

Comparison of Capillary and Venous Drug Concentrations After Administration of a Single Dose of Risperidone, Paliperidone, Quetiapine, Olanzapine, or Aripiprazole

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Abstract

Risperidone, paliperidone, quetiapine, olanzapine, and aripiprazole are antipsychotic drugs approved for treating various psychiatric disorders, including schizophrenia. The objective of this randomized, parallel-group, open-label study was to compare finger-stick-based capillary with corresponding venous whole-blood and plasma concentrations for these drugs after administration of a single dose to healthy volunteers. All whole-blood and plasma drug concentrations were measured with validated liquid chromatography–tandem mass spectrometry methods. Capillary and venous concentrations (both in plasma and whole blood) were in close agreement, although a time-dependent difference was observed, most obviously for olanzapine and paliperidone, with slightly higher capillary versus venous drug concentrations during the first hours after administering a single dose. The observed difference between capillary and venous plasma drug concentrations is expected not to be relevant in clinical practice, considering the wide window of therapeutic concentrations and the wide range of drug concentrations in the patient population for a given dose. Based on these results, finger-stick-based capillary drug concentrations have been shown to approximate venous drug concentrations.

Keywords

capillary concentrations, venous concentrations, risperidone, paliperidone, quetiapine, olanzapine, aripiprazole, antipsychotics

Risperidone, paliperidone, quetiapine, olanzapine, and aripiprazole are antipsychotic medications approved for treating various psychiatric disorders, including schizophrenia. Schizophrenia is a chronic, debilitating psychiatric disorder. Quantification of antipsychotic blood levels may be useful for managing medication therapy and evaluating patient adherence to prescription instructions. A major reason to use blood levels to guide psychopharmacotherapy is the considerable variability in the pharmacokinetics of the medications between patients.¹ At the very same dose, a more than 20-fold interindividual variation in the medication's systemic steady-state concentration may occur, as patients differ in their ability to absorb, distribute, metabolize, and excrete drugs because of concurrent disease, age, concomitant medication, or genetic polymorphism.^{1–4} Questionable drug adherence, suboptimal tolerability, nonresponsiveness at therapeutic doses, or pharmacokinetic drug–drug interactions are typical situations when measurement of medication concentrations is deemed helpful to guide therapy.¹ Monitoring of blood

levels, combined with clinical evaluations, may aid in identifying the causes of medication nonresponse and aid in therapeutic decision making. However, integration of the assessment of drug blood levels into the clinical decision-making process has been suboptimal, often because of long delays (up to 2 weeks and longer) in obtaining the antipsychotic concentrations from specialized laboratories. Ideally, a point-of-care (POC)

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device would enable instantaneous decision making during a regular visit to the clinician. POC devices usually analyze finger-stick-based blood samples to enable blood sampling in a nonhospital environment. In addition, finger-stick-based capillary sampling may be preferred by patients.^{5,6} However, multiple cases are reported in the literature that suggest that drug concentrations of finger-stick-based blood (a mixture of arterial, venous, and capillary blood) and venous blood may differ.⁷⁻⁹ Therefore, the primary objective of this study was to compare finger-stick-based capillary and venous whole-blood and plasma concentrations for 5 commonly prescribed atypical antipsychotics (risperidone, paliperidone, quetiapine, olanzapine, and aripiprazole) after administration of a single dose to healthy participants. To our knowledge, the publication of well-designed studies evaluating the correlation between capillary and venous concentrations of antipsychotic medications is limited to 1 study comparing capillary and venous concentrations in dried blood spots under steady-state conditions.¹⁰

Materials and Methods

The Independent Ethics Committee (Commissie voor Medische Ethiek, UZ Antwerpen, Belgium) at the study site (Clinical Pharmacology Unit, Merksem, Belgium) approved the protocol. This study was conducted in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with International Conference on Harmonisation Good Clinical Practice guidelines and applicable regulatory requirements and in compliance with the protocol. All participants provided written informed consent. The study is registered at clinical trials.gov as NTC01607762.

Study Design

This phase 1 randomized, parallel-group, open-label study was conducted between February and October 2012 at a single center in Belgium. A single dose of 1 of the 5 studied antipsychotics was administered. On administration, samples were collected during a 5-day (for participants receiving risperidone, paliperidone, quetiapine, or olanzapine) or an 18-day (for participants receiving aripiprazole, because of its longer half-life) observation period.

