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Original article

ANTIHYPERALGESIC ACTIVITY OF PROPOXAZEPAM IN THE OXALIPLATIN-INDUCED COLD ALLODYNIA IN RATS

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Background. Oxaliplatin (OXP), a third-generation chemotherapeutic platinum compound, is widely used in treating metastatic colorectal cancer. However, its clinical utility is limited by oxaliplatin-induced peripheral neuropathy (OIPN), a dose-dependent and often persistent adverse effect characterized by sensory dysfunction such as cold allodynia. Current pharmacological options for OIPN management are limited, with duloxetine being the only drug recommended with moderate confidence by clinical guidelines. Novel analgesics with alternative mechanisms of action are urgently needed.

Objective. This study aimed to evaluate the antihyperalgesic (analgesic) effect of propoxazepam, a novel benzodiazepine derivative with known GABAergic and glycinergic activity, in a rat model of OXP-induced peripheral neuropathy.

Methods. Chronic peripheral neuropathy was induced in male Sprague–Dawley rats via repeated intraperitoneal injections of OXP (4 mg/kg, twice weekly for 3 weeks). Cold allodynia was assessed using the paw immersion test at 10 °C. Rats received a single oral dose of propoxazepam (0.5–8 mg/kg) or duloxetine (100 mg/kg) on days 4, 11, and 18, with paw withdrawal latency (PWL) measured at 60, 120, and 180 minutes post-administration. Data were analyzed using Student's *t*-test with $p \leq 0.05$ as the threshold for statistical significance.

Results. OXP administration significantly reduced PWL, indicating development of cold allodynia. Propoxazepam demonstrated a dose-dependent analgesic effect starting as early as Day 4. Significant increases in PWL were observed at doses of 4 and 8 mg/kg, with maximal effects on Day 11 (up to 62% relative to the control). While duloxetine induced a stronger initial effect (~70–75%), it diminished rapidly to 19% by 180 minutes. Lower doses (0.5–2 mg/kg) of propoxazepam did not show statistically significant effects. The analgesic effect of propoxazepam peaked at 120 minutes post-administration and declined by 180 minutes.

Conclusions. Propoxazepam effectively reduces cold allodynia in a rat model of OIPN in a dose- and time-dependent manner. Its analgesic efficacy, mediated through GABAergic and glycinergic modulation and supported by anti-inflammatory properties, positions it as a promising candidate for treating chemotherapy-induced neuropathic pain. Given its favorable safety profile and novel mechanism, propoxazepam warrants further investigation in clinical trials.

Keywords: oxaliplatin-induced peripheral neuropathy; chemotherapy-induced neuropathic pain; propoxazepam; allodynia; GABAergic modulation; anti-inflammatory action; preclinical model.

Introduction

Oxaliplatin (OXP) is a third-generation organoplatinum chemotherapeutic agent commonly employed as a first-line treatment for metastatic colorectal cancer [1]. Although it demonstrates significant antitumor activity, its clinical use is limited by dose-dependent neurotoxicity, which remains one of its most severe adverse effects. This neurotoxicity typically presents as paresthesia and dysesthesia in the hands and feet [2], and approximately 85 to 95% of patients experience rapid onset of acute neuropathic pain following an oxaliplatin infusion, usually without accompanying motor impairment [3].

When combined with other drugs, such as in the FOLFOX protocol (leucovorin, fluorouracil, and OXP) used in colorectal cancer treatment, a 71% incidence of neuropathy symptoms was observed among study participants, with 84% experiencing some degree of functional impairment or reduced quality of life up to 25 months after chemotherapy cessation [4].

The development of oxaliplatin-induced peripheral neuropathy involves multiple mechanisms, including the dysregulation of calcium, potassium, and sodium ion channels, changes in transient receptor potential channel activity, as well as oxidative stress and neuroinflammatory processes [5]. Several drugs (e.g. gabapentin and duloxetine) are

recommended to mitigate this side effect [6]. Unfortunately, these analgesics cause another side effects, such as somnolence and nausea [7].

