HUMAN PSYCHOPHARMACOLOGY
Hum. Psychopharmacol Clin Exp 2009; **24**: 532–539.
Published online 19 August 2009 in Wiley InterScience
(www.interscience.wiley.com) **DOI**: 10.1002/hup.1049

No pharmacokinetic interaction between paliperidone extended-release tablets and trimethoprim in healthy subjects[§]

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Objective The effect of trimethoprim, a potent organic cation transport inhibitor, on the pharmacokinetics (PK) of paliperidone extended-release tablets (paliperidone ER), an organic cation mainly eliminated via renal excretion, was assessed.
Methods Open-label, two-period, randomized, crossover study in 30 healthy males. Single dose of paliperidone ER 6 mg was administered either alone on day 1 or day 5 during an 8-day treatment period of trimethoprim 200 mg twice daily. Serial blood and urine samples were collected for PK and plasma protein binding of paliperidone and its enantiomers. The 90% confidence interval (CI) of ratios with/without trimethoprim for PK parameters of paliperidone and its enantiomers calculated.
Results Creatinine clearance decreased from 119 to 102 mL min^{-1} with trimethoprim. Addition of trimethoprim increased unbound fraction of paliperidone by 16%, renal clearance by 13%, AUC_∞ by 9%, and $t_{½}$ by 19%. The 90% CIs for ratios with/without trimethoprim were within the 80–125% range for C_{max}, AUC_{last}, and renal clearance. For AUC_∞, 90% CI was 79.37–101.51, marginally below the lower bound of the acceptance range. Paliperidone did not affect steady-state plasma concentrations of trimethoprim.
Conclusions No clinically important drug interactions are expected when paliperidone ER is administered with organic cation transport inhibitors. Copyright © 2009 John Wiley & Sons, Ltd.

KEY WORDS — Paliperidone; trimethoprim; drug interaction; pharmacokinetics

INTRODUCTION

Paliperidone is an antipsychotic of the second generation that belongs to the chemical class of benzoxisoxazole derivatives. Paliperidone extended-release tablets (paliperidone ER; INVEGA™, Janssen Pharmaceuticals, Titusville, NJ, USA) are approved for the treatment of schizophrenia in the United States and European regions. It is formulated as an ER tablet, employing the patented OROS® PushPull™ technology developed by ALZA Corporation.

Paliperidone is a centrally active dopamine D_2 and serotinergic 5-HT_{2A} antagonist, both in *in vitro* and *in vivo* animal and human studies. Paliperidone is also active as an antagonist at α_1- and α_2-adrenergic receptors and H_1-histaminergic receptors. It has no affinity for cholinergic muscarinic or β_1- and β_2-adrenergic receptors (Megens and Awouters, 1994; Schotte et al., 1996). Positron emission tomography in healthy subjects showed that paliperidone occupies central D_2 and $5HT_2$ receptors (Karlsson *et al*., 2006).

Paliperidone pharmacokinetics (PK) have been assessed with intravenous and oral administration of immediate-release (IR) and ER formulations of paliperidone. The controlled rate of release of paliperidone from the ER formulation results in a pharmacokinetic profile with a slower rate of absorption than an IR formulation. After administration of paliperidone ER, the plasma concentrations of paliperidone rise steadily to reach maximum plasma concentration (t_{max}) approximately 24 h after dosing. On subsequent days of treatment, reduced fluctuations in plasma concentrations,

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§ This work was presented in part at the 2006 Annual Meeting of the American Society of Clinical Pharmacology and Therapeutics (8–11 March 2006, Baltimore, MA).

Received 18 March 2009
Accepted 17 June 2009

with a peak to trough ratio of 1.7, are observed (INVEGA Prescribing Information, Accessed November 2007, Paliperidone ER tablets. http://www.invega.com/invega/shared/pi/invega.pdf#zoom=100). The terminal elimination half-life ($t_{½}$) of paliperidone ER is 23 h. The absolute bioavailability is approximately 28%, likely due to reduced absorption in the lower gastrointestinal tract, with negligible first-pass elimination. Paliperidone ER exhibits linear and time-independent PK (INVEGA Prescribing Information, Accessed November 2007, Paliperidone ER tablets. http://www.invega.com/invega/shared/pi/invega.pdf#zoom=100), which are dose-proportional within the dose range of 3–15 mg (Rossenu *et al*., 2006a).

