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**Title:** Human pharmacology of current and new treatments for schizophrenia

**Issue Date:** 2012-03-08

# THE EFFECTS OF A GLYCINE REUPTAKE INHIBITOR R231857 ON THE CENTRAL NERVOUS SYSTEM AND ON SCOPOLAMINE INDUCED IMPAIRMENTS IN COGNITIVE AND PSYCHOMOTOR FUNCTION IN HEALTHY SUBJECTS

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J PSYCHOPHARMACOL 2010; 24: 1681-7

## Abstract

The effects of the selective inhibitor of the glycine transporter 1, might be an indication that R231857 penetrated the CNS, they were not R231857, in development for schizophrenia, on the central nervous system consistent or dose-related. R231857 had some small effects on (CNS) were investigated in healthy males in the absence and presence of scopolamine-induced CNS-impairment, which were also not clearly scopolamine. This was a double-blind, placebo-controlled, four-period dependent on dose. Scopolamine proved to be an accurate, reproducible crossover ascending dose study. Pharmacokinetics, body sway, saccadic and safe model to induce CNS impairment by an anticholinergic and smooth pursuit eye movements, pupillometry, pharmaco-mechanism. R231857 lacked consistent dose-related effects in this study, electroencephalogram (EEG), Visual Analogue Scales (VAS) for alertness, probably because CNS concentrations were too low to produce significant/ mood, calmness and psychedelic effects, adaptive tracking, finger tapping, reproducible CNS-effects or to affect the scopolamine challenge in healthy Stroop test, Visual and Verbal Learning Task (VVLTL) and hormone levels volunteers. The effects of higher doses in healthy volunteers and the were assessed. R231857 was administered alone and together with clinical efficacy in patients remain to be established. scopolamine to investigate the potential reversal of anticholinergic CNS impairment by the glycine reuptake inhibitor. Forty-two of the 45 included subjects completed the study. Scopolamine significantly affected almost every CNS parameter measured in this study. R231857 alone showed some pharmacodynamic changes compared with placebo. Although these effects might be an indication that R231857 penetrated the CNS, they were not consistent or dose-related. R231857 had some small effects on scopolamine-induced CNS-impairment, which were also not clearly dependent on dose. Scopolamine proved to be an accurate, reproducible and safe model to induce CNS impairment by an anticholinergic mechanism. R231857 lacked consistent dose-related effects in this study, probably because CNS concentrations were too low to

produce significant/reproducible CNS-effects or to affect the scopolamine challenge in healthy volunteers. The effects of higher doses in healthy volunteers and the clinical efficacy in patients remain to be established.

## Introduction

As extensively reviewed in previous reports, hypofunction of N-methyl-D-aspartate (NMDA) neurotransmission is hypothesised to play an important role in the pathophysiology of schizophrenia (Javitt, 2006; Stone, *et al*, 2007). R231857 (Figure 1 - structural formula) selectively inhibits the glycine transporter 1 (GlyT<sub>1</sub>). Tsai and Lane *et al* have shown that the glycine reuptake inhibitor sarcosine causes some improvements of positive and negative symptoms and cognitive function in schizophrenia (Lane, *et al*, 2005; Tsai, *et al*, 2004). Hence, the hypothesis is that R231857 may also have beneficial effects on these symptoms.

Preclinical studies have supported a potential therapeutic potential of this compound (Johnson and Johnson, data on file). R231857 is more potent than sarcosine, evidenced by a lower IC<sub>50</sub> (the half maximal inhibitory concentration). It increased extracellular glycine levels in the prefrontal cortex in rats and glycine levels in the cerebrospinal fluid in dogs. It was also effective in some animal models of schizophrenia. Importantly, R231857 normalised the disturbed prepulse inhibition paradigm in dopamine transporter knockout mice. It also decreased amphetamine-induced hyperactivity in rats with neonatal lesions of the hippocampus and reduced the potentiation of amphetamine-induced dopamine release in the prefrontal cortex of rats receiving phencyclidine. R231857 was well tolerated by healthy men in single and multiple doses up to 640 mg but central nervous system (CNS) effects of electroencephalogram (EEG), Cognitive Drug Research (evaluating memory function and attention) and Addiction Research Center Inventory 49-Item Questionnaire (ARC149) were not observed in these studies (Johnson and Johnson, data on file).

