Research Results in Pharmacology

Research Results in Pharmacology 7(3): 41–47
UDC: 615.212.7
DOI 10.3897/rrpharmacology.7.68025

Research Article

Effect of adjuvant drugs on the analgesic activity of opioid morphine analgesics and compound RU-1205

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Academic editor: Oleg Gudyrev ♦ **Received** 28 April 2021 ♦ **Accepted** 17 July 2021 ♦ **Published** 21 September 2021

Citation: Spasov AA, Grechko OIu, Eliseeva NV, Lifanova YuV, Aleksandrenkova AN (2021) Effect of adjuvant drugs on the analgesic activity of opioid morphine analgesics and compound RU-1205. Research Results in Pharmacology 7(3): 41–47. https://doi.org/10.3897/rrpharmacology.7.68025

Abstract

Introduction: Adjuvant medications can be used to increase the analgesic effect of opioid analgesics, reduce the manifestation of side effects, and also for premedication. This paper provides information on the effect of clonidine, haloperidol, metocloparmide, diazepam, midazolam on opioid analgesics: - morphine and the selective kappa-opioid agonist compound RU-1205.

Materials and methods: A probable interaction between RU-1205, morphine and adjuvant drugs in pain behaviors was carried out on the model of somatogenic pain. 95 male mice received either RU-1205 (5 mg/kg, i.p.) and morphine (1 mg/kg, i.p.) separately or in combination with haloperidol (0.45 mg/kg, i.p.); midazolam (0.3 mg/kg, i.p.); diazepam (1 mg/kg, i.p.); metoclopramide (5 mg/kg, i.p.), and clonidine (1 mg/kg, i.p.). The analgesic effect was assessed by tail flick test. Registration of the latent period of the reaction was carried out 30, 60 and 90 minutes after the adjuvant drug administration.

Results: When studying the interaction with morphine, it was found that clonidine, haloperidol and metoclopramide enhanced the effects; diazepam offset them, and midazolam had no affect on the analgesic properties. In the course of the studies, RU-1205 showed an increase in analgesic activity when combined with clonidine, a slight increase with midazolam, and a decrease when co-administered with diazepam. Haloperidol had no influence on the effect of RU-1205, while metoclopramide both potentiated and reduced the analgesic effect.

Discussion: Pharmacodynamic and pharmacokinetic interactions of RU-1205 with an α2AR agonist, benzodiazepine receptor agonists, D2P antagonist, and σ-receptor blocker were established.

Conclusion: The presented data make it possible to more accurately formulate ideas about the localization and action mechanism of the kappa-agonist of opioid receptors, the compound RU-1205.

Keywords

opioids, adjuvant drugs, morphine, kappa agonists, clonidine, haloperidol, metoclopramide, diazepam; midazolam.

Introduction

The etiology and pathogenesis of pain are variable; therefore, each of the types of pain (nociceptive somatic, nociceptive visceral, neuropathic, dysfunctional) requires an individual therapeutic approach. For severe pain, opioid analgesics are recommended (Mills et al. 2016). For purposes of increasing their analgesic effect, reducing the incidence of side effects, as well as for premedication, adjuvant drugs can be used (Clinical guidelines 2018). As adjuvant agents (can be used to relieve pain, though not intended for this purpose), alpha-adrenergic receptor agonists, neuroleptics, benzodiazepine receptor agonists are most often used; in addition, symptomatic therapy medications, for example, antiemetics, are often included (Fallon and McConnell 2006). When developing new anesthetic drugs at the stage of preclinical studies, it is necessary to determine possible coanalgesic interactions.

This paper provides information on the effect of adjuvant drugs (clonidine, haloperidol, metocloparmide, diazepam, midazolam) on opioid analgesics: a non-selective opioid receptor agonist – morphine and a selective kappa-opioid agonist (Spasov et al. 2018), not having narcogenic potential (Spasov and Zvartau 2020) – compound RU-1205. This compound is a derivative of imidazobenzimidazole, and exhibits analgesic activity with a central and peripheral mechanism of action (Spasov et al. 2014a, 2014b, 2018; Grechko et al. 2017).

