

A PRECLINICAL SET UP OF A RAT MODEL OF FOLFOX-INDUCED NEUROPATHY: EFFECT OF DIMIRACETAM

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Oxaliplatin is the main responsible of chronic neuropathy induced by the Folfox therapy. Clinical treatments are unsatisfactory as well as preclinical models of Folfox-induced neuropathy are absent.

The aim of this study was to set up a model of Folfox-induced neuropathy and to assess the effect of the new anti-neuropathic compound dimiracetam in comparison with referenced drugs.

Male Sprague-Dawley rats were treated i.p. with Folfox components (oxaliplatin 6 mg kg⁻¹, 5-FU 50 mg kg⁻¹, leucovorin calcium salt 90 mg kg⁻¹) or oxaliplatin alone (6 mg kg⁻¹) on days 0, 7, 14, 21 whereas a separate group received one more injection of Folfox on day 28. Pain behavioural measurements (Paw pressure, Cold plate, electronic Von Frey) and motor coordination (Rota rod test) were assessed before and after treatments. Behavioural, motor, neurological and autonomic parameters (Open field test, Irwin test) were evaluated on days 22 and 42.

Folfox reduced the pain threshold in response to noxious mechanical and non noxious thermal (cold) stimuli from day 14 up to day 42, comparably to oxaliplatin alone. Otherwise, five injections of Folfox enhanced the severity but not the duration of painful alterations. Spontaneous activity, behavioural, autonomic and neurological functions were also affected whereas the motor coordination was not altered. On day 22, duloxetine (15 mg kg⁻¹, p.o.), morphine (10 mg kg⁻¹, s.c.) or pregabalin (20 mg kg⁻¹, p.o.), acutely injected, reduced the Folfox-dependent hypersensitivity. Repeated administrations of dimiracetam (150 mg kg⁻¹, p.o., twice daily, from day 22 to 42), significantly protected rats from Folfox-induced painful threshold, behavioural, autonomic, and neurological alterations taking effect after 7 day treatment. Pregabalin repeatedly administered b.i.d. (20 mg kg⁻¹, p.o.) was less effective in reducing mechanical hypersensitivity.

A rat model of Folfox-induced neuropathic pain has been shown. Repeated administrations of dimiracetam fully prevented Folfox-induced alterations.