Genotyping Facilitates Individualized Prediction of Pharmacokinetic Exposure of Iloperidone in Extensive and Poor CYP2D6 Metabolizers

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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. Iloperidone metabolism involves CYP450 enzymes 2D6 and 3A4, and results in a major active metabolite, P88, and an inactive metabolite (with respect to central nervous system activity), P95. A study was conducted characterizing iloperidone pharmacokinetics in CYP2D6-genotyped extensive (EM) and poor (PM) metabolizers. Iloperidone interaction with dextromethorphan, a CYP2D6 prototype substrate, was assessed.

Methods: A 2-cohort, open-label study was completed in healthy subjects genotyped as CYP2D6 EM (Cohort 1, n = 19) or PM (Cohort 2, n = 8). All subjects received a single 3-mg iloperidone dose in period 1. In periods 2 and 3, subjects in Cohort 1 received either 80 mg of dextromethorphan or 3 mg of iloperidone + 80 mg of dextromethorphan in random order. Subjects in Cohort 2 did not participate in periods 2 and 3. Plasma samples were collected for 72 hours after administration of iloperidone and iloperidone + dextromethorphan. Serum samples were collected for 24 hours after administration of dextromethorphan and 72 hours after administration of iloperidone + dextromethorphan.

Results: Iloperidone and P88 area under the plasma concentration-time curve (AUC) values were substantially increased (57% and 95%, respectively) in PM, and P95 exposure was substantially decreased (80%). Elimination half-life was prolonged by 88% for iloperidone, 46% for P88, and 33% for P95. In contrast, dextromethorphan did not influence pharmacokinetic parameters of iloperidone: C_{max} of iloperidone alone (2.79 ng/mL) and in combination with dextromethorphan (2.75 ng/mL) appeared at the same median time of 2.5 hours. In general, pharmacokinetic parameters of iloperidone were similar in the presence or absence of dextromethorphan.

Conclusions: CYP2D6 genotyping of patients as EM or PM facilitates individualized prediction of the pharmacokinetic profile of iloperidone. Although iloperidone was well-tolerated by EM and PM, the ultimate clinical goal of achieving the best balance of efficacy/tolerability/side-effects can be better realized considering CYP2D6 status.

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 $NE_{\alpha1}$ 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.[1-4]
- Iloperidone is extensively metabolized in the liver via multiple pathways, including pathways mediated by the cytochrome P450 enzymes CYP2D6 and CYP3A4.[5] The 2 major metabolites of iloperidone are an active metabolite, P88, and an inactive metabolite (with respect to central nervous system activity), P95.
- CYP2D6 is known to be polymorphic, and approximately 5% to 10% of the Caucasian population carries a genotype of poor metabolizer (PM).[6,7]
- The objectives of this study are
  - To compare the pharmacokinetic (PK) profiles of iloperidone and its metabolites, P88 and P95, in subjects CYP2D6-genotyped as extensive metabolizers (EM) or PM
  - To assess the PK interactions of iloperidone and dextromethorphan, a CYP2D6 prototype substrate, in subjects CYP2D6-genotyped as EM

METHODS

Trial Design

- A 2-cohort, randomized, open-label, 3-period, crossover study (**Table 1**)
  - Cohort 1: n = 19; healthy subjects CYP2D6-genotyped as EM
  - Cohort 2: n = 8; healthy subjects CYP2D6-genotyped as PM

Table 1. Study Treatment Design.

	Period 1	Period 2	Period 3
Cohort 1/ Sequence 1	Iloperidone 3 mg	Dextromethorphan 80 mg + Iloperidone 3 mg	Dextromethorphan 80 mg
Cohort 1/ Sequence 2	Iloperidone 3 mg	Dextromethorphan 80 mg	Dextromethorphan 80 mg + Iloperidone 3 mg
Cohort 2/ Sequence 1	Iloperidone 3 mg	—	—

- Iloperidone plasma samples were colleted for 72 hours after administration of iloperidone and iloperidone + dextromethorphan to assess PK parameters of iloperidone and its metabolites.
- Dextromethorphan serum samples were collected for 24 hours after administration of dextromethorphan alone and for 72 hours after administration of dextromethorphan + iloperidone to assess PK parameters of dextromethorphan and its metabolite dextrorphan.
- Urine samples were collected up to 72 hours after dosing of iloperidone to assess PK parameters of iloperidone and its metabolites.