The aim of the work was to study the effect of adjuvant drugs on the analgesic activity of morphine and kappa-opioid agonist under laboratory code RU-1205, when co-administered intraperitoneally, on a model of somatogenic pain.

Materials and methods

Experimental animals

The experiments were carried out on 95 male outbred white mice weighing 20–25 g (source: Federal State Unitary Enterprise Nursery of Laboratory Animals ”RAPPOLOVO”, veterinary certificate No. 15702 dated 08.12.2020).

The animals were kept in standard conditions: Ordinance No. 51 ”On the Approval of sanitary regulations 2.2.1.3218-14 “Sanitary and Epidemiological Requirements for the Design, Equipment and Maintenance of Experimental Biological Clinics (Vivariums)” of August 29, 2014, and Directive of the European Parliament and the Council of the European Union 2010/63/EU of September 22, 2010 “On the Protection of Animals Used for Scientific Purposes”. The experiments were approved by the Regional Research Ethics Committee of Volgograd Region (registration number IRB 00005839 IORG 0004900 (OHRP), minutes No. 2077-2018 of October 30, 2018).

Drugs and treatment

The object of the study was 9-(2-morpholinoethyl)-2-(4-fluorophenyl) imidazo [1,2-a]-benzimidazole dihydrochloride (compound RU-1205) synthesized at the Research Institute of Physical Chemistry, Southern Federal University, Rostov-on-Don, by Candidate of Chemical Sciences, senior researcher at the Laboratory of Organic Synthesis, Zhukovskaya O.N. (Patent of the Russian Federation 2009).

The study used thedrugs in the following doses: compound RU-1205 (5 mg/kg); morphine hydrochloride (1 mg/kg) (Moscow Endocrine Plant, Russia) (license for circulation of narcotic drugs, psychotropic substances and their precursors No. FS-34-03-000004-16 of October 25, 2016). Haloperidol (0.45 mg/kg) (Ozone LLC, Russia); midazolam (0.3 mg/kg) (Cenexi SAS, Switzerland); diazepam (1 mg/kg) (Moscow Endocrine Plant, Russia); metoclopramide (5 mg/kg) (Novosibkhimpharm JSC, Russia); and clonidine (1 mg/kg) (Organika JSC, Russia). Doses of the compounds used in the study are based on previous studies and literature data (Pang et al. 2001; Leppert et al. 2014; Stone et al. 2014; Semenova 2020; Semenova et al. 2020).

Experimental design

The animals were randomized into 13 groups receiving: 1. compound RU-1205; 2. morphine hydrochloride; 3. morphine hydrochloride + haloperidol; 4. compound RU-1205 + haloperidol; 5. morphine hydrochloride + midazolam; 6. compound RU-1205 + midazolam; 7. morphine hydrochloride + diazepam; 8. compound RU-1205 + diazepam; 9. morphine hydrochloride + metoclopramide; 10. compound RU-1205 + metoclopramide; 11. morphine hydrochloride + clonidine; 12. connection RU-1205 + clonidine; 13. solvent – distilled water (control group).

The study of analgesic activity of the drugs was carried out on the model of somatogenic pain (tail flick from heat) in accordance with the method described in the manual for preclinical studies (Voronina and Guzeevatykh 2012). The substances under study were dissolved in distilled water and injected intraperitoneally as a single dose, in the volume of 100 µl per 10 g of animal weight. The drug was registered three times: 30, 60 and 90 minutes after the adjuvant drug administration (Leppert et al. 2014). When studying the coanalgesic effects, morphine/compound RU-1205 were administered 15 minutes before the adjuvant drugs.

