The Pharmacogenomics Journal (2003) 3, 105–113

www.nature.com/tpj

ORIGINAL ARTICLE

Pharmacokinetics and QT interval pharmacodynamics of oral haloperidol in poor and extensive metabolizers of *CYP2D6*

M Desai[1,2]
JE Tanus-Santos[2]
L Li[1]
JC Gorski[1]
M Arefayene[1,2]
Y Liu[1]
Z Desta[1,2]
DA Flockhart[1,2]

[1]*Divisions of Clinical Pharmacology, Indiana University School of Medicine, Indianapolis, IN, USA;* [2]*Georgetown University Medical Center, Washington, DC, USA*

Correspondence:
DA Flockhart, Department of Medicine/ Division of Clinical Pharmacology, Indiana University School of Medicine, Wishard Memorial Hospital, Myers Bldg. Room W7123, 1001 W. 10th St., Indianapolis, IN 46202-2879, USA.
Tel: +1 317 630 8795
Fax: +1 317 630 8185
E-mail: dflockha@iupui.edu

Received: 26 September 2002
Revised: 2 January 2003
Accepted: 6 January 2003

ABSTRACT

We studied the pharmacokinetics and QT interval pharmacodynamics of a single 10 mg dose of oral haloperidol in a randomized, double-blind, placebo-controlled, crossover trial of healthy poor (PMs) and extensive (EMs) metabolizers of *CYP2D6*. There was a statistically significant greater mean QT_c on haloperidol (421.6±20.1 ms) than on placebo (408.4±18.5 ms, $P=0.0053$) occurring 10 h post haloperidol/placebo administration. Men and women had similar ranges of QT_c changes from placebo. Despite a statistically significant greater mean elimination half-life (19.1±3.6 *vs* 12.9±4.0 h, $P=0.04$) and lower mean apparent oral clearance (12.8±4.1 *vs* 27.0±11.3 ml/min/kg, $P=0.02$) of haloperidol in *CYP2D6* PMs than in EMs, this exposure change did not translate into marked QT_c changes from baseline that could be considered clinically important. Although the magnitude of the mean QT_c prolongation on haloperidol relative to placebo is relatively small, it may assume significance in the presence of other risk factors for QT prolongation.
The Pharmacogenomics Journal (2003) **3,** 105 113. doi:10.1038/sj.tpj.6500160

Keywords: haloperidol; CYP2D6 genotype; QT

INTRODUCTION

Schizophrenia is a common psychiatric disease with a lifetime prevalence of nearly 1% of the general population[1] that is associated with an increased risk of premature death. A recent meta-analysis revealed that schizophrenic patients are 1.5 times more likely of dying from all causes compared to an age- and gender-matched cohort of the general population.[2] While it is not known how much of this excess risk can be attributed to antipsychotic-induced cardiotoxicity, it is clear that many antipsychotics are arrhythmogenic.[3]

Among the antipsychotic drugs, haloperidol remains one of the most widely used worldwide. Haloperidol-induced ventricular arrhythmias of the torsades de pointes (TdP) type have been reported with a range of doses starting as low as 4 mg[4] administered over a 24 h period and as high as 825 mg[5] over a 24-h period. Cardiac side effects at high doses likely involve excessive exposure to haloperidol. However, the extent to which low doses of haloperidol contribute to QT interval prolongation in the absence of risk factors[6] such as age, concomitant medications, electrolyte imbalances, ischemic heart disease, or congenitally prolonged QT intervals is less well characterized. Prolongation of the QT interval is a biomarker for the malignant ventricular arrhythmia of TdP.