To obtain an indication of CNS penetration and pharmacological activity, a battery of quantitative CNS-tests was used that is sensitive

to a wide range of CNS-active drugs including neuroleptics (de Visser, *et al*, 2001, 2003; Gijsman, *et al*, 2002; Kemme, *et al*, 2003; van der Post, *et al*, 2004). It is difficult to demonstrate cognitive improvements in healthy volunteers, which would be an important therapeutic objective in schizophrenic patients. To induce transient and reversible thought and memory disturbances, which in some ways mimic those observed in patients with negative symptoms and cognitive dysfunction, a scopolamine challenge test was used (Ebert, *et al*, 1998; Green, *et al*, 2005; Koller, *et al*, 2003; Riedel, *et al*, 1995). Various preclinical experiments have demonstrated a reversal of scopolamine-induced impairments using agonists for the glycine site on the NMDA receptor (Andersen, *et al*, 2002; Kishi, *et al*, 1998; Zajackowski and Danysz, 1997). Similar findings were obtained in one study in healthy volunteers with the partial glycine site agonist, D-cycloserine (Jones, *et al*, 1991). The neuropharmacological mechanism behind the cholinergic-glutamatergic interaction has not been elucidated. It has been proposed that glycine increases acetylcholine release in the striatum and hippocampus (Nishimura and Boegman, 1990; Ransom and Deschenes, 1989; Scatton and Lehmann, 1982). Another is the presence of NMDA receptor sites on cell bodies of cholinergic neurons and a subsequent increased acetylcholine release by glycine (agonists) due to depolarisation of the receptor (Fishkin, *et al*, 1993; Matsuoka and Aigner, 1996).

In the current study, the objectives were to study the CNS profile of R231857 alone and its effects on scopolamine-induced (cognitive and psychomotor) impairments in healthy male subjects.

## Methods

### Subjects

A total of 45 male subjects aged 18-55 with body mass index (BMI) of 18-28.5 kg/m<sup>2</sup> were recruited by the Centre of Human Drug Research. After signing an informed consent, subjects were medically screened within 3 weeks before study participation. Exclusion criteria included

the use of agents known to affect CNS performance (including nicotine, drugs or alcohol), history or presence of psychiatric disease and evidence of relevant clinical abnormalities (checked by a physical examination and haematology, biochemistry and virology). The use of medication was not allowed during the study period. The Ethics Review Board of the Leiden University Medical Center approved the study protocol.

### Study design

This study was a double-blind, placebo-controlled, four-period crossover ascending dose study. The periods were separated by a washout period of at least 1 week.

### Drugs and study design

Scopolamine 0.5 mg or placebo was given intravenously over a period of 15 min starting at T = 0 and 80, 160 or 320 mg of R231857 or placebo was orally administered at T = 0.5 h. This study was a double-blind, placebo-controlled, four-period crossover ascending dose study. The four treatments given, separated by at least 1 week, were scopolamine + placebo, scopolamine + R231857, placebo + placebo and placebo + R231857. After these four periods, the dose of R231857 was escalated and given to another group of 15 subjects in a four-period crossover fashion. Three dose groups of R231857 were treated, resulting in 45 subjects in total. The three doses of R231857 used in this study (80, 160 and 320 mg) were expected to cause plasma concentrations, corresponding to levels that block the GlyT<sub>1</sub> site for more than 50% in preclinical experiments, which was considered sufficient to cause a significant functionally relevant effect. Exploration of higher levels of exposure and inhibition was thwarted by pharmaceutical formulation issues that occurred with the production of higher doses.

The selection of the scopolamine dose was based on an earlier study of Ebert, *et al* showing that an intravenous dose of 0.5 mg scopolamine demonstrated clear concentration-dependent effects using electroencephalography, while still having an acceptable side-effect profile (Ebert, *et al*, 2001).

## Safety

Adverse events, electrocardiogram (ECG), body temperature, blood pressure and heart rate measurements were performed throughout the study. ECGs were assessed using Cardioperfect ECG recorder (Welch Allyn, New York, US). Blood pressure and heart rate were measured using an automated device (Nihon Kohden, Life Scope EC, Tokyo, Japan). Haematology, biochemistry and urinalysis were performed.

