Effects of the Prostaglandin E<sub>1</sub> Analog Limaprost on Mechanical Allodynia Caused by Chemotherapeutic Agents in Mice

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Abstract. This study examined in mice whether limaprost, a prostaglandin E<sub>1</sub> analog, would relieve allodynia induced by chemotherapeutic agents. Single intraperitoneal injections of paclitaxel, oxaliplatin, and vincristine sulfate induced and gradually increased mechanical allodynia. Repeated administration of limaprost alfadex inhibited the late, but not early, phase of mechanical allodynia induced by paclitaxel and oxaliplatin, but not vincristine. Paclitaxel and oxaliplatin, but not vincristine, gradually decreased peripheral blood flow, which was prevented by limaprost. These results suggest that limaprost is effective against mechanical allodynia induced by paclitaxel and oxaliplatin, which may be due to inhibition of the decrease in peripheral blood flow.

Keywords: limaprost, chemotherapeutic agent–induced mechanical allodynia, peripheral blood flow

Chemotherapy-induced pain is a dose-limiting side-effect of anti-cancer drugs, including the vinca alkaloid vincristine, the taxane paclitaxel, and the platinum-based drug oxaliplatin. Many patients receiving the chemotherapeutic drugs experience pain including mechanical allodynia, which first appears in the feet or simultaneously in the fingers and toes (1). Chemotherapy-induced pain not only decreases quality of life but also interrupts cancer therapy. Therefore, the control of pain is important, but little is known about the pain mechanisms and there are few efficacious analgesics. In animal experiments, pain has been generally developed by repeated administration of chemotherapy drugs for 1 – 2 weeks (2, 3), but chemotherapy drugs are clinically administered once in one treatment course of 1 – 2 weeks. In this study, therefore, we compared mechanical allodynia after single administration of paclitaxel, oxaliplatin, and vincristine at the clinically recommended dose.

The effects of some agents, for example, gabapentin, on pain induced by chemotherapeutic agents have been studied using animal models (3 – 5). Regarding the prevention of chemotherapy-induced neuropathy, intramuscular gene transfer of vascular endothelial growth factor has been shown to prevent decreases in nerve blood flow and the number of vasa nervorum induced by paclitaxel (6). The findings raise the possibility that the increase of nerve blood flow alleviates pain induced by chemotherapeutic agents. In this context, limaprost, an orally active prostaglandin E<sub>1</sub> analog, suppresses pain-associated claudication induced by spinal stenosis (7) and thermal hyperesthesia induced by constriction injury to the sciatic nerve in rats (8). In the present study, therefore, we tested the effects of limaprost on mechanical allodynia after administration of paclitaxel, oxaliplatin, and vincristine.

Male C57BL/6 mice (6-week-old at the start of experiment; Japan SLC, Shizuoka) were used. Animals were housed 4 – 6 per cage in a room under controlled temperature (22 ± 1°C), humidity (55 ± 10%), and light (lights on 07:00 – 19:00 h). Food and water were freely available. Procedures for animal experiments were approved by the Committee for Animal Experiments at University of Toyama and were conducted in accordance with the animal experiment guidelines of the Japanese Pharmacological Society.

Paclitaxel, oxaliplatin, and vincristine sulfate (all from Sigma, St. Louis, MO, USA) were dissolved in 10%
cremophor® EL (Sigma), saline, and 5% glucose, respectively, and were injected intraperitoneally. Limaprost alfadex, a gift from Ono Pharmaceutical Co., Ltd. (Osaka), was dissolved in tap water and administered orally everyday after chemotherapeutic drug injection. The dose (0.3 mg/kg) of limaprost alfadex was selected from the published literature on the effect of limaprost on spinal stenosis-induced walking dysfunction in rodents (7).

Mechanical allodynia of the hind paw was assessed as described (9). After an acclimation period of at least 30 min, von Frey filament with the bending force of 0.69 mN was pressed perpendicularly against the plantar skin and was held for 1 – 3 s with it slightly buckled. Responses to the stimulus were ranked as follows: 0, no response; 1, lifting of the hind paw and 2, flinching or licking of the hind paw. The stimulation of the same intensity was applied six times to each hind paw at intervals of several seconds and the average served as a response score.

Blood flow of the dorsal part of the proximal tail was measured under pentobarbital (50 mg/kg) anesthesia with a laser Doppler flowmeter (ALF21N; Advance Co., Ltd., Tokyo). Measurement was repeated ten times every 30 s just before limaprost administration and the average served as blood flow.

Data are presented as means and S.E.M. Results were analyzed with Student’s t-test or the Mann-Whitney rank sum test; *P<0.05 was considered significant.

In the first series of experiments, we examined the intensity and time-course of mechanical allodynia after the recommended clinical doses of three chemotherapeutic agents. The recommended dose of paclitaxel is 210 mg/m² body surface area (package insert of Taxol®). If body height and weight are 170 cm and 60 kg, respectively, body surface area is 1.69 m², according to Du Bois’s formula for calculating the body surface area. Therefore, the amount is 355 mg and the dose is 5.9 mg/kg. Thus, paclitaxel was administered at a dose of 5 mg/kg. A recommended dose of oxaliplatin is 85 mg/m² body surface area (package insert of Elplat®). If body surface area is 1.69 m², the amount is 144 mg and the dose is 2.4 mg/kg. Thus, oxaliplatin was administered at a dose of 3 mg/kg. Since recommended doses of vincristine sulfate are 0.02 – 0.1 mg/kg (package insert of Oncovin®), it was administered at a dose of 0.1 mg/kg.