Paliperidone is a racemate. The pharmacologic profiles of the racemate and its enantiomers R078543 (+) and R078544 (−) are similar in *in vitro* binding assays, *in vitro* receptor occupancy studies and *in vivo* functional interaction studies (unpublished data). Interconversion of the enantiomers occurs rapidly and reproducibly in humans (Rossenu *et al*., 2006b).

Paliperidone exhibits moderate protein binding (74%), binding to α_1-acid glycoprotein and albumin. It is metabolised to a limited extent and renal excretion is the major route of elimination, with 59% of the dose excreted unchanged in urine. About half of the renal excretion occurs by active secretion. Four independent metabolic pathways were identified—dealkylation, hydroxylation, dehydrogenation, and benzizoxazole scission—none of which accounted for more than 6.5% of the absorbed dose (Vermeir *et al*., 2008). *In vitro* studies suggested a role for cytochrome P450 (CYP) 2D6 and CYP3A4 in the metabolism of paliperidone; however, *in vivo* results indicate that these isoenzymes play a limited role in the metabolism of paliperidone (Vermeir *et al*., 2008). It has, therefore, little propensity to cause, or be subject to, metabolism-based interactions.

Paliperidone is a cation at physiologic pH and eliminated mainly via renal excretion; 59% of the dose is excreted unchanged in the urine. Approximately, half of the renal excretion occurs by active secretion (Vermeir *et al*., 2008). Several transporters can be involved in active secretion, including cation transporters or P-glycoprotein (Tanigawara, 2000). Co-administration of inhibitors or inducers of such transporters may result in the alteration of the PK (Du Buske, 2005).

The purpose of this study was to assess the impact of an inhibitor of the organic cation transporter system in the kidney, such as trimethoprim, on the PK and renal excretion of paliperidone.

Trimethoprim, an organic base transported by the organic cation transporter system, has been shown to decrease the renal clearance of zidovudine and its glucuronide metabolite, both actively secreted in the renal tubule (Chatton *et al*., 1992). Trimethoprim is an antibacterial that belongs to the class of diaminopyrimidines. It is used for treatment and prophylaxis of uncomplicated urinary tract infections and upper respiratory infections. It is often used in combination with sulfamethoxazole. Trimethoprim is rapidly absorbed after oral administration, with a t_{max} ranging between 1 and 4 h. $T_{½}$ ranges from 8 to 10 h. Steady-state concentrations are achieved within 2–3 days of dosing. Trimethoprim is mainly excreted by the kidneys, 80% of the dose is excreted unchanged in the urine through glomerular filtration and tubular secretion. Protein binding was reported to be 44% (Proloprim Prescribing Information, Accessed May 2008, http://www.fda.gov/medwatch/safety/2006/Jan_PI/Proloprim_PI.pdf).

MATERIALS AND METHODS

Subjects

The study was executed at the Clinical Pharmacology Unit in the Academic Hospital Jan Palfijn (Merksem, Antwerp, Belgium). The study protocol and consent form were reviewed and approved by the Ethics Committee of the University Hospital of Antwerp, Belgium. The study was performed according to the ethical principles if the Declaration of Helsinki and applicable European laws. All subjects gave written informed consent before participation.

Healthy normotensive males aged between 18 and 55 years with a body mass index of 18–28 kg m^{-2} and a creatinine clearance (CL_{CR}) of $\geq$80 mL min^{-1} were enrolled. Subjects were healthy based on a prestudy medical history, physical examination, electrocardiogram (ECG), laboratory tests, and urine analysis. Subjects were excluded if they had a relevant drug allergy; a history of alcohol or drug abuse (as confirmed by negative alcohol and drug screen); orthostatic hypotension; heart rate of $<$45 bpm; positive tests for hepatitis B and C, and HIV; or abnormal bowel movements (i.e., $<$1 bowel movement on average every other day, or $>$2 bowel movements per day).