Pharmacokinetic Parameters

The following PK parameters were determined using noncompartmental methods using WinNonlin Pro (Version 2.1):

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

Safety Evaluations

- Safety assessments included medical history, physical examination, vital signs, electrocardiography, laboratory evaluations, and adverse event (AE) monitoring.

Statistical Methods

- An analysis of variance (ANOVA) model based on a parallel group design was used to compare iloperidone, P88, and P95 profiles between cohorts.
- An ANOVA model based on a 2×2 crossover design was used to compare dextromethorphan and dextrorphan PK profiles from periods 2 and 3.
- An ANOVA model based on a randomized block design was used to compare iloperidone, P88, and P95 profiles from all 3 periods in Cohort 1.

RESULTS

Subject Demographics

- 25 males and 2 females; mean age of 29.84 years
- 66.6% (n = 18) Caucasian, 3.7% (n = 1) black, 3.7% (n = 1) Asian, and 25.9% (n = 7) other racial origins
  - 19 subjects were CYP2D6-genotyped as EM
  - 8 subjects were CYP2D6-genotyped as PM

Pharmacokinetics: Iloperidone Alone in CYP2D6-genotyped Extensive versus Poor Metabolizers

- Comparison of the PK parameters between the cohorts showed (**Table 2**)
  - V_z/F was similar between the groups
  - Iloperidone exposure ($AUC_{0-\infty}$) was substantially greater in the PM group
  - Half-life of iloperidone was prolonged and CL_r/F was decreased in the PM group
- Comparison of the P88 PK parameters between the cohorts showed (**Table 3**)
  - P88 exposure ($AUC_{0-\infty}$) and C_{max} of P88 were substantially greater in the PM group
  - Half-life of P88 was prolonged and CL_r/f_m was decreased in the PM group
- Comparison of the P95 PK parameters between the cohorts showed (**Table 4**)
  - P95 exposure ($AUC_{0-\infty}$) and C_{max} of P95 were substantially lower in the PM group
  - Half-life of P95 was prolonged in the PM group
  - CL_R was approximately the same between the groups

Table 2. Mean Iloperidone Pharmacokinetic Parameters in CYP2D6-genotyped Extensive and Poor Metabolizers After a Single 3-mg Oral Iloperidone Dose.

	Mean (CV%)		
Pharmacokinetic Parameter	Extensive Metabolizers (EM)	Poor Metabolizers (PM)	Difference (%)*
T_{max} (h)†	2.5 (2-3)	3 (1-4)	—
C_{max} (ng/mL)	2.79 (27)	2.26 (13)	–19.0
$AUC_{0-\infty}$ (ng·h/mL)	29.4 (36)	46.3 (17)	57.4
$t_{1/2}$ (h)	17.6 (36)	32.8 (21)	86.4
CL_r/F (L/h)	116.5 (39)	66.4 (16)	–43.0
V_z/F (L)	2868 (49)	3095 (19)	7.9
Amount excreted (% of dose)	0.45 (69)	0.70 (34)	55.6
CL_R (mL/min)	8.2 (56)	9.28 (25)	13.1

CV = coefficient of variance. *Difference (%) = (PM – EM)/EM × 100. †Median (range).

Table 3. Mean P88 Pharmacokinetic Parameters in CYP2D6-genotyped Extensive and Poor Metabolizers After a Single 3-mg Oral Iloperidone Dose.