Propoxazepam, as a promising analgesic drug, is undergoing clinical studies in Ukraine. Similar to gabapentinoid drugs (derivatives of the inhibitory neurotransmitter gamma-aminobuturyc acid, GABA), which are used in general medical practice in the treatment of neuropathic pain, propoxazepam also has an anticonvulsant effect [8–10], which is considered a predictor of analgesic action and thus explains the analgesic component in the pharmacological spectrum of compound. Data [11] suggest that the mechanism of propoxazepam's analgesic and anticonvulsant properties includes GABAergic and glycinergic systems. Propoxazepam similar to gabapentin reduced hyperglycemia, clinical signs of polyneuropathy with course of administration for 5 weeks, and also showed analgesic effect, as evidenced by an increase in the threshold of pain sensitivity [11]. Taking into account these facts it was suggested that the drug may inhibit oxaliplatin-induced hyperalgesia in rats.

Propoxazepam successfully passed the first stage of clinical studies in healthy volunteers, in which the safety and proper pharmacokinetics of the compound were proven [12]. The second phase of clinical research involves studying the analgesic effect of the drug on patients with neuropatic pain.

The purpose of this study was to assess the antihyperalgesic effect of a single oral administration of Propoxazepam in the model of OXP-induced peripheral neuropathy in rats. Duloxetine was used as a reference substance to validate the assay.

Materials and Methods

Chemical source

Propoxazepam was first synthesized at the A.V. Bogatsky Physico-Chemical Institute of the National Academy of Sciences of Ukraine, the scaling-up process was then developed at the SLC "INTERCHEM", Odesa, Ukraine. For this study, it was provided as previously described in the patent USA [13]. The characterization data for Propoxazepam, including nuclear magnetic resonance and mass spectrometry details as well as the melting point, have been published previously [14]. General purpose reagents and solvents were of analytical grade (or a suitable alternative) and were obtained principally from VWR International Ltd, Rathburn Chemicals Ltd, Sigma Aldrich Chemical Company Ltd and Fisher Scientific UK Limited.

Animals and housing conditions

Seventy male Sprague–Dawley rats, weighing 155–202 g during the induction day were used. Rats were housed in a temperature (20–24 °C) and relative humidity (45–65%) controlled room and acclimated to an artificial day/night cycle of 12 hours light/12 hours darkness. Rats had free access to tap water and were fed ad libitum with pelleted complete diet. Animals were housed 4 per cage (relative to the standard housing conditions) and were acclimated for a period of at least 5 days before any testing. The animal study was conducted according to the European legislation (Directive 2010/63/EU) and Ukraine Government regulation (60 № 416/20729) regarding the protection of animals used for scientific purposes and was in full compliance with to the recommendations of the International Association for the Study of Pain (Test facility accreditation number for the use of laboratory animals is D63.300.12).

Experiment design

Chronic peripheral neuropathy was induced by repeated intraperitoneal injections of OXP (4 mg/kg, i.p., 10 ml/kg) 2 times a week for 3 weeks (course dose = 24 mg/kg, i.p.). Seven experimental groups were treated with OXP (4 mg/kg, i.p.) and one (group 1, Sham group) was treated with 5% Glucose (vehicle of OXP) following the same sequence of administration. On Day 0, latency of hindpaw withdrawal was measured on both paws using the cryothermostat (baseline pre-induction).

On the first week, two intraperitoneal injections of OXP (4 mg/kg, groups 2–8) or 5% Glucose (group 1) were performed (Day 0 and Day 3). On Day 4, the latency of hindpaw withdrawal was measured (pre-treatment baseline), then, rats were treated with vehicle or propoxazepam (groups 3–7, doses 0.5, 1.0, 2.0, 4.0 and 8.0 mg/kg orally) and 120 min later, the latency of hindpaw withdrawal was measured on both paws using the cryothermostat. Rats from duloxetine group were measured 60 min after treatment (Fig. 1).

