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The analgesic properties of a promising antidepressant –2-methyl-3-(phenylaminomethyl)-1H-quinolin-4-one

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Abstract
The article presents the results of the experimental study of the analgesic properties of a promising antidepressant with the polymodal action on CNS – 2-methyl-3-(phenylaminomethyl)-1H-quinolin-4-one (atristamine). The study was carried out in male mice using the acetic acid-induced writhing test (to evaluate the effect on the visceral type of pain) and the tail immersion test (to estimate the impact on the somatic nociceptive system). Metamizole sodium (500 mg/kg) and imipramine hydrochloride (25 mg/kg) were chosen as reference drugs. The results of the study showed that in the acetic acid-induced writhing test atristamine in the dose of 100 mg/kg had no antinociceptive effect. At the same time, the analgesic activity of this compound in the same dose has been proven in the tail immersion test. It has been shown that atristamine provides antinociception starting not less than in 90 min after introduction and has the optimal effect in the 120-min time point. Certain differences in the analgesic action compared to imipramine have been discussed.

Keywords: 2-methyl-3-(phenylaminomethyl)-1H-quinolin-4-one, atristamine, antidepressant, analgesic activity, writhing test, tail immersion test

1. Introduction
Antidepressants are widely used for pain management and often referred to as "adjuvant analgesics". An adjuvant (co-analgesic) is a drug that is not primarily identified as a painkiller in nature in its indications for use but that has been found in clinical practice to have either an independent analgesic effect or additive analgesic properties when used with opioids [1]. Antidepressants do not provide a direct pain relief in the same way as opioids or NSAIDs and can not compete with painkillers in intensity of their effect, but it is well known that antidepressants provide excellent antinociception for many pain conditions.
Currently, tricyclic antidepressants (TCAs) together with anticonvulsants are considered to be the first-line drugs for the treatment of neuropathic pain [2]. Most of the published guidelines on neuropathic pain still recommend TCAs as the first-line drugs [3-5].
The analgesic action of TCAs was extensively studied and proven over 30 years ago. Furthermore, newer duloxetine and milnacipran are the only serotonine norepinephrine reuptake inhibitors (SNRIs) that are FDA-approved as analgesics; the analgesic effect of venlafaxine is also demonstrated by multiple studies. Duloxetine is currently the only drug approved by the FDA for the treatment of depression and pain [6].
Antidepressants are effective as analgesics in patients with chronic pain and no concomitant depression that indicates independence of analgesic and antidepressant effects [2]. This is an argument to state that antidepressants have a genuine analgesic effect. Furthermore, pain is a frequent symptom of depression, and the multiple studies supported great prevalence of depression in chronic pain patients. It confirms the hypothesis that pain and depression share overlapping biochemical mechanisms.
The antidepressant-induced analgesia seems to be centrally mediated [7], moreover, consistent evidence also indicates a peripheral site of action [8]. Several mechanisms account for their analgesic effect but inhibition of monoamine transporters (and, consequently, the facilitation of descending inhibition pain systems) is implicated on the basis of mechanistic and knockout-mouse studies [2].
The object of the present study is a promising antidepressant with the polymodal action on the CNS – 2-methyl-3-(phenylaminomethyl)-1H-quinolin-4-one (Fig. 1).

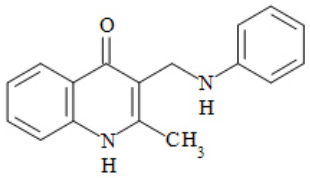

Fig 1: The structural formula of 2-methyl-3-(phenylaminomethyl)-1H-quinolin-4-one (atristamine).

This compound was chosen as a leader for the in-depth study under the conditional name of "atristamine" after screening of the series of 3-(N-R,R′-aminomethyl)-2-methyl-1H-quinolin-4-ones where it showed the excellent antidepressant activity in the tail suspension test in combination with the high anti-amnesic activity studied in the passive avoidance test after scopolamine-induced anterograde amnesia in the dose of 100 mg/kg [9-10]. The unique spectrum of additional neuropharmacological properties of this molecule (antihypoxic, anti-amnesic, alcoprotective) was studied [11-13]. Using the ELISA methods it was shown that a significant decrease in the concentration of 5-hydroxitriptamine was consistent with the increased levels of dopamine and epinephrine in the brain of mice after administration of atristamine in the dose of 100 mg/kg [14]. It was also proven that atristamine (100 mg/kg) had protective effects against a traumatic brain injury in rats [15].