At the start of the open-label observation period, participants were randomly assigned to 1 of the 5 cohorts: 1 mg risperidone, 3 mg paliperidone, 100 mg quetiapine extended release (XR), 5 mg olanzapine, or 5 mg aripiprazole. Randomization was performed based on a computer-generated randomization schedule. At least 12 participants were randomized per cohort. Two additional participants who were poor metabolizers of CYP2D6, as determined by pharmacogenomic testing,

were directly assigned to the risperidone cohort without randomization.

Medication was administered as a single oral dose. Dosing was to occur after an overnight fast. All drugs were swallowed whole and not chewed, divided, dissolved, or crushed and were taken with 240 mL of non-carbonated water. Participants then fasted for at least 1 hour, after which they received breakfast. Lunch was provided approximately 4 hours after dosing.

Study Population

Healthy participants of either sex aged 18 to 55 years (inclusive) with a body mass index (BMI) between 17 and 35 kg/m² and a body weight not less than 50 kg were enrolled. Participants were judged to be in good health based on their medical history and physical examinations, including vital signs, electrocardiogram, and clinical laboratory test results. Women of childbearing potential enrolled in the study were not pregnant or breast-feeding, and agreed to take appropriate precautions to avoid pregnancy from screening until completion of the study. Nonstudy medications, except for paracetamol, hormonal contraceptives, and hormone replacement therapy, were not allowed for 14 days before the study drug administration and until completion of the study, unless deemed necessary by the investigator. The use of paracetamol was allowed until 3 days before study drug administration. Hormonal contraceptives and hormone replacement therapy were to be continued throughout the study.

Study Drugs

The following formulations were administered as a single dose: risperidone, 1 Risperdal 1-mg immediate-release tablet; paliperidone, 1 Invega 3-mg extended-release tablet; quetiapine, 2 Seroquel XR 50-mg extended-release tablets; olanzapine, 1 Zyprexa 5-mg immediate-release tablet; aripiprazole: 1 Abilify 5-mg immediate-release tablet. All study drugs were stored at controlled room temperature ranging from 15°C to 30°C.

Blood Collection

Venous (3 mL) and finger-stick (0.5 mL) capillary blood samples were collected before dosing and 2, 4, 6, 12, 24, 36, 48, 60, 72, 84, 96, and 108 hours after dosing. For participants who were randomized to the aripiprazole cohort, additional venous and finger-stick capillary blood samples were collected 5, 9, 13, and 17 days after dosing. Finger-stick-based capillary samples were collected within 10 minutes after the venous samples. For venous and capillary samples, whole-blood and derived plasma aliquots were stored frozen for further analysis.

Analytical Methods

For participants taking paliperidone, quetiapine, or olanzapine, concentrations of the parent compound, and for participants taking risperidone or aripiprazole, concentrations of the parent compound and the major metabolite (9-hydroxyrisperidone and dehydroaripiprazole, respectively) were determined in whole blood and derived plasma, using validated liquid chromatography–tandem mass spectrometry methods.¹¹ In addition, the sums of parent drug and major metabolite were calculated for participants taking risperidone (“risperidone active moiety”) or aripiprazole (“aripiprazole active moiety”).

Using 0.025-mL aliquots of sample for analysis, the lower limits of quantification for whole-blood and plasma assays were as follows: 0.100 ng/mL for risperidone, paliperidone (9-hydroxyrisperidone), and olanzapine; 1 ng/mL for quetiapine, quetiapine metabolites, aripiprazole, and dehydroaripiprazole.

Intrabatch accuracy for quality-control samples ranged from 86% to 115% for the plasma assays and from 90% to 113% for the whole-blood assays. Interbatch accuracy ranged from 98% to 106% for the plasma assays and from 92% to 107% for the whole-blood assays. Interbatch precision ranged from 3.3% to 7.0% for the plasma assays and from 2.3% to 6.2% for the whole-blood assays.

The blood samples from 6 participants were not analyzed for olanzapine, as stability experiments pointed out that the addition of ascorbic acid to whole blood was necessary to safeguard the stability of olanzapine during freezing and thawing. For these 6 participants, whole-blood aliquots were not sampled with ascorbic acid.

In the venous plasma samples collected, quetiapine metabolites were determined using qualified research methods, the performance of which is described below per analyte: quetiapine sulfoxide, quetiapine sulfone, 7-hydroxyquetiapine, norquetiapine, and *O*-desalkylquetiapine were quantified.¹¹ For this qualified analytical method, the generally accepted criteria on accuracy of 15%^{12,13} (European Medicines Agency, 2011; Food and Drug Administration, 2001) could not be met for all metabolites. Only for quetiapine sulfoxide and quetiapine sulfone did the intrarun accuracy meet the 15% accuracy criterion. For 7-hydroxyquetiapine and *O*-desalkylquetiapine the intrarun accuracy was within 20%, whereas for norquetiapine it was within 25%.