Mice given a single injection of paclitaxel, oxaliplatin, and vincristine developed mechanical allodynia, which was evident on day 3 and peaked 10 – 14 days after injections (Fig. 1). Peak allodynia was not prominently different between these chemotherapeutic agents (Fig. 1). Allodynia almost subsided by 40, 25, and 35 days after injections of paclitaxel, oxaliplatin, and vincristine, respectively (Fig. 1).

Repeated prophylactic administration of limaprost alfadex (0.3 mg/kg) did not affect the initial development of mechanical allodynia induced by paclitaxel and oxaliplatin, but it significantly inhibited the allodynia from day 4 – 6, as compared to vehicle (Fig. 2: A and B). Limaprost at the same dose did not affect allodynia induced by vincristine until at least day 15 after the start of administration (Fig. 2C).

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Single injection of paclitaxel and oxaliplatin gradually decreased peripheral blood flow, which was prevented by repeated administration of limaprost alfadex (0.3 mg/kg) (Fig. 3: A and B). The peripheral blood flow had a tendency to decrease after vincristine administration, which was not affected by limaprost at the same dose (Fig. 3C).

Single injections of three kinds of chemotherapeutic drugs induced mechanical allodynia at clinically recom-
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Recommended doses. Allodynia was similar to each other in the peak intensity and spontaneously decreased, although the time-course was different between these agents. The results show that these agents cause comparable mechanical allodynia, which gradually increases over about 10 days and then spontaneously abates without additional dosing.

The time-course of mechanical allodynia after paclitaxel (5 mg/kg) is similar to another group’s report, in which paclitaxel (4 mg/kg) caused mechanical hypersensitivity with a peak around 2 weeks and had a 4-week duration (5). The time-course of mechanical hypersensitivity, including allodynia, may not significantly vary after different doses of paclitaxel (10). Single intravenous injection of oxaliplatin (0.5 – 5 mg/kg) in rats has been shown to cause mechanical hypersensitivity that is rapid in onset and present even 3 weeks after; the duration was not dependent on the dose (11). In this study, single intraperitoneal injection of oxaliplatin (5 mg/kg) caused gradual increase in mechanical allodynia, which almost subsided by 3 weeks after. Differences in the time-course may be partly due to differences in the route of administration and animals. Vincristine has been generally administered daily or every two days at doses of 0.05 – 0.2 mg/kg in animal experiments. Five intravenous injections of vincristine (0.05 – 0.15 mg/kg) every two days for 9 days gradually increases mechanical hyperalgesia, which peaks around 2 weeks after the start of administration and then gradually subsides (12). The time-course is similar to the present study, in which animals were given single injection of vincristine (0.1 mg/kg).

Repeated administration of limaprost significantly inhibited the late phase of mechanical allodynia induced by paclitaxel and oxaliplatin. Paclitaxel and oxaliplatin gradually decreased peripheral blood flow. Similarly, paclitaxel chronically decreases blood flow in the sciatic nerve (6). The results that limaprost significantly inhibited blood flow decrease and mechanical allodynia at the late phase suggest that a decrease in peripheral blood flow is partly involved in this allodynia. Limaprost has pharmacological properties similar to prostaglandin E₁, acting on IP and EP₁,₄ prostanoid receptors (13), which may be responsible for the inhibition of blood flow decrease and platelet aggregation (7, 14). Limaprost increases the reduced blood flow in the stenosed area, but not normal blood flow (7). Paclitaxel and oxaliplatin have a risk of thrombosis (package inserts of Taxol and Elplat) and paclitaxel inhibits angiogenesis in the peripheral tissue (15). Thus,
an ischemic pain mechanism may be involved in the allodynia induced by paclitaxel and oxaliplatin. However, further experiments are needed to address this issue.

Limaprost did not inhibit the early phase of allodynia induced by paclitaxel and oxaliplatin, suggesting that changes in peripheral blood flow are not involved in this allodynia. In this context, paclitaxel and oxaliplatin exert acute effects on primary afferents to elicit hyperexcitability (1), which may be involved in the early phase of allodynia.

Vincristine did not markedly decrease peripheral blood flow, which was not affected by limaprost. This is consistent with previous reports that vincristine acutely decreases blood flow in the tumor, but not in the skin and muscle, and the effect almost disappears by 24 h (16). Vincristine also did not chronically affect angiogenesis in the peripheral tissue (15). It is suggested that blood flow decrease is not involved in vincristine-induced allodynia. Vincristine and paclitaxel chronically cause spontaneous activity of primary afferents (2). Thus, blood flow–independent mechanisms might be involved in allodynia induced by these chemotherapy agents.

In conclusion, the present results suggest that limaprost is effective against neuropathic allodynia caused by paclitaxel and oxaliplatin and that remedies against chemotherapy-induced allodynia should be selected depending on chemotherapeutic agent used.

References