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Anticonvulsant activity of a newly synthesized analgesic from the hexaazaisowurtzitane class (experimental study)

© S.G. Krylova[1], E.A. Kiseleva[1], D.A. Kulagina[2], T.N. Povetyeva[1], Yu.V. Nesterova[1], A.I. Lopatina[3], V.V. Eremina[2], S.V. Sysolyatin[2], V.V. Zhdanov[1]

[1] Goldberg Research Institute of Pharmacology and Regenerative Medicine, Tomsk, Russia;
[2]Institute for Issues of Chemical and Energetic Technologies, Biysk, Russia;
[3]Pirogov Russian National Research Medical University, Moscow, Russia

ABSTRACT

Objective. To study anticonvulsant activity of thiowurtzine in seizure models induced by pentylenetetrazol and thiosemicarbazide.

Material and methods. Experiments were conducted on male CD-1 mice. Thiowurtzine was administered intragastrically at doses of 50, 100 and 200 mg/kg. Carbamazepine (100 mg/kg) was used as a reference drug. Anticonvulsant activity was investigated in antagonism tests with pentylenetetrazol (PTZ 140 mg/kg subcutaneously) and thiosemicarbazide (TSC 30 mg/kg subcutaneously). Anticonvulsant activity was assessed considering latency of various seizure stages, their frequency, and animal survival.

Results. In PTZ test, thiowurtzine 100 mg/kg significantly prolonged latent period of myoclonic seizures by 92% and clonic seizures by 95%, as well as survival time by 73% compared to the control group. All changes were significant. Survival reached 41.7% that was comparable to the effect of carbamazepine. At 200 mg/kg, efficacy decreased that indicated a narrow therapeutic window. In TSC model, thiowurtzine did not significantly affect survival. However, dose 100 mg/kg reduced the number of the most severe tonic seizures by 31%.

Conclusion. Thiowurtzine possesses anticonvulsant activity, most pronounced in GABA-dependent pentylenetetrazol model. These data indicate membrane-stabilizing effect and expand potentials for this compound in comorbid conditions.

Keywords: *analgesic, hexaazaisowurtzitane, thiowurtzine, anticonvulsant activity, pentylenetetrazol, thiosemicarbazide.*

INFORMATION ABOUT THE AUTHORS:
Krylova S.G. — https://orcid.org/0000-0003-0249-1395
Kiseleva E.A. — https://orcid.org/0000-0003-3732-1302
Kulagina D.A. — https://orcid.org/0000-0002-4673-5817
Povetyeva T.N. — https://orcid.org/0000-0001-8644-489X
Nesterova Yu.V. — https://orcid.org/0000-0002-1382-926X
Lopatina A.I. — https://orcid.org/0009-0008-8622-158X
Eremina V.V. — https://orcid.org/0000-0002-1467-0051
Sysolyatin S.V. — https://orcid.org/0000-0002-1405-171X
Zhdanov V.V. — https://orcid.org/0000-0002-9516-0204
Corresponding authors: Krylova S.G. e-mail: krylova5935@gmail.com; Kulagina D.A. e-mail: imbiri@rambler.ru

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Introduction

Despite the centuries-long history of pain pharmacotherapy, available arsenal of analgesics is still imperfect. Key disadvantages, such as some side effects of non-steroidal anti-inflammatory drugs (gastroduodenopathy, nephrotoxicity, hepatotoxicity and hematotoxicity, cardiovascular effects, etc.), risk of mental and physical dependence of opioids, as well as ceiling of effectiveness for many painkillers dictate the need for fundamentally new therapeutic strategies and molecular structures [1]. Virtual screening methods are currently used for reducing the cost and accelerated development of new drugs in modern pharmacology. Available web-based tools not only enable development of bioactive molecules and drug repurposing, but also stimulate generation of new ideas and testing of hypotheses. This ultimately makes a significant contribution to creation of fundamentally new substances. Thus, computer drug-design and directed chemical synthesis technologies were followed by creation of a first-in-class molecule based on pharmacophore — high-energy substance 2,4,6,8,10,12-hexaazatetracyclo[5,5,0,03,11,05,9]dodecane (hexaazaisowurtzitane). The newly synthesized compound was used as a pharmaceutical substance to create a prototype of effective and low-toxic analgesic thiowurtzine (capsules 120 mg). Comprehensive in silico and in vivo studies established that analgesic effect of thiowurtzine is realized through modulation of TRPA1 and TRPV1 receptors, as well as voltage-dependent calcium channels. This unique mechanism ensures that the drug lacks both opioid (morphine-like) effects and side effects typical for non-steroidal anti-inflammatory drugs. No effect in tests with arecoline tremor together