The same sequence of OXP injections, administration of compounds and test were performed on the second week (administrations on day 7, day 10, test on day 11) and on the third week (administrations on day 14, day 17, test on day 18). On the third week, animals were tested 60, 120 and 180 min after oral administration of Propoxazepam or positive reference (duloxetine) or vehicle.

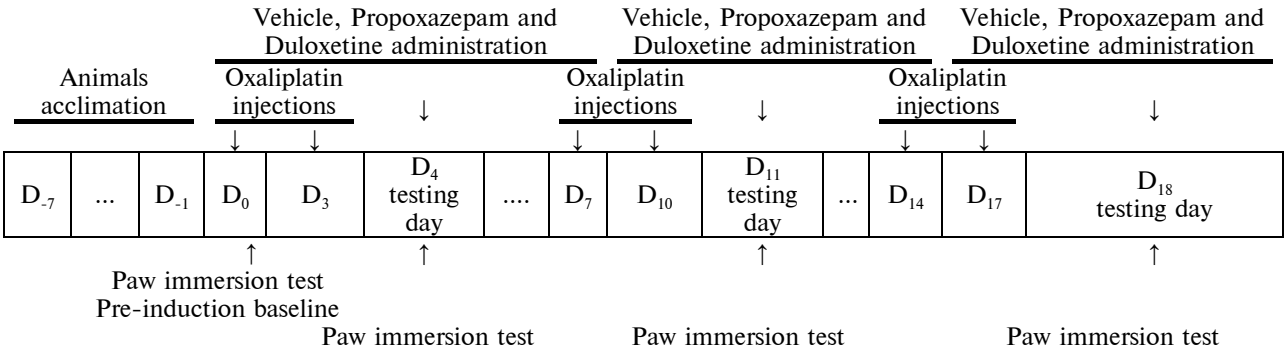

Figure 1: Study design

Pain test cold allodynia

Pain test cold allodynia was measured using the paw immersion test [15], where the latency of hindpaw withdrawal is measured after immersion of the hindpaw in the cryothermostat with a temperature fixed at 10 °C (±0.5 °C).

Calculations

Data were presented as mean ± standard error of the mean ($M \pm m$). The relative effect (in per cents from the maximum values) was calculated as following:

$$\text{Effect}, \% = \frac{\text{LT}_{\text{exp.group}} - \text{LT}_{\text{neuropat.group}}}{\text{LT}_{\text{sham.group}} - \text{LT}_{\text{neuropat.group}}} \cdot 100,$$

where $\text{LT}_{\text{exp.group}}$ – paw withdrawal latency time in the experimental group; $\text{LT}_{\text{neuropat.group}}$ – paw withdrawal latency time in the oxaliplatin-treated group with neuropathy (assumed to be "0%"); $\text{LT}_{\text{sham.group}}$ – paw withdrawal latency time in the oxaliplatin-treated group (assumed to be "100%").

Statistics

Shapiro–Wilk test was used for data normality assessing. Data of experimental groups were compared to the vehicle treated group using *t*-Student to determine the significance of the difference between the means. The significance level was set at $p \le 0.05$ and $p \le 0.01$.

Results

Induction of cold allodynia in rats by intraperitoneal administration of OXP

Intraperitoneal administration of oxaliplatin at a dose of 4 mg/kg statistically significantlly ($p \le 0.01$ compared to Control group) decreased the paw withdraw latency time in all the experimental groups already by the Day 4 witch decreased gradually up to Day 18 (Fig. 2). Treatment with vehicle alone (Control group) had no effect on mechanical and cold sensitivity and the anumals of the Control group demonstrated a stable paw withdrawal latency throughout the time of the study. At the same time, single oral administrations of Duloxetine (100 mg/kg) induced the marked and statistically significant ($p \le 0.01$ by already the Day 4) increase in paw withdraw latency time compared to Neuropathy group (Figs. 3–5), which validated the used neuropathic model.

