ANTINOCICEPTIVE EFFECTS OF DULOXETINE ON OXALIPLATIN-INDUCED PERIPHERAL NEUROPATHY IN RATS AND NONHUMAN PRIMATES MODELS

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POSTER
 # PTU-12

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Background & Aims

- Chemotherapeutic oxaliplatin is effective for the treatment of advanced metastatic colorectal cancer. However, oxaliplatin treatment leads to signs of acute and chronic neuropathy including dysesthesia, paresthesia and spontaneous pain.
- Cold allodynia, hypersensitivity to non-painful cold, is observed in nonhuman animals, consistent with clinical symptoms.
- Analgesic treatments that reduce oxaliplatin-associated neuropathic pain would be highly desirable to ensure that cancer patients receive all scheduled treatments.
- To further enhance preclinical translation to the clinical setting, multiple, distinct test species could be utilized.
- Brain activation could be utilized as a supplemental objective measure of pain.

Materials and Methods

Male Sprague-Dawley **rats** (100-140 g; SPF status, Janvier, France) were used in two oxaliplatin-induced cold allodynia models. In the **acute** model, rats were treated with oxaliplatin (10 mg/kg, i.p.). In the **chronic** model, rats were treated with oxaliplatin (2 x 4mg/kg/week, i.p., for 3 weeks). The hind paw immersion test (10°C), latency (sec.) to remove the paw from the water, was used to quantify cold allodynia.

Oxaliplatin (5 mg/kg) was i.v. infused over a 2 hr. period in male **cynomolgus macaques** (EBS, Japan). A second oxaliplatin infusion was performed 3 weeks later. The distal 10 cm of the macaque's tail was immersed in 10°C water. The latency (sec.) to withdraw the tail from the water was recorded.

<u>Functional magnetic resonance imaging (fMRI)</u>

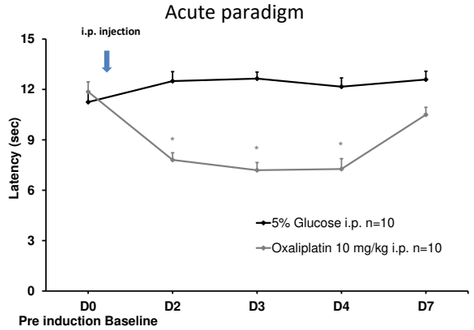
Three days after oxaliplatin infusion, brain activation during application of cold to the tail was measured (3T MRI, Philips Ingena). Brain activity was measured before duloxetine treatment and 1 hr. after duloxetine treatment.

Duloxetine, a serotonin-norepinephrine reuptake inhibitor approved for use in "major depressive disorder" and several chronic pain states, has demonstrated moderate efficacy in reducing painful oxaliplatin-induced neuropathy. Thus, the efficacy of duloxetine on cold allodynia in the rat and NHP models of oxaliplatin-induced neuropathy was examined. The effect of duloxetine on NHP brain activation was also examined.

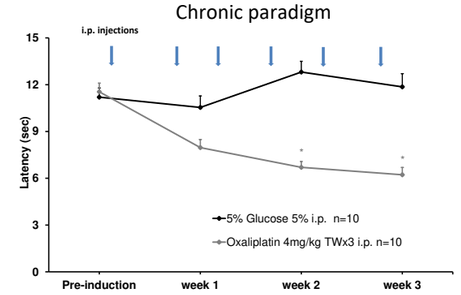
RAT

Single or repeated administrations of oxaliplatin-induced cold allodynia in rats: time course studies.

Acute paradigm

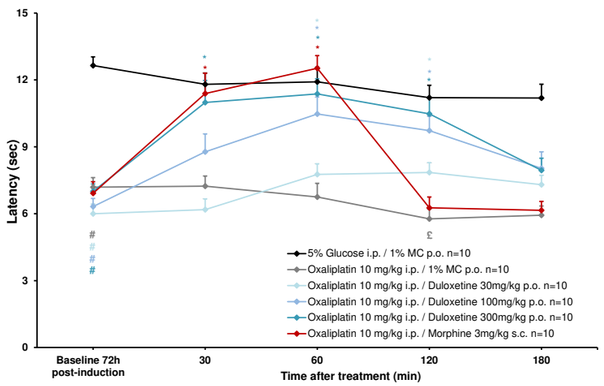


Chronic paradigm



Results are expressed as mean ± s.e.m. *: p<0.05 as compared to baseline of the corresponding group, Tuckey's test after significant Friedman repeated measures ANOVA on ranks.