	Mean (CV%)		
Pharmacokinetic Parameter	Extensive Metabolizers (EM)	Poor Metabolizers (PM)	Difference (%)*
T_{max} (h)†	4.0 (3-6)	4.5 (3-6)	—
C_{max} (ng/mL)	2.32 (30)	3.33 (20)	43.5
$AUC_{0-\infty}$ (ng·h/mL)	49.4 (43)	96.4 (21)	95.1
$t_{1/2}$ (h)	25.5 (45)	37.3 (20)	46.3
CL_r/f_m·F (L/h)	68.7 (32)	32.3 (20)	–53.0
V_z/F (L)	2343 (45)	1715 (21)	–26.8
Amount excreted (% of dose)	4.2 (57)	8.0 (30)	90.5
CL_R (mL/min)	46.5 (35)	51.3 (16)	10.3

CV = coefficient of variance. *Difference (%) = (PM – EM)/EM × 100. †Median (range).

Table 4. Mean P95 Pharmacokinetic Parameters in CYP2D6-genotyped Extensive and Poor Metabolizers After a Single 3-mg Oral Iloperidone Dose.

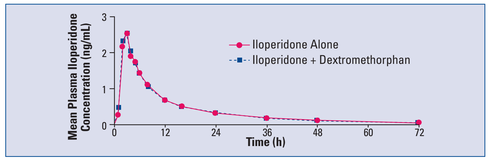
	Mean (CV%)		
Pharmacokinetic Parameter	Extensive Metabolizers (EM)	Poor Metabolizers (PM)	Difference (%)*
T_{max} (h)†	6.0 (3-16)	8.0 (3-12)	—
C_{max} (ng/mL)	4.5 (34)	0.67 (44)	–85.0
$AUC_{0-\infty}$ (ng·h/mL)	153.8 (26)	32.1 (36)	–79.1
$t_{1/2}$ (h)	23.0 (20)	30.6 (31)	33.0
CL_r/f_m·F (L/h)	21.5 (41)	101.4 (26)	380.9
V_z/F (L)	730.3 (53)	4520 (53)	519.1
Amount excreted (% of dose)	19.2 (31)	4.5 (24)	–76.5
CL_R (mL/min)	66.4 (26)	75.0 (25)	12.9

CV = coefficient of variance. *Difference (%) = (PM – EM)/EM × 100. †Median (range).

Pharmacokinetics: Coadministration of Iloperidone and Dextromethorphan in CYP2D6-genotyped Extensive Metabolizers

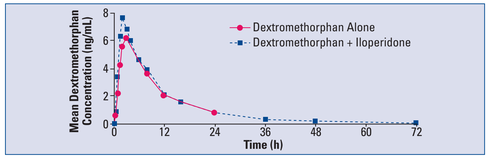
- Time courses of mean plasma concentrations of iloperidone after administration of iloperidone alone and in combination with dextromethorphan were indistinguishable (**Figure 1**).
- PK parameters for iloperidone were similar when iloperidone was administered alone or in combination with dextromethorphan.
- Time courses of mean plasma concentrations of P88 and P95 after administration of iloperidone alone and in combination with dextromethorphan were also indistinguishable.
- PK parameters of P88 were similar when iloperidone was administered alone or in combination with dextromethorphan. Differences in the PK parameters between the treatments were all <10%.
- PK parameters of P95 were similar when iloperidone was administered alone or in combination with dextromethorphan. Differences in the PK parameters between the treatments were <14%.

Figure 1. Mean Plasma Concentration of Iloperidone After Administration of a Single 3-mg Oral Dose of Iloperidone Alone and in Combination With a Single 80-mg Oral Dose of Dextromethorphan.



- Most PK parameters of dextromethorphan were similar when dextromethorphan was administered alone or in combination with iloperidone (**Figure 2**).
- There was a <10% difference between the treatments for AUC, $t_{1/2}$, CL_r/F, and V_z/F, and a 24% difference between treatments in mean C_{max}.
- Formation of dextrorphan, the metabolite of dextromethorphan resulting from CYP2D6 metabolism, occurred at the same rate after administration of iloperidone.
- The differences between treatments for dextrorphan C_{max} and AUC were 5% and 1%, respectively.
- Coadministration of iloperidone prolonged $t_{1/2}$ of dextrorphan by 58% (4.55 vs 7.17 hours).

Figure 2. Mean Plasma Concentration of Dextromethorphan After Administration of a Single 80-mg Oral Dose of Dextromethorphan Alone and in Combination With a Single 3-mg Oral Dose of Iloperidone.