## Pharmacodynamics

Eleven blocks of pharmacodynamic measurements were performed: predose (twice before scopolamine administration) and 0.75, 1.0, 1.5, 2.0, 2.5, 3.5, 4.5, 6.5 and 8.5 h post-dose. Average baseline values for each variable were obtained by calculation of the mean of two baseline assessments. Pharmacodynamic tests were performed in a quiet room with ambient illumination with only one subject in the same room per session. Tests were performed in the following order: body sway, saccadic eye movements, smooth pursuit measurement, pupillometry, pharmacoe-EEG, Visual Analogue Scales (VAS) Bond and Lader, Bowdle, adaptive tracking, finger tapping, Stroop test and Visual and Verbal Learning Task (VULT). Blood for hormones (follicle-stimulating hormone [FSH], luteinizing hormone [LH] and prolactin) was taken regularly from 4 min until 24 h after scopolamine administration. LH and FSH were measured as animal studies of both R231857 and the related compound R213129 showed an increase in serum prolactin levels and decrease in LH. The prolactin rise was confirmed after single and multiple administration of R231857 in healthy volunteers (Johnson and Johnson, data on file). Because of the presumed role of excitatory amino acids in the regulation of the release of such hormones, these hormones are potentially interesting endocrine markers for pharmacodynamic activity of GlyT<sub>1</sub> inhibitors (Brann and Mahesh, 1995; Mahesh and Brann, 2005). Subjects had a standardised breakfast 1 h before scopolamine administration. All subjects were thoroughly trained and familiarised with the

psychometric tests within 14 days before start of the study to minimise learning effects during the study. The pharmacodynamic measurements are described extensively elsewhere (Liem-Moolenaar, 2009).

## Pharmacokinetics

### R231857

Blood samples (5 mL) for plasma concentrations of R231857 were drawn predose and at 1.0, 1.5, 2.0, 2.5, 3.5, 4.5, 8.5, 10 and 24 h post-dose. Samples were protected from light at all times to prevent degradation of the compound. Plasma samples were analysed to determine R231857 concentrations using a validated, selective and sensitive liquid chromatography-tandem mass spectrometry (LC-MS/MS) (Lower Limit Of Quantification (LLOQ) = 1 ng/mL). R231857 was performed by the Department of Bioanalysis, J&J PRD, Belgium.

### SCOPOLAMINE

Blood samples (4 mL) for plasma concentrations of scopolamine were drawn at 0.5, 0.75, 1.0, 2.5 and 6.5 h after the scopolamine infusion was stopped. Samples were protected from light at all times. Plasma samples were analysed to determine scopolamine concentrations using a validated, selective and sensitive liquid LC-MS/MS method (LLOQ = 10 pg/mL). Scopolamine bioanalysis was performed by Pharma Bio-Research Group B.v., Zuidlaren, the Netherlands.

## Statistical analysis

### PHARMACODYNAMICS (PD)

PD parameters were analysed by mixed model analyses of variance (using SAS PROC MIXED) with treatment, period, time and treatment by time as fixed effects, with subject, subject by time and subject by treatment as random effects and with the baseline value as covariate, where baseline is defined as the average of the available values obtained before dosing. This resulted in least square means (LSM) estimates that indicate the

change from baseline, where baseline in the graph is set at 0 for  $t = 0$  min. Treatment effects were reported as the contrasts between placebo and scopolamine, where the average of the measurements up to and including 8.5 h (22 h for neuroendocrine parameters) were calculated within the statistical model. Contrasts were reported along with 95% confidence intervals and analyses were two sided with a significance level of 0.05.

## PHARMACOKINETICS (PK)

Summary statistics of the plasma concentration data and estimated pharmacokinetic parameters for R231857 and scopolamine were calculated. The following pharmacokinetic parameters for R231857 and scopolamine were determined using Pharsight's WinNonlin pharmacokinetic analysis software (version 4.0.1):  $C_{MAX}$ ,  $C_{0.5h}$  (scopolamine),  $T_{MAX}$ ,  $AUC_{last}$ ,  $AUC_{\infty}$ ,  $t_{1/2term}$ ,  $CL/F$  (clearance/bioavailability) (R231857) and  $CL$  (scopolamine).

## Results

### *Participant characteristics*

Forty-two of the 45 included healthy male subjects completed the study. There was no difference in demographics (age and BMI) between the three different dose groups of R231857.

Three subjects decided to stop participation in the study for personal reasons. Subjects were on average 27.5 years old (range: 18-55).

### *Clinical effects*

Scopolamine induced the well-known anticholinergic effects (characterised by increased pupil size, dry mouth, drowsiness and impaired eye focusing) in 43 of the 44 subjects. Other reported effects were dizziness in 4 and headache in 3 of the 44 subjects.

The most frequently reported adverse events for R231857 were headache (12 of 45), somnolence (10 of 45) and nausea (5 of 45).

