Iloperidone Is Well Tolerated by Subjects With Renal or Hepatic Impairment in Single-Dose Clinical Pharmacokinetic Studies

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VANDA PHARMACEUTICALS INC.

ABSTRACT

Introduction: Iloperidone is an investigational mixed D_2/5-HT_2 antagonist antipsychotic with affinity for 5-HT_{1A}, 5-HT_{2A}, and 5-HT_6 receptors. This profile predicts clinical efficacy for schizophrenia with reduced extrapyramidal side-effect risk. Open-label studies were conducted to determine single-dose pharmacokinetics (PK) of iloperidone, an active metabolite, P88, and an inactive metabolite (with respect to central nervous system activity), P95, in adults with renal or hepatic impairment compared with healthy controls.

Methods: *Study 1 (S1):* Ten adults with chronic severe renal impairment (CrCL <30 mL/min) and 13 healthy controls (CrCL >80 mL/min) received single iloperidone 3-mg oral doses. *Study 2 (S2):* Eight adults with mild-to-moderate hepatic impairment and 8 healthy controls received single iloperidone 2-mg doses. Assay results for blood and urine samples collected predose and frequently for up to 65 hours (S1) and 48 hours (S2) postdose were used to determine iloperidone, P88, and P95 PK.

Results: *Renal impairment vs controls:* Iloperidone clearance was reduced by 19%, and mean maximum plasma concentration (C_{max}) was unaltered, although half-life ($t_{1/2}$) was significantly prolonged (33.7 hours [impaired subjects] vs 15.0 hours [control subjects]; P = .02). P88 PK, including area under the plasma concentration-time curve from zero to the last time point with detectable concentration (AUC_{0-t}), was not significantly altered. PK parameters for P95 showed that the appearance (mean T_{max} = 8 vs 24; P = .04) and elimination (mean $t_{1/2}$ = 19.3 vs 82.8; P = .008) of P95 in plasma were slower in renally impaired subjects compared with healthy control subjects; higher plasma concentrations were found in renally impaired subjects. *Hepatic impairment vs controls:* Iloperidone T_{max}, C_{max}, AUC_{0-t}, and $t_{1/2}$ were essentially unaltered. P88 C_{max} (1.74 vs 1.02 ng/mL; 90% confidence interval [CI], 1.29, 2.88) and AUC_{0-t} (34.3 vs 22.9 ng·h/mL; 90% CI, 1.06, 2.56) were significantly increased in hepatically impaired subjects without altering renal clearance. Protein binding (98%) was unaffected by renal or hepatic impairment (97%). Iloperidone was well tolerated by all subjects in both studies.

Conclusion: Renal dysfunction did not alter iloperidone and P88 PK to a clinically significant extent. Iloperidone exposure was unaffected by mild to moderate hepatic impairment. P88 PK was virtually unchanged in renal impairment, but in hepatic impairment P88 exposure was moderately increased, suggesting a potentially increased combined exposure to pharmacologically active moieties (iloperidone + P88). While the metabolism of iloperidone to P95 decreased slightly in hepatically impaired subjects, P95 levels significantly increased in renally impaired subjects. Protein binding was unaffected by renal or hepatic impairment. Single low doses of iloperidone were well tolerated by all subjects.

INTRODUCTION

- Iloperidone, an investigational mixed D_2/5-HT_2 antagonist antipsychotic with high affinity for 5-HT_{2A}, D_2, and D_3 receptors; moderate affinity for D_4, 5-HT_6, 5-HT_7, and $NE_{\alpha 1}$ receptors; and low affinity for 5-HT_{1A}, D_1, and H_1 receptors, is expected to have clinical efficacy for a broad range of schizophrenia symptoms and a reduced potential for extrapyramidal side effects.[1,2]
- Because medical comorbidities may be frequent in patients with schizophrenia, 2 open-label studies were conducted to determine the single-dose pharmacokinetics (PK) of iloperidone and its metabolites, P88 and P95, in adults with renal or hepatic impairment compared with healthy, matched controls.

METHODS

Study Design 1: Renal Impairment

- Open-label, single-dose, parallel-group study
- Subjects: 18 to 65 years of age with chronic, severe renal impairment (CrCL <30 mL/min and receiving hemodialysis 3 times/wk) (Group 1), and matched healthy controls (Group 2)
- Single-dose treatment period (3 × 1-mg iloperidone capsules)
- Plasma samples were collected at predetermined time points predosing and up to 65 hours postdosing to assess PK parameters and the percentage of iloperidone protein binding.
- Eight-hour urine samples were collected from healthy subjects at predetermined time points for up to 65 hours.

Study Design 2: Hepatic Impairment

- Open-label, single-dose, parallel-group study
- Subjects: 18 to 65 years of age with mild (Child-Pugh score of 5-6) to moderate (Child-Pugh score of 7-9) hepatic impairment (Group 1) and matched healthy controls (Group 2)
- Single-dose treatment period (2-mg iloperidone capsule)
- Plasma samples were collected at predetermined time points predose and for up to 48 hours postdose to assess PK parameters.
- Eight-hour urine samples were collected at predetermined time points for up to 48 hours.

Pharmacokinetics Parameters

The following PK parameters were determined using noncompartmental methods:

- Area under the plasma concentration-time curve from zero to the last time point with detectable concentration (AUC_{0-t})
- Area under the plasma concentration-time curve from zero to infinity ($AUC_{0-\infty}$)
- Maximum plasma concentration observed postdosing (C_{max})
- Time at which C_{max} occurred (T_{max})
- Apparent clearance of parent drug (CL_r/F)
- Apparent clearance of metabolite (CL_r/f_m·F)
- Total amount excreted in urine (measured in healthy subjects in Study 1)
- Elimination half-life ($t_{1/2}$)
- Apparent volume of distribution of parent drug (V_z/F)
- Apparent volume of distribution of metabolite (V_z/f_m·F)
- Renal clearance (CL_R) (measured only in Study 2)

Safety Evaluations

- Safety assessments included physical examinations, electrocardiography (ECG), vital signs, laboratory evaluations (biochemistry, urinalysis, hematology), and adverse event monitoring.