Safety Assessments

Safety assessments during the observation period included monitoring treatment-emergent adverse events, clinical laboratory tests, electrocardiograms, vital sign measurements and physical examinations.

Statistical Methods

Regression analyses were performed for each analyte and sampling matrix (whole blood or plasma). A linear regression model was fitted to the data with capillary concentration as the dependent variable and venous concentration as the independent predictor. Each regression model was fitted initially with a nonzero intercept term. If the intercept was found not to be significantly different from 0, the regression model was refitted without the intercept term. The estimates of slope and 95% confidence intervals (CIs) were obtained.

Both for whole blood and plasma, the individual percentage difference (%difference, capillary versus venous) was calculated at each time as follows: $(\text{concentration capillary}/\text{concentration venous}) \times 100\% - 100\%$. Mean \pm SD %difference was presented as a function of time after drug administration.

Capillary and venous whole blood-to-plasma ratios were calculated at each time for each analyte and the active moieties, and descriptive statistics were calculated per analyte and time.

The safety analysis set included all participants who received study drug.

Statistical analyses were performed using Microsoft Excel (version 2007; Microsoft, Redmond, Washington) and SAS (version 9.3; SAS Institute Inc., Cary, North Carolina). SigmaPlot version 11, R package (version 3.1.0; The R Foundation for Statistical Computing, Vienna, Austria), and SAS version 9.3 were used to produce plots. Pharmacokinetic parameters for quetiapine metabolites were calculated using Phoenix WinNonlin software (Pharsight Corporation, Certara, L.P., St. Louis, Missouri).

Results

Study Population

Sixty-four healthy participants were randomized in this study, of whom 62 completed the study. Two participants in the aripiprazole cohort were withdrawn from the study because of adverse events. Demographic and baseline characteristics were comparable across the different cohorts. The majority of the participants were white ($n = 60$), and there were slightly more women ($n = 34$) than men ($n = 30$). Participants had a median age of 44 years (range, 18 to 55 years), a median body weight of 72.9 kg (range, 52.1 to 109.4 kg), and a median BMI of 25.1 kg/m² (range, 18.4 to 34.0 kg/m²).

Drug Concentrations

For 1 of the 2 withdrawn participants no postdose samples were available, and for the other participant no samples were available after the 4-hour sample. For 6 subjects in the olanzapine group whole-blood concentrations were not reported because of stability issues

Table 1. Regression Analysis Results

Cohort	Analyte	Number of Paired Samples	Estimate	95%CI	r ²	
Plasma	Risperidone	Risperidone	0.880	0.843–0.918	0.967	
		9-Hydroxyrisperidone	0.925	0.891–0.960	0.945	
		Risperidone active moiety ^a	0.892	0.863–0.921	0.957	
	Paliperidone	Paliperidone	1.026	0.985–1.067	0.946	
	Quetiapine	Quetiapine	0.946	0.918–0.974	0.981	
	Olanzapine	Olanzapine	1.169	1.117–1.221	0.933	
		Aripiprazole	Aripiprazole ^c	0.889	0.842–0.937	0.887
		Dehydroaripiprazole ^c	0.716	0.638–0.793	0.715	
		Aripiprazole active moiety ^{b,c}	0.878	0.825–0.931	0.860	
Whole blood	Risperidone	Risperidone	0.953	0.926–0.980	0.986	
		9-Hydroxyrisperidone	0.946	0.933–0.960	0.992	
		Risperidone active moiety ^a	0.947	0.931–0.963	0.989	
	Paliperidone	Paliperidone	0.950	0.936–0.964	0.993	
	Quetiapine	Quetiapine	0.944	0.923–0.966	0.989	
	Olanzapine	Olanzapine	1.000	0.951–1.050	0.960	
	Aripiprazole	Aripiprazole	0.925	0.909–0.940	0.925	
			Dehydroaripiprazole ^c	0.643	0.509–0.777	0.543
			Aripiprazole active moiety ^{b,c}	0.949	0.916–0.983	0.951

Cohort risperidone, single oral dose of a 1-mg risperidone tablet; cohort paliperidone, single oral dose of 3-mg paliperidone tablet; cohort quetiapine, single oral dose of two 50-mg quetiapine extended-release tablets; cohort olanzapine, single oral dose of a 5-mg olanzapine tablet; cohort aripiprazole, single oral dose of a 5-mg aripiprazole tablet.