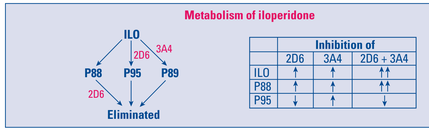
Safety

- AEs were reported by 20 of 27 subjects. The most common AEs suspected to be related to study medications were
  - Dizziness (16 episodes in 12 subjects)
  - Rhinitis (10 episodes in 8 subjects)
  - Tachycardia (5 episodes in 4 subjects)
- When iloperidone was administered alone, the frequency of AEs was not different between EM (12 in 19 subjects) and PM (5 in 8 subjects).
- After administration of iloperidone, clinical laboratory findings were similar between the groups.

CONCLUSIONS

- The PK profile of iloperidone was altered in CYP2D6-genotyped PM compared with EM.
- In EM, dextromethorphan did not alter the PK profile of iloperidone, and iloperidone did not alter the PK profile of dextromethorphan during concurrent administration.
- Interaction between iloperidone and other CYP2D6 substrates is unlikely.
- CYP2D6 genotyping of patients as EM or PM facilitates prediction of the individualized PK profile of iloperidone (**Figure 3**).

Figure 3. Metabolism of Iloperidone (ILO) and CYP450-inhibitor Effects.



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Cohort 1/ Sequence 2	Iloperidone 3 mg	Dextromethorphan 80 mg	Dextromethorphan 80 mg + Iloperidone 3 mg
Cohort 2/ Sequence 1	Iloperidone 3 mg	—	—

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The following PK parameters were determined using noncompartmental methods using WinNonlin Pro (Version 2.1):

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- Area under the plasma concentration-time curve from zero to infinity ($AUC_{0-\infty}$)
- Elimination half-life ($t_{1/2}$)
- Apparent clearance of parent drug (CL_τ/F)
- Apparent clearance of metabolite ($CL_\tau/f_m \cdot F$)
- Apparent volume of distribution (V_z/F)
- Total amount excreted in urine
- Renal clearance (CL_R)

Safety Evaluations

- Safety assessments included medical history, physical examination, vital signs, electrocardiography, laboratory evaluations, and adverse event (AE) monitoring.

Statistical Methods

- An analysis of variance (ANOVA) model based on a parallel group design was used to compare iloperidone, P88, and P95 profiles between cohorts.
- An ANOVA model based on a 2×2 crossover design was used to compare dextromethorphan and dextrorphan PK profiles from periods 2 and 3.
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RESULTS

Subject Demographics

- 25 males and 2 females; mean age of 29.84 years
- 66.6% (n = 18) Caucasian, 3.7% (n = 1) black, 3.7% (n = 1) Asian, and 25.9% (n = 7) other racial origins
  - 19 subjects were CYP2D6-genotyped as EM
  - 8 subjects were CYP2D6-genotyped as PM

Pharmacokinetics: Iloperidone Alone in CYP2D6-genotyped Extensive versus Poor Metabolizers

- Comparison of the PK parameters between the cohorts showed (**Table 2**)
  - V_z/F was similar between the groups
  - Iloperidone exposure ($AUC_{0-\infty}$) was substantially greater in the PM group
  - Half-life of iloperidone was prolonged and CL_τ/F was decreased in the PM group
- Comparison of the P88 PK parameters between the cohorts showed (**Table 3**)
  - P88 exposure ($AUC_{0-\infty}$) and C_{max} of P88 were substantially greater in the PM group
  - Half-life of P88 was prolonged and CL_τ/f_m was decreased in the PM group
- Comparison of the P95 PK parameters between the cohorts showed (**Table 4**)
  - P95 exposure ($AUC_{0-\infty}$) and C_{max} of P95 were substantially lower in the PM group
  - Half-life of P95 was prolonged in the PM group
  - CL_R was approximately the same between the groups

Table 2. Mean Iloperidone Pharmacokinetic Parameters in CYP2D6-genotyped Extensive and Poor Metabolizers After a Single 3-mg Oral Iloperidone Dose.

