Evaluation of behavioral pain phenotype and optimization of the rat paclitaxel and oxaliplatin models of chemotherapy-induced peripheral neuropathy.

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In collaboration with the NIH HEAL Initiative Preclinical Screening Platform for Pain (PSPP), the paclitaxel and oxaliplatin models of chemotherapy-induced peripheral neuropathy in the rat were optimized and validated. Adult male and female Sprague Dawley rats (n=10, each sex) were used in these studies. For the paclitaxel model studies, paclitaxel was injected at several doses (2 mg/kg, i.p.; 4 mg/kg, i.p.; 2 mg/kg, i.v.) on alternate days (Day 0, 2, 4, 6) to determine the optimal dose and route of administration. For the oxaliplatin model studies, oxaliplatin (3 mg/kg, i.v.) was injected 2 days per week for a period of 4 weeks. Hind paw tactile sensitivity was determined with von Frey filaments using the "up-down" testing method, and hind paw cold sensitivity was determined using the acetone test. In the paclitaxel model studies, 4 injections of paclitaxel on alternate days (Day 0, 2, 4, 6) produced bilateral hind paw tactile and cold hypersensitivity which was maximal by Week 5 and persisted through Week 6. The paclitaxel dose of 4 mg/kg, i.p. was found to be optimal for this model, and results from rat pharmacokinetic studies demonstrated that Cmax and AUC values associated with this dose were consistent with values associated with efficacy in the clinic. Interestingly, hind paw priming with acetone during Week 2 enhanced acetone cold hypersensitivity in this model during Weeks 3-6, while mechanical priming with von Frey filament stimulation did not affect the development of tactile hypersensitivity. In the oxaliplatin model studies, oxaliplatin injection (3 mg/kg, i.v.) 2 days per week for a period of 4 weeks produced bilateral hind paw tactile and cold hypersensitivity which was maximal by Week 6 and persisted through Week 8. The magnitude of tactile and cold hypersensitivity was similar in the paclitaxel and oxaliplatin models. Initial pharmacological characterization was performed in these models by examining the effects of morphine sulfate (0.3-3 mg/kg, s.c.) on bilateral hind paw hypersensitivity, and morphine sulfate (3 mg/kg, s.c.) was found to significantly inhibit bilateral tactile and cold hypersensitivity in the paclitaxel and oxaliplatin models at Week 6 and Week 7, respectively. The validation of the paclitaxel and oxaliplatin models of chemotherapy-induced peripheral neuropathy further highlights efforts within the NIH HEAL Initiative's PSPP program to validate clinically relevant endpoints and models to be incorporated into evaluating novel assets towards accelerating the development of novel non-opioid, non-addictive therapeutics.