Thus, there are no doubts about the necessity for studying the analgesic properties of atristamine as a promising antidepressant in the order to find new pharmacological features of this molecule, as well as to investigate possible mechanisms of the main action comparing the results obtained with the common data for antidepressants.

2. Materials and methods

2.1 Drugs

2-Methyl-3-(phenylaminomethyl)-1H-quinolin-4-one (atristamine) was synthesized as previously described [16]. Purity and identity of the compound obtained was confirmed using NMR spectroscopy and TLC.

Metamizole sodium was chosen as a reference drug due to its evidenced analgesic properties and used in the form of solution for injection 500 mg / 1 mL (trade name "Analgin-Zdorovye", Zdorovye, Kharkiv, Ukraine).

Imipramine hydrochloride was chosen as the second reference drug since it belonged to TCAs with potent antinociceptive properties and the well-studied mechanism of this action. Imipramine was used in the form of solution for injection 25 mg / 2 mL (trade name "Melipramine", EGIS Pharmaceuticals PLC, Hungary).

2.2 Animals

Adult random-bred albino male mice weighing 20-25 g were included in the present study. The animals were obtained from the vivarium of the Central Research Laboratory at the National University of Pharmacy (Kharkiv, Ukraine) and maintained at 19-24 °C and 50% humidity in a well-ventilated room with a 12h light/dark cycle. Mice were housed in standard polypropylene cages with free access to food ("Mouse diet", LabDiet, St. Louis, MO, USA) and water. All the experimental protocols were in accordance with "Directive 2010/63/EU of the European Parliament and the Council of 22 September, 2010 on protection of animals used for scientific purposes".

All experimental animals were randomly divided into 8 groups of 8 mice:

Group I – Control for the writhing test (treated with only distilled water at a dose of 0.1 mL / 10 g);

Group II – treated with atristamine (100 mg/kg), for the writhing test;

Group III – treated with metamizole (500 mg/kg), for the writhing test;

Group IV – treated with imipramine (25 mg/kg), for the writhing test;

Group V – Control for the tail immersion test (treated with only distilled water at a dose of 0.1 mL / 10 g);

Group VI – treated with atristamine (100 mg/kg), for the tail immersion test;

Group VII – treated with metamizole (500 mg/kg), for the tail immersion test;

Group VIII – treated with imipramine (25 mg/kg), for the tail immersion test.

2.3 Pharmacology

2.3.1 Acetic acid-induced writhing test

The writhing test is a chemical method used to induce pain of the peripheral origin by injection of irritant agents such as acetic acid in mice and allows estimating the effect on the visceral nociceptive system.

For the writhing test [17], the mice were first habituated to a plastic observation chamber for 60 min. Then, the mice were given atristamine (100 mg/kg, *per os* in the form of a fine aqueous suspension stabilized with Tween-80), metamizole sodium (500 mg/kg, i.p.) and imipramine hydrochloride (25 mg/kg, i.p.) 45 min before the test. Subsequently, the mice were treated i.p. with 0.7% acetic acid solution (10 mL / kg). The number of abdominal constrictions and extensions of the trunk and hind limbs (writhings) was counted for each mouse starting in 15 min after acetic acid injection over a period of 30 min. The percentage of protection was calculated using equation:

$$\%\ \boldsymbol{of\ protection} = \frac{C-T}{C} \times 100\%,$$

where C – mean number of writhing (control);
T – mean number of writhing (test).