with suppression of tryptophan hyperkinesis allows us to conclude that substance inhibits activation of serotonergic system, but lacks antimuscarinic (m-anticholinergic) properties [2, 3].

Research of anticonvulsant properties of a potential analgesic is logical and important, since anticonvulsants have long been successfully used for chronic pain syndromes, especially neuropathic pain, fibromyalgia, and migraine. Chronic pain syndromes and epilepsy have common pathophysiological mechanisms, including central sensitization, imbalance between excitatory (glutamatergic) and inhibitory (GABAergic) systems, and ion channel dysfunction [4–7]. Models of seizures induced by GABA proconvulsants (corazol, thiosemicarbazide), differing in mechanism of action, can be used to study anticonvulsant properties of analgesic and participation of GABAergic system in analgesia [8].

The purpose of the study was to analyze anticonvulsant activity of the first synthesized analgesic from the hexaazaisowurtzitane class (thiowurtzine) in models of seizures caused by corazol and thiosemicarbazide.

Material and methods

Experiments were performed on 108 male CD-1 mice (weight 28—32 g) obtained from the Department of Experimental Biomodeling of the Goldberg Research Institute of Pharmacology and Regenerative Medicine. Maintenance of animals and design of experiments were approved by local bioethics commission (JACUC protocol no. 96092015) and complied with Directive 2010/63/EU of the European Parliament and European Council on protection of animals used for scientific purposes.

We randomized animals into groups considering body weight (±10%); each group had at least 10 animals. Animals were euthanized in a CO_2 chamber.

The object of study was pharmaceutical substance thiowurtzine (odorless white crystalline powder). Thiowurtzine contains at least 97.0% $C_{19}H_{20}Br_2N_6O_5S$ (empirical formula) on a dry matter basis. Thiowurtzine is easily soluble in acetone, dimethyl sulfoxide (DMSO), Tween-80, slightly soluble in alcohol (96%), almost insoluble in water. Melting point – 328—330°C. Characteristics of thiowurtzine are fully confirmed by physicochemical research methods: IR spectrum, ν/cm^{-1}, 1H nuclear magnetic resonance (NMR) spectrum (DMSO-d, δ, ppm), C NMR spectrum (DMSO-d6, δ, ppm). Molecular weight of compound (Mw) is 604.27.

The doses were 50, 100 and 200 mg/kg. Intragastric administration was selected considering previous experiments devoted to analgesic activity [2, 3]. Purified water was used as a solvent for thiowurtzine with addition of Tween-80 20 μl (polysorbate LAUROPAN T/80, Italy) per 1 ml of water. Negative control animals were administered a water-Tween solution (0.2 ml per 20 g of body weight). Positive control implied intragastric carbamazepine (Sigma, China) 100 mg/kg (purified water 0.2 ml per 20 g of body weight) [9, 10]. We studied anticonvulsant activity in antagonism tests with corazole (pentylenetetrazole (PTZ), Sigma, Germany) and thiosemicarbazide (Sigma, Germany) [11].

