Evaluation of the relationship between pharmacokinetics and the safety of aripiprazole and its cardiovascular effects in healthy volunteers

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Running title

Aripiprazole: pharmacokinetics and safety.

Abstract

Aims –Evaluation of the possible relationship between pharmacokinetics and the safety of aripiprazole, and its influence on blood pressure, heart rate and corrected QT (QTc) interval. **Materials and Methods** – The study population comprised 157 healthy volunteers from 6 bioequivalence clinical trials. Subjects were administered a single 10-mg oral dose of each formulation separated by a 28-days washout period. Plasma concentrations were measured using high performance liquid chromatography coupled to mass spectrometry. Blood pressure was measured at the following times: pre-dose and 0.5, 2, 4, 6 and 8 hours post-dose. An electrocardiogram (ECG) was recorded at pre-dose, 4 and 8 hours post-dose. **Results** –AUC, C_{max}, $T_{1/2}$ and V_d/W were higher in women. Aripiprazole treatment produced a decrease of blood pressure (9.3 mmHg on systolic and 6.2 mmHg on diastolic pressure) and an increase in heart rate (12.1 bpm) and QTc interval (9.1 ms). There were sex differences in blood pressure, heart rate and QTc interval. Women and subjects with higher AUC and C_{max} values were more prone to suffer adverse drug reactions (ADRs) and gastrointestinal adverse reactions. AUC was related with systolic blood pressure (SBP) and diastolic blood pressure (DBP) decrease and heart rate (HR) increase but there was no relationship between aripiprazole concentrations and QTc increase.

Conclusions – Aripiprazole decreases blood pressure and increases heart rate and QTc interval. Pharmacokinetics, pharmacodynamics and safety of aripiprazole are affected by sex. There is a directly proportional relationship between pharmacokinetic parameters and ADRs and effect on BP and HR.

Key words: aripiprazole; pharmacokinetics; pharmacodynamics; safety.

Tables included: 4

Figures included: 1

Introduction

Aripiprazole is an atypical antipsychotic indicated for the treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder. The recommended dose for patients with schizophrenia is 10-15 mg/day and for patients with manic episodes is 15 mg/day (1, 2).

Due to its mechanism of action aripiprazole belongs to a new generation of antipsychotics called "third-generation" antipsychotics (3). It acts as a partial agonist of the dopamine D_2, dopamine D_3 and serotonin 5-HT_{1A} receptors and as an antagonist of the serotonin 5-HT_{2A} and 5-HT_7 receptors (4, 5, 6, 7). Also, it exhibits a moderate affinity for α1 adrenergic and histamine H_1 receptors (8, 9).

Aripiprazole has a linear pharmacokinetic within the dose ranges of 5-30 mg/day (10). It is metabolized by the liver by dehydrogenation (CYP2D6), hydroxylation (CYP2D6), and N-dealkylation (CYP3A isozymes). It has an active metabolite, dehydro-aripiprazole, representing about 40% of aripiprazole AUC in plasma at steady state. Dehydro-aripiprazole has an affinity for dopamine D_2 receptors similar to aripiprazole (11). The peak plasma concentration of aripiprazole occurs within 3 to 5 hours post dose. The mean volume of distribution at steady state is 4.9 L/kg. Half-life of aripiprazole is 75 hours for *CYP2D6* extensive metabolizers and 146 hours for poor metabolizers while for dehydro-aripiprazole it is about 94 hours (1). Aripiprazole and its metabolite are widely bound to plasma proteins, primarily to albumin (12).

According to drug label (1), most common adverse drug reactions (ADRs) to aripiprazole are akathisia and nausea with an incidence of 3% among patients. Other ADRs produced by aripiprazole are: agitation, insomnia, anxiety, extrapyramidal disorders, somnolence, headache, blurred vision, vomiting, constipation, fatigue, tachycardia and postural hypotension (1).

In general, aripiprazole has a better safety profile than other atypical antipsychotics; it has a lower rate of extrapyramidal symptoms, weight gain or hyperprolactinemia (10).