In vitro cardiac electrophysiology studies that we have conducted demonstrate that supratherapeutic concentrations of haloperidol prolong the heart rate corrected QT interval (QT_c) by approximately 26% in an isolated perfused feline heart model.[7] The mechanism of haloperidol-mediated QT prolongation

involves blockade of the rapidly acting delayed rectifier potassium channel (I_{Kr}). Haloperidol, has been shown to block this channel expressed in Xenopus oocytes in a concentration-dependent manner with an IC_{50} of 1 μM.[8] Despite the clear ability of haloperidol to bring about relevant changes in ion channel activity *in vitro* and a number of incriminating case reports of cardiotoxicity,[9] the ability of therapeutic doses of haloperidol to prolong the QT_c interval in healthy subjects without the presence of interacting drugs is not known.

Cytosol reductase is the enzyme that converts haloperidol to reduced haloperidol, an active metabolite.[10,11] Reduced haloperidol can be oxidized back to haloperidol by cytochrome *P*450 isoforms CYP3A4 and CYP2D6.[12,13] Multiple clinical studies have shown that *CYP2D6* genotype influences haloperidol and reduced haloperidol pharmacokinetics.[14–16] However, it is not known to what extent *CYP2D6* genotype influences haloperidol-induced QT interval pharmacodynamics.

The primary objective of the present study was to determine the potential for a commonly used clinical dose of haloperidol to alter the QT_c interval in healthy subjects in a prospective, randomized controlled trial. The secondary objectives of the study were to determine the influence of *CYP2D6* genotype on haloperidol disposition and QT interval pharmacodynamics.

RESULTS

A total of 16 healthy subjects participated in the study. Subject demographics are presented in Table 1. The body mass index (BMI) ranged from 21.4 to 31.6 kg/m^2 in all subjects with males (25.8±3.6 kg/m^2) having a greater BMI compared to females (22.4±1.4 kg/m^2) ($P=0.036$). In all, eight of the volunteers were *CYP2D6* *1 homozygotes, two were *4 heterozygotes, two were *10 heterozygotes, one was a *17 homozygote, and three were *4 homozygotes. One subject who started the study dropped out because of severe anxiety and restlessness 4 h postdosing. At 10 h postdosing, the mean heart rate was 62.3±6.5 beats per minute (bpm) and 56.3±8.1 bpm on haloperidol and placebo, respectively ($P=0.003$ pre-Bonferonni and $P=0.039$ post-Bonferonni). The heart rate was not statistically significantly different between the two groups at any other time point during the study.

Table 1 Demographics

	Female (n=8)	*Males* (n=8)
Age (years)	26.9±8.0	32.1±4.0
Weight (kg)	62.3±6.7	82.5±14.2
Height (cm)	166.7±7.4	178.5±6.2
Ethnicity		
Caucasian	5	4
African-American	1	3
Asian	2	1

Values are reported as the mean±SD of subjects completing the study.

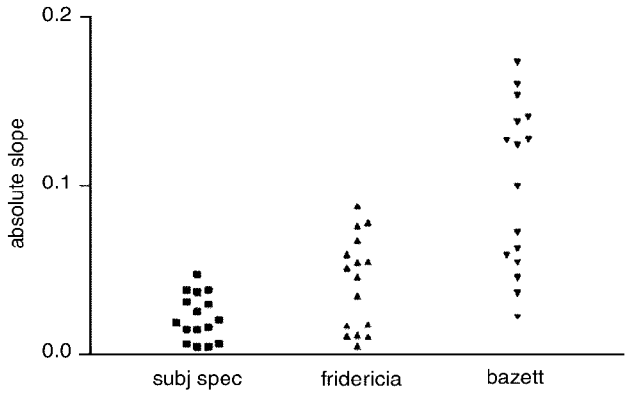

Figure 1 Absolute slope comparisons of each subject's ($N=16$) linear regression line between QT_c *vs* RR using the subject-specific correction, Fredericia's correction, and Bazett's correction (based on placebo period data only). A lower slope suggests less potential for over or under correction of the heart rate corrected QT interval (QT_c).

