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Research Article

Distribution, excretion and metabolic pathways of a single parenteral administration of kappa-opioid receptor agonist RU-1205

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Abstract

Introduction: The purpose was to study the pharmacokinetic properties of RU-1205 with the previously identified kappa-agonistic and analgesic effects after parenteral administration.

Materials and methods: Pharmacokinetic parameters of RU-1205 after intravenous and subcutaneous administration at doses of 10 mg/kg and 50 mg/kg, respectively, were investigated, using the method of high-performance liquid chromatography with measurement of the compound according to a pre-established calibration curve. The indices of the area under the pharmacokinetic curve, clearance, half-life, residence time of the drug molecule in the body, total (apparent) volume of distribution, as well as the indicator of absolute bioavailability for subcutaneous administration were calculated. Tissue distribution and excretion of RU-1205 were also studied. Evaluation of metabolism of RU-1205 was conducted *in silico*, using the PALLAS 3.00 software, with the use of specific tests with CYP 450 substrates and by studying the ability of RU-1205 to form conjugates with endogenous acids.

Results and discussion: It was found that after a single intravenous administration, the investigated substance was determined in the blood for 12 h; the half-life was 8.49 hours. The absolute bioavailability after subcutaneous administration is 57.35%. RU-1205 is eliminated within 3–4 days. The main route of excretion is extrarenal. The biotransformation of the substance probably proceeds mainly with the formation of oxidized forms of the initial molecule according to the reactions of the first phase of metabolic transformation, so the chance to observe phase 2 of the metabolism could be very low.

Conclusion: The test substance undergoes a long process of elimination, has the highest tropism to the elimination organs and undergoes active biotransformation processes in the body of animals.

Keywords

imidazobenzimidazoles, kappa-agonists, analgesics, pharmacokinetic, tissue distribution, excretion, biotransformation.

Introduction

It is well know that opioid analgesics currently used in clinical practice are associated with serious nervous system related adverse events, such as euphoria, hallucinations, anxiety, respiratory depression, development of opioid addiction, abuse and misuse, and development of tolerance and physical dependence, which significantly limit the use of opioid analgesics in clinical practice. Therefore, there is an unmet medical need in development of new well-tolerated pain-relieve medications (Stein 2018).

One of the promising approaches to address these adverse events is development of new class of analgesics that are selective agonists of opioid receptors, such as kappa receptors. Unlike well-known mu- and delta- receptors agonists, these analgesics are characterised by absence of euphoria, respiratory depression and physical dependence (Prisinzano et al. 2005; Minervini et al. 2018).

RU-1205 [9-(2-morpholinoethyl)-2-(4-fluorophenyl) imidazo[1,2-α]benzimidazole] is imidazo [1,2-α] bensimidazole based compound. *In vitro*, this drug was found to have a significant analgesic activity due to its agonistic effect on kappa opioid receptors (Grechko et al. 2017). *In vivo*, RU-1205 demonstrated a significant pain relieving effect exceeding that of butorphanol and morphine (Spasov et al. 2018), without any respiratory depression, development of analgesic tolerance and physical dependency (Grechko et al. 2017; Litvinov et al. 2017).

An analysis of pharmacokinetic parameters and tissue and organ distribution of pharmacological substance is an important and useful tool for further drug development and for a better understanding of the results of non-clinical and toxicological studies (Normative Legal Acts 2017). Understanding the pharmacokinetic characteristics can affect a decision about the way of administration of the drug and about choosing the optimal dose to be further tested in clinical trials. An analysis of tissue and organ distribution is important for a better understanding of the effects of the drug based on its mechanism of action and for predicting the potential tissue specific toxicity.

The aim of this study was to evaluate pharmacokinetic characteristics and tissue and organ distribution of the novel therapeutic agent RU-1205 after intravenous and subcutaneous administrations.