The role of aripiprazole on corrected QT (QTc) prolongation is contradictory. Even though aripiprazole is thought not to affect QTc interval (13, 14) several cases of long QTc after aripiprazole treatment have been described (15, 16). Furthermore, there is no "Thorough QT/QTc Study" (a study to determine if a drug can prolong QTc) of aripiprazole available in the literature.

Several studies have shown that it is less likely to produce long QT syndrome (10) than other antipsychotics like pimozide (17), haloperidol, ziprasidone and clozapine (18, 19). Moreover, evidence of its effects on heart rate and blood pressure remains unclear (12, 20).

Our aim was to evaluate the relationship between pharmacokinetics and safety profile of aripiprazole, and also, to study its influence on the electrocardiogram and the blood pressure in healthy subjects receiving a single dose.

Materials and methods

Study population

One hundred and fifty-seven healthy volunteers (89 men and 68 women) were enrolled in six bioequivalence clinical trials performed at the Clinical Trial Unit of Hospital Universitario de la Princesa. These trials were conducted following approval by the Research Ethics Committee of Hospital de la Princesa (Madrid, Spain), duly authorized by the "Agencia Española de Medicamentos y Productos Sanitarios" (AEMPS) and under the guidelines of Good Clinical Practice. All the volunteers gave written informed consent for the study.

Subjects who fulfilled all of the inclusion criteria and none of the exclusion criteria were included in the study. The inclusion criteria were: age from 18 to 55 years-old, subjects free from any organic or psychic conditions, normal vital signs and electrocardiogram, no clinically significant abnormalities in hematology, biochemistry, serology, and urine test. Exclusion criteria were: subjects who have received prescribed pharmacological treatment in the last 15 days or any kind of medication in the 48 hours prior to receiving the study medication, body mass index (BMI) outside the 18.5-30.0 range, smokers, history of sensitivity to any drug, pregnant women or lactose intolerance.

Study design and procedures

All the clinical trials were phase I, oral single dose, randomized, open-label, two periods, two sequences, crossover, single-center studies with blind determination of the plasma concentrations of aripiprazole by the responsible analyst. In half of the trials the volunteers received aripiprazole 10 mg tablets, while in the other half the volunteers received aripiprazole 10 mg orodispersible tablets. In the first period, each volunteer received a single dose of one formulation of aripiprazole (test or reference). In the second

period after a washout period of 28 days, each volunteer received the same dose of the other formulation. Volunteers fasted from 10 hours before until 5 hours after drug administration. For tablets, each administration was with at least 240 ml (8 ounces) of water and for orodispersible tablets, previous to drug administration volunteers rinsed their mouth with 20 ml of water. In all the studies the reference formulation was Abilify® (Otsuka Pharmaceutical Laboratories Europe).

Blood samples were collected in 6 ml sterile EDTA-K2 tubes. Samples were centrifuged at 3500 rpm (1900 g) for 10 minutes and then, plasma was collected and stored at -20ºC until its shipment to the accredited external laboratory which determined plasma concentrations of aripiprazole. These concentrations were measured by reverse phase high performance liquid chromatography coupled to a tandem mass spectrometry detector (LC/MS/MS), with a lower limit of quantification of 0.5 ng/ml. The method involved solid-phase extraction procedure with strong cation-exchange and reversed phase 10 mg plates. Chromatographic separations were performed on a reversed-phase column (Zorbax SB-C18, 4.6 x 50 mm, 3.5µm, from Agilent Technologies). The mobile phase was ammonium formate 1 mM, 0.1% formic acid prepared in Milli-Q water: methanol (42:58 v/v). The chromatographic separation was isocratically performed at room temperature at a flow-rate of 1.00 mL/min.

Pharmacodynamic analysis

Blood pressure was measured in supine position using an automatic monitor at pre-dose, 0.5, 2, 4, 6 and 8 hours after dosing. Also, a 12-lead electrocardiogram was obtained at pre-dose, 4 and 8 hours post dose. As the QT interval has an inverse relationship to heart rate, it might be corrected for heart rate; for this purpose we used Bazett's correction formula (21). According to the ICH E14 clinical guidance (22), we considered corrected QT (QTc) interval prolongation an absolute QTc interval > 450 ms or a change from baseline in QTc interval >30 ms.