PTZ-induced seizures. There was intragastric administration of thiowurtzine through a tube once in doses of 50, 100 and 200 mg/kg 1 hour before subcutaneous administration of corazol 140 mg/kg in the neck of the animal. Carbamazepine 100 mg/kg was administered in the same fashion. After administration of effective dose of corazol (140 mg/kg subcutaneously), negative control animals develop convulsive manifestations in the following se-

Table 1. **Effect of thiowurtzine in preventive single intragastric administration (50, 100, and 200 mg/kg) on corazole-induced (140 mg/kg subcutaneously) seizures in outbred male CD1 mice (*M±m*)**

Group, dose (number of animals)	Myoclonus (stage 1), s/number	Clonic seizures (stage 2), s/number	Generalized clonic seizures (stage 3), s/number	Tonic extension (stage 5), s/ number	Life expectancy, s	Survivors, %
1. Control (n=12)	114,3±9,4/16,3±3,0	362,0±117,7/1,2±0,4	405,7±102,6/1,0±0,3	521,7±87,6/1,0±0,1	659,9±158,4	8,3 (1/12)
2. Carbamazepine, 100 mg/kg (n=12)	153,2±14,3^{1-2*}/55,8±8,8^{1-2**}	486,4±125,9/3,8±1,2^{1-2*}	747,2±115,5^{1-2*}/1,3±0,3	1151,6±154,7^{1-2**}/0,3±0,1^{1-2**}	1229,8±138,1^{1-2*}	33,3 (4/12)$^{1-2*}$
3. Thiowurtzine, 50 mg/kg (n=11)	147,6±26,5/26,8±7,5^{1-3*}	619,6±132,0/0,6±0,3^{2-3*}	245,0±34,0^{2-3**}/2,4±0,5^{1-3*}	484,9±69,1^{2-3**}/1,2±0,2^{2-3**}	815,8±156,6^{2-3*}	9,1 (1/11)$^{2-3*}$
4. Thiowurtzine, 100 mg/kg (n=12)	219,7±56,3^{1-4**}/13,3±3,9^{2-4**}	707,3±199,2^{1-4*}/1,4±0,5	307,6±59,9^{2-4**}/1,6±0,4	517,9±85,9^{2-4**}/1,0±0,0^{2-4**}	1141,2±177,8^{1-4*}	41,7 (5/12)$^{1-4*}$
5. Thiowurtzine, 200 mg/kg (n=11)	188,6±36,4^{1-5*}/19,7±7,5^{2-5**}	484,8±85,8/0,3±0,1$^{1-5*; 2-5**, 4-5*}$	316,1±69,7^{2-5**}/1,1±0,3	542,3±69,8^{2-5**}/1,0±0,0^{2-5**}	726,4±142,0^{2-5*}	9,1 (1/11)$^{4-5*}$

Note: here and in table 2: * — $p \leqslant 0.05$, ** — $p \leqslant 0.01$.

quence: 1) ⩾ 1 myoclonic contractions of the whole body; 2) repeated clonic spasms of the fore and/or hind limbs > 3 s without lost turning over reflex; 3) generalized clonic convulsions of the fore and hind limbs with lost turning over reflex; 4) tonic extension of the forelimbs with lost turning over reflex; 5) tonic extension of the fore and hind limbs with lost turning over reflex [11]. Corazol-induced seizures were recorded 1 hour after administration of substances and within 30 min after administration of corazol. All control animals had convulsive manifestations after administration of corazol (points 1–3). Animals without seizures described in point 2 or subsequent stages 3–5 within 30 minutes after administration of test substances and then corazol were considered "protected". The main criterion for effectiveness was life expectancy of animals and number of survivors (%) [10].

Thiosemicarbazide-induced seizures. Thiowurtzine was administered through a gastric tube in single doses of 50, 100 and 200 mg/kg 1 hour before subcutaneous administration of thiosemicarbazide 30 mg/kg in the neck of the animal. Carbamazepine 100 mg/kg was administered in the same fashion. Criteria of anticonvulsant activity were prolonged time to the first convulsive attack (latent period), frequency of clonic-tonic seizures and death of animals (%). Mice survived 90 min after injection of thiosemicarbazide were classified as "protected" [9, 10].