Statistical Methods

- Concentrations below the limit of quantitation were treated as zero in summary statistics and for the calculation of PK parameters.
- The analysis of variance model (ANOVA) was used to evaluate differences between Groups 1 and 2 in each respective study design.
- The PK parameters $t_{1/2}$ and T_{max} were analyzed by the nonparametric Wilcoxon signed rank test.

RESULTS

Patient Characteristics

Table 1. Demographics in Renal Impairment and Hepatic Impairment Studies.

	Age, y Mean (SD)	Height, cm Mean (SD)	Weight, kg Mean (SD)
Study 1: Renal Impairment			
Men			
Group 1/Impaired (n = 7)	47.4 (7.4)	178.9 (7.7)	79.0 (7.1)
Group 2/Healthy (n = 9)	43.2 (6.3)	175.6 (7.4)	79.9 (6.7)
All (n = 16)	45.1 (6.9)	177.0 (7.5)	79.5 (6.7)
Women			
Group 1/Impaired (n = 3)	53.7 (14.6)	162.6 (12.7)	70.9 (19.0)
Group 2/Healthy (n = 4)	53.8 (13.3)	156.2 (11.8)	64.0 (15.1)
All (n = 7)	53.7 (12.6)	158.9 (11.6)	67.0 (15.7)
Study 2: Hepatic Impairment*			
Men			
Group 1/Impaired (n = 6)	53.3 (8.4)	172.1 (6.0)	84.8 (9.1)
Group 2/Healthy (n = 6)	52.8 (8.0)	172.7 (5.3)	84.4 (9.7)
All (n = 12)	53.1 (7.9)	172.4 (5.4)	84.6 (9.0)
Women			
Group 1/Impaired (n = 2)	52.0 (5.7)	160.0 (0.0)	67.5 (1.0)
Group 2/Healthy (n = 2)	49.5 (6.4)	159.5 (3.5)	64.6 (2.6)
All (n = 4)	50.8 (5.1)	159.8 (2.1)	66.0 (2.4)

SD = standard deviation.
*All subjects in Study 2 were CYP2D6-genotyped as extensive metabolizers.

Study 1: Pharmacokinetic Parameters in Renally Impaired Subjects Compared With Healthy Subjects

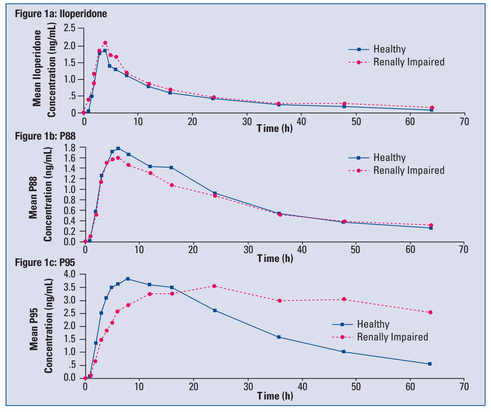
- Iloperidone was quickly absorbed, had a median T_{max} of 3 to 4 hours in healthy and renally impaired subjects, and reached a comparable C_{max} in the 2 groups (**Table 2**).
- Iloperidone clearance was reduced by 19%, and mean C_{max} was unaltered in renally impaired subjects.
- Iloperidone half-life ($t_{1/2}$) was significantly prolonged (33.7 vs 15.0 hours; P = .02) and $AUC_{0-\infty}$ was 80% higher (47.9 vs 26.6 ng·h/mL) in renally impaired subjects (**Figure 1**).
  - This large increase may be, at least in part, an artifact due to mean plasma concentrations in renally impaired subjects at 48 hours being higher than what would be expected from concentrations at the preceding time points. This contributes to the difference in $AUC_{0-\infty}$ being much larger (80%) than in AUC_{0-t} (24%)
- PK parameters for P88, including AUC_{0-t}, were not significantly altered in renally impaired subjects compared with healthy control subjects.
- PK parameters for P95 showed that the appearance (mean T_{max} = 8 vs 24 hours; P = .04) and elimination (mean $t_{1/2}$ = 19.3 vs 82.8 hours; P = .008) of P95 in plasma were slower, and plasma concentrations were significantly higher in renally impaired subjects compared with healthy control subjects.
- Protein binding (98%) was unchanged by renal impairment (97%).

*Table 2. Mean (CV%) Pharmacokinetic Parameters for Iloperidone and Metabolites (P88 and P95) in Healthy and Renally Impaired Subjects Following a Single Oral 3-mg Dose of Iloperidone.**