Pharmacokinetic analysis

Pharmacokinetic parameters were estimated by non-compartmental analysis using WinNonlin Professional, version 2.0. (Pharsight Corporation, USA). The maximum plasma concentration (C_{max}) and time to reach the maximum plasma concentration (T_{max}) were obtained directly from raw data. The total area under the curve from administration

to infinity ($AUC_{0-\infty}$) was calculated as the sum of AUC_{0-t} and the residual area (C_t divided by k_e, with C_t as the last measured concentration and k_e as the apparent terminal elimination rate, which was estimated by log-linear regression from the terminal portion of the log-transformed concentration-time plots). Half-life ($t_{1/2}$) was calculated by dividing 0.693 by k_e.

The total drug clearance adjusted for bioavailability (Cl/F) was calculated by dividing the dose by the $AUC_{0-\infty}$ and adjusting for weight (Cl/FW). AUC and C_{max} were adjusted for dose and weight and logarithmically transformed for statistical analysis.

Safety and tolerability assessments

The safety and tolerability of aripiprazole was assessed by clinical evaluation of adverse events (AEs) and other parameters including: vital signs, physical examinations and 12-lead ECGs. During the development of the study, volunteers were asked if they had suffered any AE and also, those AEs spontaneously notified by the volunteer were recorded. Karch and Lasagna criteria (23) were used to determine causality. On the basis of these criteria, AEs can be classified as: definite, probable, possible, unlikely and unrelated. Only those AEs which were definite, probable, or possible, were considered as adverse drug reactions (ADRs) and taken into account for the statistical analysis. Intensity (mild, moderate and severe), time sequence and outcome of AEs were also recorded.

According to the drug label (1), ADRs were classified using "System Organ Class" (SOC) allocation as: general (asthenia, back pain), cardiovascular (hypotension, QT_C prolongation, syncope and tachycardia), gastrointestinal (gastroenteritis, nausea/vomiting and abdominal pain), genitourinary (polyuria), neurological (dizziness, headache, hiccups and somnolence), psychiatric (nightmares, insomnia and nervousness) and respiratory (shortness of breath).

Statistical analysis

Statistical analysis was carried out using the SPSS 15.0 software (SPSS Inc., Chicago, IL, EEUU); p values less than 0.05 were considered statistically significant. We have analyzed the data of both formulations (reference and test formulations of tablets and orodispersible tablets) together due to the fact that they have proved to be bioequivalent. For the statistical analysis of pharmacokinetics and ADRs we have considered data from each period separately. For the statistical analysis of the ADRs, it was only considered whether or not an ADR had developed, not including the number of times that this ADR

took place. Pharmacokinetic data were logarithmically transformed for data analysis, except T_{max}, in accordance with EMA guidelines (24). The corrected Pearson χ^2-test was applied to compare the incidence of ADRs between men and women and between age groups (above or below 30 years old). Also, we determined the influence of the pharmacokinetics on ADRs using t-test. We used the same test to study if pharmacokinetics parameters differ between age groups. We perform a logistic regression to study the influence of age and sex in the development of ADRs. Furthermore, to study the capacity of AUC and C_{max}, to discriminate patients with ADRs and nauseas/vomiting ROC curves were plotted and sensitivity and specificity computed.

We evaluated whether sex had influence on pharmacokinetics and pharmacodynamic parameters (SBP, DBP, QTc and HR) using t-test. Correlation between AUC, C_{max} and concentration of aripiprazole (at 4 h and 8 h) and decrease in BP and increase in QT_C and HR was analyzed by lineal regression.

Results

Demographic characteristics

We analyzed 157 healthy volunteers (89 men and 68 women). Demographic data are shown in table 1. Average age was similar between men and women. However, men had a greater weight, height and BMI than women.

There were volunteers who participated in more than one clinical trial: 1 subject participated in four, 1 subject participated in three and 17 subjects participated in two clinical trials. 121 subjects only participated in one clinical trial. There were 17 subjects who only completed one period.