Subject-specific QT Correction Model

The slopes of the QT_c *vs* RR linear regression lines derived from Bazett's, Fredericia's, and the subject-specific heart rate correction formulae were compared using placebo (off-drug) response data. The goal of heart rate correction of the QT interval was to obtain a QT_c *vs* RR linear regression line with a slope as close to zero as possible. As shown in Figure 1, the mean absolute slope±SD of the QT_c interval (ms) *vs* RR interval (ms) regression line for placebo period data using the subject-specific correction (0.022±0.014) was significantly lower than the mean absolute slopes using Fredericia's correction (0.043±0.028, $P=0.04$) or Bazett's correction (0.10±0.049, $P<0.0001$). Since the subject-specific correction generated QT_c *vs* RR linear regression lines with the smallest absolute slopes, we chose to present study results using this correction method. Using linear mixed modeling for QT correction, the mean α±standard error of the mean (SEM) for our study sample was 0.29±0.02 (range 0.23–0.38). Alpha (α) was defined as the slope of the log transformed QT *vs* RR relation using the subject-specific heart correction method. The terms corresponding to α in both the Bazett and Fredericia heart rate correction formulae were constant at 1/2 and 1/3, respectively.

Pharmacokinetics

The mean±SD pharmacokinetic parameters of haloperidol for the 16 subjects are shown in Table 2. As shown in Table 3, there was no statistically significant difference between females and males with respect to clearance (25.2±12.3 *vs* 23.3±11.8 ml/min/kg, $P=0.72$), half-life (15.1±2.4 *vs* 13.1±5.9 h, $P=0.28$), and AUC (132.1±66.8 *vs* 107.1±47.6 ng h/ml, $P=0.50$) for the 10 mg dose. Reduced haloperidol, an active metabolite of haloperidol, was below detectable limits in the majority of subjects and therefore a pharmacokinetic profile of this metabolite is not reported. All but one of the subjects in whom this metabolite was detected

Table 2 Haloperidol pharmacokinetic parameters (n=16)

C_{max} (ng/ml)	7.6±3.6
T_{max} (h)	2.9±1.3
AUC (ng h/ml)	119.6±57.4
V_d/F (l/kg)	27.0±11.9
Clearance/*F* (ml/min/kg)	24.3±11.7
Half-life(h)	14.1±4.5

Values are reported as the mean±SD after administration of 10 mg of oral haloperidol. C_{max} is the maximal plasma concentration recorded in each subject. T_{max} is the time at which C_{max} occurred. AUC is the area under the plasma concentration *vs* time curve extrapolated to infinity. V_d/F is the apparent oral volume of distribution. Clearance/*F* is the apparent oral clearance.

Table 3 Haloperidol pharmacokinetics and sex

	Females (n=8)	*Males* (n=8)	P-*value*
AUC (ng h/ml)	132.1±66.8	107.1±47.6	0.51
Clearance/*F* (ml/min/kg)	25.3±12.3	23.3±11.8	0.72
Half-life (h)	15.1±2.4	13.1±6.0	0.29

Values are reported as the mean±SD of subjects receiving 10 mg oral haloperidol. AUC is the area under the plasma concentration *vs* time curve extrapolated to infinity. Clearance/*F* is the apparent oral clearance. *P*-values calculated using a nonparametric statistical test.