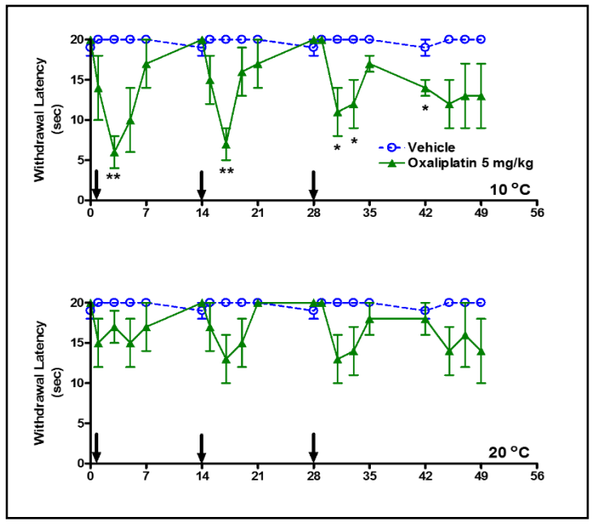
Effect of a single administration of duloxetine and morphine in the model of oxaliplatin-induced cold allodynia in rats (acute model – D3).



Results are expressed as mean ± s.e.m. £ :p<0.05 as compared to T30 timepoint of the corresponding group, Tuckey's test after significant Friedman ANOVA. *: p<0.05 as compared to baseline of the corresponding group, Tuckey's test after significant Friedman ANOVA. # : p<0.05 as compared to the 5% glucose-treated animals at the same time point, Tuckey's test after significant Kruskal-Wallis ANOVA.

NHP

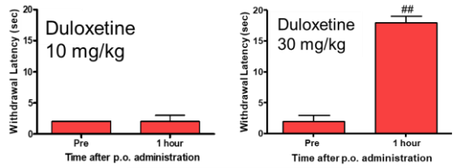
Acute cold allodynia following oxaliplatin treatment.



Decreased latency to respond to a cold (10°C) but not neutral (20°C) temperature. (↓)Oxaliplatin infusion.

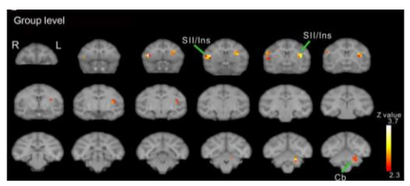
Mean ± SEM, n = 5-6 oxaliplatin-treated, n = 3 vehicle-treated. *$p < 0.05$, **$p < 0.01$ vs. baseline ("0").

Duloxetine increases tail withdrawal latency.

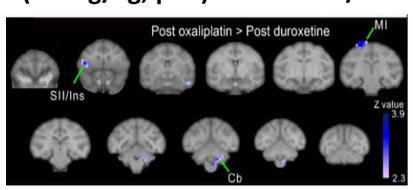


mean ± S.E., n = 3-4 ##$P < 0.01$ vs. Pre

Activation of secondary somatosensory cortex (SII) and insular cortex (Ins) in oxaliplatin-infused macaques.



Duloxetine (30 mg/kg, p.o.) reduced SII/Ins activation.



Results

Rat: Oxaliplatin significantly reduced latencies to withdrawal from non-painful cold in rats following either acute or chronic oxaliplatin treatment. Duloxetine dose-dependently alleviated cold allodynia. A single dose of morphine reversed oxaliplatin-induced cold allodynia.

NHP: Significantly reduced latencies to withdrawal from non-painful cold were observed three days following oxaliplatin treatment. A single dose of duloxetine alleviated cold allodynia.

In oxaliplatin-infused macaques, non-painful cold activated Ins/SII. Duloxetine reduced Ins/SII activation.

Conclusions

An acute dose of duloxetine suppressed cold hypersensitivity induced by acute and chronic oxaliplatin treatment in both rats and nonhuman primates. These findings suggest a similar drug efficacy in either chronic or acute oxaliplatin-induced neuropathy and furthermore replicate clinical findings of duloxetine reducing oxaliplatin-induced neuropathy.

A possible mechanism of action of duloxetine is a reduction of activation of brain areas involved in pain perception.

The preclinical models used in this study are relevant for the evaluation of antiallodynic drugs which attenuate or prevent peripheral neuropathic pain caused by oxaliplatin.

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Conflict of Interest

Authors are employees of their respective institutions.

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