Pharmacokinetic analysis

Mean and standard deviation of pharmacokinetic parameters are included in table 2. We found statistically significant differences between men and women in some pharmacokinetic parameters, even after adjusting for weight. AUC, C_{max}, $T_{1/2}$ and V_d/W were higher in women, as table 2 shows. Also, we analyzed if there was a relationship between subject withdrawal and higher values of AUC and C_{max}. Volunteers who dropped out due to vomiting (after administration) or other ADRs (N=11) showed a tendency in having higher values of AUC (1759.3± 658.5 ng·h/mL vs 1605.2±412.1 ng·h/mL;

P=0.988) and C_{max} (56.4±17.4 ng/mL vs 48.3±10.5 ng/mL; *P*=0.068) than those volunteers who did not leave the study or those who left the study for personal reasons (N=146). However, these findings were not statistically significant. Volunteers older than 30 years old had higher levels of $T_{1/2}$ (62.2±28.3 vs 50.3±21.6; *P*=0.044) and V_d/W (4.6±0.8 vs 4.1±0.9; *P*=0.004) compared to those younger than 30 years old, but there were no differences in AUC and C_{max}.

Pharmacodynamics

As table 3 shows aripiprazole has a blood pressure lowering effect: systolic blood pressure (SBP) decreased a maximum mean of 9.3 mmHg and diastolic blood pressure (DBP) decreased a mean of 6.2 mmHg. There was a significant inverse relationship between AUC and SBP (nonstandardized β coefficient= -0.005, *P*= 0.005) and DBP (nonstandardized β coefficient= -0.002, *P*= 0.012). Similarly, there was a statistically significant increase in heart rate at 4 h (4.5 lpm, *P*=0.001) and even higher at 8 h (12.1 lpm, *P*<0.001) compared with pre-dose value. We found a directly proportional relationship between AUC and heart rate (nonstandardized β coefficient= 0.005, *P*= 0.024). We did not find relationship between C_{max} and SBP, DBP and heart rate.

There was a 9.1 ms increase in QTc interval from baseline to 4 and 8 hours post-dose (Table 3). Following EMA criteria (22), at 4 h post-dose there were 18 volunteers with long QTc and at 8 h post-dose there were 24 volunteers with long QTc. A QTc interval prolongation > 500 ms or an increase from baseline > 60 ms is considered an increased risk of Torsade de Pointes (25, 26). There were 3 subjects in which increase of QTc from baseline was >60 ms. In our study, aripiprazole plasmatic concentrations were not related to increase in QTc interval at 4 h (nonstandardized β coefficient= 0.239, *P*= 0.265) or 8 h post-dose (nonstandardized β coefficient= 0.247, *P*= 0.329.). There was also no relationship between long QTc interval and higher concentrations of aripiprazole at the time of ECG, AUC and C_{max} values.

In relation to sex, there were significant differences in SBP, DBP, QTc and HR at all measured times. Blood pressure was higher in men than in women, while heart rate and QTc interval were higher in women than in men, as table 3 shows. However, the pharmacodynamic effect of aripiprazole was similar in men and women.

Adverse drug reactions

During the course of the study there were no severe, serious or life threatening AEs. 19 volunteers (12.1%, 14 women and 5 men) dropped out of the study for different reasons; including vomiting within 2 hours after drug administration (47.4%), personal reasons (42.1%) or other ADRs (10.5%). In these cases, only pharmacokinetic parameters of the first period were considered. Study withdrawal was associated with sex, with a dropout rate higher in women than in men (20.6% vs 5.6%; P =0.006).

A total of 108 volunteers (68.8%) suffered at least one ADR, being the most frequently reported: dizziness (38.9%), nausea/vomiting (29.9%) and headache (18.5%). Using SOC allocation, the most frequent were neurological (51.0%) and gastrointestinal ADRs (31.8%).

In general, ADRs incidence was greater among women (77.9% vs 61.8% in men, P=0.037). Particularly, gastrointestinal ADRs were more frequent in women than in men (45.6% vs 21.3%, P =0.002), including nausea/vomiting (42.6% vs 20.2%, P=0.003).

Our results demonstrate a significant association between pharmacokinetics and ADRs. Volunteers who suffered at least one ADR or gastrointestinal ADRs had higher AUC and C_{max} values than those who did not, as shown in table 4. Also, we found higher AUC and C_{max} values in volunteers who suffered nausea/vomiting, but these results only were statistically significant for C_{max} (Table 4).