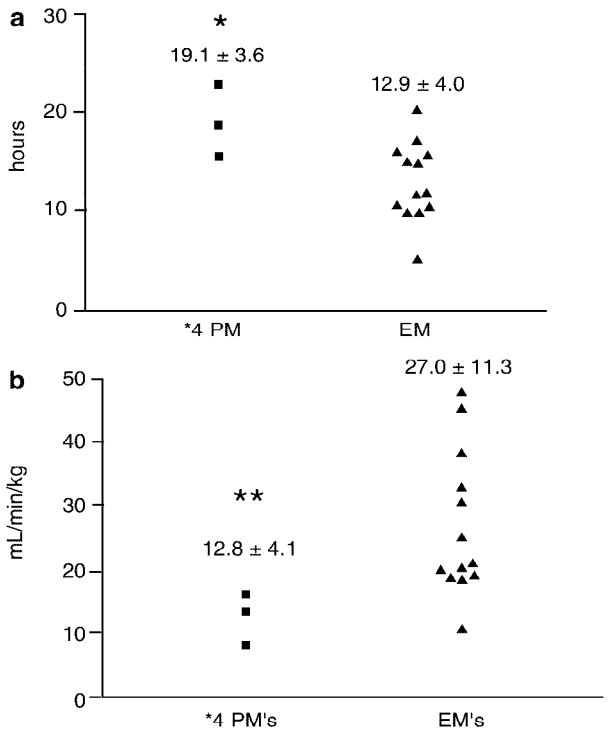

Figure 2 (a) Distribution of half-lives (h) as a function of *CYP2D6* genotype. (b) Distribution of apparent oral clearances (ml/min/kg) as a function of *CYP2D6* genotype (mean half-life and clearance/*F*±SD are as shown in the figure): *$P=0.04$; **$P=0.02$.

were poor metabolizers (PMs). In the three PMs receiving the 10 mg dose, the mean C_{max} was 1.23 ng/ml occurring between 24 and 48 h after haloperidol administration. In the single extensive metabolizer (EM) in whom it was detected, the C_{max} was 0.696 ng/ml occurring at 8 h postdose.

The effects of *CYP2D6* genotype on haloperidol pharmacokinetics are shown in Figure 2. The mean terminal elimination half-life of haloperidol was statistically significantly higher in PMs (19.1±4.0 h) compared to EMs (12.9±4.0 h, $P=0.04$) (Figure 2a). The mean apparent oral clearance of haloperidol was significantly lower in PMs (12.8±4.1 ml/min/kg) compared to EMs (27.0±11.3 ml/min/kg) ($P=0.02$) (Figure 2b). The maximal plasma concentrations of haloperidol achieved were 6.1±0.3 and 7.9±3.9 in PMs and EMS, respectively and were not statistically significantly different.

QT Interval Pharmacodynamics

As expected, the time averaged QT_c's±SD off drug (placebo only) were 416.8±17.9 and 408.9±16.6 ms in females and

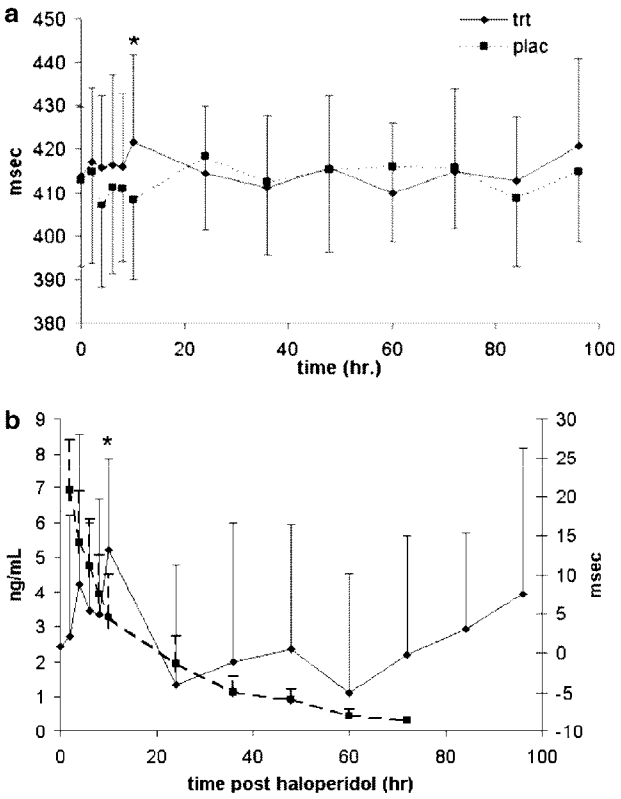

Figure 3 (a) Mean QT_c±SD (ms) on haloperidol and placebo as a function of time post haloperidol/placebo administration. (b) Mean QT_c change±SD (ms) and mean plasma haloperidol concentrations±SD (ng/ml) as a function of time posthaloperidol administration. The QT_c change is defined as QT_c on haloperidol minus the QT_c on placebo at the corresponding time point. *$P=0.0053$ (after Bonferonni correction).

males, respectively ($P=0.001$), which is consistent with findings in the medical literature that suggest females in general have longer QT intervals than males in the absence of drug therapy.