Study design

In this open-label, randomized, two-way crossover study, all healthy male subjects received each of the two treatments in random order. Treatment A consisted

DOI: 10.1002/hup

of a single oral dose of 6 mg *rac*-paliperidone ER on Day 1. Treatment B included trimethoprim 200 mg tablet twice daily (b.i.d.) from day 1 to day 8 and a single dose of 6 mg paliperidone ER on Day 5. Successive paliperidone ER administrations were separated by at least 14 days. Paliperidone ER 6 mg tablets were administered in the morning under fasting conditions with 240 mL of water. In Treatment B, subjects took a 200 mg trimethoprim tablet in the morning and in the evening (12 h after morning intake) on days 1 to 8 (inclusive) with 240 mL of water.

To avoid possible interactions, caffeine consumption is limited to less than 450 mg of caffeine per day, and consumption of methylxanthine or caffeine was not allowed during the stay at the testing facility. Furthermore, grapefruit juice or food containing Seville oranges was not allowed from 3 days before the first dose through completion of the study, and alcohol or quinine were not allowed from 24 h before the first dose until the end of the study. Smoking was permitted, but limited to 10 cigarettes per day.

No medication other than the study drug was allowed from 14 days prior to the first study drug intake until the end of the study, with the exception of paracetamol to treat certain adverse events (AEs). Clinical laboratory tests were performed at the end of each treatment period. Blood pressure to assess orthostasis and pulse rate were measured up to 96 h after paliperidone ER dosing in each treatment group, as well as on day 1 prior to trimethoprim dosing. ECGs were recorded predose on day 1 in each treatment.

Blood and urine sampling for pharmacokinetics

Blood samples (sodium heparin anticoagulated) for determination of paliperidone enantiomers were collected immediately before and at 2, 4, 6, 9, 12, 16, 18, 20, 22, 24, 26, 28, 30, 33, 36, 48, 60, 72, 84, and 96 h after administration of paliperidone ER. Plasma samples for determination of trimethoprim were collected in Treatment B prior to trimethoprim dosing on Days 4–8. A plasma sample for determination of creatinine was collected at 12 h after administration of paliperidone ER in both treatments. A blood sample for *in vitro* determination of plasma protein binding of paliperidone enantiomers was collected predose on Day 1. Complete urinary output was collected during 120 h following paliperidone ER administration on day 1 for Treatment A and day 5 for Treatment B (0–8, 8–12, 12–24, 24–36, 36–48, 48–72, and 72–96 h). Samples were frozen at −20°C or below until analysis.

Sample analysis

Plasma and urine samples for the determination of plasma and urine concentrations of the paliperidone enantiomers R078543 ((+)-paliperidone) and R078544 ((−)-paliperidone) were analyzed by the Department of Bioanalysis (Beerse, Belgium). The concentrations of paliperidone were calculated as the sum of the two enantiomers.

For the determination of paliperidone enantiomers in plasma, a validated liquid chromatography–tandem mass spectrometry assay was applied as described by De Meulder *et al*. (2008). The data support the accurate and precise quantitation of both the paliperidone enantiomers in 200 μL heparin plasma over a concentration range of 0.2–100 ng mL^{-1}, with a lower limit of quantification of 0.2 ng mL^{-1}. Accuracy, expressed as percentage bias and precision, ranged from −4.5% to 2.3% and from 4.2% to 7.4%, respectively.

An analogous method (De Meulder *et al*., 2008) was applied for the determination of paliperidone enantiomers in urine, as used for the determination of paliperidone enantiomers in plasma. The method was verified by means of a full validation. The data support the accurate and precise quantitation of both the paliperidone enantiomers in 100 μL urine over a concentration range of 1–2000 ng mL^{-1}, with a lower limit of quantification of 1.0 ng mL^{-1}. Accuracy, expressed as percentage bias and precision, ranged from –2.2% to 1.3% and from 2.6% to 3.8%, respectively.