^aRisperidone active moiety: risperidone + 9-hydroxyrisperidone.

^bAripiprazole active moiety: aripiprazole + dehydroaripiprazole.

^cIntercept was significant. In plasma: for aripiprazole, intercept estimate = 0.755 (*P* = .034); dehydroaripiprazole, intercept estimate = 0.474 (*P* < .0001); aripiprazole active moiety, intercept estimate = 0.969 (*P* = .024). In whole blood: for dehydroaripiprazole, intercept estimate = 0.393 (*P* = .0003); aripiprazole active moiety, intercept estimate = -0.338 (*P* = .030).

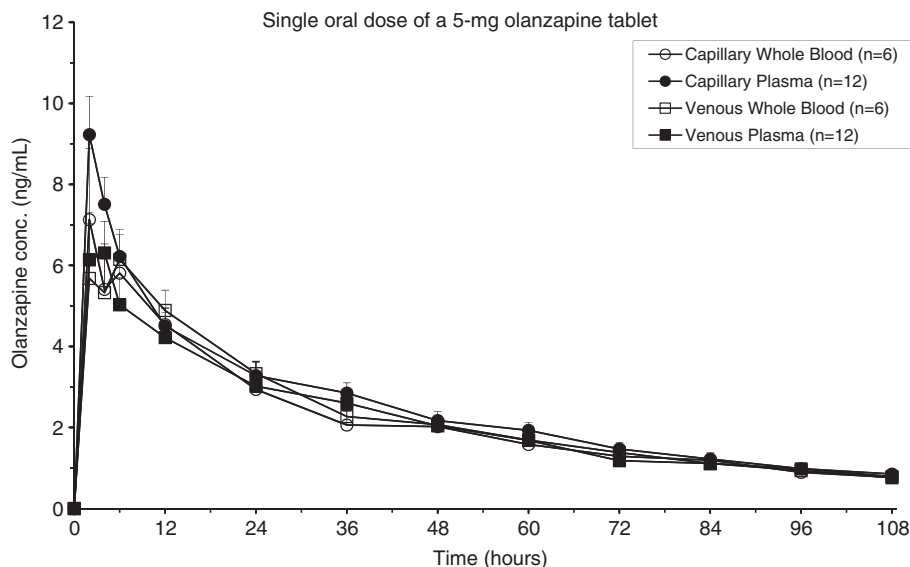


Figure 1. Olanzapine: mean ± SE concentration–time profiles, in capillary and venous whole blood and plasma.

with the sample. The numbers of capillary–venous data pairs of quantifiable concentration data that were included in the statistical analysis are listed in Table 1.

Mean ± SE concentration–time profiles in capillary and venous whole blood and plasma are shown in

Figures 1 (olanzapine) and 2 (risperidone active moiety) and in Supplementary Figures S7 (aripiprazole active moiety), S8 (paliperidone), and S9 (quetiapine). In the initial regression analysis, the intercept for plasma was significantly different from 0 for aripiprazole,

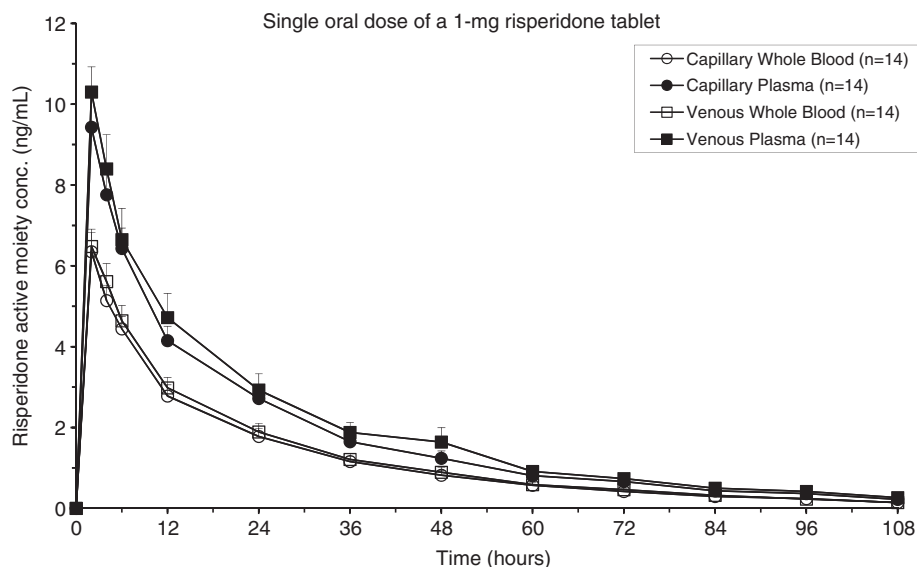


Figure 2. Risperidone active moiety: mean \pm SE concentration–time profiles, in capillary and venous whole blood and plasma.

dehydroaripiprazole, and the aripiprazole active moiety (the sum of aripiprazole and dehydroaripiprazole), and the intercept for whole blood was significantly different from 0 for dehydroaripiprazole and the aripiprazole active moiety (Table 1). For all other analytes the intercept was not significantly different from 0, and hence the reduced models without intercept were fitted.