Statistical processing

Statistical processing was carried out using the GraphPad Prism7.0 software package with the determination of the M±m parameters and the subsequent use of the two-way analysis of variance (Bonferroni post-test).

The changes were assessed using the value of the maximum possible effect (**MPE**, %) (Voronina and Guzeevatykh 2012):

$$\mathbf{MPE} = \frac{\text{LPtest - LPcontrol}}{\text{MAXtime - LP control}}, \text{ where}$$

$\mathbf{LP}_{test}$ is a latent period of the reaction after the substance administration, $\mathbf{LP}_{control}$ is the latent period of the reaction before the substance administration, $\mathbf{MAX}_{time}$ is the maximum time of the stimulus application (15 s).

Results

The results of the effect of the adjuvant drugs on the analgesic activity of agents that have an agonistic effect on opioid receptors are shown in Table 1. When studying the tail flick latent period, the mean values in the control group were 3.70 ± 0.51 s (Table 1).

At the first stage, the interaction of morphine and compound RU-1205 with an alpha-adrenergic agonist, clonidine, was studied.

When co-administered with opioid receptor agonists, clonidine significantly potentiated the analgesic effect of morphine and RU-1205 (Fig. 1). MPE, %, compared with that of the groups of single administration of opioids, significantly increased (by 45%, 27% and 44% for morphine and by 59%, 46% and 42% for compound RU-1205, respectively) ($p \leq 0.05$).

At the second stage, the interaction of morphine and compound RU-1205 with the neuroleptic, haloperidol, was studied.

Haloperidol, when used simultaneously with morphine, significantly increased MPE, % relative to the indicators of the morphine group by 2.3, 1.8 and 2.8 times at each of the time points, respectively (Fig. 2) ($p \leq 0.05$). When co-administered with RU-1205 compound, 30 minutes later, haloperidol exceeded MPE, %, by 9 units, compared with that of the group receiving only the kappa agonist, while there were no significant differences at other points.

Table 1. Effects of adjuvant drugs on the analgesic activity of morphine and compound RU-1205 in the Tail flick test in male mice after intraperitoneal administration

№	Drug and/or combination	Latency period, M±m, s		
		30 minutes	**60 minutes**	**90 minutes**
1	solvent	3.60 ± 0.51	3.93 ± 0.47	3.58 ± 0.46
2	compound RU-1205	5.12 ± 0.12*	6.38 ± 0.44*	6.80 ± 0.36*
3	morphine	5.48 ± 0.35*	6.04 ± 0.42*	7.08 ± 0.65*
4	morphine + clonidine	10.98 ± 1.55*#	9.50 ± 1.23*#	11.14 ± 1.56*#
5	compound RU-1205 + clonidine	11.9 ± 1.52*#$	11.7 ± 1.54*#$	11.66 ± 1.56*#$
6	morphine + haloperidol	8.86 ± 0.6*#	8.63 ± 0.46*#	10.48 ± 0.69*#
7	compound RU-1205 + haloperidol	6.14 ± 0.43*	6.20 ± 0.49*	7.12 ± 0.9*
8	morphine + metoclopramide	6.53 ± 0.65*#	7.23 ± 0.82*#	6.93 ± 0.63*
9	compound RU-1205 + metoclopramide	5.91 ± 0.31*	6.30 ± 0.53*	5.77 ± 0.48*#$
10	morphine + diazepam	4.17 ± 0.38#	3.88 ± 0.61#	3.78 ± 0.37#
11	compound RU-1205 + diazepam	4.81 ± 0.64*	5.47 ± 0.60*	6.04 ± 0.41*#
12	morphine + midazolam	5.46 ± 0.99*	6.35 ± 0.75*	6.23 ± 0.55*
13	compound RU-1205 + midazolam	6.36 ± 0.31*$	6.42 ± 0.83*	6.27 ± 0.43*

Notes: * – significant differences from the two-way ANOVA control group. Bonferroni post-test $p \leq 0.05$; # – significant differences from the group of the reference drug – morphine. Two-way ANOVA. Bonferroni post-test $p \leq 0.05$; $ – significant differences from the compound RU-1205 group. Two-way ANOVA. Bonferroni post-test $p \leq 0.05$.