PK Parameters	Mean (CV%) Healthy Subjects (n = 9)	Renally Impaired Subjects (n = 9)	Difference (%)†
Iloperidone			
T_{max} (h)‡	3.0 (2-5)	4.0 (3-4)	–
C_{max} (ng/mL)	2.2 (35)	2.3 (71)	5
AUC_{0-t} (ng·h/mL)	27.8 (38)	34.5 (84)	24
$AUC_{0-\infty}$ (ng·h/mL)	26.6 (23)	47.9 (82)	80
$t_{1/2}$ (h)	15.0 (20)	33.7 (48)	124
CL_r/F (L/h)	120.2 (32)	97.3 (59)	–19
V_z/F (L)	2527 (23)	4049 (45)	60
Amount excreted (µg)	17.5 (96.8)	–	–
P88			
T_{max} (h)‡	6.0 (3-16)	6.0 (3-12)	–
C_{max} (ng/mL)	2.01 (38)	2.0 (39)	–5
AUC_{0-t} (ng·h/mL)	51.1 (52)	48.1 (49)	–6
$AUC_{0-\infty}$ (ng·h/mL)	62.5 (62)	44.9 (40)	–28
$t_{1/2}$ (h)	25.6 (15)	22.8 (27)	–11
Amount excreted (µg)	142.9 (64)	–	–
P95			
T_{max} (h)‡	8 (5-24)	24 (8-24)	–
C_{max} (ng/mL)	4.2 (58)	3.9 (54)	–7
AUC_{0-t} (ng·h/mL)	126.2 (50)	192.3 (62)	52
$AUC_{0-\infty}$ (ng·h/mL)	141.2 (48)	447.4 (61)	217
$t_{1/2}$ (h)	19.3 (20)	82.8 (34)	329
Amount excreted (µg)	277.4 (50)	–	–

CV = coefficient of variance; PK = pharmacokinetics.
*Subjects 9, 14, 15, 18, and 19 excluded. †Difference (%) = (healthy – renally impaired)/healthy × 100. ‡Median (range).

Figure 1. Mean Concentration–Time Profiles of Iloperidone and Metabolites (P88 and P95) in Healthy and Renally Impaired Subjects Following a Single Oral 3-mg Dose.



Study 2: Pharmacokinetic Parameters in Hepatically Impaired Subjects Compared With Healthy Subjects

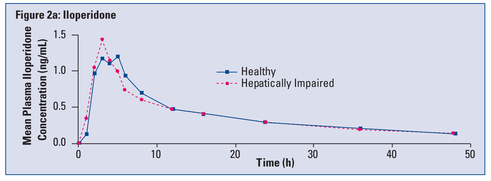
- Iloperidone T_{max}, C_{max}, AUC_{0-t}, and $t_{1/2}$ were similar in hepatically impaired and healthy subjects (**Table 3**; **Figure 2**).
- P88 C_{max} (1.74 vs 1.02 ng/mL; 90% confidence interval [CI], 1.29, 2.88) and AUC_{0-t} (34.3 vs 22.9 ng·h/mL; 90% CI, 1.06, 2.56) were significantly increased by approximately 71% and 50%, respectively, in hepatically impaired subjects without altering renal clearance.
- P95 C_{max} was decreased by 19%, and P95 exposure was slightly lower (AUC_{0-t} 20%, $AUC_{0-\infty}$ 5%) in hepatically impaired subjects, without alteration in CL_R.
- Protein binding (98%) was unchanged by hepatic impairment (97%).

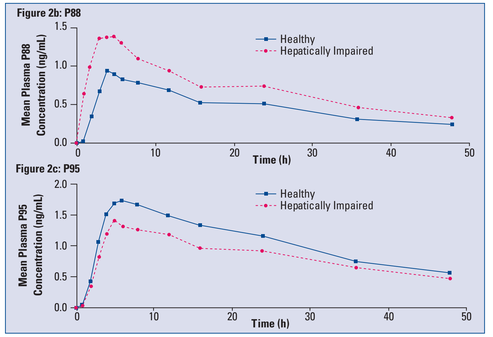
Table 3. Mean (CV%) Pharmacokinetic Parameters for Iloperidone and Metabolites (P88 and P95) in Healthy and Hepatically Impaired Subjects Following a Single Oral 2-mg Dose of Iloperidone.

PK Parameters	Mean (CV%) Healthy Subjects	Hepatically Impaired Subjects	Difference (%)*
Iloperidone	(n = 7)	(n = 7)	
T_{max} (h)†	3.5 (2-5)	3.0 (1-5)	–
C_{max} (ng/mL)	1.75 (56)	1.68 (40)	–4.0
AUC_{0-t} (ng·h/mL)	18.8 (40)	18.2 (47)	–3.2
$AUC_{0-\infty}$ (ng·h/mL)	22.0 (36)	26.2 (38)	19
$t_{1/2}$ (h)	24.5 (30)	24.5 (18)	0.0
CL_r/F (L/h)	101.3 (33)	91.4 (53)	–9.8
V_z/F (L)	3702 (53)	3063 (41)	–17
Amount excreted (% of dose)	0.40 (70)	0.38 (55)	5.0
CL_R (mL/min)	7.0 (44)	9.8 (91)	40
P88	(n = 8)	(n = 7)	
T_{max} (h)†	4.5 (4-12)	3.5 (1-8)	–
C_{max} (ng/mL)	1.02 (63)	1.74 (21)	74
AUC_{0-t} (ng·h/mL)	22.9 (58)	34.3 (36)	50
$AUC_{0-\infty}$ (ng·h/mL)	32.3 (53)	47.8 (40)	48
$t_{1/2}$ (h)	26.9 (22)	22.6 (32)	–16
CL_r/f_m·F (L/h)	77.0 (47)	47.8 (39)	–
V_z/f_m·F (L)	3174 (63)	1481 (35)	–
Amount excreted (% of dose)	2.94 (73)	3.9 (33)	33
CL_R (mL/min)	43.0 (35)	45.3 (54)	5.3
P95	(n = 8)	(n = 6)	
T_{max} (h)†	5.5 (4-12)	6.0 (4-24)	–
C_{max} (ng/mL)	1.90 (32)	1.54 (70)	–19
AUC_{0-t} (ng·h/mL)	50.3 (40)	40.0 (59)	–20
$AUC_{0-\infty}$ (ng·h/mL)	71.5 (39)	68.1 (32)	–4.8
$t_{1/2}$ (h)	25.2 (35)	25.2 (27)	0
CL_r/f_m·F (L/h)	31.3 (33)	32.5 (38)	–
Vz/fm·F (L)	1102 (34)	1219 (51)	–
Amount excreted (% of dose)	168.0 (38)	145.2 (70)	–14
CL_R (mL/min)	56.2 (26)	58.6 (27)	4.3

CV = coefficient of variance; PK = pharmacokinetics.
*Difference (%) = (healthy – renally impaired)/healthy × 100. †Median (range).