Trimethoprim in plasma was analyzed at Pharma Bio-Research (The Netherlands). Aliquots of 250 μL of plasma, 250 μL of internal standard working solution and 250 μL of 0.1 M borate buffer (pH 10.0) were subsequently added to an extraction tube. After vortex mixing for 10 s, 5.0 mL of a mixture of diethylether and dichloromethane (6:4 v/v%) was added and extraction was performed in a tumble mixer at 36 rpm for 10 min. After centrifugation at 3846*g* (4000 rpm) for 5 min at 20°C, the aqueous layer was frozen in a mixture of acetone and dry ice and the organic layer transferred to a clean extraction tube. A sample of 250 μL of 0.1 M sulfuric acid was added and the extraction was performed in a tumble mixer at 60 rpm for 10 min. After centrifugation at 3846*g* (4000 rpm) for 5 min at 20°C, the aqueous layer was frozen in a mixture of acetone and dry ice. After the organic layer was discarded and the aqueous layer was thawed, the remaining organic layer was evaporated under nitrogen at 40°C for 5 min. The sample was transferred to an injection glass insert and centrifuged

DOI: 10.1002/hup

at 8000 rpm for 10 min and an aliquot of 30 μL was injected into the Alliance Separations Module 2690 (Waters Associates, Milford, MA, USA) chromatographic system with an Applied Bio-Systems 759A absorbance detector set at 231 nm (Applied Bio-Systems, Maarssen, The Netherlands). A Lichrospher 100 (C18 endcapped, 125 × 4 mm^2, 5 μm) (Merck, The Netherlands) analytical column was used, set at 30°C by means of an Alliance column oven (Waters Associates, Milford, MA, USA). As mobile phase a mixture of 17% (v/v) of A (1400 μL triethylamine added to 1700 mL water, adjusted to pH 4.0 with acetic acid) and 83% (v/v) B (acetonitrile) was run at 0.9 mL min^{-1}. The data support the accurate and precise quantitation of trimethoprim in 250 μL heparin plasma over a concentration range of 50–2000 ng mL^{-1}, with a lower limit of quantification of 50 ng mL^{-1}. Accuracy, expressed as percentage bias and precision, ranged from −5.9% to −3.1% and from 0.9% to 1.6%, respectively.

Pharmacokinetic analysis

Pharmacokinetic parameters for paliperidone and its enantiomers were calculated using standard non-compartmental methods: observed maximum plasma concentration (C_{max}) and time to reach C_{max} (t_{max}) (both determined by visual inspection of the data), area under the plasma concentration–time curve (AUC; calculated by linear trapezoidal summation from time zero to the time of the last quantifiable measurement [AUC_{last}] extrapolated to infinity by dividing the last observed quantifiable blood concentration by the terminal exponential rate constant [λ_z]), elimination $t_{1/2}$ (calculated as $\ln 2/\lambda_z$; λ_z was determined from linear regression analysis of data points during the terminal exponential phase of the log plasma concentration–time plot), apparent total oral clearance (CL/*F*; calculated as dose divided by AUC_∞), renal clearance of paliperidone (calculated as total amount excreted unchanged in urine [Ae] divided by AUC_∞); CL_{CR} (calculated as the total amount excreted in 24 h urine divided by the serum creatinine concentration, for both treatment periods); clearance by glomerular filtration (CL_{GFR}; calculated as CL_{CR} multiplied by the fraction unbound (f_u) of paliperidone), active renal clearance (CL_{act}; calculated as the difference between CL_R and CL_{GFR}). The protein binding of the individual enantiomers of paliperidone was determined *in vitro* as described by Mannens *et al*. (1994). The fraction of unbound paliperidone was calculated as $((f_{u,R078543} \times AUC_{\infty,R078543}) + (f_{u,R078544} \times AUC_{\infty,R078544}))/AUC_{\infty,paliperidone}$.

Statistical evaluation

A sample size of 25 subjects was considered to be sufficient to estimate the ratio of geometric mean pharmacokinetic parameters of paliperidone with and without co-administration of trimethoprim to within 15% of the true value with 90% confidence. Thirty subjects were enrolled, to take into account an anticipated 15% dropout rate.

All pharmacokinetic parameters were summarized using descriptive statistics. An analysis of variance (ANOVA) for a two-treatment, two period, randomized, crossover design was performed for C_{max}, AUC_{last}, AUC_∞, and CL_R. All subjects were included in the statistical analysis. ANOVA models were fitted to the data with the pharmacokinetic parameters of interest as the dependent variable, treatment-sequence group, period and treatment as fixed effects, and subject (nested within sequence) as a random effect. The 90% confidence interval (CI) for the ratio of paliperidone and trimethoprim co-treatment over paliperidone mono-treatment was constructed. The absence of a drug–drug interaction was concluded if the 90% CI fell within the prespecified interval of 80–125%.