Materials and methods

Animals

The studies were conducted on non-linear male rats, weighing 200–230 g each, received from The Laboratory Animals Nursery of the Academy of Medical and Technical Sciences (Moscow). The animals were kept at the animal testing site as per the State standard (GOST R 50258-92). All the procedures were performed after the approval by The Regional Ethic Committee (Protocol № 2077-2018 issued on 30.10.2018). The animals had constant access to water and food and received standardized diet (granules, 5 mm in diameter, GOST R 50258-92 51899-02). The animals were deprived of food 12 hours prior to the trial.

Drugs and administration route

RU-1205 drug substance was synthesized in the Research Institute of Physical and Organic Chemistry, Southern Federal University (Fig 1). The purity was at least 99.46%.

The study drug RU-1205 was administered intravenously and subcutaneously at doses of 10 mg/kg and 50 mg/kg respectively. The drug was diluted with saline.

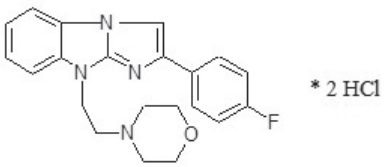

Figure 1. RU-1205 Structured formula.

Study design

Blood and organ sampling was performed after decapitation of the animals – 5 min, 10 min, 20 min, 40 min, 1 hour, 2 hours, 4 hours, 8 hours, and 12 hours after intravenous administration, after 30 minutes, 1 hour, 2 hours, 4 hours, 8 hours, and 12 hours after subcutaneous administration and 5 minutes after administration of the saline in the control group. The rats were randomly assigned to one of the study groups (n = 5 for each time interval). 5% sodium citrate was used for blood stabilisation. Plasma was obtained by 15 min centrifugation at 3000 rpm. Drug distribution was studied in the organs responsible for excretion – liver and kidneys, in the targeted organ – brain, in the organs and tissues with variable vascularisation – heart and lungs (strong vascularisation), musculus quadriceps femoris (moderate vascularisation), and omentum (low vascularisation). The organs under study were ground and homogenized to form 20% water homogenate. The drug concentration was also evaluated in the animals' feces and urine, which were sampled in metabolic cages (Termoplast, Italy) 2, 4, 8, 12, 24, 48, 72 and 96 hours after drug administration.

The concentration of RU-1205 in plasma and 20% organ homogenate was evaluated using high performance liquid chromatography (HPLC) with a diode array UV detector (Shimadzu, Japan) on a SUPERCOSIL LC-18 column (5 μm particle; 4.6 mm × 100 mm) at a temperature of 50 °C. For a mobile phase, acetonitrile (UF210, Russia) was used with a buffer system at a ratio of 1:1 (potassium phosphate monobasic 50 mmol, titrated with 0.5 M of NaOH solution, pH = 5.0). Before chromatography, the mobile phase was degassed by ultrasonication and filtered. The detection wavelength was set at λ 205 nm, a flow rate of 1 mL/min (Smirnova et al. 2013).

The pharmacokinetic properties of the study drug included AUC (area under the curve) (Piotrovsky 1986), K_{el}

(elimination constant), Cl (clearance), $T_{1/2}$ (half-life of the drug), MRT (mean residence time), Vd (volume of distribution), and ft (tissue distribution).

To evaluate potential metabolites of drug RU-1205, PALLAS 3.00 software (CompuDrug Chemistry Ltd, Budapest, Hungary) was used. To evaluate the effect of RU-1205 on cytochrome P450, specific tests with CYP 450 substrates were used (Omiecinski et al. 1999; Perloff et al. 2000; Nebert et al 2002). Hexenal (MedPro Inc, Latvia) at a dose of 70 mg/kg was administered intraperitoneally (isoforms CYP2C9, CYP2B1 and CYP2B2). Midazolam (Roche, Switzerland) at a dose of 80 mg/kg was administered intraperitoneally (isoforms CYP3A1 and CYP2C). Alprazolam (Organica JSC, Russia) at a dose of 50 mg/kg was administered intraperitoneally (isoform CYP3A1). A possible effect of the study drug on the second biotransformation phase was evaluated by studying its ability to change the sleep onset latency and sleep duration of the UDP-glucuronosyltransferase substrate – chloral hydrate (MedPro Inc, Latvia), which had been administered intraperitoneally at a dose of 70 mg/kg.

