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Short Communication

Mexiletine Reverses Oxaliplatin-Induced Neuropathic Pain in Rats

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Abstract. Oxaliplatin is a platinum-based chemotherapy drug characterized by the development of acute and chronic peripheral neuropathies. Mexiletine, an orally available Na^+-channel blocker, has widely been used in patients with chronic painful diabetic neuropathy. In the present study, we examined the effect of mexiletine on oxaliplatin-induced neuropathic pain in rats. Mexiletine (100, but not 10 and 30, mg/kg, p.o.) completely reversed both mechanical allodynia and cold hyperalgesia induced by oxaliplatin (4 mg/kg, i.p., twice a week). Lidocaine (30, but not 3 and 10, mg/kg, i.p.) also significantly relieved both pain behaviors. These results suggest that mexiletine may be effective in relieving the oxaliplatin-induced neuropathic pain clinically.

Keywords: mexiletine, oxaliplatin, neuropathic pain

Oxaliplatin, a third-generation platinum-based chemotherapy drug, is a key drug in the treatment of colorectal cancer. Unlike other platinum compounds, oxaliplatin induces an acute painful neuropathy, which appears soon after administration (1). The patients suffer from extremity and perioral paresthesias and in particular from severe cold hypersensitivity. After multiple cycles the patients develop a clinically different peripheral neuropathy that is characterized by a sensory axonal nerve damage closely resembling that induced by cisplatin. This chronic neuropathy can become very disabling and is, in fact, often a dose-limiting toxicity. For this reason, peripheral neuropathy associated with the administration of oxaliplatin is a major clinical problem in chemotherapy.

Mexiletine, an orally available Na^+-channel blocker, has been reported to be effective on chronic painful diabetic neuropathy in clinical trial (2), and it is prescribed for treating patients with these symptoms. In animal models, acute administration of mexiletine has been reported to relieve the mechanical allodynia in rats treated with vincristine, a chemotherapeutic agent, and streptozotocin-induced diabetic rats (3, 4). No experimental study, however, has been conducted to date to determine the effect of mexiletine on pain behavior in a rat model of oxaliplatin-induced neuropathy. In the present study, we examined the effect of mexiletine on the oxaliplatin-induced mechanical allodynia and cold hyperalgesia after the development of neuropathy in rats.

Male Sprague-Dawley rats weighing 200 – 250 g (Kyudo Co., Saga) were used in the present study. Rats were housed in groups of four to five per cage, with lights on from 08:00 to 20:00 h. Animals had free access to food and water in their home cages. All experiments were approved by the Experimental Animal Care and Use Committee of Kyushu University according to the National Institutes of Health guidelines, and we followed IASP Committee for Research and Ethical Issues guidelines for animal research (5).

Oxaliplatin (Elplat®) was obtained from Yakult Co., Ltd. (Tokyo). Mexiletine hydrochloride was purchased from Sigma-Aldrich, Inc. (St. Louis, MO, USA). Lidocaine (Xylocaine® 2% for intravenous injection) was obtained from Astra Zeneca K.K. (Osaka). Oxaliplatin was dissolved in 5% glucose solution. The vehicle-treated rats were injected with 5% glucose solution. Oxaliplatin (4 mg/kg) or vehicle was injected intraperitoneally (i.p.) twice a week for 4 weeks (Days 1, 2, 8, 9, 15, 16, 22, and 23). Mexiletine was dissolved in sterile water and administered orally. Lidocaine was dissolved in saline and administered i.p. The doses of these drugs were chosen based on previous reports (3, 4, 6). Behavioral tests were performed blindly with respect to drug administration.

The mechanical allodynia was assessed by the von Frey test. Rats were placed in a clear plastic box

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(20 × 17 × 13 cm) with a wire mesh floor and allowed to habituate for 30 min prior to testing. von Frey filaments (The Touch Test Sensory Evaluator Set; Linton Instrumentation, Norfolk, UK) of 1 – 15 g bending force were applied to the midplantar skin of each hind paw with each application held for 6 s. Fifty percent paw withdrawal thresholds were determined by up-down methods (7).

The cold hyperalgesia was assessed by the acetone test described by Flatters and Bennett (8). Rats were placed in a clear plastic box (20 × 17 × 13 cm) with a wire mesh floor and allowed to habituate for 30 min prior to testing. A 50-μL aliquot of acetone (Wako Pure Chemical, Ltd., Osaka) was sprayed onto the plantar skin of each hind paw three times with a Micro Sprayer® (Penn Century Inc., Philadelphia, PA, USA), and the number of withdrawal responses was counted for 40 s from the start of the acetone spray.

We confirmed the incidence of mechanical allodynia and cold hyperalgesia on Days 24 and 3, respectively. We carried out the drug evaluation on the next day. In the case of mexiletine, the von Frey and acetone tests were performed immediately before (0 min) and at 60, 120, and 180 min after administration. In the case of lidocaine, the von Frey and acetone tests were performed immediately before (0 min) and at 30, 60, and 120 min after administration.