For all analytes there was a close agreement between capillary and corresponding venous drug concentrations; both in plasma and whole blood (eg, for plasma; Figure 3, Figure 4, and, as supplementary online information, Supplementary Figure S1, Supplementary Figure S2, and Supplementary Figure S3). Capillary whole-blood and plasma drug concentrations were, in general, slightly lower than corresponding venous concentrations (eg, Figure 5 and, as supplementary online information, Supplementary Figure S1 and Supplementary Figure S2). Despite the overall similarity of the concentrations, the difference in the estimated slope was statistically significant for all the analytes except paliperidone in plasma (95% CIs for the slope included 1) and olanzapine in whole blood (95% CIs for the slope included 1); see Table 1.

A time dependence was observed in the difference between capillary and venous plasma drug concentrations. For olanzapine, the finger-stick capillary plasma concentrations were generally higher than the venous plasma concentrations (mean difference up to 12 hours after dosing between +26% and +65%), but the difference was smaller at later times (mean difference from 12 hours onward ranged between +2% and +18%); see Figure 6. For the other drugs, capillary plasma concentrations were generally higher than venous plasma concentrations during the first hours after dosing (eg,

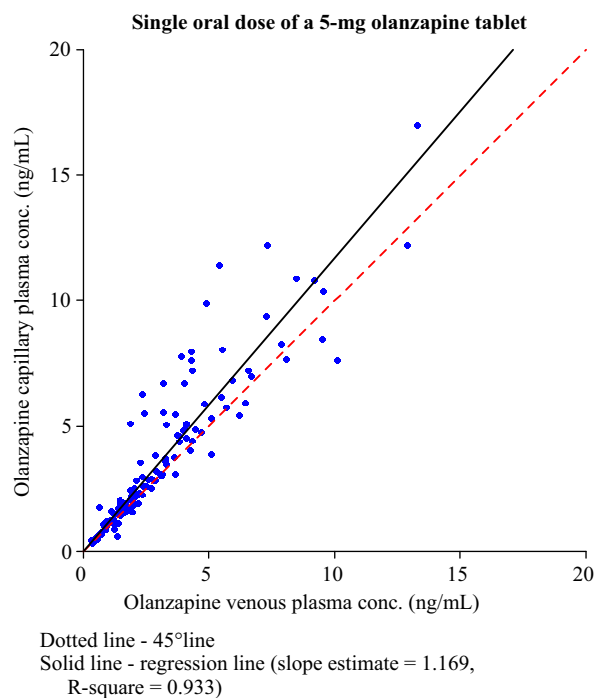


Figure 3. Olanzapine: regression analysis of capillary versus venous plasma concentrations after a single oral dose of 5 mg olanzapine in healthy subjects.

mean difference of +26% 2 hours after dosing of paliperidone) and slightly lower at later times (eg, mean difference ranged between -4% and -9% from 36 to 72 hours after dosing of paliperidone); see Figure 5 and, as supplementary online information, Supplementary Figures S4, S5, and S6.

Mean venous whole-blood/plasma ratios varied within the following ranges: risperidone active moiety,

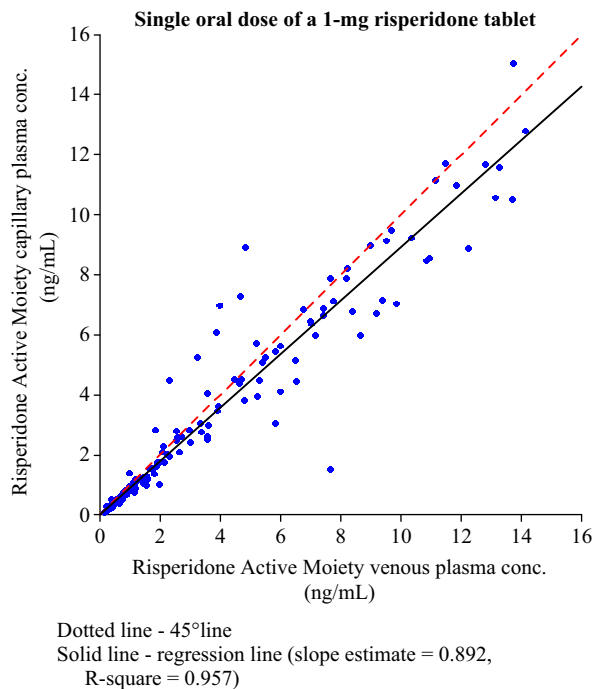


Figure 4. Risperidone active moiety: regression analysis of capillary versus venous plasma concentrations after a single oral dose of 1 mg risperidone in healthy subjects.