The ability of RU-1205 to form conjugates with endogenous acids in excreta was studied using various hydrolyses of urine samples: fermentative hydrolysis, acid hydrolysis, and alkaline hydrolysis. Fermentative hydrolysis was conducted by 24-hour incubation of urine samples in the acetate buffer (0.1M, pH = 5.0) with beta-glucuronides and arylsulphatase (extracted from Helix pomatia snails, Boehringer Mannheim, Germany) at a temperature of 37 °C (Thomas et al. 1999). Acid hydrolysis was conducted by 2-hour incubation with 5M of HCl solution at a temperature of 37 °C (Dix et al. 1999; Manini et al. 1999). Alkaline hydrolysis was conducted using 5M of NaOH solution.

Statistical analyses

For the statistical analysis, the following software was used: GraphPad.Prism.5.0 and Microsoft Office Excel 2007.

Results and discussion

When evaluating the pharmacokinetic parameters of RU-1205, it was found that ,following intravenous administration to the study animals, it demonstrated a long plasma circulation time. A dose of 10 mg/kg of RU-1205 was traced in plasma 12 hours after administration, which confirmed a long elimination process (Fig. 2A, B). Prolonged elimination of the drug was supported by the following parameters: T1/2 and MRT were 8.49 hours and 7.14 hours, respectively (Table 1). The apparent volume of distribution (Vd=8.30 L/kg) exceeded 12-fold the real liquid volume in rats (0.67 L/kg). According to the literature, this supported that RU-1205 can penetrate intensively into organs and tissues (Davies and Morris 1993).

After subcutaneous administration of RU-1205, $T_{1/2}$ was reported to be 4.28 hours and MRT – 3.1 hours. The

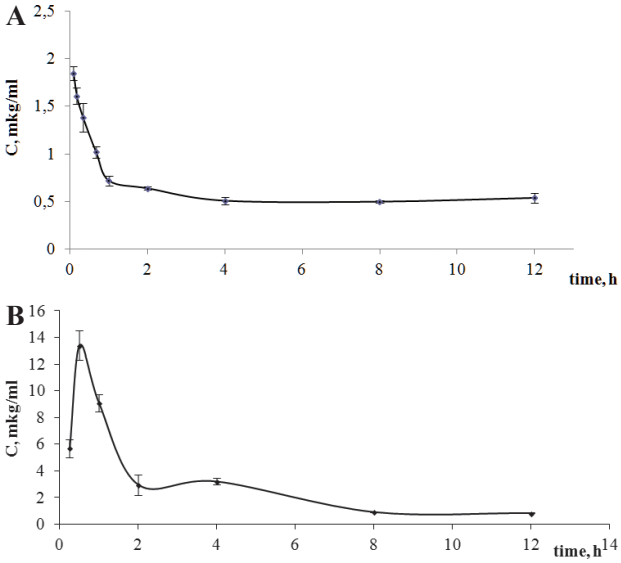

Figure 2. A. The mean plasma profiles of RU-1205 after intravenous (i/v) administration at a dose of 10 mg/kg. **B.** The mean plasma profiles of RU-1205 after subcutaneous (s/c) administration at a dose of 50 mg/kg.

Table 1. Pharmacokinetic Parameters of RU-1205 in Plasma Following Intravenous and Subcutaneous Administration in Rats

Parameter	Intravenously 10 mg/kg	Subcutaneously 50 mg/kg
AUC (μg*h/mL)	14.76	36.18
K_{el} (hour^{-1})	0.08	0.242
Cl (L/h/kg)	0.68	2.43
$T_{1/2}$ (hours)	8.49	4.28
MRT (hour)	7.14	3.1
Vd (L/kg)	8.3	13.23
F, %	–	57.35

apparent volume of distribution significantly exceeded real liquid volume in the body after intravenous and subcutaneous administrations, which can indicate that RU-1205 could actively penetrate into organs and tissues. When subcutaneously administrated, the study compound is intensively absorbed from the injection site. C_{max} was reached 30 minutes after administration. Absolute bioavailability of RU-1205 was reported to be 57.35%.