Statistical analysis of data was carried out using the Statistica 10 software. Non-parametric distribution of variables (Shapiro-Wilk test) required Kruskal-Wallis test for multiple comparisons. The Wilcoxon-Mann-Whitney U test was used for between-group comparisons, and the Fisher angular transformation test (φ) was used to identify significance of differences in qualitative indicators. For each sample, we estimated arithmetic mean (M) and standard error of mean (m). These values are presented in tables together with *n* (number of animals). In all cases, the null hypothesis was rejected at $p<0.05$ [11].

Results

Carbamazepine demonstrated high anticonvulsant activity for PTZ-induced seizures. Compared to the control group, carbamazepine prolonged latent period for myoclonic, generalized clonic and tonic seizures, significantly reduced the number of episodes of tonic seizures and increased the number of survivors from 8.3% in the control group to 33.3% under significantly (1.9 times) longer life expectancy ($p<0.05$).

A single dose of thiowurtzine (50 mg/kg) was weakly effective (Table 1). There was prolonged latent period of myoclonic seizures (by 29%), clonic seizures (by 71%) and tonic seizures (by 18%), as well as increased life expectancy (by 24%), but these changes demonstrated only statistical trend. For some parameters (number of myoclonic seizures and generalized clonic seizures), the drug significantly worsened results compared to negative control animals. Survival of animals corresponded to negative control. Thiowurtzine 100 mg/kg had protective effect relative to the negative control. This effect consisted of prolonged latent period of myoclonic seizures by 92% ($p<0.01$) and clonic seizures by 95% ($p<0.05$). Increased life expectancy was one of the most significant manifestations of effectiveness of thiowurtzine (by 73% compared to the negative control group) **(Table 1)**. This result was comparable to the effect of carbamazepine. Thiowurtzine ensured 41.7% survival of mice that exceeded appropriate value in the carbamazepine group (33.3%). Protective effect of thiowurtzine at a dose of 200 mg/kg was manifested in increased latent period of myoclonic seizures by 65% ($p<0.05$)

Table 2. **Effect of thiowurtzine in preventive single administration on thiosemicarbazide-induced seizures (30 mg/kg subcutaneously) in male CD-1 mice**

Group, dose (number of animals)	Clonic seizures (stage 2), s/number	Generalized clonic seizures (stage 3), s/number	Tonic extension (stage 5), s/ number	Life expectancy, s	Survivors, %
1. Control ($n=10$)	3036,4±275,0/0,1±0,1	2975,8±197,8/0,4±0,2	2523,8±69,6/1,6±0,2	3251,1±362,8	10 (1/10)
2. Carbamazepine, 100 mg/kg ($n=10$)	$4164,6\pm348,3^{1-2*}$/$1,6\pm0,7^{1-2*}$	$3535,4\pm126,8^{1-2*}$/$2,1\pm178,0^{1-2**}$	$4418,2\pm356,8^{1-2**}$/$0,4\pm0,2^{1-2**}$	$4815,5\pm324,1^{1-2**}$	70 (7/10) $^{1-2**}$
3. Thiowurtzine, 50 mg/kg ($n=10$)	$2739,0\pm118,5^{2-3**}$/$1,0\pm0,5$	$2940,8\pm141,6^{2-3**}$/$0,5\pm0,2^{2-3**}$	$2652,9\pm59,3^{2-3**}$/$1,6\pm0,3^{2-3**}$	$3052,2\pm173,2^{2-3**}$	0^{2-3**}
4. Thiowurtzine, 100 mg/kg ($n=10$)	$3050,8\pm295,0^{2-4*}$/$0,5\pm0,3$	$3064,7\pm253,1$/$0,5\pm0,2^{2-4**}$	$3100,3\pm286,8^{2-4*}$/$1,1\pm0,2^{1-4*,\ 2-4*}$	$3413,3\pm348,9^{2-4**}$	20 (2/10)$^{2-4**}$
5. Thiowurtzine, 200 mg/kg ($n=10$)	$2626,6\pm89,8^{2-5**}$/$0,4\pm0,2$	$2536,0\pm67,6^{1-5*,\ 2-5**}$/$0,8\pm0,4$	$2569,4\pm81,4^{2-5**}$/$1,5\pm0,3^{2-5**}$	$2768,2\pm96,7^{2-5**}$	0^{2-5**}

and reduced number of clonic seizures by 25% ($p<0.05$) compared to negative control. However, the substance at this dose did not increase survival of mice (9.1% as in negative control). Anticonvulsant activity of thiowurtzine at a dose of 200 mg/kg was significantly weaker compared to 100 mg/kg that can indicate narrow therapeutic range of thiowurtzine.