To establish the best cutoff to discriminate volunteers in risk of ADRs from AUC and C_{max} values, ROC curve were plotted (Figure 1). Area under ROC curve were significantly higher than 0.5 (P < 0.001 in both); AUC, 0.631 (95%CI: 0.572 – 0.691) and C_{max}, 0.613 (95%CI: 0.553 – 0.673). The best cutoff for AUC was 1570.3 ng·h/mL (sensitivity, 55.8%, specificity, 70.3%) and for C_{max} 55.61 ng/mL (sensitivity, 36.8%, specificity, 82.3%). In multivariate logistic regression models age was not significantly associated to ADRs. Since nausea/vomiting were more frequent in women, Odds Ratio 2.789 (95%CI: 1.510 – 5.154), cutoff were studied separately for men and women. Area under ROC curve to predict nausea/vomiting from AUC and C_{max} values, were significantly higher than 0.5 for men (P = 0.010 and P = 0.002, respectively); AUC, 0.680 (95%CI: 0.549 – 0.812) and C_{max} 0.721 (95%CI: 0.617 – 0.825, but area under ROC curve were not significantly higher than 0.5 for women (AUC, P = 0.460 and Cmax, P = 0.687). For men, the best cutoff for AUC was 1688.9 ng·h/mL (sensitivity, 68.4%, specificity, 75.8%) and for C_{max} the best cutoff was 43.88 ng/mL (sensitivity, 94.7%, specificity, 51.6%).

The percentage of subjects with ADRs did not differ statistically between young (≤30 years), 70.1%, and older volunteers (> 30 years), 63.3% (P=0.514).

Discussion

Sex influence on pharmacokinetics

The pharmacokinetic parameters obtained in our study are similar to those published in the literature (27, 28) and shown in the drug label (1). Sex differences were observed in the pharmacokinetics of aripiprazole. AUC, C_{max}, $T_{1/2}$ and V_d/W were higher in women than in men. These results are consistent with information in the drug label (1), which states that: "C_{max} and AUC of aripiprazole are 30 to 40% higher in women than in men. These differences, however, are largely explained by differences in body weight (25%) between men and women". However, we found statistically significant differences after adjusting all the parameters for weight.

Influence of sex on drug pharmacokinetics is a quite well-known aspect. There are different factors causing these differences, such as hormonal changes and differences in body weight (29, 30). Women present a higher V_d/W than men, due to their highest fat percentage (30). These findings are discrepant with a previous study analyzing different antipsychotics, in which differences between sex and plasmatic concentrations were only found with clozapine and olanzapine but not with aripiprazole (31). Moreover, other studies did not find influence of sex on plasma concentration of aripiprazole (32, 33). These different results could be explained by the differences in study design (these clinical trials are multiple dose, whereas our study is single dose).

Pharmacodynamics

In our study aripiprazole increased heart rate and decreased blood pressure. These results are consistent with other study on which aripiprazole increased heart rate from baseline (mean increase of 4 bpm vs 1 bpm after placebo). This could be due to a compensatory response to a decrease of blood pressure (34). Orthostatic hypotension is a known side effect of many antipsychotic drugs, although some cases of hypertension after aripiprazole treatment have been described (35, 36).

QTc prolongation is a known risk factor of sudden death. Many studies have reported the effect of antipsychotics on QTc prolongation (37, 38), being the most common thioridazine (withdrawn from the Spanish market in 2005) and ziprasidone (39). The effect of aripiprazole on the QTc interval in electrocardiograms remains unclear. We

described an increase on QTc interval after the administration of aripiprazole. In a study with psychiatric patients the QTc interval decreased 6.94 ms from baseline to the end of treatment (40). Another study reported a reduction in QTc with aripiprazole (41). However, in a recently controlled crossover study for 90 drugs with 59,467 subjects (42) aripiprazole showed a mean QTc prolongation of 7.6 ms, that is similar to our data. In addition, Torsade de Pointes (a form of ventricular tachycardia) was reported in a patient without history of cardiovascular risk after administration of 2.5 mg of aripiprazole (43). This is the first study to demonstrate a relationship between AUC of aripiprazole and change in SBP, DBP and HR. Surprisingly, it was not related to QT_C prolongation, maybe, because it also depends on the concentrations of the active metabolite.