RESULTS

Demographics, safety, and tolerability

Thirty healthy male subjects received study drug and completed the study. Subject age ranged from 19 to 51 years (mean: 37.8 years), body weight ranged from 56 to 97 kg (mean: 77.1 kg) and body mass index ranged from 19 to 28 kg m^{-2} (mean: 24.0 kg m^{-2}). All subjects were Caucasian.

Paliperidone mono-treatment as well as paliperidone and trimethoprim co-treatment were well tolerated. No serious AEs occurred and no subjects discontinued due to an AE. The most common treatment-emergent AEs in both treatment groups combined were flatulence (37%), postural hypotension (30%), somnolence (23%), headache (20%), fatigue (17%), diarrhea (10%), dry mouth (10%), and dizziness (10%). There were no laboratory abnormalities reported as AEs.

Clinical laboratory tests, ECGs, and vital signs showed no evidence of any safety problems related to paliperidone.

Pharmacokinetics

The mean plasma concentration–time profiles of paliperidone and its enantiomers, R078543 ((+)-paliperidone) and R078544 ((−)-paliperidone), were

DOI: 10.1002/hup

similar after administration of a single dose of 6 mg paliperidone ER taken alone or with 200 mg trimethoprim b.i.d. (Figure 1). In both treatment groups, peak plasma concentrations—which were slightly increased by 9% when trimethoprim was co-administered—were reached approximately 24 h after dosing. Plasma exposure decreased by 5% (AUC_{last}) and 9% (AUC_{∞}), as elimination of paliperidone was slightly increased by trimethoprim intake. This is reflected by a decrease in $t_{½}$ from approximately 27 to 22 h (average values).

In both treatments, R078543 plasma concentrations were higher than those of R07644 at all time points (Figure 1), and this is reflected in the C_{max} and AUCs. The t_{max} and $t_{½}$ were similar for both enantiomers (Table 1).

Statistical analysis for C_{max} and AUC revealed that all 90% CIs for the paliperidone with trimethoprim treatment versus paliperidone alone treatment ratios were included within 80–125%, except for AUC_{∞}, with a lower bound of the 90% CI of 79.37%, which is marginally outside the acceptance range (Table 1). For both paliperidone enantiomers, similar results were obtained as for the racemate (Table 1).

The urinary excretion of paliperidone and its enantiomers was similar in the presence or absence of co-treatment with trimethoprim. The intake of trimethoprim slightly increased the paliperidone CL_R when taken together with trimethoprim; however, the 90% CI of the ratio was included within 80–125% (Table 1). CL_{act} increased by the same magnitude as the renal clearance (Table 1). CL_{CR} was 14% lower in the paliperidone/trimethoprim co-treatment compared to the paliperidone alone treatment (Table 1).

Trimethoprim increased the unbound fraction in plasma of paliperidone and its enantiomers by approximately 4% (Table 2). In both treatment groups, the fraction unbound of R076544 was twice as high as that of R076543.

Steady-state trimethoprim plasma concentrations were not affected by a single dose of 6 mg paliperidone (Table 3).

DISCUSSION

Paliperidone ER is approved in the United States and Europe for the treatment of schizophrenia, which frequently presents with a variety of psychotic, mood and anxiety symptoms, often in combination with substance abuse and comorbid medical conditions. As a result, co-treatment with a number of other drugs occurs frequently. This increases the risk of drug–drug and drug–disease interactions and AEs. Paliperidone is excreted in part by active renal secretion, and therefore, the influence of inhibition of this excretion route was investigated. As paliperidone is an organic cation at physiologic pH, the effect of an organic cation transport inhibitor on the renal excretion of paliperidone ER was investigated. Trimethoprim was selected as an organic cation transport inhibitor rather than cimetidine, because the latter is not only an organic