At the third stage, the interaction of morphine and compound RU-1205 with the antiemetic drug, metoclopramide, was studied.

When administered simultaneously with morphine, metoclopramide increased the analgesic effect after 30 and 60 minutes (MPE, % increased by an average of 10 units) (Fig. 3). Metoclopramide, when administered together with RU-1205 compound, after 30 minutes increased MPE, % by 7 units; after 60 minutes it did not change the values, but after 90 minutes, it decreased MPE, % by 9 units.

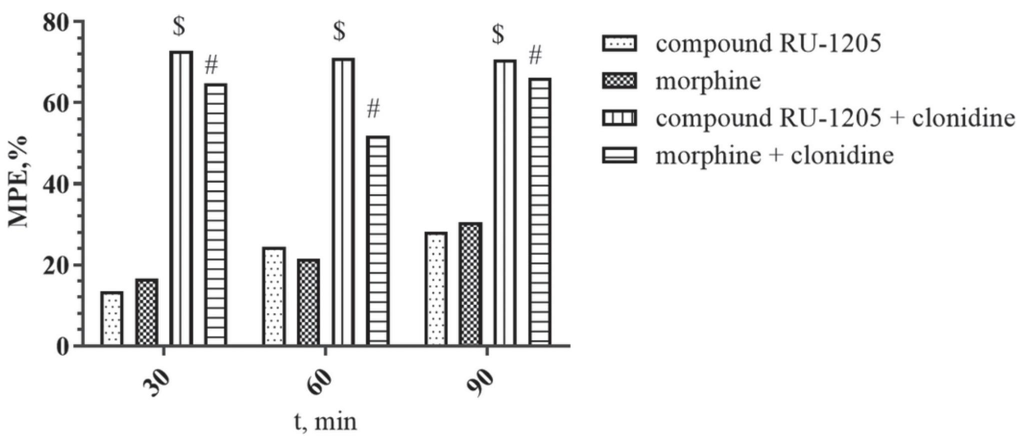

Figure 1. Effects of clonidine on the analgesic activity of morphine and compound RU-1205 in the tail flick test in male mice after intraperitoneal administration. **Note:** # – significant differences from the group of the reference drug – morphine. Two-way ANOVA. Bonferroni post-test $p \leq 0.05$; $ – significant differences from the compound RU-1205 group. Two-way ANOVA. Bonferroni post-test $p \leq 0.05$.