Pharmacokinetic Parameter	Mean (CV%)		
	Extensive Metabolizers (EM)	Poor Metabolizers (PM)	Difference (%)*
T_{max} (h)†	2.5 (2-3)	3 (1-4)	—
C_{max} (ng/mL)	2.79 (27)	2.26 (13)	–19.0
$AUC_{0-\infty}$ (ng·h/mL)	29.4 (36)	46.3 (17)	57.4
$t_{1/2}$ (h)	17.6 (36)	32.8 (21)	86.4
CL_τ/F (L/h)	116.5 (39)	66.4 (16)	–43.0
V_z/F (L)	2868 (49)	3095 (19)	7.9
Amount excreted (% of dose)	0.45 (69)	0.70 (34)	55.6
CL_R (mL/min)	8.2 (56)	9.28 (25)	13.1

CV = coefficient of variance. *Difference (%) = (PM – EM)/EM × 100. †Median (range).

Table 3. Mean P88 Pharmacokinetic Parameters in CYP2D6-genotyped Extensive and Poor Metabolizers After a Single 3-mg Oral Iloperidone Dose.

Pharmacokinetic Parameter	Mean (CV%)		
	Extensive Metabolizers (EM)	Poor Metabolizers (PM)	Difference (%)*
T_{max} (h)†	4.0 (3-6)	4.5 (3-6)	—
C_{max} (ng/mL)	2.32 (30)	3.33 (20)	43.5
$AUC_{0-\infty}$ (ng·h/mL)	49.4 (43)	96.4 (21)	95.1
$t_{1/2}$ (h)	25.5 (45)	37.3 (20)	46.3
$CL_\tau/f_m \cdot F$ (L/h)	68.7 (32)	32.3 (20)	–53.0
V_z/F (L)	2343 (45)	1715 (21)	–26.8
Amount excreted (% of dose)	4.2 (57)	8.0 (30)	90.5
CL_R (mL/min)	46.5 (35)	51.3 (16)	10.3

CV = coefficient of variance. *Difference (%) = (PM – EM)/EM × 100. †Median (range).

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Table 4. Mean P95 Pharmacokinetic Parameters in CYP2D6-genotyped Extensive and Poor Metabolizers After a Single 3-mg Oral Iloperidone Dose.

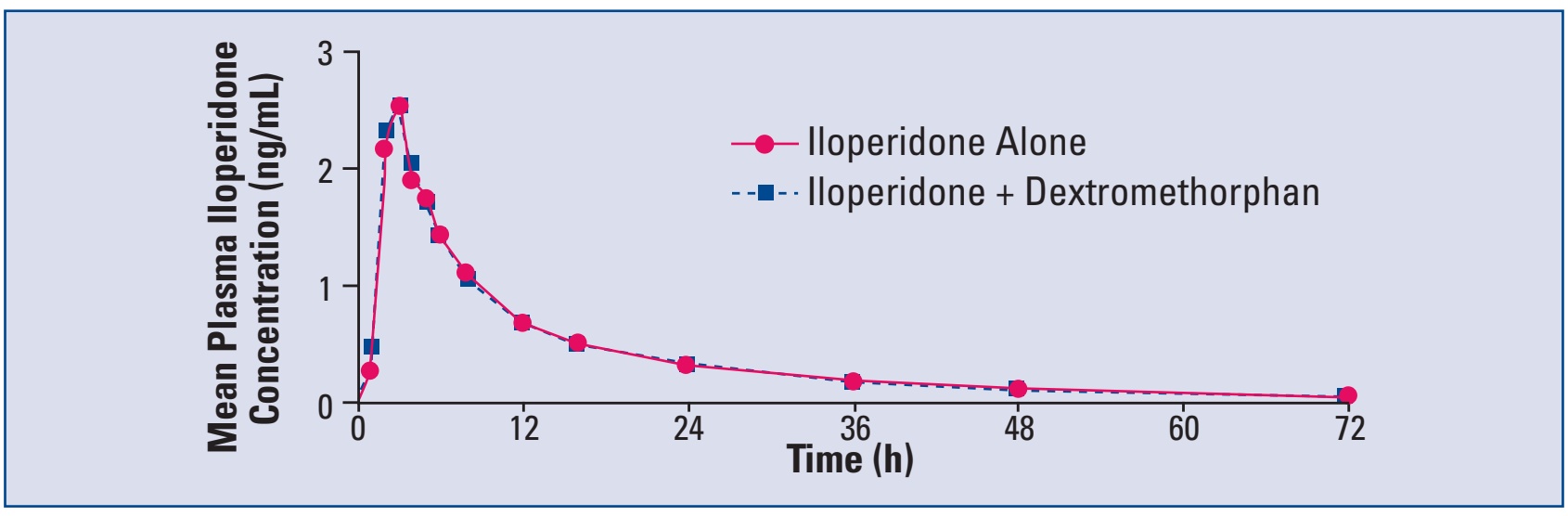
Pharmacokinetic Parameter	Mean (CV%)		
	Extensive Metabolizers (EM)	Poor Metabolizers (PM)	Difference (%)*
T_{max} (h)†	6.0 (3-16)	8.0 (3-12)	—
C_{max} (ng/mL)	4.5 (34)	0.67 (44)	–85.0
$AUC_{0-\infty}$ (ng·h/mL)	153.8 (26)	32.1 (36)	–79.1
$t_{1/2}$ (h)	23.0 (20)	30.6 (31)	33.0
$CL_\tau/f_m \cdot F$ (L/h)	21.5 (41)	101.4 (26)	380.9
V_z/F (L)	730.3 (53)	4520 (53)	519.1
Amount excreted (% of dose)	19.2 (31)	4.5 (24)	–76.5
CL_R (mL/min)	66.4 (26)	75.0 (25)	12.9