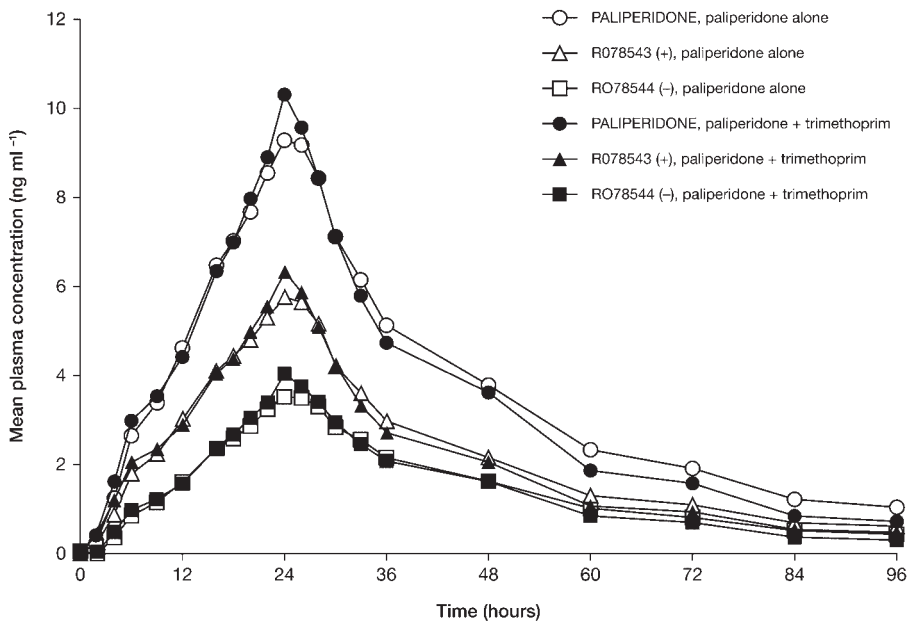

Figure 1. Mean plasma concentration versus time profiles of paliperidone and its enantiomers, R078543 (+) and R078544 (−), after a single dose of 6 mg paliperidone ER taken alone or with 200 mg twice daily trimethoprim

DOI: 10.1002/hup

Table 1. Pharmacokinetic parameters of paliperidone and its enantiomers, R078543 (+) and R078544 (−), after a single dose of 6 mg paliperidone ER taken alone or with 200 mg twice daily trimethoprim

Parameter[a] ($n = 30$)	Paliperidone mono-treatment	Paliperidone plus trimethoprim co-treatment	Treatment ratio (90% confidence interval)
Paliperidone			
C_{max}, ng mL^{-1}	9.78 (3.45)	10.7 (3.67)	109.53 (96.20–124.71)
t_{max}, h[b]	24.0 (16.0–28.0)	24.0 (11.4–28.0)	—
AUC_{last}, ng.h mL^{-1}	348 (119)	330 (130)	93.59 (82.39–106.32)
AUC_{∞}, ng h mL^{-1}	391 (138)	356 (148)	89.75 (79.37–101.51)
$t_{1/2}$, h	26.8 (5.09)	21.8 (3.57)	—
$Ae_{0-96\,h}$, % dose	19.2 (5.82)	19.6 (5.85)	—
CL/F, mL min^{-1}	290 (108)	327 (135)	
CL_R, mL min^{-1}	52.4 (16.1)	59.2 (17.9)	113.24 (108.23–118.47)
CL_{CR}, mL min^{-1}	119 (21.4)	102 (19.9)	—
CL_{GFR}, mL min^{-1}	30.7 (7.88)[c]	30.4 (7.61)	—
CL_{act}, mL min^{-1}	21.7 (11.8)	28.7 (13.8)	—
R078543 (+)			
C_{max}, ng mL^{-1}	6.11 (2.23)	6.51 (2.38)	106.86 (93.37–122.31)
t_{max}, h[b]	24.0 (16.0–28.0)	24.0 (9.0–28.0)	—
AUC_{last}, ng.h mL^{-1}	209 (75.7)	195 (81.3)	91.55 (80.47–104.15)
AUC_{∞}, ng.h mL^{-1}	235 (87.2)	210 (92.8)	87.86 (77.63–99.43)
$t_{1/2}$, h	27.2 (5.18)	22.0 (3.71)	—
$Ae_{0-96\,h}$, % dose	7.68 (2.50)	7.68 (2.66)	—
R078544 (−)			
C_{max}, ng mL^{-1}	3.71 (1.25)	4.17 (1.33)	112.95 (99.65–128.03)
t_{max}, h[b]	24.0 (18.0–28.0)	24.0 (11.4–28.0)	—
AUC_{last}, ng.h mL^{-1}	138 (44.5)	135 (50.4)	96.19 (84.67–109.28)
AUC_{∞}, ng.h mL^{-1}	156 (51.9)	147 (56.5)	93.17 (82.75–104.91)
$t_{1/2}$, h	26.5 (5.15)	21.7 (3.58)	—
$Ae_{0-96\,h}$, % dose	11.5 (3.42)	11.9 (3.32)	—