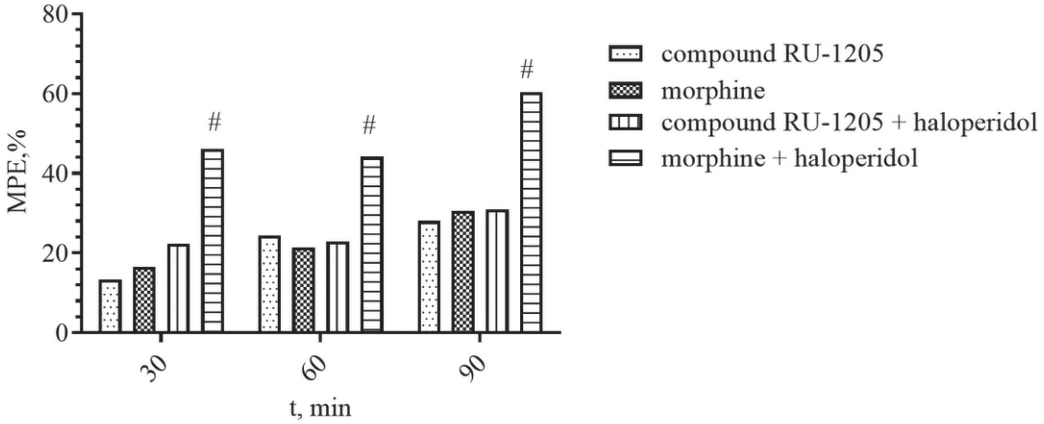

Figure 2. Effects of haloperidol on the analgesic activity of morphine and compound RU-1205 in the tail flick test in male mice after intraperitoneal administration. **Note:** # – significant differences from the group of the reference drug – morphine. Two-way ANOVA. Bonferroni post-test $p \leq 0.05$; $ – significant differences from the compound RU-1205 group. Two-way ANOVA. Bonferroni post-test $p \leq 0.05$.

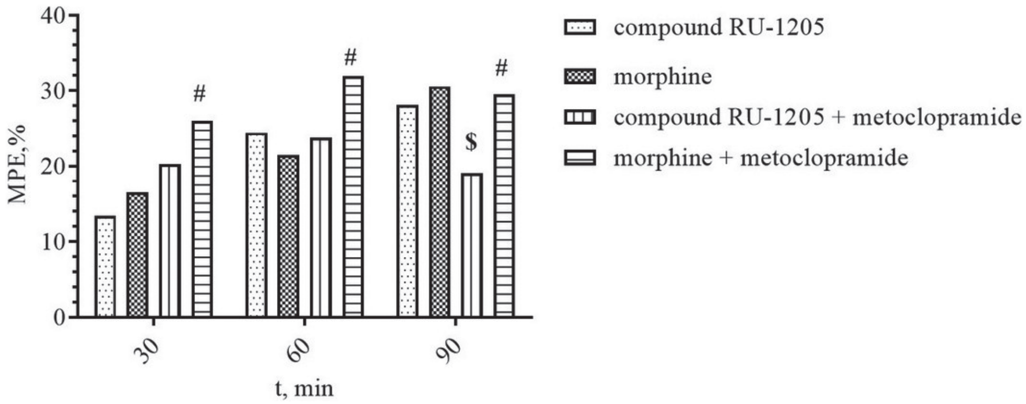

Figure 3. Effects of metoclopramide on the analgesic activity of morphine and compound RU-1205 in the tail flick test in male mice after intraperitoneal administration. **Note:** # – significant differences from the group of the reference drug – morphine. Two-way ANOVA. Bonferroni post-test $p \leq 0.05$; $ – significant differences from the compound RU-1205 group. Two-way ANOVA. Bonferroni post-test $p \leq 0.05$.

At the fourth stage, the interaction of morphine and compound RU-1205 with benzodiazepine receptor agonists, diazepam and midazolam, was assessed.

Diazepam, when administered with morphine, completely neutralized its analgesic effect at all time points to the level of the control values (MPE, % 5.08%, 2.54%, 1.67%, respectively $p \leq 0.05$) compared with the group receiving only morphine (Fig. 4); the results obtained are consistent with the literature data (Gear et al. 1997; Nemmani and Mogil 2003). At the same time, diazepam slightly reduced the analgesic activity of RU-1205 when they are used together.

Midazolam had practically no effect on the severity of morphine analgesia with these drugs administered together (Fig. 5) at any of the time points ($p \leq 0.05$). When studying the interaction of RU-1205 with midazolam, it was found that the benzodiazepine receptor agonist potentiated the analgesic effect of the kappa agonist 1.8 times after 30 minutes, but no differences were observed at time points of 60 and 90 minutes.