The incidence of these events seemed slightly higher following dosing with R231857 than with placebo. For headache, this was 6 of 43 after all three doses of R231857 compared with 4 of 44 for placebo, for somnolence 5 of 43 compared with 2 of 44 and for nausea 2 of 43 compared with 0 of 44. However, these numbers are too small to draw any conclusions.

## *Pharmacokinetic results*

The mean concentration-versus-time profile of R231857 is presented in Figure 2. After administration, R231857 was rapidly absorbed with a time of maximum concentration 1 h or less after dose administration and a maximum concentration of 370, 1200 and 2050 ng/mL for the three different doses. The terminal elimination half-life was short, that is, less than 3 h (range: 1.6-2.8 h) and clearance ranged between 125 and 160 L/h. Pharmacokinetics were dose-linear for the tested doses, with the exception of slightly more than dose proportional pharmacokinetics between 80 and 160 mg. When combined with scopolamine, the pharmacokinetic profile of R231857 was slightly altered for some parameters (see Figure 2). For all doses, but mainly at the highest dose, the maximum concentration was reduced. Consequently, exposure was also reduced when 320 mg R231857 was combined with scopolamine (from approximately 2700 to 1900 ng.h/mL).

The average scopolamine concentration 0.5 h after the end of dosing (with and without R231857) was 1335 pg/mL and the terminal elimination half-life was 1.5 h. Clearance was 186 L/h. Scopolamine was not affected by the addition of R231857.

## *Pharmacodynamic results*

### SCOPOLAMINE

Scopolamine resulted in a considerable number of CNS-effects and affected almost every parameter measured in this study (Table 1). Scopolamine deteriorated adaptive tracking, body sway and finger tapping rate performance compared with placebo. Both saccadic peak

velocity and smooth pursuit performance decreased after scopolamine compared with placebo administration.

Powers of alpha (Fz-Cz and Pz-Oz) and beta Pz-Oz were statistically significantly lower after scopolamine than after placebo. Delta power (Fz-Cz and Pz-Oz) was statistically significantly higher after scopolamine than after placebo. Beta Fz-Cz and theta power (Fz-Cz and Pz-Oz) after scopolamine was not statistically significantly different from placebo.

Scopolamine deteriorated all parameters of the vvLT (Table 1): delayed word recall (number correct), immediate word recall (number correct) and delayed word recognition (number correct). Similarly, the following parameters of the Stroop test were deteriorated compared with placebo: number correct in both basic and conflict situation and reaction time in conflict situation. The delayed word recognition (reaction time) and the Stroop parameter reaction time in basic situation after placebo were not statistically significantly different than after scopolamine.

The VAS alertness and VAS mood were significantly lower after scopolamine than after placebo and the VAS calmness was not changed by scopolamine. The VAS internal perception, external perception, the VAS feeling high and the VAS colour perception were all higher after scopolamine than after placebo.

All hormone levels increased after scopolamine compared with placebo.

## R231857

R231857 80 mg marginally decreased adaptive tracking performance by 1.41% (95% CI -2.78, -0.05). The 160 mg dose marginally decreased the number correct of the immediate word recall test by 2.0 (95% CI -4.0, -0.1) and the VAS alertness scale by 3.4 mm (95% CI -6.2, -0.6).

## R231857 AND SCOPOLAMINE

EEG beta power (Fz-Cz), which was not changed by scopolamine alone, was decreased after 160 mg R231857 by 6.7% (95% CI -12.7, -0.4%). The VAS calmness scale, which was also not changed after scopolamine alone, was increased after 320 mg R231857 by 2.5 mm (95% CI 0.2, 4.8).

Scopolamine-induced increases in the VAS colour perception scale were further increased after 320 mg R231857 by 1.2 mm (95% CI 0.4, 2.0) and scopolamine-induced hormone increases were reversed after 160 mg R231857 by 6.3% for FSH (95% CI -9.6, -2.8%) and by 17.3% for LH (95% CI -25.9, -7.7%).

## Discussion

Scopolamine showed similar effects to our previous study in another cohort of healthy subjects (Liem-Moolenaar, 2009), which demonstrates the accuracy and reproducibility of this model for cognitive and psychomotor impairment. Scopolamine impaired almost every tested CNS-parameter. The concentration effect relationships of the scopolamine challenge will be discussed in more detail elsewhere (data on file).