Figure 2. Mean Concentration–Time Profiles of Iloperidone and Metabolites (P88 and P95) in Healthy and Hepatically Impaired Subjects Following a Single Oral 2-mg Dose.





Safety (Studies 1 and 2)

- No increase in adverse events was observed in subjects with hepatic or renal impairment compared with healthy control subjects (**Table 4**).
- No clinically significant ECG changes were observed.

Table 4. Summary of Adverse Events.

Adverse Event	Renal Impairment Study Group 1* (n = 8)	Renal Impairment Study Group 2* (n = 8)	Hepatic Impairment Study Group 1* (n = 10)	Hepatic Impairment Study Group 2* (n = 13)
Somnolence	–	1	1	1
Dizziness	1	2	1	1
Headache	1	1	1	–
Watery eyes	–	–	1	–
Dry mouth	–	–	1	–
Diarrhea	–	–	1	–
Rhinitis	–	2	–	1
Dyspnea	1	–	–	–

*Group 1 = impaired subjects; Group 2 = healthy control subjects.

CONCLUSIONS

- In renally impaired subjects, iloperidone C_{max} and AUC_{0-t} were modestly increased (by 5% and 24%, respectively). Iloperidone half-life doubled, and $AUC_{0-\infty}$ increased by 80%, but these values are probably exaggerated because of unexpected plasma concentration values at 48 hours.
- P88 PK were virtually unchanged, and exposure to P95 was significantly higher in renally impaired subjects.
- Iloperidone exposure was unaffected by mild to moderate hepatic impairment.
- Exposure to P88 was moderately higher in hepatically impaired subjects compared with healthy controls, suggesting a potentially increased combined exposure to pharmacologically active moieties (iloperidone + P88) of approximately 30%.
- The metabolism of iloperidone to P95 is slower in hepatically impaired CYP2D6-genotyped subjects considered extensive metabolizers.
- Protein binding was unaffected by renal or hepatic impairment.
- Single low doses of iloperidone were well tolerated by all subjects.

ACKNOWLEDGMENTS

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REFERENCES

1. Kalkman HO et al. *Neuropsychopharmacology.* 2001;25:904-914.
2. Kalkman HO et al. *Life Sci.* 2003;73:1151-1159.

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Iloperid

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ABSTRACT

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Methods: *Study 1 (S1):* Ten adults with chronic severe renal impairment (CrCL <30 mL/min) and 13 healthy controls (CrCL >80 mL/min) received single iloperidone 3-mg oral doses. *Study 2 (S2):* Eight adults with mild-to-moderate hepatic impairment and 8 healthy controls received single iloperidone 2-mg doses. Assay results for blood and urine samples collected predose and frequently for up to 65 hours (S1) and 48 hours (S2) postdose were used to determine iloperidone, P88, and P95 PK.

Results: *Renal impairment vs controls:* Iloperidone clearance was reduced by 19%, and mean maximum plasma concentration (C_{max}) was unaltered, although half-life ($t_{1/2}$) was significantly prolonged (33.7 hours [impaired subjects] vs 15.0 hours [control subjects]; $P = .02$). P88 PK, including area under the plasma concentration-time curve from zero to the last time point with detectable concentration ($AUC_{0\text{-}t}$), was not significantly altered. PK parameters for P95 showed that the appearance (mean T_{max} = 8 vs 24; $P = .04$) and elimination (mean $t_{1/2}$ = 19.3 vs 82.8; $P = .008$) of P95 in plasma were slower in renally impaired subjects compared with healthy control subjects; higher plasma concentrations were found in renally impaired subjects. *Hepatic impairment vs controls:* Iloperidone T_{max}, C_{max}, $AUC_{0\text{-}t}$, and $t_{1/2}$ were essentially unaltered. P88 C_{max} (1.74 vs 1.02 ng/mL; 90% confidence interval [CI], 1.29, 2.88) and $AUC_{0\text{-}t}$ (34.3 vs 22.9 ng·h/mL; 90% CI, 1.06, 2.56) were significantly increased in hepatically impaired subjects without altering renal clearance. Protein binding (98%) was unaffected by renal or hepatic impairment (97%). Iloperidone was well tolerated by all subjects in both studies.

Conclusion: Renal dysfunction did not alter iloperidone and P88 PK to a clinically significant extent. Iloperidone exposure was unaffected by mild to moderate hepatic impairment. P88 PK was virtually unchanged in renal impairment, but in hepatic impairment P88 exposure was moderately increased, suggesting a potentially increased combined exposure to pharmacologically active moieties (iloperidone + P88). While the metabolism of iloperidone to P95 decreased slightly in hepatically impaired subjects, P95 levels significantly increased in renally impaired subjects. Protein binding was unaffected by renal or hepatic impairment. Single low doses of iloperidone were well tolerated by all subjects.

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METHODS

Study Design 1: Renal Impairment

- Open-label, single-dose, parallel-group study
- Subjects: 18 to 65 years of age with chronic, severe renal impairment (CrCL <30 mL/min and receiving hemodialysis 3 times/wk) (Group 1), and matched healthy controls (Group 2)
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- Apparent clearance of metabolite ($CL_\tau/f_m \cdot F$)
- Total amount excreted in urine (measured in healthy subjects in Study 1)
- Elimination half-life ($t_{1/2}$)
- Apparent volume of distribution of parent drug (V_z/F)
- Apparent volume of distribution of metabolite ($V_z/f_m \cdot F$)
- Renal clearance (CL_R) (measured only in Study 2)

Safety Evaluations

- Safety assessments included physical examinations, electrocardiography (ECG), vital signs, laboratory evaluations (biochemistry, urinalysis, hematology), and adverse event monitoring.