Figure 3a shows the mean QT_c's $\pm$SD in the treatment and placebo groups at each time point during the study. At the 10 h time point, the mean QT_c's were 421.6 ± 20.1 and 408.4 ± 18.5 ms on haloperidol and placebo, respectively ($P=0.00041$ pre-Bonferonni, $P=0.0053$ post-Bonferonni). At the 4- and 6-h time points, there were trends towards a greater mean QT_c on treatment than placebo but after Bonferonni's correction the trend was nullified. Figure 3b shows both the haloperidol-induced mean QT_c changes from placebo and the mean haloperidol plasma concentrations as a function of time post dosing. The QT_c change is defined as the QT_c on treatment at a given time point less the QT_c on placebo at the corresponding time point. Males and females had significant overlap in their maximal QT_c changes from placebo as shown in Figure 4a. There was also significant overlap in QT_c changes from placebo at T_{max} (the time point where maximal haloperidol plasma concentrations were achieved) (Figure 4b). Similarly among PMs and EMs of CYP2D6, there was significant overlap between the QT_c changes from placebo as shown in Figure 4c and 4d.

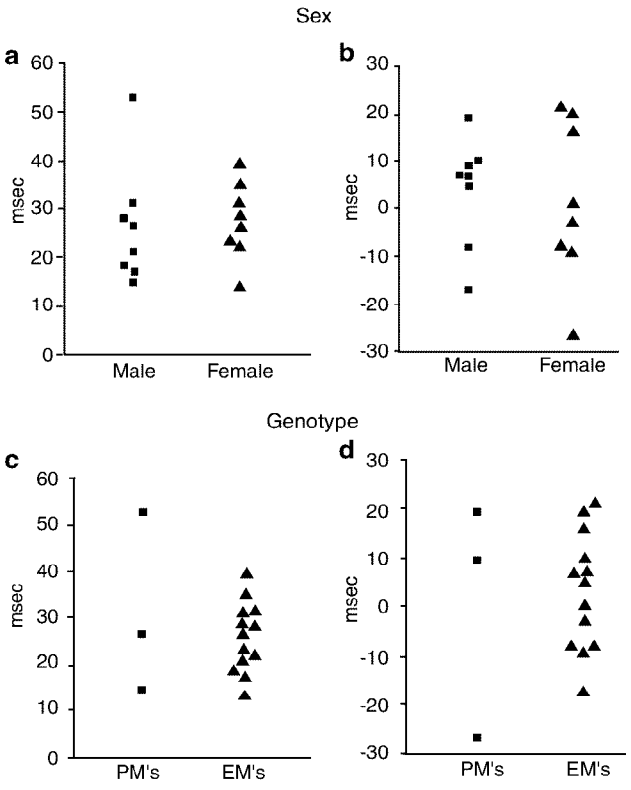

Figure 4 Haloperidol-induced QT_c changes from placebo as a function of sex and genotype. (a) and (c) show maximal QT_c changes in milliseconds from placebo occurring at any time postdose. (b) and (d) QT_c changes in milliseconds from placebo occurring at T_{max} (time point where maximal haloperidol concentrations were achieved).