[a]Mean (standard deviation).
[b]Median (range).
[c]CL_{CR} of trimethoprim co-treatment was used for the calculation. Treatment ratio: ratio of least-square means of paliperidone, plus trimethoprim versus least-square means of paliperidone alone treatment. C_{max}, observed maximum plasma concentration; t_{max}, time to reach maximum plasma concentration; AUC_{last}, area under the plasma concentration–time curve from time zero to the time of the last quantifiable measurement; AUC_{∞}, area under the plasma concentration–time curve from time zero to infinity; $t_{1/2}$, half-life; $Ae_{0-96\,h}$, total amount of paliperidone excreted unchanged in urine from time 0 to 96 h; CL/F, apparent total oral clearance; CL_R, renal clearance; CL_{CR}, creatinine clearance; CL_{GFR}, clearance by glomerular filtration; CL_{act}, active renal clearance.

cation transport inhibitor but is also a potent CYP3A4 (Ohno *et al*., 2007) and P-glycoprotein inhibitor (Yasui-Furukori *et al*., 2005). As paliperidone may, in part, be metabolized by CYP3A4 (Vermeir *et al*., 2008) and transported by P-glycoprotein (Annaert *et al*., 2005), the use of cimetidine may have led to confounding results. In order to show the maximum inhibition potential, the organic cation transport inhibitor trimethoprim was administered at the highest registered dosage regimen of 200 mg twice daily. Trimethoprim administration was continued for 3 days after paliperidone ER administration to fully cover the elimination phase of paliperidone.

Steady state of trimethoprim was reached by Day 4. The trough trimethoprim concentrations were not affected by the addition of 6 mg paliperidone ER and are in the same range as those reported by Niemi *et al*. (2004).

The glomerular filtration rate (GFR) is the accepted parameter to estimate renal function. GFR is usually

Table 2. Fraction unbound for paliperidone and its enantiomers, R078543 (+) and R078544 (−), in the presence and absence of trimethoprim

Substance	Paliperidone alone ($n = 30$)	Paliperidone plus trimethoprim ($n = 30$)
Paliperidone, %	25.7 (3.81)	29.7 (3.77)
R078543 (+), %	18.7 (3.55)	22.6 (3.67)
R078544 (−), %	36.1 (4.43)	39.5 (3.84)

Data expressed as mean (standard deviation).

Table 3. Plasma concentrations (ng mL^{-1}) for trimethoprim 200 mg twice daily before and after 6 mg of paliperidone ER administration

	Day 4		Day 5		Day 6		Day 7	Day 8	Day 9
	a.m.	p.m.	a.m.	p.m.	a.m.[a]	p.m.	p.m.	p.m.	a.m.
Mean	2480	2320	2240	2080	2310	2020	2170	2210	2400
SD	718	697	727	669	695	684	729	763	805

Paliperidone ER was administered in the morning of Day 5. All samples collected just prior to dosing except:
[a]Sample collected 2 h prior to dosing. SD, standard deviation.

DOI: 10.1002/hup

determined using serum or plasma creatinine concentrations. This, however, generally leads to an overestimation of the GFR as about 28% of CL_{CR} occurs by active tubular secretion (Kastrup *et al*., 1985). CL_{CR} closely approximates the GFR when the active tubular secretion of creatinine is inhibited (Hellerstein *et al*., 1998). Trimethoprim decreased the mean (SD) CL_{CR} by about 14%, from 119 (21.4) to 102 (19.9) mL min^{-1}, which is in line with literature data (Hellerstein *et al*., 1998) and consistent with an inhibition of the active tubular secretion of creatinine by trimethoprim. Therefore, we considered the CL_{CR} data obtained in the co-administration paliperidone and trimethoprim to be the product of glomerular filtration only. Consequently, we used the CL_{CR} measured in paliperidone and trimethoprim co-administration to estimate the clearance by glomerular filtration in the paliperidone alone treatment as well.