Discussion

The combination of α2 -adrenergic agonists (α2AP) with opioid analgesics reduces the side effects of each of the groups used (Paech et al. 2004). According to immunohistochemical studies (Stone et al. 2007), opioid receptors (OR) are co-expressed in the same population of sensory neurons as α2AP, and antinociceptive synergy requires the activation of calcium channels and protein kinase C. The observed synergistic effects are explained by the physical link between μ-OR and adrenergic receptors. It is well known that co-expression of GPCRs leads to the formation of heteromeric complexes with altered functional and ligand-binding properties. Such interactions can occur at the level of primary afferent neurons, the spinal cord and other parts of the central nervous system (e.g., locus caeruleus), as well as at the periphery (Milligan 2009).

There is evidence that haloperidol can inhibit Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII α), thereby reducing tolerance to opioids and physical addic-

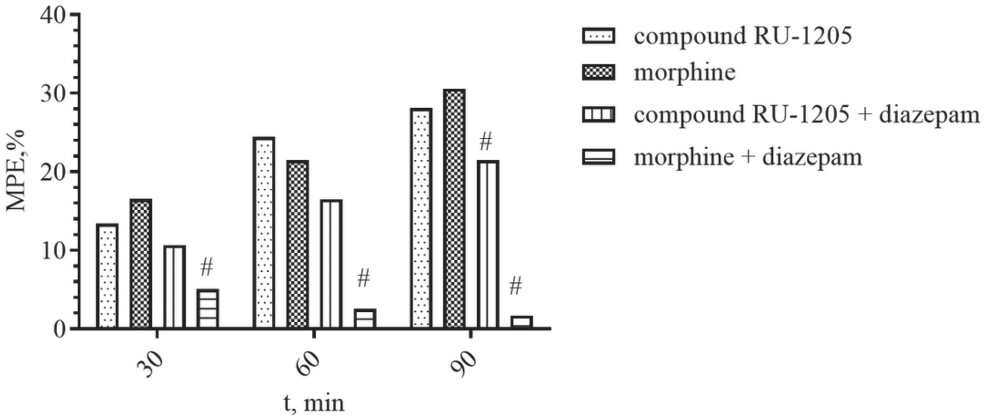

Figure 4. Effects of diazepam on the analgesic activity of morphine and compound RU-1205 in the tail flick test in male mice after intraperitoneal administration. **Note:** # – significant differences from the group of the reference drug – morphine. Two-way ANOVA. Bonferroni post-test $p \leq 0.05$; $ – significant differences from the compound RU-1205 group. Two-way ANOVA. Bonferroni post-test $p \leq 0.05$.

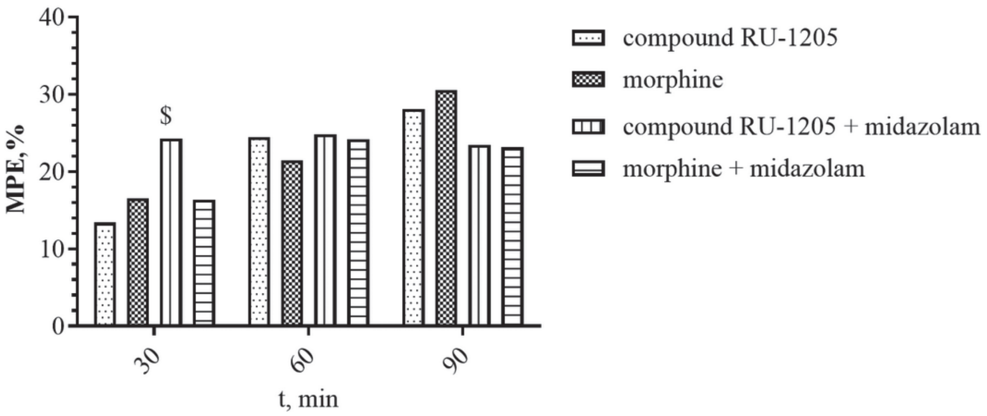

Figure 5. Effects of midazolam on the analgesic activity of morphine and compound RU-1205 in the tail flick test in male mice after intraperitoneal administration. **Note:** # – significant differences from the group of the reference drug – morphine. Two-way ANOVA. Bonferroni post-test $p \leq 0.05$; $ – significant differences from the compound RU-1205 group. Two-way ANOVA. Bonferroni post-test $p \leq 0.05$.

tion to their long-term intake. It is assumed that CaMKII causes desensitization of μ-OR and κ-OR in cells, in neurons of the dorsal root ganglia, and in the superficial laminae of the dorsal horn of the spinal cord (Brüggemann et al. 2000). Modeling of opioid-mediated analgesia can be accomplished by sigma receptor antagonism with haloperidol (Chien and Pasternak 1995).

