transpharmation A global leader in translational biology

Poster # 2302

Pregabalin attenuates mechanical allodynia in a rat model of oxaliplatin induced peripheral neuropathy

A. Fisher[1], R. Magnusdottir[1,2], C. Chenu[2], N. Upton[1]

1 Transpharmation Ltd, London, UK | **2** Comparative Biomedical Sciences, The Royal Veterinary College, London, UK.

Aim of Investigation:

Chemotherapy- induced peripheral neuropathy (CIPN) is a dose limiting side effect in the use of the platinum-based antineoplastic drug oxaliplatin as a treatment for colorectal cancer. Currently there is no treatment available to reverse the neurotoxicity which presents as pain, sensory loss and cold allodynia in up to 80% of patients[1]. The aim of this study is to investigate if pregabalin can reverse the mechanical allodynia caused by oxaliplatin in CIPN.

Methods:

CIPN was induced in 10 male C57BL/6 mice (6 weeks-old) with a single intraperitoneal injection of oxaliplatin (15 mg/kg i.p.) and in male SD rats (180-210 gr) (5 or 10 mg/kg i.p.). Signs of thermal and mechanical allodynia were assessed from baseline to 14-19 days after injection by Cold/Hot plate (Bioseb, France) at 15°C (rats) and 20°C (mice) and hand-held von Frey (vF) hairs of gradually increasing weights (0.07, 0.16, 0.4, 0.6 and 1g). Pregabalin at 3 mg/kg and 10 mg/kg p.o. was administered to reverse the mechanical allodynia in mice and at 30mg/kg p.o. in rats.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska Curie grant agreement No 642720

Results: Mice

Figure 1

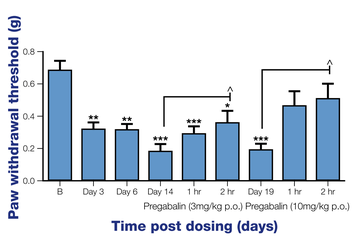
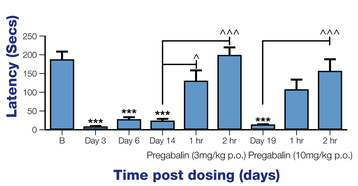


Figure 2



Results: Rats

Figure 3

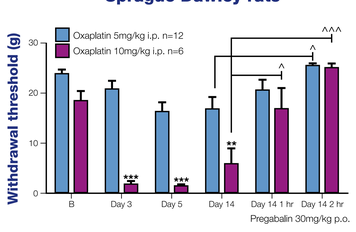
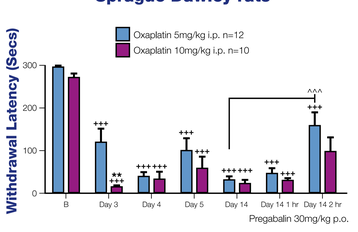


Figure 4



Results: Correlation analysis of the responses to thermal and mechanical stimuli showed no significant trend, indicating that oxaliplatin- induced peripheral neuropathy affects the mechanical and thermal modalities in different ways.

Figure1: Development of mechanical allodynia in C57Bl6 mice. In mice, a neuropathic baseline was established 3 days post-oxaliplatin injection and remained stable for 14 days. At day 14 pregabalin (3 mg/kg p.o.) reduced mechanical allodynia at 2 hours (H) post-dosing but not 1H. Following a 2 day wash-out where scores returned to neuropathic baseline, pregabalin (10 mg/kg p.o.) increased paw withdrawal threshold (PWT) again at 2H only. Values are mean ± s.e.m. n=12. *P<0.05, **P<0.01 and ***P<0.001 compared with baseline (B). ^P<0.05, ^^P<0.01 and ^^^P<0.001 compared with day 14 or day 19.

Figure 2: Development of thermal allodynia in C57Bl6 mice. Thermal allodynia was also assessed and followed a similar trend in development as the mechanical allodynia. Thermal testing was performed either immediately after vF or alone. The results in both test situations were similar showing no iatrogenic effects of vF on thermal sensitivity.

Pregabalin (3mg/kg p.o.) reduced the thermal allodynia at both the 1H and 2H time-point. Pregabain (10mg/kg p.o.) reduced the thermal allodynia only at the 2H time point. Values are mean ± s.e.m. n=10. *P<0.05, **P<0.01 and ***P<0.001 compared with baseline (B). ^P<0.05, ^^P<0.01 and ^^^P<0.001 compared with day 14 or day 19.

Figure 3: Development of mechanical allodynia in Sprague Dawley rats. Little effect on PWT following vF testing was observed with oxaliplatin at 5 mg/kg i.p. across the test days. Although there was only a modest reduction in PWT resulting from oxaliplatin (5mg/kg i.p.), Pregabalin did increase the PWT at the 2H time point, on day 14, in this group of animals. Oxaliplatin (10mg/kg i.p) produced a more marked effect on PWT apparent by day 3. Pregabalin (30mg/kg p.o.) reduced the mechanical allodynia at both the 1H and 2H time-point on day 14. Values are mean ± s.e.m. *P<0.05, **P<0.01 and ***P<0.001 compared with oxaliplatin (5mg/kg i.p.). ^P<0.05, ^^P<0.01 and ^^^P<0.001 compared with day 14 or day 19.

Figure 4: Development of thermal allodynia in Sprague Dawley rats. Thermal allodynia was established 3 days after injection of oxaliplatin at both 5 and 10mg/kg i.p. and remained stable for 14 days. There were no real differences in the effects, on thermal sensitivity, between the two doses of oxaliplatin. Thermal allodynia was attenuated slightly, but significantly, by Pregabalin (30mg/kg p.o.) in rats dosed with oxaliplatin (5mg/kg i.p.) at the 2H time-point only.

Conclusion:

The phenotype produced by systemic administration of oxaliplatin in rodents i.e. that of both thermal and mechanical hypersensitivity is similar to that observed in man; supporting the clinical translatability of this model.

In the rat, oxaliplatin produced dose-dependent effects on mechanical and thermal allodynia.

A single dose of pregabalin was able to reverse mechanical allodynia in the rat and mouse models of oxaliplatin-induced peripheral neuropathy.

Pregabalin was clearly more potent against mechanical allodynia than thermal allodynia in rats supporting the different pahtological mechanisms underlying these two symptoms.

References: 1) 1. Ventzel L, Jensen A, Jensen A, Jensen T, Finnerup N. Chemotherapy-induced pain and neuropathy. PAIN. 2016;157(3):560-568.