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 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

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Mexiletine, an orally available Na+-channel blocker, has been reported to be effective on chronic painful diabetic neuropathy. In the present study, we examined the effect of mexiletine on 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
(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.

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, 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
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 therapeu-
tic 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 ad-
ministration of lidocaine relieved the oxaliplatin-induced cold allodynia in rats. Our finding is essentially consist-
tent with the previous finding. Moreover, we found that mexiletine and lidocaine at the effective dose had no ef-
flect on pain behavior in intact rats. Therefore, the ame-
liorative effects of mexiletine and lidocaine were not at-
tributable 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 therapeu-
tic 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 descend-
ing β-endorphinergic system is involved in the antinoci-
ceptive effect of mexiletine. The β-endorphinergic system
is generally accepted as an antinociceptive system, which selectivity has antinociceptive effect on painful condi-
tions. In the in vitro studies, application of oxaliplatin to dorsal root ganglion (DRG) neurons resulted in an in-
crease 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 neuro-
pathic pain, but may be ineffective in reducing pain-re-
lated behaviors in intact rats.

In the present study, mexiletine reversed mechanical
todynia and cold hyperalgesia to the same degree. Li-
docaine also relieved both pain-related behaviors. Re-
cently, we demonstrated that oxalate and platinum me-
tabolite are involved in the cold hyperalgesia and me-
chanical 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 expres-
sion 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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