Values were expressed as the mean ± S.E.M. The values were analyzed by Student's *t*-test or one-way analysis of variance (ANOVA) followed by the Tukey-Kramer's post-hoc test (StatView; Abacus Concepts, Berkeley, CA, USA) to determine differences among the groups. A probability level of $P < 0.05$ was accepted as statistically significant.

Oxaliplatin (4 mg/kg, i.p.) significantly reduced the 50% paw withdrawal threshold compared with the vehicle in the von Frey test on Day 24 ($P < 0.01$, Figs. 1A and 2A). Oxaliplatin at the same dose significantly increased the number of withdrawal responses compared with vehicle in the acetone test on Day 3 ($P < 0.01$, Figs. 1B and 2B). The incidence of mechanical allodynia and cold hyperalgesia was 92% and 81%, respectively. Acute administration of mexiletine (100 mg/kg, p.o.) completely reversed the reduction of 50% paw withdrawal threshold by oxaliplatin at 60 min after administration in the von Frey test ($P < 0.01$, Fig. 1A). Moreover, mexiletine (100 mg/kg, p.o.) completely reversed the increase of number of withdrawal responses by oxaliplatin at 60 and 120 min after administration in the acetone test ($P < 0.05$, Fig. 1B). These effects of mexiletine disappeared by 180 min after administration. Similarly, acute administration of lidocaine (30 mg/kg, i.p.) significantly inhibited the reduction of 50% paw withdrawal threshold by oxaliplatin at 30 min after administration in the von Frey test ($P < 0.05$, Fig. 2A). Moreover, lidocaine (3, 10, and 30 mg/kg, i.p.) significantly inhibited the increase of number of withdrawal responses by oxaliplatin at 30 min after administration in the acetone test ($P < 0.01$, Fig. 2B). These effects of lidocaine had disappeared by 120 min after administration. In addition, mexiletine (100 mg/kg, p.o.) and lidocaine (30 mg/kg, i.p.) had no effect on the 50% paw withdrawal threshold in the von Frey test and the number of withdrawal responses in the acetone test in intact rats (data not shown).

Our data in this study revealed that acute administration of mexiletine completely reversed both mechanical

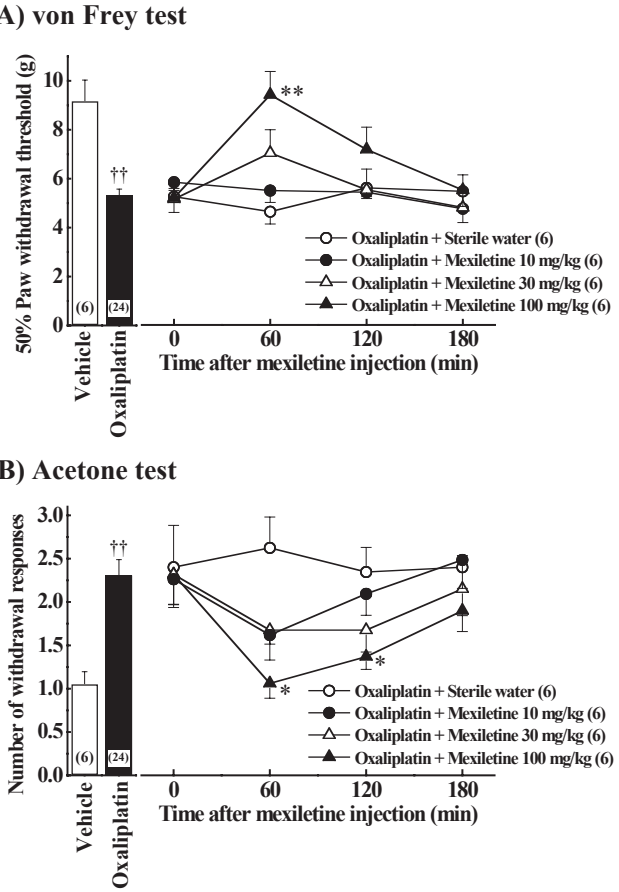

Fig. 1. Effect of mexiletine on mechanical allodynia in the von Frey test (A) and cold hyperalgesia in the acetone test (B) in oxaliplatin-treated rats. Oxaliplatin (4 mg/kg) was administered i.p. twice a week for 4 weeks (Days 1, 2, 8, 9, 15, 16, 22, and 23). We confirmed the incidence of mechanical allodynia and cold hyperalgesia on Days 24 and 3, respectively. We carried out the drug evaluation on the next day. Mexiletine was administered orally. The von Frey and acetone tests were performed immediately before (0 min) and at 60, 120, and 180 min after administration. Number of animals is shown in parenthesis. Values are expressed as the mean ± S.E.M. $^{\dagger\dagger}P < 0.01$, compared with vehicle; $^{*}P < 0.05$, $^{**}P < 0.01$, compared with oxaliplatin alone.

allodynia and cold hyperalgesia induced by oxaliplatin. Mexiletine has widely been used in the treatment of chronic painful diabetic neuropathy. It has also been reported that mexiletine produced no major adverse events and was superior to placebo to relieve neuropathic pain in controlled clinical trials (9). Taken together, the present results suggest that mexiletine is useful as a therapeutic drug for oxaliplatin-induced neuropathic pain if it is used with caution as needs arise.

