Pharmacological characterization of paclitaxel-induced neuropathic pain in rats

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Introduction

Peripheral neuropathic pain is a well-documented side effect of chemotherapy in 25-35% of cancer patients undergoing treatment.

Paclitaxel (Taxol®) is a widely-used anticancer agent for treatment of ovarian, breast, lung, head, and neck cancer. There are two well-documented side effects of this treatment: myelosuppression and peripheral sensory neurotoxicity. These side effects often necessitate the use of suboptimal doses (dose-liming therapy), or even a complete suspension of treatment.

In patients, paclitaxel-induced peripheral neuropathy is characterized by degeneration of sensory axons and is clinically manifested as numbness, pain, and thermoesthesia in hands and feet.

This poses a growing, significant clinical problem as the average life span increases and cancer becomes more prevalent. Additionally, in some cases this neuropathy may become a chronic problem even after cessation of treatment.

Hypothesis

Paclitaxel-induced neuropathic pain in rats can be attenuated by gabapentin, antidepressants, and opioids.

Methods

Animals: Male Sprague Dawley rats from Harlan Laboratories were used in these studies. Upon receipt, rats were assigned unique identification numbers (tail marked) and group housed with 3 rats per cage in polycarbonate cages with micro-isolator filter tops. All rats were examined, handled, and weighed prior to initiation of the study to assure adequate health and suitability. During the course of the study, 13/12 light-dark cycles were maintained. The room temperature was maintained between 20° and 23° with a relative humidity maintained around 50%. Chow and water were provided ad libitum for the duration of the study. In each test, animals were randomly assigned across treatment groups. Animals were not disturbed between test days.

Treatment: Rats received an intraperitoneal injection of paclitaxel (2 mg/kg) on days 1, 4, and 8. Paclitaxel-induced neuropathy was assessed using von Frey filaments. The following compounds were assessed, with all compounds administered at an injection volume of 0.5 ml/kg: gabapentin (50 and 100 mg/kg) was dissolved in 0.5% carboxymethyl cellulose (CMC) and administered (i.p.) 30 minutes prior to testing. Tramadol (30, 100, and 150 mg/kg) was dissolved in 0.5% CMC and administered (p.o.) 60 minutes prior to testing. Morphine (2, 5, and 10 mg/kg), p.o., and antipodaline (3, 10, and 30 mg/kg) were dissolved in sterile injectable saline and administered 60 minutes prior to testing.

Von Frey Testing: Withdrawal from a mechanical stimulus was measured by applying von Frey (VF) filaments of ascending bending force to the plantar surface of the hind paws (ipsilateral and contralateral). A positive response was defined as withdrawal from the von Frey filament. Conformation of the paw withdrawal threshold (PWT) was tested by assessing the response to the filament above and below the withdrawal response. Rats were brought to the experimental room and allowed to habituate to the room for one hour prior to testing, and acclimated to the observation chambers for 15 minutes prior to 15 minutes prior to taking all PWT measurements.

Baseline response: Baseline PWT responses were measured prior to paclitaxel or test compound administration. Rats were subsequently balanced and assigned to treatment groups based on baseline PWT values of left and right hind paws between washouts.

Statistical Analysis: Left and right von Frey data were averaged together, and analyzed by ANOVA (ANOVA) followed by Fisher PLSD post-hoc comparisons. An effect was considered significant if p<0.05. Data are presented as the mean ± standard error of the mean (S.E.M.).

Result

Paclitaxel-induced neuropathy started day 12 after injection and continued throughout the study. Acute administration of gabapentin on day 23 reversed paclitaxel-induced neuropathy. The effect of gabapentin persisted with chronic administration up to day 44 when the study ended. Data represents mean ± SEM. *p<0.05 vs. Vehicle-Vehicle; #p<0.05 vs. Paclitaxel-Vehicle.

Summary

The present studies, we evaluated various analgesics and antidepressants on mechanical hyperalgesia induced by paclitaxel. In the present studies, we evaluated gabapentin, antidepressants and morphine.

In summary, gabapentin was effective in reversing paclitaxel-induced neuropathy. Gabapentin showed a full reversal.

Further studies are ongoing to evaluate the efficacy of different classes of analgesic agents in this model.

References


On test days, baseline PWT was assessed. Following pretreatment with test compound, PWT was again assessed.

Table 1: Summary of drugs tested in these studies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/kg)</th>
<th>Route</th>
<th>Vehicle</th>
<th>Pretreatment (min)</th>
<th>Route</th>
<th>PVT</th>
<th>Vehicle</th>
<th>Pretreatment (min)</th>
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<tr>
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<td>p.o.</td>
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<td>0.5% CMC</td>
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<tr>
<td>Tramadol</td>
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<td>p.o.</td>
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<td>30</td>
<td>p.o.</td>
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