In this study, the glycine reuptake inhibitor R231857 alone showed some marginal and inconsistent effects compared with placebo. The 80 mg dose caused a small deterioration of adaptive tracking performance and the 160 mg dose decreased the number of correct responses of the immediate word recall test and the subjective alertness. Although these effects might be an indication for limited CNS depression, these were not consistent or dose-related. The study does not allow an interpretation whether this lack of consistent effects is due to insufficient brain penetration, low pharmacological activity, the absence of physiological changes during glycine reuptake inhibition in healthy humans or a methodological reason (i.e., we were not able to detect small CNS-effects with our tests).

The combination of R231857 with scopolamine caused a reduction of  $C_{MAX}$  and exposure of the GlyT<sub>1</sub>-reuptake inhibitor. This could be due to the anticholinergic action of scopolamine, which can lead to delayed gastric emptying and resorption of the highest dose of R231857. Scopolamine also changed the subtle pharmacodynamic effects of R231857, although these changes were small and inconsistent and could not be clearly attributed to either the doses of the GlyT<sub>1</sub> reuptake inhibitor or the small scopolamine-related reductions of plasma concentrations.

There were changes in EEG power and subjective calmness, subjective colour perception and hormones, which does not seem to point to alterations of any specific brain network or physiological system. Glycine reuptake inhibition would be expected to cause some glutamatergic effects in the CNS, but also in this respect, we could not identify any trends in the results (such as CNS stimulation). In healthy subjects, the literature has only reported one study on the effects of the glycine reuptake inhibitor D-cycloserine on scopolamine-induced memory impairment (Jones, *et al*, 1991). The only other studies investigating D-cycloserine alone in healthy volunteers on cognitive function report contradictory results (Bailey, *et al*, 2007; D'Souza, *et al*, 2000; Trevisan, *et al*, 2008). Therefore, it is difficult to make useful comparisons to previously published reports.

The lack of clear and consistent R231857 effects on scopolamine-induced CNS-impairment could have several causes. These include non-optimal dosing of the glycine reuptake inhibitor, the unsuitability of the scopolamine model or a dose that was too high to detect effects of glycine reuptake inhibitors and the composition of the CNS battery (which may have consisted of tests that were too insensitive to pick up effects). Because previous studies have shown some reversal of scopolamine effects with D-cycloserine, the most plausible explanation is that the doses of R231857 were too low. If so, the small and non-dose-related effects that were observed in this study could have been an indication of very early CNS-effects, which and may have been too small and/or too variable to consistently surpass the detection limit. In this case, higher doses will cause both larger and more consistent effects. A limited blood-brain-barrier penetration of R231857 may also have increased the variability of its CNS-effects in the low 80- 320 mg dose range. The doses used in this study were based on the in-vitro IC<sub>50</sub> for the GlyT<sub>1</sub>-transporter. Based on pre-clinical experiments, this level was considered to be sufficient to cause pharmacologically relevant and functionally detectable effects in healthy volunteers, but it was actually based on practical limitations with the formulation of higher doses. In hindsight, and particularly if CNS-exposure was low, this exposure level may have been too small.

In summary, the scopolamine challenge test proved to be accurate,

reproducible and a safe model for CNS-impairment. Most of the scopolamine-induced changes were in agreement with the findings of previous studies. Both alone and in combination with scopolamine, R231857 only showed marginal, inconsistent effects, which could not be readily attributed to any consistent functional or pharmacological modification. This absence of consistent effects seems most logically explained by R231857 concentrations in the CNS that were too low to cause any reliable changes in healthy volunteers. To show pharmacological activity of this compound in healthy volunteers, studies with higher doses would be required. In addition, clinical trials are needed to investigate which level of glycine reuptake inhibition is needed to show efficacy in patients.



Table1 Pharmacodynamic effects of placebo, scopolamine and the combination of scopolamine and R231857