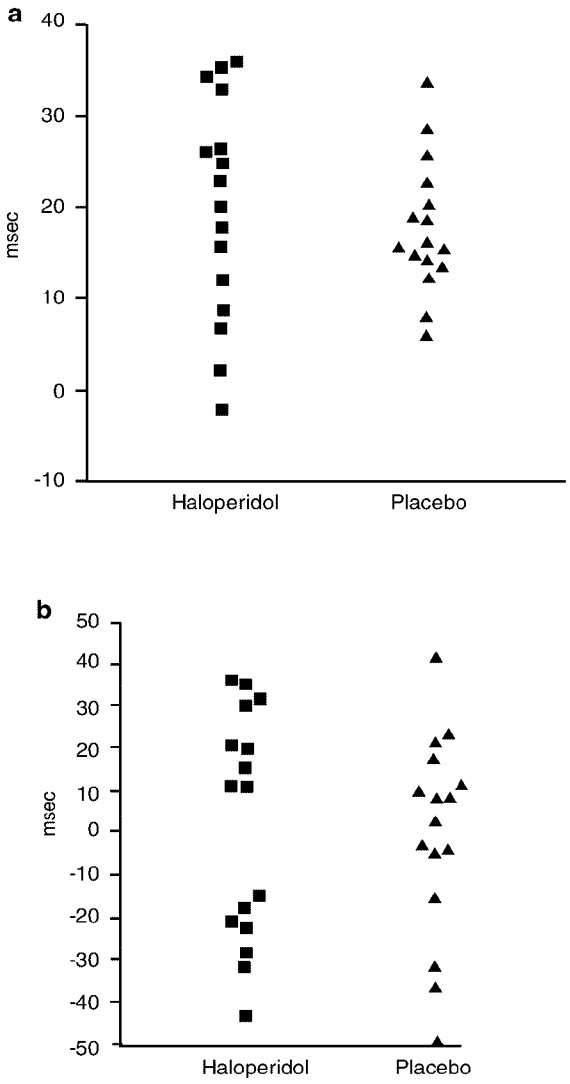

Figure 5 QT_c changes from baseline: haloperidol *vs* placebo. (a) Maximal QT_c change in milliseconds from baseline occurring at any time postdose. (b) QT_c change in milliseconds from baseline occurring at T_{max} (time point where maximal haloperidol concentrations were achieved).

There was significant overlap in the maximal QT_c change from baseline (time 0 time point) in the treatment and placebo groups as shown in Figure 5a. Similarly, significant overlap in the QT_c change from baseline occurred at the time point when maximal haloperidol plasma concentrations were achieved as shown in Figure 5b.

The maximal change in QT_c relative to baseline observed in a single individual at any time post haloperidol administration was 8.8%. Similarly, the maximal change in QT_c relative to baseline observed in any subject receiving

placebo was 7.2%, illustrating potential for significant variability of this measurement in the absence of any treatment.

There was poor correlation between plasma haloperidol concentrations and QT_c change from placebo during the first 10 h of the study ($R^2 = 0.007$, $P > 0.30$) (figure not shown).

Adverse Effects

No subject was discontinued from the study because of haloperidol-induced arrhythmia or other cardiac adverse event. One volunteer who started the study, dropped out because of severe anxiety and restlessness starting 4 h after receiving haloperidol. The most common side effects seen with haloperidol were anxiety and restlessness of variable intensity that occurred in 12 of 16 subjects (75%) completing the study. Other less common side effects that occurred at a frequency of between 10 and 40% were difficulty concentrating, feeling tired or sleepy, decreased appetite, dry mouth, blurred vision, dystonia, and vivid dreams. Three subjects experienced dystonia between 24 and 36 h after dosing and were successfully treated with diphenylhydramine 25 mg orally.

Subjects experiencing dystonia requiring diphenylhydramine did not differ significantly in haloperidol pharmacokinetic parameters compared with those not experiencing these side effects. Subjects experiencing dystonia showed a mean clearance of 15.3 ± 4.1 ml/min/kg, while those not experiencing this side effect showed a mean clearance of 26.02 ± 12.4 ml/min/kg ($P = 0.071$). The mean C_{max} of haloperidol in subjects experiencing dystonia was 9.4 ± 4.2 ng/ml, while the C_{max} in subjects not experiencing dystonia was 7.1 ± 3.4 ng/ml ($P = 0.35$). Similarly, there was no statistically significant difference in the mean plasma concentration *vs* time area under the curve between the two groups (158 ± 94 *vs* 111 ± 47 ng h/ml, $P = 0.35$). The *CYP2D6* genotypes for the three subjects who experienced dystonia were *4 heterozygote, *10 heterozygote, and *4 homozygote.