2.3.2 Tail immersion test

The tail immersion test was carried out as described by Janssen *et al*. [18] and allowed us to evaluate the effect on the somatic nociceptive system. Twenty-four hours before the experiment all mice were habituated to the experimental procedure (measurement of the tail withdrawal latency) in order to minimize novelty-induced antinociception. The experiment was started in 60 min after drug introduction taking into account the route of atristamine administration (intragastric) and possible pharmacokinetic features. Drugs were administered in the same doses like in the writhing test. Four time points with 30 min interval for measurements of the tail withdrawal latency were considered for the tail immersion test. The tail withdrawal latency (the reaction time) of each animal was determined by immersing the lower 2.0 cm of the tail into a water-bath with the constant temperature (60 °C) and recording the tail withdrawal latency (in seconds) using a manual stopwatch.

2.4 Statistical analysis

The results were expressed as the mean (M) ± standard error

of the mean (SEM). Statistical differences between groups were analyzed using Student's t-test (in the case of normal distribution) and Mann-Whitney U test. The level of statistical significance was considered to be $p<0.05$.

3. Results

3.1 Acetic acid-induced writhing test

The results of the study of the analgesic activity of atristamine in comparison with metamizole sodium and imipramine in the writhing test are given in Tab. 1.

Table 1: Effects of atristamine, metamizole sodium and imipramine on acetic acid-induced writhing in mice

Group, the number of animals	Control, n=8	Atristamine, 100 mg/kg, n=8	Metamizole sodium, 500 mg/kg, n=8	Imipramine, 25 mg/kg, n=8
Number of writhings (M±SEM)	32.6±5.7	32.6±3.8	5.9±4.9* (p=0.006)	6.4±2.8* (p=0.002)
% of protection	–	0	81.9	80.4

Notes. * – significant compared to the control group.

As can be seen from Tab. 1, atristamine in the dose of 100 mg/kg had no effect on the number of writhings in this study, whereas metamizole sodium (500 mg/kg) and imipramine (25 mg/kg) exhibited an excellent protection up to 80-82%. The results of the reference drugs are absolutely agreed with data published [19-20].

3.2 Tail immersion test

As can be seen from Tab. 2 and Fig. 2, in 60 min after drug administration only metamizole showed a significant effect on the reaction time of mice prolonging this indicator up to 50% ($p<0.05$). Other drugs had no action in this time point.

Table 2: The effect of atristamine, metamizole and imipramine on the tail withdrawal latency (reaction time) of mice in the tail immersion test, s

Group, the number of animals	Control, n=8	Atristamine, 100 mg/kg, n=8	Metamizole sodium, 500 mg/kg, n=8	Imipramine, 25 mg/kg, n=8
60 min	2.40±0.48	2.98±0.33	3.59±0.33* (p=0.024)	1.84±0.29
90 min	1.85±0.13	3.10±0.50* (p=0.018)	6.24±1.33* (p=0.002)	2.38±0.47
120 min	2.87±0.36	5.92±1.25* (p=0.041)	3.83±0.76	2.43±0.32
150 min	2.26±0.21	3.97±0.60* (p=0.010)	3.08±0.46	3.06±0.90

Notes. * – significant compared to the control group.

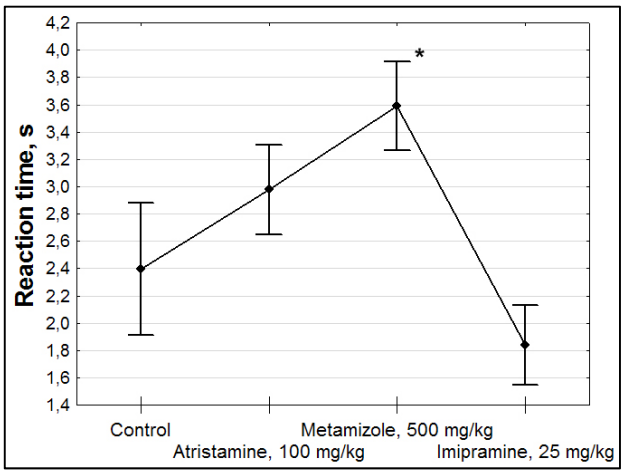

Fig 2: The effect of atristamine, metamizole and imipramine on the reaction time of mice in the 60-min time point.