In the model of thiosemicarbazide-induced seizures after subcutaneous administration of substance at a dose of 30 mg/kg, carbamazepine significantly increased latent period of all seizures, decreased the number of tonic seizures by 25% ($p<0.01$) and prolonged life expectancy by 48% ($p<0.01$) compared to negative control **(Table 2)**. Significant increase in survival rate (up to 70% vs. 10% in the control group) confirms validity of experimental model.

Thiowurtzine 50—200 mg/kg had no protective anticonvulsant effect comparable to carbamazepine **(Table 2)**. Regarding latent period of seizures, none dose of thiowurtzine demonstrated consistent and significant increase in time to onset of all types of seizures. Indicators in groups of substance were either comparable with control or significantly less than in the carbamazepine group. However, administration of thiowurtzine at a dose of 100 mg/kg decreased the number of the most severe tonic seizures by 31% ($p<0.05$) and prolonged their latent period by 23% ($p>0.05$) compared to the negative control group. Moreover, survival rate in this group was 20%, similar to the control group (10%) and significantly lower than in the carbamazepine group. The substance had no effect on overall lifespan of mice. In all experimental groups of thiowurtzine, this indicator was comparable to the negative control group and significantly less than in the carbamazepine group. Thiowurtzine 50 and 200 mg/kg did not increase survival (0%) that did not differ from negative control (10%).

Discussion

Similar pathophysiological mechanisms of chronic pain syndromes and epilepsy, including central sensitization and dysfunction of ion channels, determines therapeutic effectiveness of anticonvulsants for neuropathic pain [4, 6]. Anticonvulsant activity of thiowurtzine confirms the prospects of this substance for comorbid conditions when epilepsy and pain disorders have a common neuronal substrate [6].

Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter of the central nervous system. Its main function is to reduce neuron excitability and suppress excess activity. GABA system dysfunction is a common pathological mechanism underlying seizures and chronic pain. In this regard, correction of this dysfunction is a key mechanism of many highly effective analgesics and antiepileptic drugs [6, 8, 9].

The key to interpreting anticonvulsant effect of thiowurtzine in tests with PTZ and thiosemicarbazide (standard chemical proconvulsants) lies in understanding the mechanism of provoking agent and its antagonism by test substance. Pentylenetetrazole is a classic non-competitive antagonist of GABA receptors, and its proconvulsant effect is due to blockade of chloride ion channels associated with these receptors. This does not exclude its nonspecific proconvulsant membranotropic effect. PTZ decreases inhibitory GABAergic tone in the central nervous system and balance shift towards excitation and synchronization of neuronal discharges. This clinically manifests in a typical sequence: myoclonic → clonic → tonic seizures. Thus, corazol-induced seizure test allows identification of compounds enhancing GABAergic neurotransmission and causing modulation of ion channels with membrane stabilization. Considering the previously established ability of thiowurtzine to modulate the activity of TRPA1 and TRPV1 receptors, as well as calcium channels [3], its protective effect in this test may be due to stabilization of neuronal membranes. Modulation of voltage-dependent calcium channels is a recognized strategy for reducing excessive excitability of the central nervous system typical for both epileptogenesis and pain hypersensitivity [5]. Protective effect of thiowurtzine at a dose of 100 mg/kg (comparable in life expectancy and even superior to the effect of carbamazepine in survival (41.7%)) allows us to put forward a hypothesis about a fundamentally different, possibly direct or indirect effect on GABAergic transmission. Prolonged latent period for all seizures and significant increase in life expectancy indicate that thiowurtzine effectively counteracts baseline triggering action of corazol. The most likely mechanism is potentiation of inhibitory effect of GABA that could compensate for corazol-induced receptor blockade. This could conceivably occur through allosteric modulation of GABA receptor (similar to benzodiazepines or barbiturates), inhibition of GABA reuptake or suppression of its metabolism (like valproates), indirect enhancement of GABAergic tone through other systems (like pregabalin and gabapentin). Weak and inconsistent activity at a dose of 50 mg/kg may indicate insufficient concentration of substance to effectively compensate for PTZ blockade. Deterioration of some parameters (number of seizures) may indicate complex, nonlinear modulation of neuronal networks by subtherapeutic dose. Significantly lower effectiveness and no improvement in survival at a dose of 200 mg/kg (despite increased latent period of tonic seizures and reduced number of clonic seizures) are the most important. This dome-shaped dose-dependent effect (with maximum activity at 100 mg/kg) is often typical for substances acting on neurotransmitter receptors. The present study suggests that thiowurtzine in optimal dose demonstrates high activity in a model whose pathogenesis is associated with inhibition of GABAergic system. Its primary mechanism of action may be due to enhanced GABA-mediated inhibition. However, narrow therapeutic range and lost efficacy at high doses require some caution in determining the therapeutic window.