Propoxazepam dose-dependent analgesic effect

The analgesic effect of Propoxazepam was observed already from the Day 4 of the developed oxaliplatin-induced peripheral neuropathy (OIPN) (Figs. 3–5) and the statistically significant ($p < 0.05$ compared to the neuropathy group) effect was demonstrated at the dose 1 mg/kg at the Day 4. The 4 and 8 mg/kg doses demonstrated a pronounced analgesic effect ($p < 0.01$ compared to the neuropathy group) lasting up to Day 18 (Fig. 5), although the values did not significantly approach those of the Control group.

Assuming that the maximum analgesic effect (100%) corresponds to the response observed in the Control group (no neuropathy), and the minimum effect (0%) corresponds to the Neuropathic group (oxaliplatin treated), the maximal significant analgesic effect of propoxazepam ranged between 34% and 45%, reaching up to 62% on Day 11 (the Table). In comparison, the reference drug duloxetine initially produced a stronger analgesic effect of approximately 70–75%, but this effect declined rapidly, dropping to 19% shortly thereafter (by 180 min after administration).

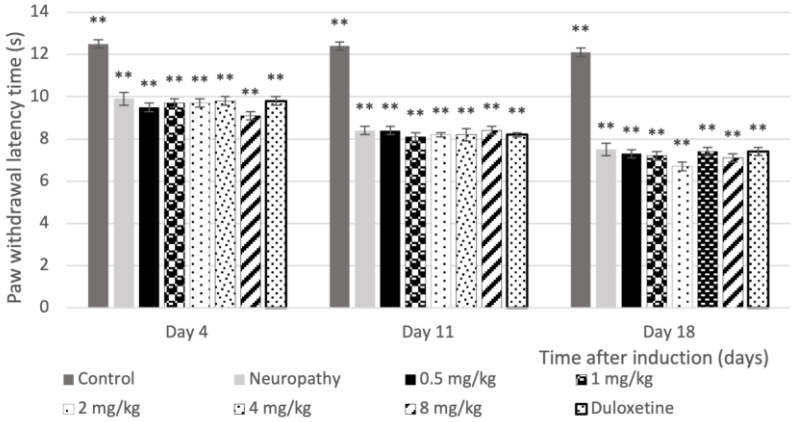

Figure 2: Pretreatment baseline D4, D11 and D18 of rats in the model of oxaliplatin-induced allodynia (rats, $n = 10$; ** – $p \le 0.01$ compared to Control group)

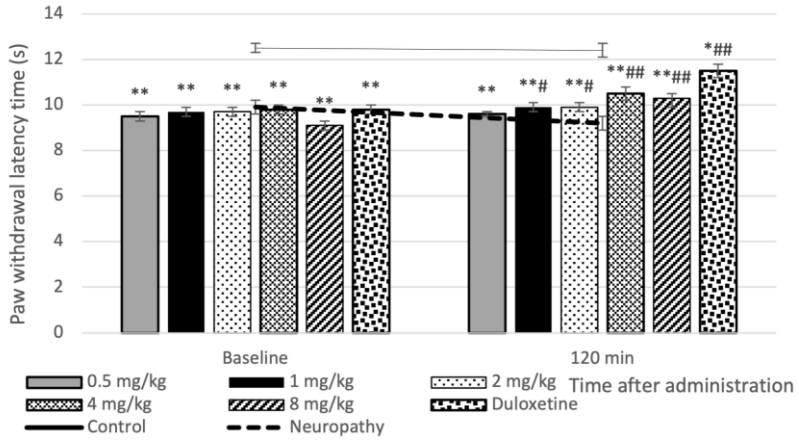

Figure 3: Analgesic effect of different doses of Propoxazepam in the oxaliplatin-induced allodynia model on Day 4 (rats, $n = 10$; 120 min after oral administration; reference drug: duloxetine, 100 mg/kg orally; * – significant at $p \le 0.05$ compared to the Control group, ** – significant at $p \le 0.01$ compared to the Control group; # significant at $p \le 0.05$ compared to the neuropathy group, ## – significant at $p \le 0.01$ compared to the neuropathy group)

