Antinociceptive Effects of Duloxetine on Oxaliplatin-Induced Peripheral Neuropathy in Rat and NonHuman Primate Models.

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Aim of Investigation: Oxaliplatin is a third-generation platinum-based chemotherapy drug widely used in the treatment of advanced metastatic colorectal cancer. Its use is limited by a cumulative and chronic neurotoxicity, characterized by dysesthesia and paresthesia in the distal extremities, spontaneous pain and loss of sensation. In nonhuman animals, oxaliplatin treatment produces significant behavioural nociceptive signs (cold allodynia), consistent with clinical symptoms. Duloxetine, a serotonin-norepinephrine reuptake inhibitor, approved for use in “major depressive disorder” and painful diabetic neuropathy, has demonstrated moderate efficacy in reducing painful oxaliplatin-induced neuropathy. The objective of this study was to assess antinociceptive effects of a single oral administration of duloxetine in oxaliplatin-induced cold allodynia in the rat and non-human primate models of oxaliplatin induced neuropathy.

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

In male cynomolgus macaques (EBS, Japan), oxaliplatin (5 mg/kg, i.v.) was infused over a 2 hr. period and a second oxaliplatin infusion was performed 2 weeks later. The distal 10 cm of the macaque’s tail was immersed in 10ºC water. The withdrawal latency (sec.) to withdraw the tail from the water was recorded.

Results: In rats, significantly reduced latencies to withdrawal from non-painful cold were observed following either acute or chronic oxaliplatin treatment, suggesting cold allodynia. Acute administration of duloxetine (30, 100 and 300 mg/kg, p.o.) ameliorated cold allodynia both acute and chronic oxaliplatin treatment in dose-related manner.

In the nonhuman primate, significantly reduced latencies to withdrawal from non-painful cold were observed three days following oxaliplatin treatment, suggesting cold allodynia. Acute administration of duloxetine (3O mg/kg p.o.) ameliorated cold allodynia.

Conclusions: A single dose of duloxetine suppressed cold hypersensitivity induced by acute and chronic oxaliplatin treatment in both rats and nonhuman primates. The findings suggest a similar drug efficacy in either chronic or acute oxaliplatin-induced neuropathy.

Our study served as models for the evaluation of antiallodynic drugs which attenuated or prevented peripheral neuropathic pain caused by oxaliplatin.

Results ANS Biotech:
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