Sex influence on pharmacodynamics

Differences in blood pressure and ECG regarding sex are well known (44, 45, 46, 47). Longer QTc in women may be due to genetic or hormonal differences (48). In a study performed in psychiatric patients with 4 antipsychotics (including aripiprazole) sex differences in QTc interval were only observed with olanzapine (49). In another study performed in psychiatric patients and healthy volunteers (50) a sex effect in the QT interval in healthy volunteers was reported, but not in the case of patients. These results agree with those found in our population, where healthy female volunteers had higher QTc values than males, but the effect of aripiprazole was similar in both groups.

Adverse drug reactions

Several studies have reported the influence of sex on ADRs (51, 52, 53). These differences might be related with differences in the exposure of women and men to drugs (53, 54). Indeed, in our study the AUC and C_{max} values were higher in women.

There are few published studies that examine the influence of pharmacokinetics on the safety of aripiprazole. A previous study (10) showed that there is not relationship between ADRs and pharmacokinetic parameters of aripiprazole. However, in a review (55) there appears to be a correlation between aripiprazole plasma levels and D_2/D_3 receptor occupancy. Greater values of AUC and C_{max} could lead to a greater D_2/D_3 receptor occupancy and therefore, to a greater percentage of ADRs. In addition, in this review two ranges of aripiprazole levels were described for ADRs. In the first one (110-249 ng/ml) ADRs were mild or absent. In the other one (210-335 ng/ml) the ADRs ranged from moderate to severe. These findings are similar to our results that show a relationship between AUC and C_{max} and ADRs/gastrointestinal reactions.

Study limitations

Our study includes six single dose bioequivalence clinical trials with healthy volunteers. The main limitation of our study is the impossibility to evaluate neither the efficacy of the drug nor the chronic ADRs (extrapyramidal symptoms, weight gain or diabetes). Also, *CYP2D6* genotyping was not performed but it is no relevant for evaluating the relationship between concentrations and adverse reactions. On the contrary, our study allows controlling typical confounding factors of studies performed on psychiatric patients such as pathologic characteristics of the disease, concomitant therapy and the motivation of patients. It is important to take into account that these results must be interpreted with caution because pharmacokinetics, pharmacodynamics, and tolerability could be different in psychotic patients. Larger studies are needed to increase the statistical power of these results.

Conclusions

Pharmacokinetic of aripiprazole is affected by sex. AUC, C_{max}, $T_{1/2}$ and V_d/W are higher in women than in men. ADRs were more common in women, specially nausea and vomiting. Subjects with higher values of AUC and C_{max} are more likely to suffer these ADRs. Aripiprazole lowers blood pressure and raises heart rate and QTc interval. AUC was related to decrease in blood pressure and increase in heart rate, but not to QTc increase. Sex is an influential factor on blood pressure and electrocardiogram parameters.

Conflict of interest

F.Abad-Santos and D.Ochoa have been consultants or investigators in clinical trials sponsored by the following pharmaceutical companies: Abbott, Alter, Chemo, Cinfa, Farmalíder, Ferrer, GlaxoSmithKline, Galenicum, Gilead, Janssen-Cilag, Kern, Normon, Novartis, Servier, Teva, and Zambon. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Table 1. Baseline demographic characteristics of the volunteers, expressed as mean ± standard deviation. $^{*}p \leq 0.01$ and $^{**}p \leq 0.001$ vs men.

	N (%)	Age (years)	Weight (kg)	Height (m)	BMI (kg/m^2)
All	157 (100%)	26.1±7.5	70.0±11.7	1.71±0.09	23.9±2.9
Men	89(56.7%)	25.1±6.4	75.1±9.7	1.76±0.07	24.5±2.6
Women	68(43.3%)	27.5±8.6	62.6±9.7**	1.64±0.06**	23.1±3.1*

Table 2. Pharmacokinetic parameters of aripiprazole following a single oral dose of 10 mg.$^{*}p \leq 0.05$, and $^{**}p \leq 0.001$ vs men, after adjusting for weight.