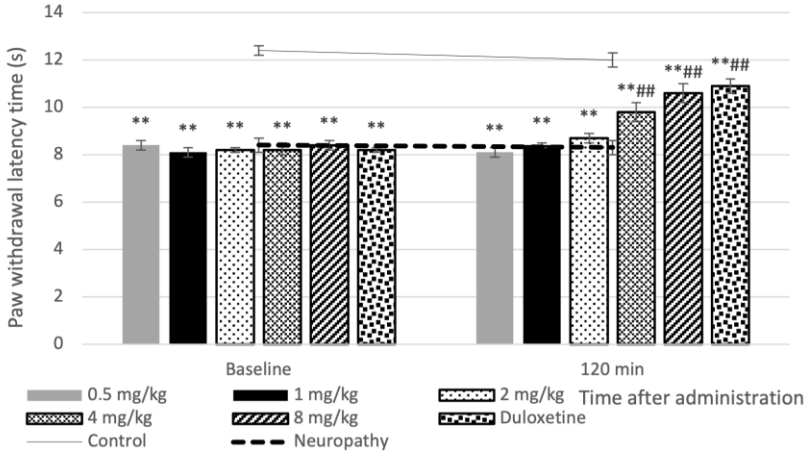

Figure 4: Analgesic effect of different doses of Propoxazepam in the oxaliplatin-induced allodynia model on Day 11 (rats, $n = 10$; 120 min after oral administration; reference drug: duloxetine, 100 mg/kg orally; ** – significant at $p \le 0.01$ compared to the Control group; ## – significant at $p \le 0.01$ compared to the neuropathy group)

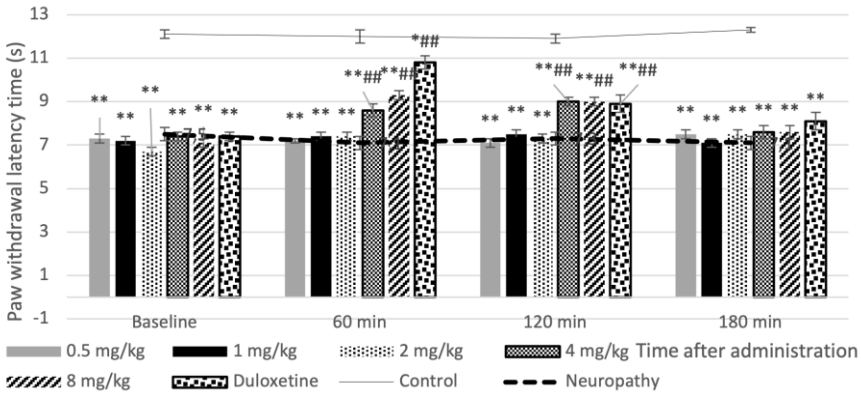

Figure 5: Analgesic effect of different doses of Propoxazepam in the oxaliplatin-induced allodynia model on Day 18 (rats, $n = 10$; 60, 120 and 180 min after oral administration; reference drug: duloxetine, 100 mg/kg orally; ** – significant at $p \le 0.01$ compared to the Control group; ## – significant at $p \le 0.01$ compared to the neuropathy group)

Table: Analgesic effect (in % of maximal effect) of different doses of Propoxazepam in the model of oxaliplatin-induced allodynia ($M \pm m$, $n = 10$)