CV = coefficient of variance. *Difference (%) = (PM – EM)/EM × 100. †Median (range).

Pharmacokinetics: Coadministration of Iloperidone and Dextromethorphan in CYP2D6-genotyped Extensive Metabolizers

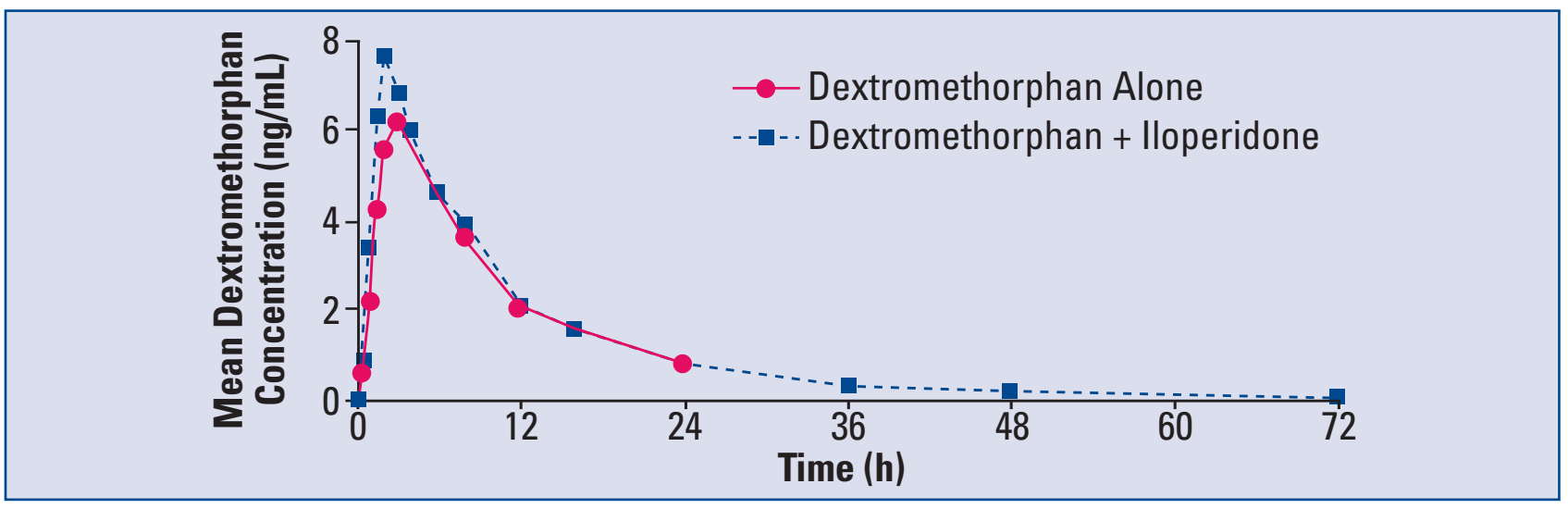
- Time courses of mean plasma concentrations of iloperidone after administration of iloperidone alone and in combination with dextromethorphan were indistinguishable (**Figure 1**).
- PK parameters for iloperidone were similar when iloperidone was administered alone or in combination with dextromethorphan.
- Time courses of mean plasma concentrations of P88 and P95 after administration of iloperidone alone and in combination with dextromethorphan were also indistinguishable.
- PK parameters of P88 were similar when iloperidone was administered alone or in combination with dextromethorphan. Differences in the PK parameters between the treatments were all <10%.
- PK parameters of P95 were similar when iloperidone was administered alone or in combination with dextromethorphan. Differences in the PK parameters between the treatments were <14%.