59% and 79%; paliperidone, 62% and 84%; quetiapine, 57% and 75%; olanzapine, 71% and 96%; and aripiprazole active moiety, 40% and 67%. Similarly, mean capillary whole-blood/plasma ratios varied within the following ranges: risperidone active moiety, 63% and 82%; paliperidone, 65% and 72%; quetiapine, 59% and

68%; olanzapine, 64% and 105%; and aripiprazole active moiety, 44% and 60%.

In 2 participants in the risperidone group who were identified as poor metabolizers of CYP2D6, the %differences between capillary and venous concentrations in whole blood and plasma were in the same range as those of the other participants.

For quetiapine, concentrations of 4 metabolites were obtained in venous plasma samples. Venous plasma concentrations only were determined for quetiapine metabolites, and consequently no evaluation of the capillary/venous correlation was performed. However, for completeness, results are summarized here. Quetiapine sulfone concentrations were below the limit of quantitation (1.00 ng/mL) in all samples analyzed. The C_{max} values (mean \pm SD) were estimated for quetiapine sulfoxide (77.3 ± 32.4 ng/mL), norquetiapine (9.08 ± 4.37 ng/mL), *O*-desalkylquetiapine (3.72 ± 1.78 ng/mL), and 7-hydroxyquetiapine (3.52 ± 1.76 ng/mL). For comparison, the estimated C_{max} value for the quetiapine concentrations measured with the qualified research method was 87.8 ± 43.0 ng/mL. The AUC_{last} values were estimated for quetiapine sulfoxide ($1,286 \pm 458$ ng·h/mL) only. For norquetiapine, *O*-desalkylquetiapine and 7-hydroxyquetiapine, no pharmacokinetic analyses could be performed because of the highly scattered data, not enabling estimation of AUC. The estimated AUC_{last} for quetiapine was $1,594 \pm 876$ ng·h/mL. For quetiapine sulfoxide, metabolic ratios decreased with time, from 119% on average 2 hours after dosing to 30% on average 72 hours after dosing. For the other metabolites, metabolic ratios

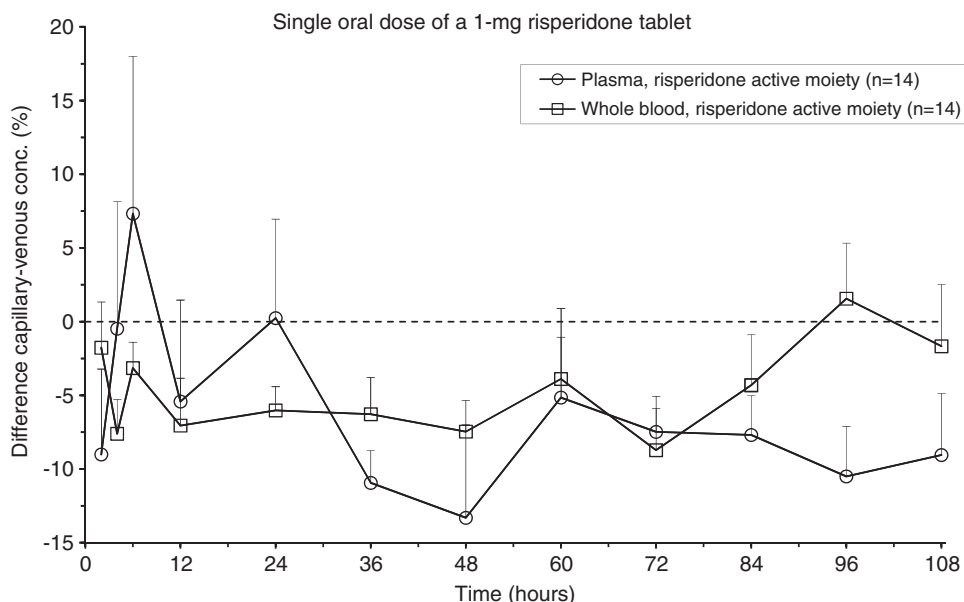


Figure 5. Risperidone active moiety: mean \pm SE %difference in capillary and venous concentration–time profiles.