Exprimental group	Day of oxaliplatin-induced neuropathy development				
	Day 4	Day 11	Day 18		
	120 min	120 min	60 min	120 min	180 min
Control	100 ± 3.2	100 ± 3.4	100 ± 5.5	100 ± 4.7	100 ± 4.4
Neuropathy	0 ± 1.3	0 ± 0.7	0 ± 1.4	0 ± 1.8	0 ± 1.2
0.5 mg/kg	12.5 ± 2	0 ± 1.1	2 ± 0.4	0 ± 0.9	7.7 ± 1.1
1 mg/kg	21.9 ± 3.5	2.7 ± 0.4	6.1 ± 1.2	4.3 ± 0.8	0 ± 1.7
2 mg/kg	21.9 ± 3.5	10.8 ± 1.6$^{\#}$	6.1 ± 1.2$^{\#}$	0 ± 0.7	7.7 ± 1.1$^{\#}$
4 mg/kg	40.6 ± 6.5$^{\#\#}$	40.5 ± 6.2$^{\#\#}$	30.6 ± 6.3$^{\#\#}$	37 ± 6.4$^{\#\#}$	9.6 ± 1.4
8 mg/kg	34.4 ± 5.5$^{\#\#}$	62.2 ± 9.3$^{\#\#}$	44.9 ± 8.8$^{\#\#}$	37 ± 6.4$^{\#\#}$	9.6 ± 1.4
Duloxetine, 100 mg/kg	71.9 ± 11.5$^{\#\#}$	70.3 ± 10.5$^{\#\#}$	75.5 ± 14.8$^{\#\#}$	34.8 ± 6.1$^{\#\#}$	19.2 ± 2.8

Notes. # – statistically significant at $p \le 0.05$ compared to the Neuropathy group; ## – statistically significant at $p \le 0.01$ compared to the Neuropathy group

Time-dependent analgesic effect of propoxazepam on Day 18

In the oxaliplatin-induced allodynia model, Propoxazepam produced its most pronounced analgesic effect on Day 18 at 60 and 120 minutes after oral administration. A significant increase ($p < 0.01$ vs. the neuropathy group) in paw withdrawal latency was observed for the 4 and 8 mg/kg doses (see Fig. 5), which then gradually decreased to control group levels by 180 minutes post-administration.

Discussion

OIPN remains a major clinical challenge, significantly limiting the quality of life of cancer patients and often necessitating dose reduction or discontinuation of oxaliplatin-based chemotherapy regimens. Despite numerous preclinical and clinical efforts, OIPN is currently not preventable, and therapeutic strategies are primarily palliative [16, 17]. The National Cancer Institute's Symptom Management and Health-Related Quality of Life Steering Committee has highlighted OIPN as a high-priority target for translational pain research [16], yet current guidelines from the American Society of Clinical Oncology (ASCO) recommend only duloxetine with moderate confidence for the treatment of chemotherapy-induced peripheral neuropathy. Compared to duloxetine – which has demonstrated clinically meaningful pain reduction in platinum- and taxane-induced CIPN (NNT (number need to treat) ≈9 for ≥50% pain relief; moderate-to-large effect sizes) and is currently the only ASCO-recommended treatment [18] – other agents show more variable results. Venlafaxine also improved neuropathic symptoms in randomized trials, inclu-

ding in oxaliplatin-induced neurotoxicity, though its efficacy appears slightly inferior to duloxetine [19]. Pregabalin and gabapentin have yielded inconsistent findings: while a meta-analysis found limited benefit in prevention and inconsistent effects in treatment trials [20], some randomized control trials and case series report significant pain alleviation with pregabalin, and occasionally show it outperforming gabapentin [19].

The study utilized a repeated OXP administration protocol to induce chronic peripheral neuropathy in rats, which is a well-validated preclinical model for chemotherapy-induced neuropathic pain. OXP-induced allodynia is believed to result from mitochondrial dysfunction, oxidative stress, and alterations in voltage-gated ion channels, leading to increased excitability of peripheral sensory neurons. Cold allodynia, a hallmark of OXP neurotoxicity, was assessed using the paw immersion test at 10 °C, allowing for quantifiable measurement of sensory hypersensitivity.