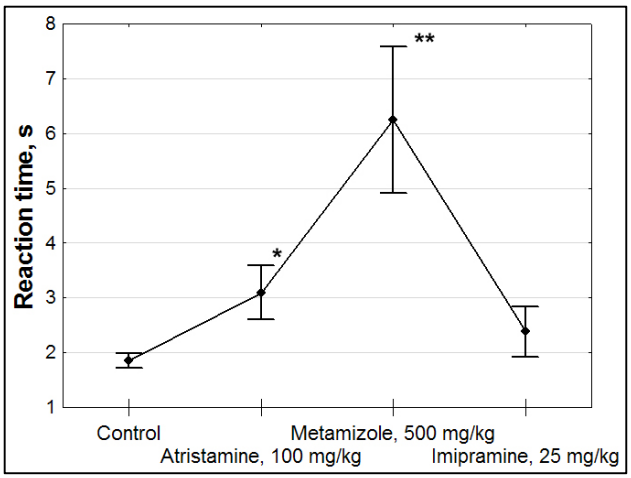

Fig 3: The effect of atristamine, metamizole and imipramine on the reaction time of mice in the 90-min time point.

The results obtained in the 90-min time point (Tab. 2 and Fig. 3) were more interesting. Further increase of the analgesic effect of metamizole was observed. It prolonged the reaction time of mice in 3.3 times ($p<0.01$) compared to the control group. Furthermore, in this time point antinociception caused by atristamine was found – it increased the tail withdrawal latency of mice up to 68% ($p<0.05$) compared to the control group, but was less effective than metamizole.

The situation dramatically changed in the next time point. As we can see (Tab. 2 and Fig. 4), in 120 min after administration metamizole had already no effect on the reaction time, whereas atristamine-induced antinociception became more apparent. There was 2-fold ($p<0.05$) prolongation of the tail withdrawal latency compared to the control group.

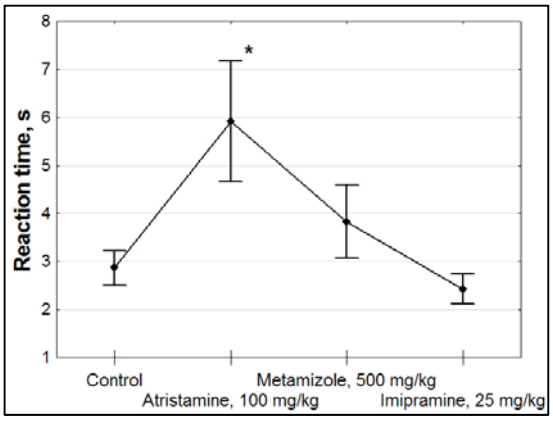

Fig 4: The effect of atristamine, metamizole and imipramine on the reaction time of mice in the 120-min time point.

The result obtained 150 min after administration of drugs (Tab. 2 and Fig. 5) showed that atristamine in this time point still provided a significant analgesia – the reaction time increased to 76% ($p<0.05$).

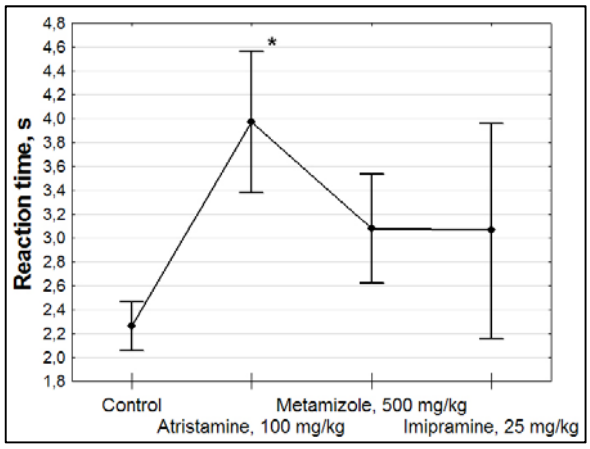

Fig 5: The effect of atristamine, metamizole and imipramine on the reaction time of mice in the 150-min time point.