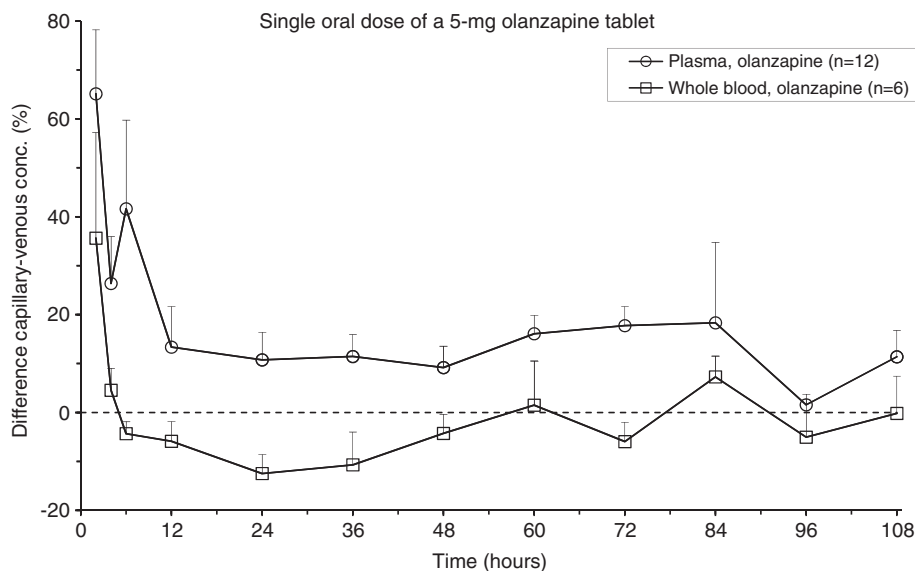


Figure 6. Olanzapine: mean \pm SE %difference in capillary and venous concentration–time profiles.

ranged from 0% to 72% without a clear relationship with time.

Safety

No deaths or other serious adverse events were reported. Two participants in the aripiprazole treatment group who experienced syncope on day 1 were withdrawn from the study because of these adverse events.

A total of 41 participants reported at least 1 treatment-emergent adverse event during the study. Most of the treatment-emergent adverse events were considered mild or moderate in intensity, except for 1 event of syncope in the aripiprazole group that was severe in intensity and considered by the investigator to be very likely related to the study drug.

Discussion

To our knowledge, published results of well-designed studies conducted to evaluate the correlation between capillary and venous concentrations of antipsychotic medications, particularly of risperidone, paliperidone (9-hydroxyrisperidone), quetiapine, olanzapine, aripiprazole, and dehydroaripiprazole, are limited to 1 study comparing capillary and venous concentrations in dried blood spots.¹⁰ However, this study evaluated the correlation under steady-state conditions only. The present study was initiated to compare the capillary and corresponding venous plasma and whole-blood concentrations of these antipsychotics after administration of a single oral dose to healthy participants. All study drugs and procedures were generally well tolerated at the relatively low doses administered. Two participants in the aripiprazole group were withdrawn from the study because of adverse events.

Because the study was performed in healthy volunteers, low doses were administered. However, because arteriovenous differences are determined by volume of distribution and clearance⁷ and because of the linear kinetics of the evaluated drugs, the data are considered relevant for higher doses.

There was a close agreement between the capillary and venous concentrations of antipsychotics in plasma. Similar results were observed when comparing capillary and venous whole-blood concentrations of the antipsychotics, albeit that for whole-blood individual values were less scattered around the regression line, resulting in slightly narrower confidence intervals for whole blood than for plasma (95%CI in Table 1). The capillary whole-blood and plasma concentrations were on average lower compared with the corresponding venous whole-blood and plasma concentrations, except for the early sampling times for most analytes, and, for olanzapine, for all sampling times. The lower mean capillary concentrations for most drugs reflect that most samples were collected during the elimination phase, during which redistribution of drug from the tissue to the venous blood may have occurred (see below).

A more in-depth analysis of the observed differences showed a clear time dependence, especially for olanzapine, but also to a lesser extent for the other drugs.

Similarly, arteriovenous differences are reported in the literature. A review by Chiou⁷ confirmed that arterial drug concentrations can be higher than venous drug concentrations on drug administration for some drugs, in particular, during the first minutes or hours after administering a single dose, because of the efficient extraction of drug from the arterioles into tissue.