Statistical Methods

- Concentrations below the limit of quantitation were treated as zero in summary statistics and for the calculation of PK parameters.
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SD = standard deviation.
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  - This large increase may be, at least in part, an artifact due to mean plasma concentrations in renally impaired subjects at 48 hours being higher than what would be expected from concentrations at the preceding time points. This contributes to the difference in $AUC_{0-\infty}$ being much larger (80%) than in AUC_{0-t} (24%)

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ceuticals Inc; [2]Vanda Pharmaceuticals Inc., Rockville

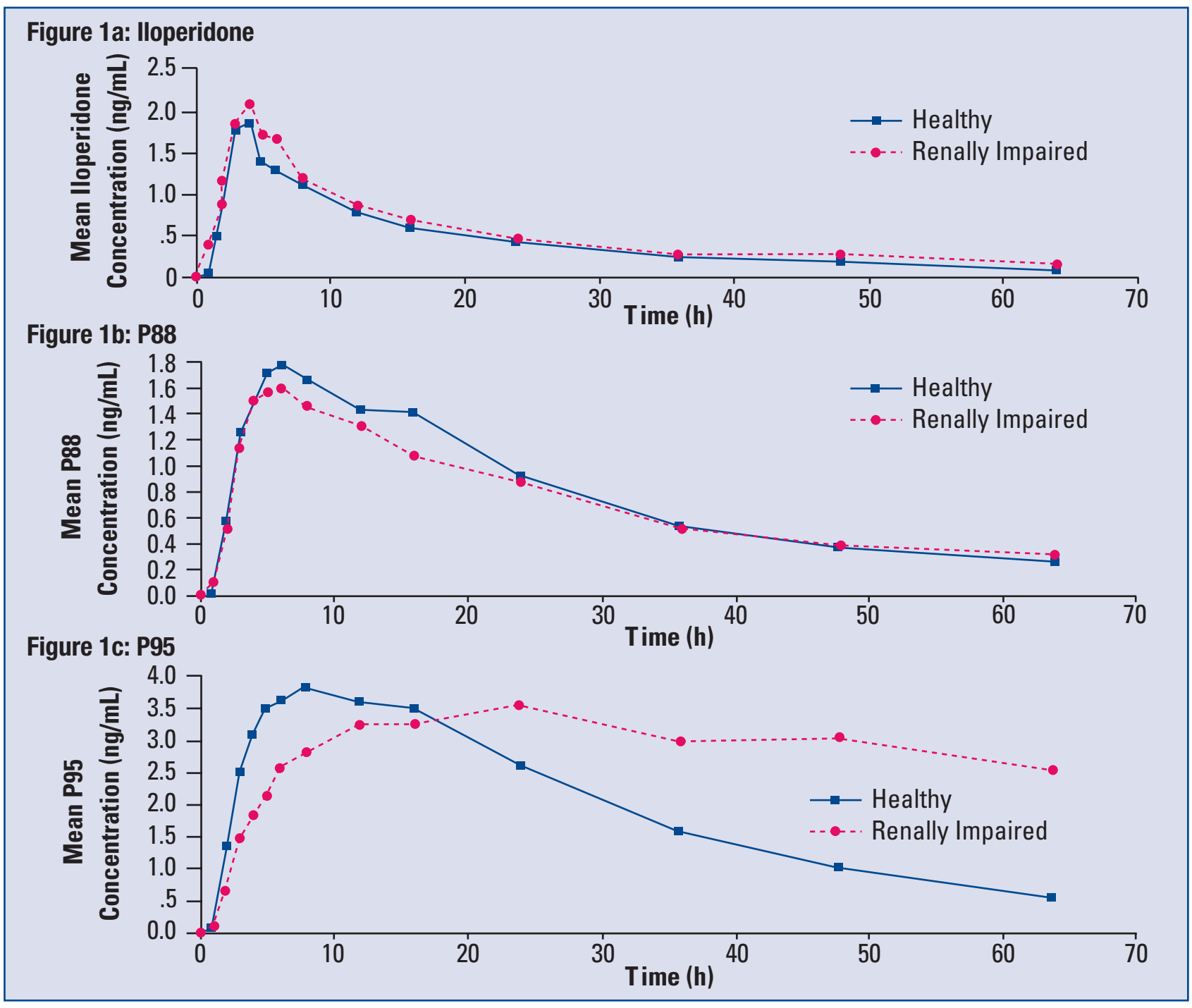
- PK parameters for P88, including AUC_{0-t}, were not significantly altered in renally impaired subjects compared with healthy control subjects.
- PK parameters for P95 showed that the appearance (mean T_{max} = 8 vs 24 hours; *P* = .04) and elimination (mean $t_{1/2}$ = 19.3 vs 82.8 hours; *P* = .008) of P95 in plasma were slower, and plasma concentrations were significantly higher in renally impaired subjects compared with healthy control subjects.
- Protein binding (98%) was unchanged by renal impairment (97%).

