

Comparative Evaluation of Paclitaxel-Induced CIPN Rat Models Using Different Dosing Regimens

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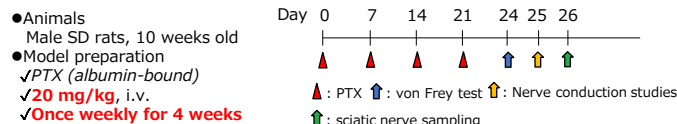
Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a major adverse effect of anticancer agents and has attracted increasing interest in preclinical pain research. In recent years, requests for pain evaluation using CIPN models have also increased at our company; however, optimal dosing regimens may vary depending on study objectives and timelines. In this study, we performed a comparative evaluation of two paclitaxel (PTX)-induced CIPN rat models using different dosing regimens to assess for preclinical pain studies.

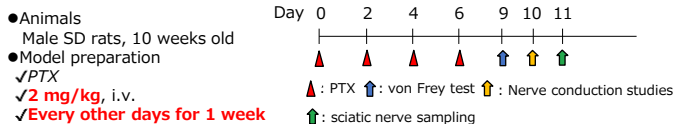
Methods

This study was conducted as approved by the International Animal Care and Use Committee of NISSEI BILIS Co., Ltd., Shiga Laboratory.

Regimen A (Long-term)



Regimen B (Short-term)



von Frey test, Nerve conduction studies, Histopathology

●von Frey test

Pain response was assessed by using the “up and-down” method, as previously described by Dixon (1965) and Chaplan et al (1994). The animals were placed individually in a cage with a wire mesh bottom (see Figure 1). After acclimation, calibrated von Frey filaments (ranging from 0.4 to 15 grams) were applied to the mid-plantar surface of the hindpaw for 3 to 4 seconds. A positive response was recorded if the animals showed withdrawal and guarding, “scratching” or “licking” of the stimulated paw. Data were calculated as the 50% withdrawal threshold. To evaluate the effects of neuropathic pain-targeted drugs, pregabalin was orally administered at dose of 20 mg/kg, followed by the von Frey test 2 hours later.

●Nerve conduction studies (NCS)

Under anesthesia, nerve conduction velocity (NCV) and compound muscle amplitude (CMAP) were measured using needle electrodes connected to an electromyography system. Stimulating electrodes were placed near the sciatic nerve (distal site) and near the Achilles tendon (proximal site), and recording electrodes were inserted into the plantar muscles (see Figure 2). NCV was calculated from the distance between the stimulation sites and the latency of the evoked response. CMAP amplitude was measured as peak-to-peak voltage. Each measurement was repeated ten times and averaged

●Histopathology

At the study endpoint, the sciatic nerve was excised under deep anesthesia, and fixed in 2.5% glutaraldehyde and 2% paraformaldehyde in a 0.1M phosphate buffer. The samples were dehydrated in a graded ethanol series and then embedded in epoxy resin for morphological preservation. Sections were stained with toluidine blue.

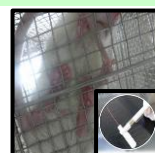


Figure 1. von Frey test

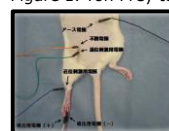
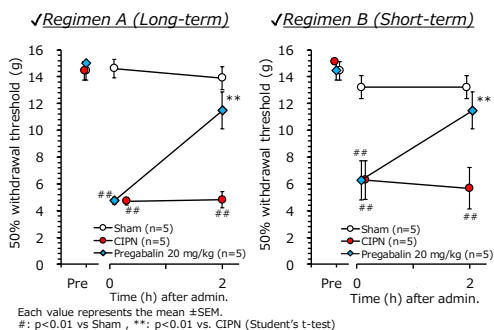


Figure 2. NCS

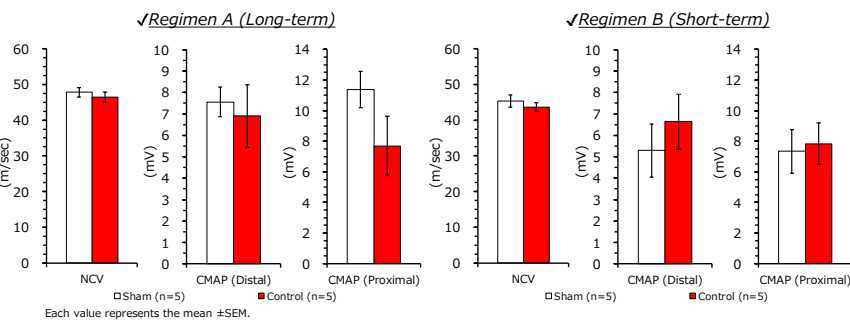
Results

von Frey test



Both paclitaxel dosing regimens produced comparable mechanical hypersensitivity. Pregabalin administration significantly increased the 50% withdrawal threshold in CIPN rats.

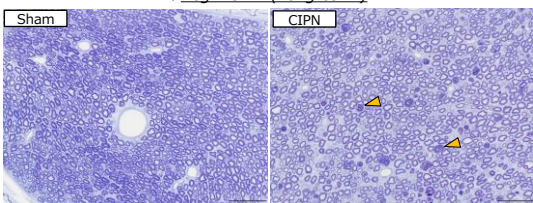
NCS (NCV and CMAP)



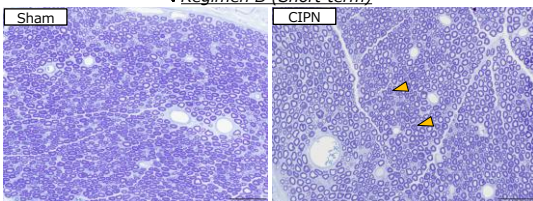
No significant differences were detected in NCV or CMAP in either dosing regimen compared with sham rats, indicating preserved peripheral nerve conduction despite marked mechanical hypersensitivity.

Histopathology

✓Regimen A (Long-term)



✓Regimen B (Short-term)



Both regimens showed axonal degeneration (▲). Regimen A exhibited marked reduction in myelinated fiber density, whereas Regimen B demonstrated axonal degeneration with only mild reduction in fiber density.

Comparison Summary of PTX-Induced CIPN Rat Models

Item	Regimen A (Long-Term)	Regimen B (Short-Term)
Paclitaxel dosing	20 mg/kg, i.v., once weekly for 4 weeks	2 mg/kg, i.v., every other days for 1 week
Total dose	Higher (cumulative)	Lower (compressed)
Study duration	Longer	Shorter
von Frey test	Comparable mechanical hypersensitivity	
NCV/CMAP	No significant change	
Sciatic nerve histopathology	Axonal degeneration Reduced myelinated fiber density	Axonal degeneration Reduced myelinated fiber density
Key characteristics	More advanced structural progression confirmed with preserved electrophysiology	Early-stage structural alteration with preserved fiber density
Recommended use	Studies requiring pathological confirmation or longer exposure	Short-term or early-detection focused studies

Conclusion

- ✓ Both paclitaxel dosing regimens produced comparable pain-related behavior, allowing flexible selection of CIPN models according to study timelines and objectives.
- ✓ Structural alterations were observed in both regimens despite preserved NCV and CMAP, with greater myelinated fiber loss in the long-term regimen, indicating that electrophysiological preservation does not preclude underlying neuropathology.
- ✓ The combined use of pain behavioral assessment, electrophysiological evaluation, and histopathological analysis enables comprehensive assessment of peripheral nerve effects, capturing both functional impairment and regimen-dependent structural progression.

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□ The author has no conflict of interest to disclose with respect to this presentation.