Parameter (unit) <sup>B</sup>	LSM <sup>C</sup> PLAC	LSM <sup>C</sup> SCOP	Difference <sup>A</sup>	95% CI	Pvalue	LSM <sup>C</sup> SCOP + R231857 <sup>D, E</sup>	Difference <sup>A</sup>	95% CI	Pvalue
Adaptive tracking (%)	21.45	11.41, 41	10.03	9.10, 10.97	<0.0001				
Body sway (mm)	258	408	58.1%	44.1, 73.9%	<0.0001				
Finger tapping rate (taps/10 sec)	66.2	62.4	3.8	2.5, 5.2	<0.0001				
Saccadic Peak Velocity (deg/sec)	458.8	442.7	16.2	8.3, 24.0	<0.0001				
Smooth pursuit (%)	50.43	43.27	7.16	4.48, 9.83	0.0001				
EEG beta Fz-Cz (µV)	2.03	2.10	3.5%	-1.0, 8.1%	0.125	1.96 (160)	93.3%	87.3, 99.6%	0.0379
Delayed word recall (# correct)	12.9	7.6	5.3	4.0, 6.6	<0.0001				
Immediate word recall (# correct)	13.0	8.5	4.5	3.5, 5.5	<0.0001				
Delayed word recognition (# correct)	24.4	22.6	1.9	0.4, 3.3	0.015				
Delayed word recognition (RT, msec)	903.9	929.3	-25.5	-65.1, 14.1	0.205				
Stroop (conflict, # correct)	19.5	19.1	0.4	0.2, 0.6	0.001				
Stroop (conflict, RT, msec)	663	756	-92	-128, -57	<0.0001				
VAS calmness (mm)	56.8	56.8	-0.1	-1.4, 1.3	0.936	59.3 (320)	2.5	0.2, 4.8	0.0305
VAS feeling high (mm)	0.19	10.23	-10.04	-13.69, -6.39	<0.0001				
VAS colour perception (mm)	0.20	0.92	-0.72	-1.25, -0.20	0.0072	2.13 (320)	1.21	0.40, 2.03	0.0038
FSH (U/L)	3.68	3.87	5.2%	2.6, 7.9%	<0.0001	3.62 (160)	93.7%	90.4, 97.2%	0.0005
LH (U/L)	4.32	5.26	21.8%	13.3, 31.1%	<0.0001	4.35 (160)	82.7	74.1, 92.3%	0.0009
Prolactin (µg/L)	8.41	9.96	18.3%	12.5, 24.7%	<0.0001				

A. Ifo is included in the 95% Confidence Interval (95% CI) the difference is not conventionally different at the 5% level; B. RT = Reaction time; C. LSM is the Least Squares Means estimate; D. The interaction effects are only indicated in case of a significant effect; E. Dose (mg) of R231857 inducing a change in scopolamine

Figure 1 Structural formula of R231857

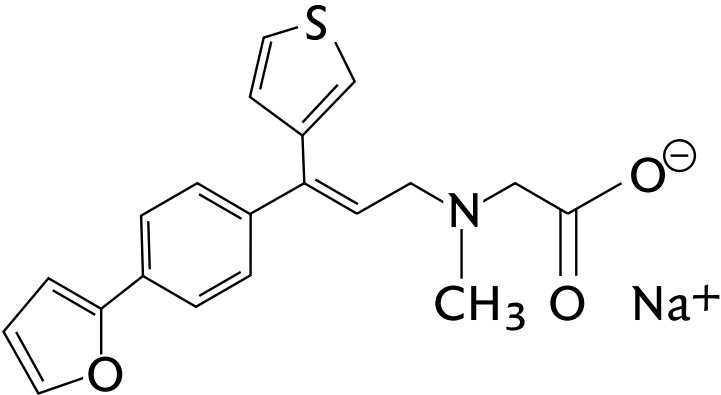
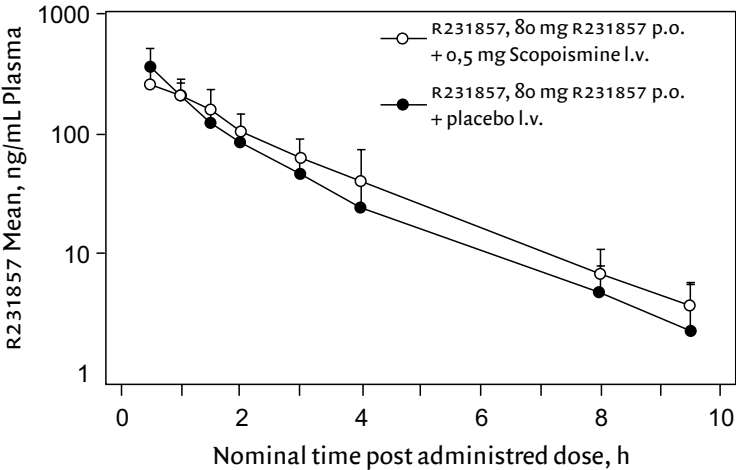


Figure 2 Mean (+SD) plasma concentration profile of 80 mg



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