*Table 2. Mean (CV%) Pharmacokinetic Parameters for Iloperidone and Metabolites (P88 and P95) in Healthy and Renally Impaired Subjects Following a Single Oral 3-mg Dose.**

PK Parameters	Mean (CV%)		
	Healthy Subjects (n = 9)	Renally Impaired Subjects (n = 9)	Difference (%)†
Iloperidone			
T_{max} (h)‡	3.0 (2-5)	4.0 (3-4)	–
C_{max} (ng/mL)	2.2 (35)	2.3 (71)	5
AUC_{0-t} (ng·h/mL)	27.8 (38)	34.5 (84)	24
$AUC_{0-\infty}$ (ng·h/mL)	26.6 (23)	47.9 (82)	80
$t_{1/2}$ (h)	15.0 (20)	33.7 (48)	124
CL_τ/F (L/h)	120.2 (32)	97.3 (59)	–19
V_z/F (L)	2527 (23)	4049 (45)	60
Amount excreted (µg)	17.5 (96.8)	–	–
P88			
T_{max} (h)‡	6.0 (3-16)	6.0 (3-12)	–
C_{max} (ng/mL)	2.01 (38)	2.0 (39)	–5
AUC_{0-t} (ng·h/mL)	51.1 (52)	48.1 (49)	–6
$AUC_{0-\infty}$ (ng·h/mL)	62.5 (62)	44.9 (40)	–28
$t_{1/2}$ (h)	25.6 (15)	22.8 (27)	–11
Amount excreted (µg)	142.9 (64)	–	–
P95			
T_{max} (h)‡	8 (5-24)	24 (8-24)	–
C_{max} (ng/mL)	4.2 (58)	3.9 (54)	–7
AUC_{0-t} (ng·h/mL)	126.2 (50)	192.3 (62)	52
$AUC_{0-\infty}$ (ng·h/mL)	141.2 (48)	447.4 (61)	217
$t_{1/2}$ (h)	19.3 (20)	82.8 (34)	329
Amount excreted (µg)	277.4 (50)	–	–

CV = coefficient of variance; PK = pharmacokinetics.
*Subjects 9, 14, 15, 18, and 19 excluded. †Difference (%) = (healthy – renally impaired)/healthy × 100. ‡Median (range).

Figure 1. Mean Concentration–Time Profiles of Iloperidone and Metabolites (P88 and P95) in Healthy and Renally Impaired Subjects Following a Single Oral 3-mg Dose.



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Study 2: Pharmacokinetic Parameters in Hepatically Impaired Subjects Compared With Healthy Subjects

- Iloperidone T_{max}, C_{max}, $AUC_{0\text{-}t}$, and $t_{1/2}$ were similar in hepatically impaired and healthy subjects (**Table 3**; **Figure 2**).
- P88 C_{max} (1.74 vs 1.02 ng/mL; 90% confidence interval [CI], 1.29, 2.88) and $AUC_{0\text{-}t}$ (34.3 vs 22.9 ng·h/mL; 90% CI, 1.06, 2.56) were significantly increased by approximately 71% and 50%, respectively, in hepatically impaired subjects without altering renal clearance.
- P95 C_{max} was decreased by 19%, and P95 exposure was slightly lower ($AUC_{0\text{-}t}$ 20%, $AUC_{0\text{-}\infty}$ 5%) in hepatically impaired subjects, without alteration in CL_R.
- Protein binding (98%) was unchanged by hepatic impairment (97%).

Table 3. Mean (CV%) Pharmacokinetic Parameters for Iloperidone and Metabolites (P88 and P95) in Healthy and Hepatically Impaired Subjects Following a Single Oral 2-mg Dose of Iloperidone.

PK Parameters	Mean (CV%)		
	Healthy Subjects	Hepatically Impaired Subjects	Difference (%)*
Iloperidone	(n = 7)	(n = 7)	
T_{max} (h)†	3.5 (2-5)	3.0 (1-5)	–
C_{max} (ng/mL)	1.75 (56)	1.68 (40)	–4.0
$AUC_{0\text{-}t}$ (ng·h/mL)	18.8 (40)	18.2 (47)	–3.2
$AUC_{0\text{-}\infty}$ (ng·h/mL)	22.0 (36)	26.2 (38)	19
$t_{1/2}$ (h)	24.5 (30)	24.5 (18)	0.0
CL_τ/F (L/h)	101.3 (33)	91.4 (53)	–9.8
V_z/F (L)	3702 (53)	3063 (41)	–17
Amount excreted (% of dose)	0.40 (70)	0.38 (55)	5.0
CL_R (mL/min)	7.0 (44)	9.8 (91)	40
P88	(n = 8)	(n = 7)	
T_{max} (h)†	4.5 (4-12)	3.5 (1-8)	–
C_{max} (ng/mL)	1.02 (63)	1.74 (21)	74
$AUC_{0\text{-}t}$ (ng·h/mL)	22.9 (58)	34.3 (36)	50
$AUC_{0\text{-}\infty}$ (ng·h/mL)	32.3 (53)	47.8 (40)	48
$t_{1/2}$ (h)	26.9 (22)	22.6 (32)	–16
$CL_\tau/f_m \cdot F$ (L/h)	77.0 (47)	47.8 (39)	–
$V_z/f_m \cdot F$ (L)	3174 (63)	1481 (35)	–
Amount excreted (% of dose)	2.94 (73)	3.9 (33)	33
CL_R (mL/min)	43.0 (35)	45.3 (54)	5.3
P95	(n = 8)	(n = 6)	
T_{max} (h)†	5.5 (4-12)	6.0 (4-24)	–
C_{max} (ng/mL)	1.90 (32)	1.54 (70)	–19
$AUC_{0\text{-}t}$ (ng·h/mL)	50.3 (40)	40.0 (59)	–20
$AUC_{0\text{-}\infty}$ (ng·h/mL)	71.5 (39)	68.1 (32)	–4.8
$t_{1/2}$ (h)	25.2 (35)	25.2 (27)	0
$CL_\tau/f_m \cdot F$ (L/h)	31.3 (33)	32.5 (38)	–
Vz/fm·F (L)	1102 (34)	1219 (51)	–
Amount excreted (% of dose)	168.0 (38)	145.2 (70)	–14
CL_R (mL/min)	56.2 (26)	58.6 (27)	4.3

CV = coefficient of variance; PK = pharmacokinetics.
*Difference (%) = (healthy – renally impaired)/healthy × 100. †Median (range).