Thiosemicarbazide as an inhibitor of glutamate decarboxylase indirectly causes seizures through suppressing the synthesis of inhibitory neurotransmitter GABA in the brain and disturbing the balance between excitatory (glutamate) and inhibitory (GABA) signals. No clear anticonvulsant effect of thiowurtzine in thiosemicarbazide-induced seizures indicates that compound is not able to compensate for severe deficiency of endogenous GABA following glutamate decarboxylase inhibition. Unlike the PTZ model with possible allosteric modulation of receptors or influence on ionic currents [10], GABA-deficient models are more resistant to drugs with indirect mechanism of action. This makes it possible to more accurately limit spectrum of neurotropic activity of thiowurtzine [10]. Thus, thiowurtzine is ineffective in GABA-deficient model of seizures, and its action "bypasses" the main cause of seizures in this test. The only positive effect (31% reduction in severe tonic seizures at 100 mg/kg) may indicate that thiowurtzine has a very narrow therapeutic window or occurs only in certain subpopulations of neurons. No change in key outcome (survival rate 20% vs. 10% in control animals, $p>0.05$) means that even partial reduction in seizure severity did not prevent death associated with uncontrolled electrical brain activity and/or systemic disorders. The absence of anticonvulsant effect of thiowurtzine in this model is not so much an indicator of complete ineffectiveness, but rather an important pharmacological marker specifying and limiting its mechanism of action in comparison with classi-

cal anticonvulsant. The above is confirmed by clear anticonvulsant effect of thiowurtzine in corazol-induced seizures (more relevant to its putative mechanism of action). At the same time, it is likely that standard screening models used for six decades (PTZ, thiosemicarbazide, etc.) detect only substances similar to existing ones and do not allow detection of more effective drugs with new mechanisms of action [8, 10].

Conclusion

Research of anticonvulsant effect of analgesic prototype is not only of academic interest, but also makes it possible to predict effectiveness of substance in chronic, especially neuropathic, pain syndromes. This also indicates possible neuronal mechanisms of its action. Available data complement preclinical assessment of a new analgesic. This makes it possible to improve safety profile, predict therapeutic capabilities and potential for the treatment of comorbid conditions.

Author contribution:
Concept and design of experiments, participation in experiments, writing the text — Krylova S.G.
Concept and design of experiments, participation in experiments, statistical analysis — Povetyeva T.N.
Concept and design of experiments, participation in experiments — Nesterova Yu.V.
Organization and participation in experiments, collection and analysis of data, statistical analysis — Kiseleva E.A.
Statistical analysis of data and design of the manuscript — Lopatina A.I.
Editing — Zhdanov V.V.
Synthesis and description of the research object — Kulagina D.A.
Synthesis of the research object — Eremina V.V.
Organization and development of synthesis of the research object — Sysolyatin S.V.

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