Our results demonstrate that propoxazepam, a novel 1,4-benzodiazepine derivative, exerts significant dose-dependent antiallodynic effects in a rat model of OIPN. Repeated intraperitoneal administration of oxaliplatin (4 mg/kg, twice a week) over 3 weeks induced cold allodynia, as evidenced by a sustained decrease in paw withdrawal latency (PWL). Treatment with propoxazepam at 4 and 8 mg/kg significantly increased PWL on Days 4, 11, and 18 post-oxaliplatin administration ($p \leq 0.01$), with maximum efficacy observed 120 minutes post-dose on Day 11. Lower doses (0.5–2 mg/kg) did not produce significant effects, indicating a clear therapeutic threshold.

Our findings build on previous work, where propoxazepam demonstrated antinociceptive activity in osteoarthritis [21], with a mean effective dose (ED_{50}) of ~33.8 mg/kg. The current study shows that much lower doses (4–8 mg/kg) are effective in a chronic neuropathic pain model, suggesting that different pain mechanisms may be involved and that propoxazepam's efficacy profile may be selectively enhanced in neuropathic conditions. The effective dose range in this study (4–8 mg/kg) corresponds approximately to 35–70 mg in human equivalent dose (HED), suggesting a feasible therapeutic window for clinical use. Though it has to be mentioned that due to the specieses difference the lower doses can be effective. Also, future studies will be necessary to evaluate the sustained efficacy and potential for tolerance development during chronic administration, particularly given the fluctuating effect observed after single-dose treatment.

The mechanisms underlying propoxazepam's analgesic effects may be multifactorial. First, previous studies confirmed that propoxazepam possesses anti-inflammatory properties, as demonstrated in carrageenan-, bradykinin-, and formalin-induced inflammation models [22]. Given the important role of neuroinflammation and cytokine release in OIPN pathogenesis [23], these anti-inflammatory effects may contribute to reduced peripheral and central sensitization. Second, propoxazepam modulates GABAergic neurotransmission via allosteric interaction with the GABAA receptor complex [24]. Importantly, in a model of GABA-deficient seizures induced by thiosemicarbazide, propoxazepam showed antagonistic activity, suggesting possible upregulation or enhanced activity of glutamate decarboxylase, the key enzyme in GABA synthesis. In the context of OIPN, previous studies have shown decreased GABA levels in the dorsal horn of the spinal cord during neuropathic pain [25]. Unlike duloxetine, which acts through monoaminergic pathways, propoxazepam's engagement with inhibitory neurotransmitter systems may provide a broader inhibition of central sensitization. Thus, restoring inhibitory tone via GABAergic potentiation may alleviate neuropathic symptoms. Finally, glycinergic transmission may also play a role. Preliminary pharmacological profiling suggests that propoxazepam interacts not only with GABAA but also with glycine-sensitive receptors, which are implicated in the modulation of nociceptive transmission. This dual mechanism of central inhibition may underlie the compound's pronounced antiallodynic effect in our OIPN model.

Despite these promising results, several limitations merit discussion. The reliance on a single modality of pain assessment (cold stimulus) may not fully represent the complexity of neuropathic pain phenotypes and additional assessments, such as mechanical and heat sensitivity, would provide a more comprehensive pain phenotype. Oral administration of Propoxazepam introduces potential variability due to interindividual differences in absorption and metabolism. Furthermore, although duloxetine was included as a positive control, the study would benefit from comparison with additional reference compounds to better contextualize the efficacy of the test agent. Also, mechanistic insights remain indirect; future studies incorporating receptor antagonists, immunohistochemical analyses, or genetic models could better elucidate the molecular pathways involved.