When intravenously administered, the study drug distributed into all the organs and tissues. Significant amounts of the compound were detected in the targeted organ – the brain, in the elimination organs – the liver and kidneys, as well as in the omentum. RU-1205 was less absorbed by tissues with increased vascularisation (heart, lungs and spleen) and had a minimal absorption in muscle tissue.

RU-1205 was detected in the targeted organ – the brain – 5 minutes after intravenous administration of a dose of 13.9 mkg/g, and then concentration gradually decreased for 14 hours until below the level of quantitation limit (Fig. 3).

During intravenous administration, the tissue availability in the brain was 5.97 (Table 2). C_{max} in the spleen, lungs and muscles was detected only within the first hour after administration of the drug. When administered intravenously, the highest concentrations of the drug was detected in the brain, kidneys and liver.

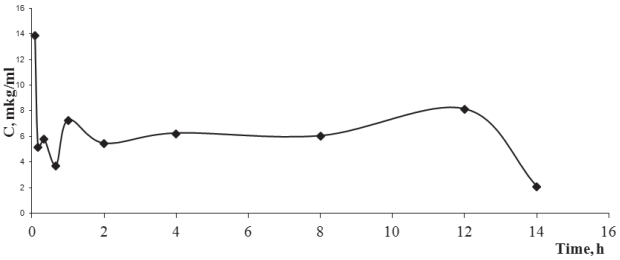

Figure 3. Maximum concentration of RU-1205 in rats' brain (10 mg/kg, intravenous administration).

Table 2. RU-1205 Pharmacokinetic Parameters of Tissue Distribution After Single Intravenous Administration of 10 mg/kg

Organ	AUC, µg*h/mL	Ft
Omentum	72.32	4.9
Brain	88.17	5.97
Kidneys	58.51	3.96
Liver	84.08	5.69
Heart	27.66	1.87

The results demonstrated that RU-1205 intensively distributed into organs and tissues, but its concentration in these organs was lower than in blood plasma. The compound has the lowest affinity to the heart, lungs, spleen and muscles. The highest concentration was detected in the elimination organs – the liver and kidneys. After subcutaneous administration, RU-1205 was detected in low quantities in the brain within the first three hours.

It was noted that when RU-1205 was administered in either of the administration routs mentioned above, its concentration was lower than the administered dose in blood plasma.

It was determined that RU-1205 could be detected in excrements within 72–96 hours following the administration, depending on the route of administration. It was also reported that only 0.7% of the unchanged substance was detected in urine and feces cumulatively following any of the two above routes of administration. More unchanged study drug substance was detected in urine than in excrements (Fig. 4). At the same time, it was found out that extrarenal (metabolic) clearance significantly prevailed over renal clearance, which indicated that RU-1205 had an active metabolism (Fagerholm 2007).

Following the intravenous administration, it took a total of 3 days (72 hours) for the drug substance to be excreted, both with urine and feces (Fig. 4A). The cumulative excretion was 50.73 µg in urine, which was approximately 2.54% of the administered dose. Hepatic clearance was 4.11 ml/h, whereas extrarenal clearance was 140.77 ml/h. The similar results were obtained after subcutaneous administration. The total excretion also took up to 72 hours (Fig. 4B). The cumulative urinary excretion was 50.63 µg, which was 0.51% of the administered dose. Therefore, the renal clearance was only 1.399 ml/h, whereas extrarenal clearance was 274.94 ml/h.

