after 200 μg , and 2/4 patients after 300 μg . The cardiovascular changes suggest a vasodilating effect of pramipexole. No significant drug-related effects on ECG or laboratory determinations were observed.

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