DISCUSSION

We conducted a study of the effects of routinely used, low doses of oral haloperidol on the electrocardiographic QT interval pharmacodynamics in healthy volunteers not on concomitant medications. To improve the mechanistic understanding of our data, we determined the pharmacokinetics of haloperidol in each subject and the effect of *CYP2D6* genotype on pharmacokinetics and QT interval pharmacodynamics. We chose to study a healthy population because of the potential for multiple, confounding, drug and disease interactions in a patient population and because of the specific potential for ion channel variants to occur in the hearts of patients with schizophrenia. Potassium channel variants have been reported in the brains of schizophrenics.[17] Single doses rather than multiple doses were used because of the intolerability of the latter study design in normal, healthy volunteers.

Our data showed a statistically significant mean QT_c prolongation of approximately 13 ms relative to placebo occurring 10 h post oral haloperidol administration. This difference could not solely be the result of intraobserver variability in QT interval assessment because there was only a mean 1.3 ms difference at time 0 (baseline) in both the placebo and haloperidol treatment periods. This 1.3-ms difference likely reflected the sum of both intra-observer variability and intraindividual variability in the QT/QT_c and accounted for about 10% of the change seen at the 10-h time point.

Our results differ from other studies in the literature that suggest haloperidol does not cause statistically significant QT_c prolongation when used in relatively low doses. Fulop *et al*[18] reported a nonsignificant QT_c prolongation of <4 ms at the end of 6 weeks of treatment with oral haloperidol (doses up to 10 mg/day) in patients with Tourette's syndrome.[19] The mean dose used in Fulop's study was approximately 5 mg a day. There are major differences in the two study designs. The obvious difference was that our study was a single-dose study whereas Fulop's was a multidose study. In our study, all subjects receiving haloperidol also served as their own controls, whereas in Fulop's study only a limited number of subjects had both a placebo and treatment period. Additionally, we had a comprehensive placebo period during which ECG sampling was intensively performed, therefore allowing us to monitor the natural fluctuations of QT_c in the absence of treatment. Intense placebo period ECG sampling was not performed in Fulop's study. Also in our study, we acquired ECGs at multiple prespecified time points post haloperidol administration allowing us to detect QT_c changes that were delayed from peak plasma concentrations. In Fulop's study, acquiring only a single ECG at the end of the study may have caused a peak QT effect that was significantly delayed from the peak plasma concentration to be missed. Additionally using a range of doses up to 10 mg may have diluted the power to detect an effect at any specific dose (eg 10 mg). Another possibility of a lack of effect in Fulop's chronic dose study could be tolerance to I_{Kr} blockade. It is unclear if this phenomenon occurs with haloperidol or other drugs. In general, we believe our study had greater sensitivity to detect an effect of haloperidol on the QT_c interval than did Fulop's study.

We found a small but statistically significant effect of *CYP2D6* genotype on haloperidol pharmacokinetics in that the terminal elimination half-life was greater and the apparent oral clearance was lower in PMs than in EMs. These findings were consistent with findings from other studies.[12,14] However, the exposure differences attributed to *CYP2D6* genotype were not sufficient to produce substantial haloperidol-induced QT_c pharmacodynamic changes in PMs relative to EMs. A likely reason for this observation could be that CYP2D6 is not exclusively responsible for haloperidol disposition. It is known that several P450s and non-P450 enzymes are involved in this process, thus making it difficult for a deficiency in any particular metabolic pathway to markedly influence QT interval pharmacodynamics. Cytosolic ketoreductase is the enzyme responsible for conversion of haloperidol to reduced haloperidol.[10,11] *In vitro* studies

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.