Analyzing time-response curves (Fig. 6) it becomes absolutely apparent that atristamine in the dose of 100 mg/kg provides antinociception starting not less than in 90 min after introduction and has the optimal effect in the 120-min time point.

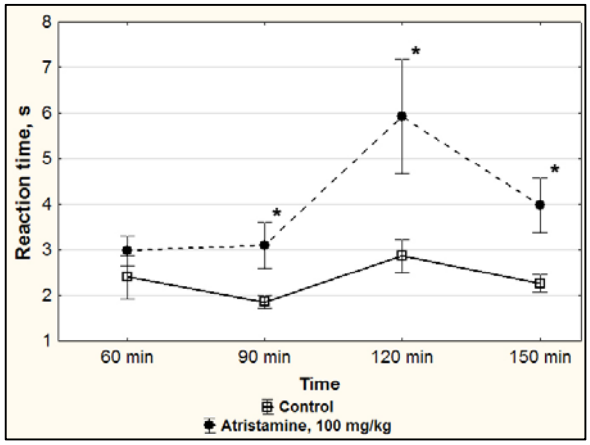

Fig 6: Time-response curves for the antinociceptive effect caused by atristamine compared to the control group.

At the same time, the reference drug metamizole acted more intensively but transiently. It may be explained by its route of administration.

4. Discussion

The result of the study of the analgesic activity of atristamine using classical TCA imipramine as a reference drug allowed revealing some peculiarities.

The analysis of the experimental data presented in Tab. 2 shows that animals treated with imipramine (25 mg/kg, i.p.) have no significant differences in the tail withdrawal latencies compared to the control group in all time points observed. This fact conflicts with the reported data [21-22] where imipramine provided the appreciable antinociceptive effect after single administration in the wide range of doses in the tail-flick test in rats. Therefore, it could be suggested that single dosing of imipramine not always provides the sufficient level of analgesia against somatic pain. At the same time, imipramine provided an excellent analgesic effect in the writhing test (Tab. 1).

Atristamine, conversely, had no action in the writhing test, but exhibited significant antinociceptive properties in the tail immersion test.

This fact reveals certain differences in the mechanisms of the analgesic action and allows us to suggest some distinctions in the mechanisms of the antidepressant effect of atristamine compared to TCAs.

5. Conclusions

The analgesic properties of a novel promising antidepressant with the polymodal action on the CNS – 2-methyl-3-(phenylaminomethyl)-1H-quinolin-4-one (atristamine) have been studied. In the acetic acid-induced writhing test atristamine in the dose of 100 mg/mg had no antinociceptive effect. At the same time, the analgesic activity of this compound in the same dose has been proven in the tail immersion test. It has been shown that atristamine provides antinociception starting not less than in 90 min after introduction and has the optimal effect in the 120-min time point. Some differences in the analgesic action compared to imipramine have been revealed. They allow suggesting certain distinctions in the mechanisms of the antidepressant effect of atristamine in comparison with TCAs. The results of this study are encouraging because the analgesic properties of atristamine can expand its application in the future as an "adjuvant analgesic", but this type of activity deserves a deeper and more detailed study.

References

1. Khan MIA, Walsh D, Brito-Dellan N. Opioid and adjuvant analgesics: compared and contrasted. The American journal of hospice & palliative care. 2011; 28(5):378-383.
2. Mico JA, Ardid D, Berrocoso E, Eschalier A. Antidepressants and pain. Trends in pharmacological sciences. 2006; 27(7):348-354.
3. Gilron I, Baron R, Jensen T. Neuropathic pain: principles of diagnosis and treatment. Mayo Clinic proceedings. 2015; 90(4):532-545.
4. Attal N, Bouhassira D. Pharmacotherapy of neuropathic pain: which drugs, which treatment algorithms? Pain. 2015; 156Suppl:S104-114.
5. Jongen JLM, Hans G, Benzon HT, Huygen F, Hartrick CT. Neuropathic pain and pharmacological treatment.