At the same time, a decrease in the severity of the analgesic effect after 90 minutes when taken together with the kappa agonist – compound RU-1205, may be associated with the pharmacokinetic characteristics of the substances (Rashchenko 2014; Ragia et al. 2016). Both haloperidol and compound RU-1205 are known to be metabolized by CYP3A from the cytochrome family. The haloperidol metabolite formed during oxidative N-dealkylation is inactive, in contrast to the analgesically active metabolites of RU-1205, which are formed as a result of hydroxylation.

According to the literature data, D2 dopaminergic neurons of the hypothalamus inhibit the production of prolactin (PRL) by the adenohypophysis (Ben-Jonathan 1985). PRL secretion is closely related to the opiodergic system (the effect of U50,488 - the agonist of κ-opioid receptors, on the concentration of PRL has been shown to a greater extent than that of morphine) (Krulich et al. 1986) and is capable of causing dose-dependent analgesia (Ramaswamy et al. 1983). Metoclopramide, in turn, is also able to stimulate prolactin release, enhancing morphine analgesia, but the mechanism of interaction with kappa agonists still remains poorly understood.

In the late 90s, Gear, Robert Wa; Miaskowski, Christine et al. (1997) observed in clinical practice the effect of reducing opioid-mediated analgesia in the presence of benzodiazepine premedication, while flumazenil (benzodiazepine receptor antagonist) enhanced postoperative morphine analgesia. Research by Nemmani and Mogil (2003) first proposed that diazepam attenuates μ- and κ-opioid analgesia through serotonergic mechanisms (in tests with morphine and the selective kappa agonist U50,488), while antiserotonergic agents (p-chlorophenylalanine methyl ester PCPA and 8-OH-DPAT) attenuate μ- and κ-opioid analgesia through (indirect) GABAergic mechanisms in the nucleus raphe dorsalis (Nemmani and Mogil 2003).

Based on the available literature data, it can be assumed that the differences between diazepam and midazolam in the severity of morphine analgesia may be associated with the peculiarities of their pharmacokinetics. The half-life ($T_{1/2}$) for midazolam is 1.7–2.6 hours, while for diazepam $T_{1/2}$, it ranges between 20 and 50 hours (Olkkola and Ahonen 2008). There is also dependence of the effect on a dose of benzodiazepines: in small doses, they have anxiolytic and anticonvulsant effects; with an increase in the dose leading to sedation, amnesia and, finally, sleep.

Conclusion

Cumulatively, the results on the effect of adjuvant drugs on analgesia caused by morphine show that clonidine, haloperidol and metoclopramide enhance the effects of morphine, diazepam neutralizes them, whereas midazolam does not affect the analgesic properties of this non-selective opioid receptor agonist. In the course of the studies conducted for RU-1205, a significant increase in analgesic activity was shown when combined with clonidine, while a slight increase – with midazolam. At the same time, a decrease in the severity of the analgesic effect was observed in the groups where RU-1205 was combined with diazepam. Haloperidol had no influence on the effect of the kappa-agonist of opioid receptors when administered together, whereas metoclopramide both potentiated and reduced the analgesic effect of RU-1205 at different time intervals. The presented data make it possible to more accurately formulate ideas about the localization and action mechanism of the kappa-agonist of opioid receptors, compound RU-1205.

Conflict of interests

The authors declare no conflict of interests.

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