The next part of the pharmacokinetic study was to evaluate the possible metabolism of RU-1205. The first step *in silico* was to conduct a computer-based prediction of potential metabolites, based on which, potential metabolites were determined. The second step involved fermentative, acid and alkaline hydrolyses of the study substance. The final step involved investigation of potential interactions of RU-1205 with specific test-substrates of some CYP450 isoforms. The substrates are known to be commonly used in other studies investigating metabolism of benzimidazole derivative compounds (Spasov et al. 2002).

We were able to detect seven possible metabolites that could be produced via an acidic reaction of hydroxylation, using a computer-based analysis *in silico*. Six out of seven molecules of these metabolites were found to have chemical fragments which are likely responsible for an analgesic effect – morpholinoethyl moiety in N^9 position of the molecular nucleus and fluorophenyl moiety in the C^2 atom of the condensed nucleus. During this analysis, it was also determined that during the RU-1205 metabolism, a morpholino moiety could be detached, which could lead to a decreased analgesic activity (Fig. 5).

During the second stage of the study, an ability of the drug RU-1205 to create conjugates with endogenous acids

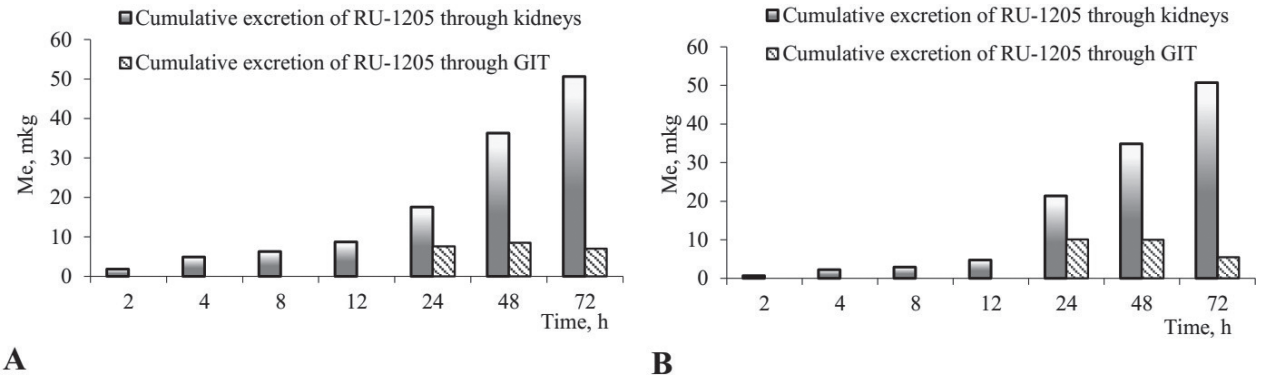

Figure 4. Cumulative excretion of RU-1205 through kidneys and liver. **A** – following10 mg/kg intravenous administration; **B** – following 50 mg/kg subcutaneous administration. **Note:** GIT – gastrointestinal tract.

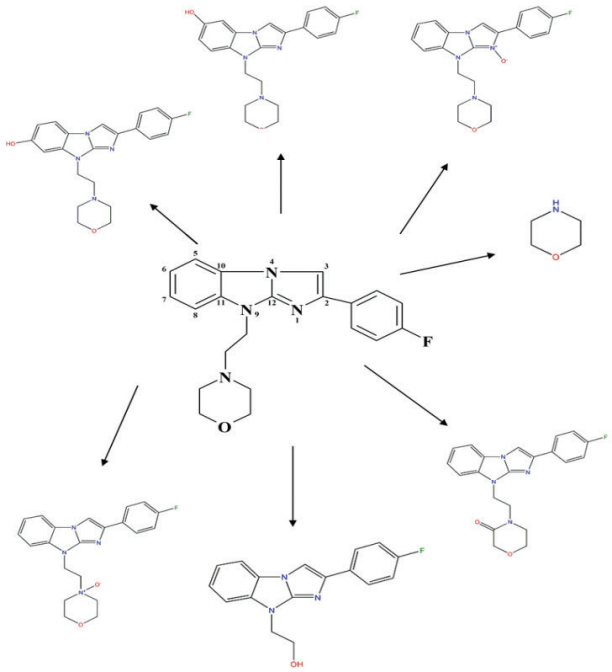

Figure 5. Potential metabolites of RU-1205 determined by computer modeling using Pallas 3.00.