Pain pract. 2014; 14(3):283-295.
6. Watson CP, Gilron I, Sawynok J, Lynch ME. Nontricyclic antidepressant analgesics and pain: are serotonin norepinephrine reuptake inhibitors (SNRIs) any better? Pain. 2011; 152:2206-2210.
7. Millan MJ. Descending control of pain. Progress in neurobiology. 2002; 66(6):355-474.
8. Sawynok J. Topical and peripherally acting analgesics. Pharmacological reviews, 2003; 55(1):1-20.
9. Shtrygol' SJu, Zubkov VO, Gritsenko IS, Podolsky IM, Shatilov OV. Screening research of 3-aminomethyl-2-methylquinolin-4-ones as potential psychotropic agents. Klìnična farmacìâ. 2010; 14(1):35-38.
10. Shtrygol' SIu, Zubkov VA, Podol'skii IN, Gritsenko IS. 2-Methyl-3-phenylaminomethylquinolin-4-one as potential antidepressant with nootropic properties. Eksperimental'naia i klinicheskaia farmakologiia. 2012; 75(4):7-9.
11. Podolsky IM, Shtrygol' SYu, Ostashko VF, Bezditko NV. The research of antihypoxic activity 2-methyl-3-phenylaminomethylquinolin-4-one of the perspective antidepressant with nootropic properties. Ukrainian biopharmaceutical journal. 2013; 2(25):46-49.
12. Podolsky IM, Shtrygol' SYu, Gritsenko IS. The influence of promising antidepressant with nootropic properties 2-methyl-3-phenylaminomethylquinolin-4-one on the phases of memory. Ukrainian Journal of Clinical and Laboratory Medicine. 2013; 8(4):104-107.
13. Podolsky IM, Shtrygol' SYu, Zubkov VA, Gritsenko IS. Interaction of perspective antidepressant with nootropic properties 2-methyl-3-phenylaminomethylquinolin-4-one with CNS stimulants and depressants. Medical Herald of the South of Russia. 2014; 1:80-84.
14. Shtrygol SYu, Zubkov VO, Podolsky IM, Gritsenko IS. The influence of 3-aminomethyl-2-methylquinolin-4-one derivatives on monoamines levels in the brain of mice. Visnyk farmaciï. 2011; 65(1):62-65.
15. Podolsky IM, Shtrygol SYu. Neuroprotective activity of 2-methyl-3-phenylaminomethylquinolin-4-one in experimental traumatic brain injury in rats. Journal of Chemical and Pharmaceutical Research. 2015; 7(4):518-524.
16. Zubkov VA, Gritsenko IS, Taran SG, Podolsky IN, Kamenetska OL. 3-Dimethylaminomethyl-2-methyl-1H-quinolin-4-one as an effective reagent in the 3-aminomethylsubstituted quinolones synthesis. Žurnal organìčnoï ta farmacevtičnoï hìmìï. 2005; 3(2):23-27.
17. Hokanson GC. Acetic acid for analgesic screening. J Nat Prod. 1978; 41:497-498.
18. Janssen PAJ, Niemegeers CJE, Dony JGH. The inhibitory effect of fentanyl and other morphine-like analgesics on the warm water induced tail withdrawal reflex in rats. Arzneimittelforschung. 1963; 13:502-507.
19. Ghelardine C, Galeotti N, Bartolini A. Antinociception induced by amitriptyline and imipramine is mediated by α2A-adrenoceptors. Jpn. J Pharmacol. 2000; 82:130-137.
20. Del Carmen R-OJ, Willam HMJ, del Carmen GMA. Antinociceptive effect of aqueous extracts from the bark of *Croton guatemalensis* Lotsy in mice. Research in Pharmaceutical Sciences. 2016; 11(1):15-22.
21. Bhargava VK, Saha L. Cholinergic mechanism in imipramine and morphine antinociception. Indian Journal of Pharmacology. 2001; 33:212-214.
22. Bhargava VK, Saha L. Serotonergic mechanism in imipramine induced antinociception in rat tail flick test. Indian Journal of Physiology and Pharmacology. 2001; 45(1):107-110.