Figure 1. Mean Plasma Concentration of Iloperidone After Administration of a Single 3-mg Oral Dose of Iloperidone Alone and in Combination With a Single 80-mg Oral Dose of Dextromethorphan.



- Most PK parameters of dextromethorphan were similar when dextromethorphan was administered alone or in combination with iloperidone (**Figure 2**).
- There was a <10% difference between the treatments for AUC, $t_{1/2}$, CL_τ/F, and V_z/F, and a 24% difference between treatments in mean C_{max}.
- Formation of dextrorphan, the metabolite of dextromethorphan resulting from CYP2D6 metabolism, occurred at the same rate after administration of iloperidone.
- The differences between treatments for dextrorphan C_{max} and AUC were 5% and 1%, respectively.
- Coadministration of iloperidone prolonged $t_{1/2}$ of dextrorphan by 58% (4.55 vs 7.17 hours).

Figure 2. Mean Plasma Concentration of Dextromethorphan After Administration of a Single 80-mg Oral Dose of Dextromethorphan Alone and in Combination With a Single 3-mg Oral Dose of Iloperidone.



Safety

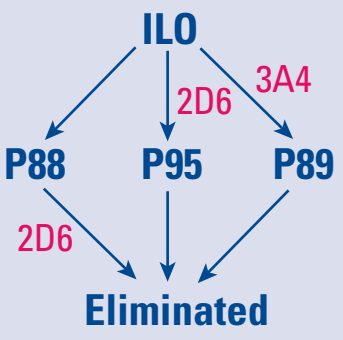
- AEs were reported by 20 of 27 subjects. The most common AEs suspected to be related to study medications were
  - Dizziness (16 episodes in 12 subjects)
  - Rhinitis (10 episodes in 8 subjects)
  - Tachycardia (5 episodes in 4 subjects)
- When iloperidone was administered alone, the frequency of AEs was not different between EM (12 in 19 subjects) and PM (5 in 8 subjects).
- After administration of iloperidone, clinical laboratory findings were similar between the groups.

CONCLUSIONS

- The PK profile of iloperidone was altered in CYP2D6-genotyped PM compared with EM.
- In EM, dextromethorphan did not alter the PK profile of iloperidone, and iloperidone did not alter the PK profile of dextromethorphan during concurrent administration.
- Interaction between iloperidone and other CYP2D6 substrates is unlikely.
- CYP2D6 genotyping of patients as EM or PM facilitates prediction of the individualized PK profile of iloperidone (**Figure 3**).

Figure 3. Metabolism of Iloperidone (ILO) and CYP450-inhibitor Effects.

Metabolism of iloperidone



	Inhibition of		
	2D6	3A4	2D6 + 3A4
ILO	↑	↑	↑↑
P88	↑	↑	↑↑
P95	↓	↑	↓

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