Finger-stick-based blood is a mixture of arterial, venous, and capillary blood, and the greater pressure in arterioles and in the arterial limb of capillaries results in a greater ratio of arterial to venous blood in finger-prick blood.¹⁴ In the present study, a time-dependent trend in %difference (capillary/venous) was observed, which was most obvious for olanzapine and paliperidone and which could reach values above 50% in some individual venous-capillary sample pairs in the first hours after dosing. Similarly, higher capillary-versus-venous concentrations were reported immediately after dosing for other drugs.^{8,9,15-17}

It was hypothesized by Chiou⁷ that during the elimination phase, the effective clearance of drug from the arterial compartment, combined with redistribution of drug from the tissues to the capillaries, can lead to higher venous drug concentrations compared with capillary concentrations. In the present study, venous concentrations were higher than capillary concentrations at later times.

Olanzapine capillary plasma concentrations were significantly higher than the corresponding venous plasma concentrations, especially during the first 6 hours after administration of a single dose. This may be related to the extensive distribution of olanzapine: the apparent volume of distribution is 22 L/kg.¹⁸ For comparison, reported apparent volumes of distribution for the other drugs are in the range of 1 to 2 L/kg for risperidone,¹⁹ 7 L/kg for paliperidone²⁰ (assuming 70 kg body weight), 10 L/kg for quetiapine,²¹ and 3.2 L/kg for aripiprazole (average, 61 kg body weight).²² In whole blood, the differences between capillary and venous olanzapine concentrations were smaller than in plasma. It is hypothesized that slow equilibration of olanzapine between red blood cells and plasma on drug administration may be another possible explanation for this finding.

From these observations, capillary-venous differences can be anticipated in clinical practice. When steady-state conditions are not met, for example in the case of nonadherence, drug kinetics are determined by elimination and redistribution processes and lower capillary concentrations may be expected. Even though most of the overall comparisons of capillary-versus-venous concentrations were statistically significantly different from 1, during the elimination phase the average difference in whole blood and plasma between capillary and venous concentrations observed in the present study was in general less than 12%. However, differences should be interpreted in the context of the broad therapeutic window and the high inter- and intra-subject variability in antipsychotic plasma levels.^{19,22-24} In other words, the variation of drug concentrations in the patient population for a given dose is much wider (concentration-to-dose ratios in 68% of subjects are an-

anticipated to span a 1.5-fold range for aripiprazole to a 4-fold range for the risperidone active moiety, whereas the 32% other subjects deviate even more), and the therapeutic windows span a 3-fold concentration range for aripiprazole, paliperidone, and risperidone up to a 5-fold concentration range for quetiapine.¹ Therefore, the differences observed in this study are not expected to be relevant in clinical practice.

That no pharmacokinetic parameters were calculated or compared is a limitation of the study. The times of pharmacokinetic sampling in this study were chosen to allow drug concentration measurements at different levels, that is, at low, intermediate, and high concentrations. Consequently, the times of sample collection were not optimal for a reliable calculation of pharmacokinetic parameters. The plasma concentrations observed in this study appeared to be consistent with published data for all evaluated drugs.²⁵⁻²⁹

Conclusions

On administration of a single dose of risperidone, paliperidone, quetiapine, olanzapine, or aripiprazole, a close agreement was observed between finger-stick-based capillary and corresponding venous drug concentrations, both in plasma and whole blood. Therefore, finger-stick-based capillary sampling can be used as an easier and patient-preferred alternative for venous blood sampling to estimate the systemic drug concentrations of these antipsychotics. However, capillary levels may overestimate the venous concentrations, in particular, for olanzapine, and during the first hours after administering a single dose. Given that the capillary-venous difference is more limited after completing the absorption phase, that is, when drug distribution between blood and tissue compartments is stabilized, smaller differences are expected after repeated administration (ie, at steady state). This was subsequently confirmed in another study, the results of which will be presented elsewhere.

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Declaration of Conflicting Interests

The authors are employees of Janssen Research & Development and potentially own stock and/or stock options in the company.

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Contributorship

All authors met ICMJE criteria for authorship, and anyone who met those criteria is listed as an author. Bart Remmerie supervised the study design, Marc De Meulder supervised the bioanalytical analysis, and Sveta Weiner supervised the statistical analysis. Bart Remmerie and Adam Savitz supervised the data interpretation and reporting of the study results. All authors critically revised and approved the final manuscript and gave permission to submit for publication.

American College of Clinical Pharmacology

None of the authors are Fellows of the American College of Clinical Pharmacology.

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Supporting Information

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