Conclusions

In conclusion, our findings support Propoxazepam as a promising candidate for the treatment of OIPN. Its combined anti-inflammatory and GABAergic/glycinergic modulatory actions, coupled with a favorable safety profile demonstrated in Phase I trials [12], position it as a novel analgesic agent worthy of further preclinical and clinical development. Considering the absence of effective preventive or curative therapies for OIPN, Propoxazepam offers a potentially valuable addition to the limited pharmacological armamentarium available for chemotherapy-induced neuropathic pain.

Interests Disclosure

A.S. Reder reported to been employee of SLC "Interchem", the financial sponsor of this study. The authors declare that this financial support did not influence the study design, data collection, analysis, interpretation, or manuscript writing.

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АНТИГІПЕРАЛГЕЗИВНА АКТИВНІСТЬ ПРОПОКСАЗЕПАМУ ПРИ ХОЛОДОВІЙ АЛОДИНІЇ, ІНДУКОВАНІЙ ОКСАЛІПЛАТИНОМ, У ЩУРІВ

Проблематика. Оксаліплатин (OXP), хіміотерапевтична сполука платини третього покоління, широко використовується для лікування метастатичного колоректального раку. Однак його клінічна корисність обмежена периферичною нейропатією (OIPN), індукованою оксаліплатином, дозозалежним і часто стійким побічним ефектом, що характеризується сенсорною дисфункцією, такою як холодова алодинія. Сучасні фармакологічні можливості лікування OIPN обмежені, і дулоксетин є єдиним препаратом, рекомендованим із помірною впевненістю клінічними настановами. Терміново потрібні нові анальгетики з альтернативними механізмами дії.

Мета. Оцінити антигіпералгетичний (знеболювальний) ефект пропоксазепаму, нового похідного бензодіазепіну з відомою ГАМКергічною та гліцинергічною активністю, на моделі OXP-індукованої периферичної нейропатії в щурів.

Методика реалізації. Хронічну периферичну нейропатію індукували в самців щурів Sprague–Dawley шляхом повторних внутрішньочеревних ін’єкцій OXP (4 мг/кг двічі на тиждень протягом 3-х тижнів). Холодову алодинію оцінювали за допомогою тесту занурення лапи при 10 °C. Щури отримували одноразово перорально дозу пропоксазепаму (0,5–8 мг/кг) або дулоксетину (100 мг/кг) на 4-, 11- та 18-й дні, при цьому латентність відведення лапи (PWL) вимірювали через 60, 120 та 180 хв після введення. Дані аналізували за допомогою *t*-критерію Стьюдента з $p \leq 0{,}05$ як порогом статистичної значущості.

Результати. Введення OXP значно зменшило PWL, що свідчить про розвиток холодової алодинії. Пропоксазепам продемонстрував дозозалежний знеболювальний ефект, починаючи вже з 4-го дня. Значне збільшення PWL спостерігалося за доз 4 і 8 мг/кг, із максимальним ефектом на 11-й день (до 62 % відносно контролю). Хоча дулоксетин викликав сильніший початковий ефект (~70–75 %), він швидко зменшився до 19 % через 180 хв. Нижчі дози (0,5–2 мг/кг) пропоксазепаму не показали статистично значущого ефекту. Знеболювальний ефект пропоксазепаму досяг піку через 120 хв після введення та зменшувався через 180 хв.

Висновки. Пропоксазепам ефективно зменшує холодову алодинію у щурів на моделі OIPN дозо- та часозалежним чином. Його знеболювальна ефективність, опосередкована ГАМКергічною та гліцинергічною модуляцією та підкріплена протизапальними властивостями, робить його перспективним кандидатом для лікування нейропатичного болю, викликаного хіміотерапією. З урахуванням його сприятливого профілю безпеки та нового механізму дії пропоксазепам заслуговує на подальше дослідження в клінічних випробуваннях.

Ключові слова: індукована оксаліплатином периферична нейропатія; індукований хіміотерапією нейропатичний біль; пропоксазепам; алодинія; ГАМКергічна модуляція; протизапальна дія; доклінічна модель.