through biotransformation was tested. Fermentative, acid and alkaline hydrolyses were conducted using rats' excreta. A chromatogram analysis, including incubation with beta-glucuronides and arylsulphatase and in combination with 5M of NaOH solution or 5M of HCl solution, demonstrated no peaks characteristic of the original chemical structure of RU-1205. Importantly, these results are similar to results obtained at the first stage (computer-based analysis), when no products of the second phase of biotransformation were detected either.

The final stage of evaluation of RU-1205 metabolism involved the investigation of the sleep duration under the influence of specific test-substrates of some of CYP450 isoforms. We determined that RU-1205 statistically significantly prolonged the sedative effect of hexenal (CYP2C9, CYP2B1, and CYP2B2) and alprazolam (CYP3A1) by 37.29% and 60.85%, respectively. However, in the combination with midazolam (CYP3A1 and CYP 2C), the sleep duration reduced by 28.74% (Table 3).

When RU-1205 was administered in combination with specific test-substrates of CYP450 isoforms, we found out that the drugs were likely metabolised though P450 CYP3A1 cytochrome isozyme (xenobiotic oxidation). CYP2B cytochromes, responsible for hydroxylation of xenobiotics, were less likely to participate in RU-1205 metabolism. Sleep duration following the midazolam and RU-1205 administration did not change significantly, which supported the hypotheses that CYP2C cytochromes are unlikely to participate in RU-1205 metabolism (xenobiotic oxidation). Changes in sleep duration following the administration of chloral hydrate and RU-1205 were not statistically significant either, which supported

Table 3. Effect of CYP450 Substrates on Sleep Duration in Rats Following Administration of RU-1205

Substrate	CYP 450 isoforms	Control (M±m)	Changes in sleep duration	
			Test,min (M±m)	Difference (%)
Phase 1				
Midazolam	CYP3A1, CYP2C	101.11±6.28	72.04±8.67*	-28.74
Alprazolam	CYP3A1	108.88±13.21	175.13±8.93*	60.85
Hexenal	CYP2C9, CYP2B1 and CYP2B2	56.44±2.23	77.5±4.24*	37.29
Phase 2				
Chloral hydrate	Glucuronosyltransferase	71.48±7.14	59.59±4.45	21.87

Note: * – statistically significant when compared with control, U Mann-Whitney test ($p \leq 0.05$).

the hypothesis that RU-1205 was unlikely to produce glucuronyl-conjugated metabolites and, therefore, the chance to observe the phase 2 reactions in the metabolism of the study substance was very low.

It was concluded that based on the results of the first phase of metabolic transformation involving CYP3A1 cytochrome, RU-1205 biotransformation is likely to involve oxygenation forms of the original formula. RU-1205 is unlikely to undergo synthetic reactions during the second phase of biotransformation, nor are new conjugates produced.

Conclusion

Therefore, this study involved the evaluation of the pharmacokinetic characteristics of new drug RU-1205, with its singular intravenous and subcutaneous administrations. Tissue and organ distribution of the study substance in rats and elimination of the drug were examined. Total bioavailability following subcutaneous administration was determined, and the potential metabolic pathways were predicted.

Based on the study results, some recommendation for using RU-1205 as an injection in clinical setting can be given. The sesults of this study also can be used for further prediction of potential interactions of RU-1205 via CYP3A1, CYP2B1, and CYP2B2 cytochromes. These results can play a significant role in planning first-in-human clinical trials.

Acknowledgments

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Conflict of interests

The authors declare no conflict of interests.

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Author contributions

- Everyone participated in the discussion of the results.

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