Co-administration of trimethoprim with a single oral dose of paliperidone ER did not cause relevant alterations on the pharmacokinetic parameters of paliperidone. The 90% CIs for the ratios with/without trimethoprim were within the acceptance range of 80–125% for C_{max}, AUC_{last}, and renal clearance. The 90% CI of AUC_{∞} was 79.37–101.51%, which was marginally below the lower bound of the acceptance range. T_{max} (around 24 h) and the amount excreted unchanged in urine (approximately 19%) were not affected by trimethoprim. Plasma and urinary exposure were in the same range as previously observed (Yang and Plosker, 2007). About 60% of paliperidone renal clearance was through excretion by passive glomerular filtration, the remaining fraction was cleared by active secretion. These findings are in line with previous findings (unpublished observations).

The intake of trimethoprim increased, rather than decreased, the mean paliperidone renal clearance from 52.4 to 59.2 mL min^{-1}. This effect was of no clinical relevance as the 90% CI of the treatment ratio was within the acceptance range of 80–125%. The active secretion of paliperidone was increased by the intake of trimethoprim by approximately the same magnitude as the renal clearance.

When comparing the apparent plasma clearance and the renal clearance, it is not obvious that renal clearance is a substantial part of paliperidone clearance. Total clearance, however, has to be corrected for the absolute bioavailability (F) of paliperidone of 28% (Rossenu *et al*., 2006b). Using this value for F, plasma clearance in this study amounts around 80 mL min^{-1}, which is in line with values observed after intravenous administration (unpublished observations).

For both paliperidone enantiomers, R078543 and R078544, similar trends were obtained as for the racemate upon co-treatment with trimethoprim. The effect of trimethoprim co-administration on the overall exposure (AUC) is slightly higher for the R078543 enantiomer. This is not clinically relevant as the pharmacological profiles of the two enantiomers are similar. When comparing the PK of both enantiomers, it is evident that in both treatments the exposure to R078543 is higher than that of R078544. The total exposure of R078543 is 50% higher than that of R078544. $t_{½}$ and t_{max} are similar for both enantiomers. The amount excreted in urine for R078543, on the other hand, is about half that of R078544. The latter can be explained by the fact that the unbound fraction of R078544 is twice is high as that of R078543 (Table 2) and, consequently, the clearance by GFR of R078544 is twice is high as that of R078543. It has been demonstrated previously that the peripheral volume of distribution for R078544 is 192 L compared with 70.6 L for R078543 (Rossenu *et al*., 2006b), which is in line with the observed difference in plasma exposure between the enantiomers.

In conclusion, no clinically relevant effects of the potent organic cation inhibitor, trimethoprim, on the exposure of paliperidone ER are observed. Trough trimethoprim concentrations were not affected by the addition of paliperidone ER. Thus, no clinically important drug interactions are expected when paliperidone ER is co-administered with organic cation transport inhibitors.

STATEMENT OF COMPETING INTERESTS

All authors were employed by the sponsor of the study, Johnson & Johnson, at the time of study preparation, conduct, analysis, and reporting. An Thyssen, Luc Janssens and Marielle Eerdekens remain full-time employees of Johnson & Johnson. Adriaan Cleton, Krishna Talluri, Jos Leempoels, and Sandra Boom were full-time employees of Johnson & Johnson at the time of study conduct.

ACKNOWLEDGEMENTS

This study was funded by Johnson & Johnson Pharmaceutical Research & Development. The authors gratefully acknowledge SGS for the assistance with the pharmacokinetics analysis, Bart Remmerie and Marc De Meulder for the bioanalytical support, Geert Mannens for the determination of plasma protein binding and Nancy van Osselaer for her scientific input. The authors would like to thank, Frances Gambling, Medicus International, for her editorial assistance. Editorial assistance was funded by Johnson &

Johnson, Pharmaceutical Services, LLC. All authors were employed by the sponsor of the study at the time of study preparation, conduct, analysis, and reporting.

Funding: This study was funded by Johnson & Johnson Pharmaceutical Research & Development.

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