Pharmacokinetic parameters	All	Men	Women
AUC (ng·h/mL)	1616.0±432.7	1552.7±396.2	1698.9±466.3*
C_{max} (ng/mL)	48.8±11.2	46.5±9.8	51.9±12.3*
T_{max}(h)	3.2 ± 1.7	3.0±1.6	3.4±1.7
$T_{1/2}$(h)	52.6 ± 23.4	46.9±16.4	60.0±28.7**
V_d/W (L/kg)	4.2 ± 0.9	3.9±0.7	4.6±0.9**
Cl/W (mL/h·kg)	63.6± 23.1	64.3±19.5	62.7±27.1

Table 3. Effects of aripiprazole on systolic (SBP) and diastolic blood pressure (DBP), heart rate (HR) and corrected QT (QTc) interval, expressed as mean±standard deviation. $^{*}p\leq0.05$, $^{**}p\leq0.01$ and $^{***}p\leq0.001$ compared with pre-dose. $^{+}p<0.05$, $^{++}p\leq0.01$ and $^{+++}p\leq0.001$ compared with men, at the same time.

	Sex	**Pre-dose**	**Post-dose**				
			0,5h	**2h**	**4h**	**6h**	**8h**
SBP (mmHg)	Men	120.5 ± 10.1	114.1 ± 8.5***	111.9 ± 10.5***	113.8 ± 8.8***	116.6 ± 9.5	116.3 ± 8.9*
	Women	111.3 ± 10.0^{+++}	105.3 ± 9.3^{**+++}	101.0 ± 8.7^{***+++}	104.0 ± 8.0^{***+++}	105.1 ± 8.5^{***+++}	105.2 ± 9.0^{***+++}
	Total	116.5 ± 11.0	110.3 ± 9.8***	107.2± 11.1***	109.6 ± 9.8***	111.6 ± 10.7***	111.5 ± 10.5***
DBP (mmHg)	Men	66.6 ± 7.4	64.0 ± 6.8	60.4 ± 7.1***	60.8 ± 6.2***	60.0 ± 5.5***	60.3 ± 5.6***
	Women	62.8 ± 6.4^{+++}	60.3 ± 5.5^{+++}	57.0 ± 5.5^{***++}	57.8 ± 4.7^{***+++}	57.2 ± 4.0^{***+++}	57.4 ± 4.3^{***+++}
	Total	65.0 ± 7.2	62.4 ± 6.5**	58.9 ± 6.7***	59.5 ± 5.8***	58.8 ± 5.1***	59.0 ± 5.3***
HR(bpm)	Men	60.6 ± 9.7			64.9 ± 10.2*		72.9 ± 11.8***
	Women	66.0 ± 10.0^{+++}			70.6 ± 11.3^{*+++}		77.9 ± 11.2^{***+++}
	Total	62.9 ± 10.0			67.4 ± 11.0***		75.0± 11.8***
QT_C (ms)	Men	392.5 ± 16.8			400.9 ± 21.1*		401.5 ± 21.6**
	Women	410.0 ± 16.9^{+++}			420.0 ± 24.9^{*+++}		419.4 ± 21.5^{*+++}
	Total	400.1 ± 18.9			409.2 ± 24.6***		409.2 ± 23.3***

Table 4. Association between pharmacokinetic parameters (AUC and $C_{max)}$ and adverse drug reactions (ADRs). $^{*}p\leq0.05$ and $^{**}p\leq0.001$ vs "No". N=number of drug administrations.

		N (%)	**AUC (ng·h/mL)**	**C_{max}(ng/ml)**
ADRs	No	175 (51.8%)	1495.2±365.0	46.6±11.3
	Yes	163 (48.2%)	1677.9±453.0**	51.5±13.1**
Nausea/vomiting	No	280 (82.8%)	1561.3±412.8	48.0±12.4
	Yes	58 (17.2%)	1689.2±437.5	53.4±12.0*
Gastrointestinal reactions	No	277 (82.0%)	1553.8±408.3	47.8±12.2
	Yes	61 (18.0%)	1717.1±445.4*	53.9±12.3**

Figure 1. ROC curves for AUC and C_{max} to discriminate subjects with adverse drug reactions (ADRs).