Figure 2. Mean Concentration–Time Profiles of Iloperidone and Metabolites (P88 and P95) in Healthy and Hepatically Impaired Subjects Following a Single Oral 2-mg Dose.

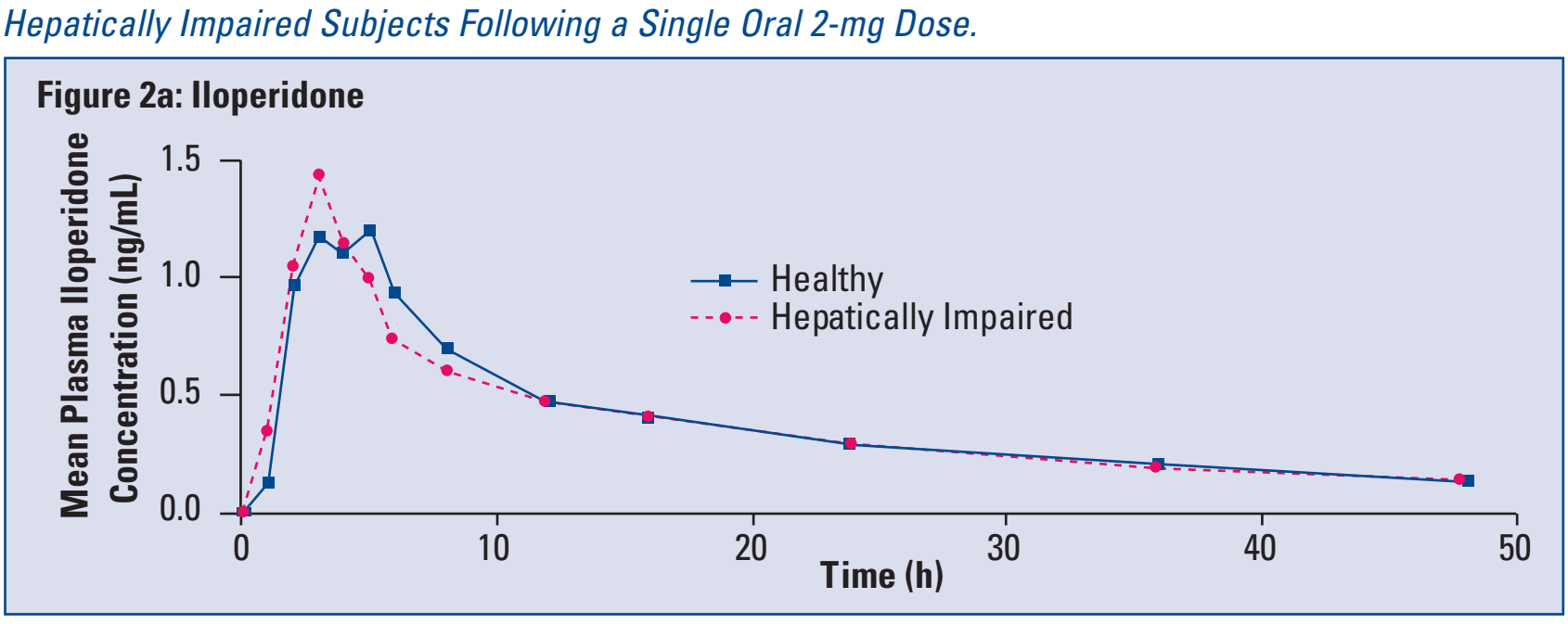


Figure 2b: P88

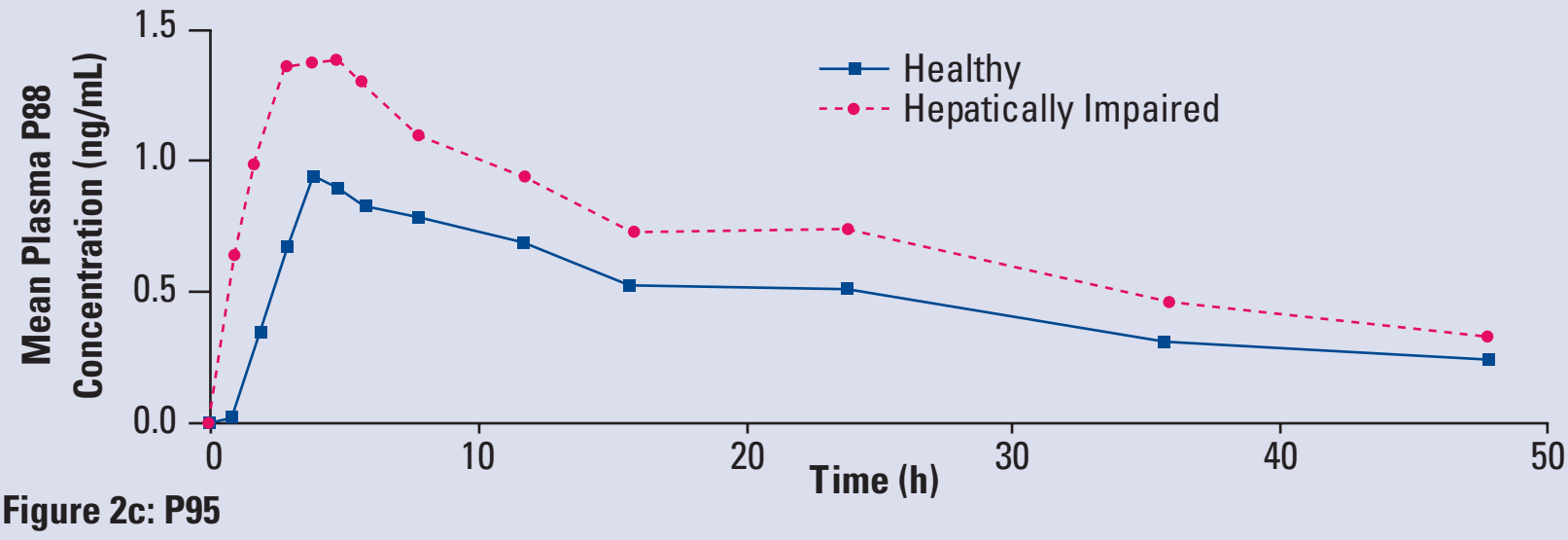
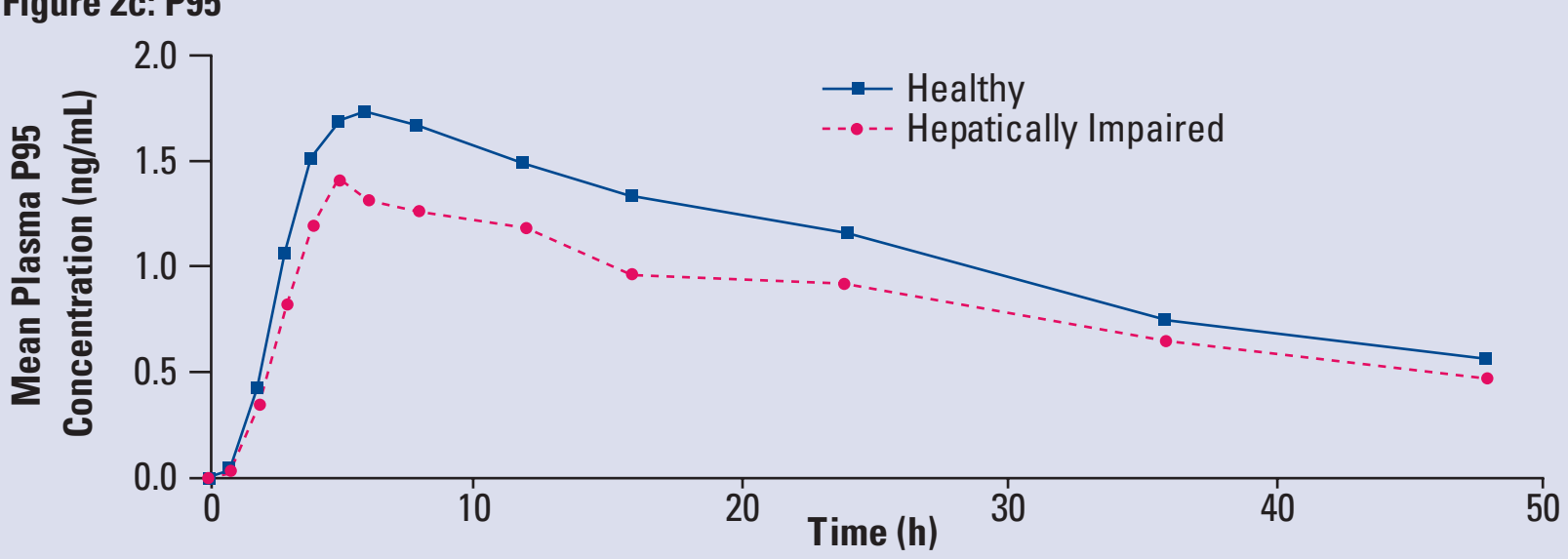


Figure 2c: P95



Safety (Studies 1 and 2)

- No increase in adverse events was observed in subjects with hepatic or renal impairment compared with healthy control subjects (**Table 4**).
- No clinically significant ECG changes were observed.

Table 4. Summary of Adverse Events.

Adverse Event	Renal Impairment Study		Hepatic Impairment Study	
	Group 1* (n = 8)	Group 2* (n = 8)	Group 1* (n = 10)	Group 2* (n = 13)
Somnolence	–	1	1	1
Dizziness	1	2	1	1
Headache	1	1	1	–
Watery eyes	–	–	1	–
Dry mouth	–	–	1	–
Diarrhea	–	–	1	–
Rhinitis	–	2	–	1
Dyspnea	1	–	–	–

*Group 1 = impaired subjects; Group 2 = healthy control subjects.

CONCLUSIONS

- In renally impaired subjects, iloperidone C_{max} and $AUC_{0\text{-}t}$ were modestly increased (by 5% and 24%, respectively). Iloperidone half-life doubled, and $AUC_{0\text{-}\infty}$ increased by 80%, but these values are probably exaggerated because of unexpected plasma concentration values at 48 hours.
- P88 PK were virtually unchanged, and exposure to P95 was significantly higher in renally impaired subjects.
- Iloperidone exposure was unaffected by mild to moderate hepatic impairment.
- Exposure to P88 was moderately higher in hepatically impaired subjects compared with healthy controls, suggesting a potentially increased combined exposure to pharmacologically active moieties (iloperidone + P88) of approximately 30%.
- The metabolism of iloperidone to P95 is slower in hepatically impaired CYP2D6-genotyped subjects considered extensive metabolizers.
- Protein binding was unaffected by renal or hepatic impairment.
- Single low doses of iloperidone were well tolerated by all subjects.

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REFERENCES

1. Kalkman HO et al. *Neuropsychopharmacology*. 2001;25:904-914.
2. Kalkman HO et al. *Life Sci*. 2003;73:1151-1159.

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