Similarly, lidocaine, another Na^+-channel blocker, significantly relieved both pain behaviors. Ling and colleagues (10) have reported that single intravenous administration of lidocaine relieved the oxaliplatin-induced cold allodynia in rats. Our finding is essentially consistent with the previous finding. Moreover, we found that mexiletine and lidocaine at the effective dose had no effect on pain behavior in intact rats. Therefore, the ameliorative effects of mexiletine and lidocaine were not attributable to non-specific sedative effects or a deficit of motor function. These findings suggest that the reduced pain behavior by Na^+-channel blockers reflects a therapeutic effect on oxaliplatin-induced neuropathic pain. Asano et al. (11) reported that mexiletine at the dose of 20 mg/kg did not affect pain-related responses in normal mice. They also indicated that activation of the descending β-endorphinergic system is involved in the antinociceptive effect of mexiletine. The β-endorphinergic system is generally accepted as an antinociceptive system, which selectively has antinociceptive effect on painful conditions. In the in vitro studies, application of oxaliplatin to dorsal root ganglion (DRG) neurons resulted in an increase of the Na^+ current (12). Interestingly, the effect of oxaliplatin is antagonized by the Na^+-channel blocker carbamazepine (12). Therefore, mexiletine and lidocaine exhibit effective relief on the oxaliplatin-induced neuropathic pain, but may be ineffective in reducing pain-related behaviors in intact rats.

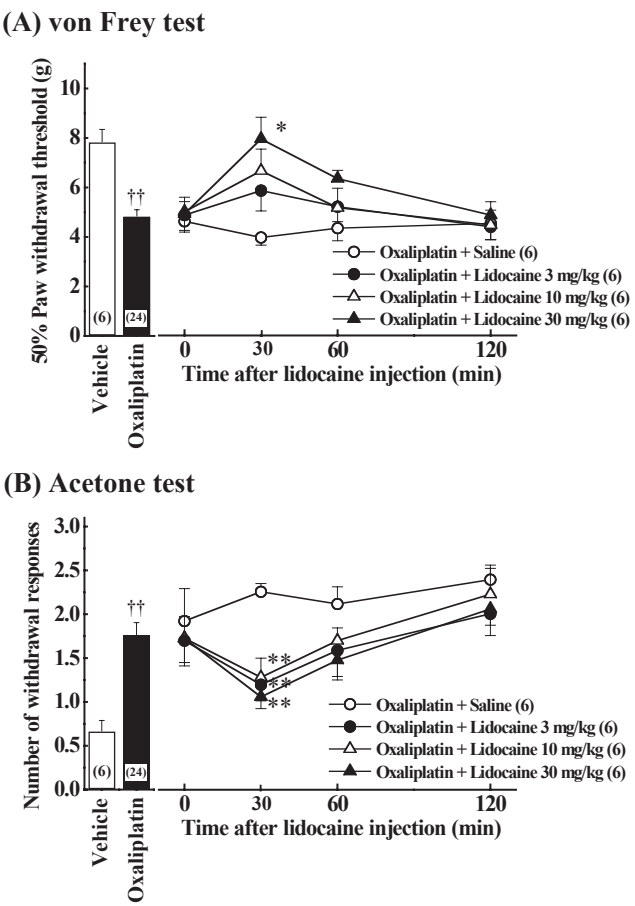

Fig. 2. Effect of lidocaine on mechanical allodynia in the von Frey test (A) and cold hyperalgesia in the acetone test (B) in oxaliplatin-treated rats. Oxaliplatin (4 mg/kg) was administered i.p. twice a week for 4 weeks (Days 1, 2, 8, 9, 15, 16, 22, and 23). We confirmed the incidence of mechanical allodynia and cold hyperalgesia on Days 24 and 3, respectively. We carried out the drug evaluation on the next day. Lidocaine was administered i.p. The von Frey and acetone tests were performed immediately before (0 min) and at 30, 60, and 120 min after administration. Number of animals is shown in parenthesis. Values are expressed as the mean ± S.E.M. $^{\dagger\dagger}P < 0.01$, compared with vehicle; $^{*}P < 0.05$, $^{**}P < 0.01$, compared with oxaliplatin alone.

In the present study, mexiletine reversed mechanical allodynia and cold hyperalgesia to the same degree. Lidocaine also relieved both pain-related behaviors. Recently, we demonstrated that oxalate and platinum metabolite are involved in the cold hyperalgesia and mechanical allodynia, respectively (6). Oxalate alters voltage-gated Na^+ channels (13) and its effect may be involved in the cold hyperalgesia. On the other hand, the mechanical allodynia may be due to the peripheral nerve injury by platinum metabolite. The change in the expression of Na^+ channels is observed after peripheral nerve injury of the rat DRG neurons (14). Taken together with these findings, the present results suggest that mexiletine and lidocaine may reverse the mechanical allodynia and cold hyperalgesia by inhibiting the hyperexcitability of Na^+ channels.

In conclusion, the study presented here demonstrates, for the first time, that acute administration of mexiletine reverses both mechanical allodynia and cold hyperalgesia induced by oxaliplatin in rats.

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