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Erratum

2017-04-01

Enhancing Translational Relevance in a Murine Model of Cisplatin-Induced Neuropathy Using a Novel Arena Apparatus

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ABSTRACT

Von Frey is used to quantify evoked allodynia in pain models for analgesic screening but is susceptible to false positives. This research explored whether behavior in a novel arena apparatus with a varied rough-textured floors in ½ fields might quantify spontaneous tactile allodynia and show better predictive validity. Mice (C57BL/6) received 6 IP administrations of 2.3mg/kg of cisplatin over 12 days to induce neuropathy (CIN). Behavioral measures were taken by eVF (g force to evoked stimuli) and arena apparatus (movement and time in ½ fields) prior to and following CIN induction, and then 1-day later 30 min after each of 3 drug exposures (Saline, 3 mg/kg Oxycodone, and 100 mg/kg Gabapentin, IP) in a Latin Square Design with 1-2 day drug holiday between testing. In eVF testing, cisplatin produced an allodynic response that was attenuated by both oxycodone and gabapentin. In the arena apparatus, cisplatin produced a reduction in overall movement that was attenuated only by oxycodone. Cisplatin produced an increase in time spent on the 60 grit ½ field, but overall drug probes had inconsistent effects on time spent on ½ field. In clinical populations, CIN is effectively treated with oxycodone but not gabapentin. This novel arena apparatus, with a more translationally relevant spontaneous allodynia endpoint, shows better predictive validity than eVF and may be useful in identifying novel pharmacotherapies in oncology settings.

INTRODUCTION & BACKGROUND

Pain research relies on evoked behavioral endpoints, such as those measured by von Frey (VF), to quantify allodynia in various chronic pain models for analgesic screening but is susceptible to false positives. False positives occur when an animal assay predicts clinical efficacy but the drug fails in clinical trials. Such poor translational relevance may reflect animal models/behavioral endpoints that do not fully replicate

features of a clinical syndrome. This may be particularly true with endpoints of allodynia where its clinical presentation is spontaneously evoked through normal activity. This research explored whether the behaviors of overall movement and time spent in ½ fields in a novel tactile arena apparatus with varied rough-textured floors might quantify spontaneous tactile allodynia and show better predictive validity in a model of cisplatin-induced neuropathy (CIN).

MATERIAL & METHODS

Mice (C57BL/6) received 6 IP administrations of 2.3mg/kg of cisplatin over 12 days to induce neuropathy (CIN). Behavioral measures were taken by Topcat, MouseMet electronic-VF in g force to an evoked stimuli and by Noldus Ethovision overall movement and time spent in ½ fields in an arena apparatus containing 60 and 220 grit sandpaper in each ½ fields (see below). These

endpoints were taken prior to and following CIN induction and then 30 min after each of 3 drug exposures (Saline, 3 mg/kg Oxycodone, and 100 mg/kg Gabapentin, IP) in a Latin Square Design with a 1-2 day drug holiday between testing. Sample sizes were n = 12-14. per group.

RESULTS

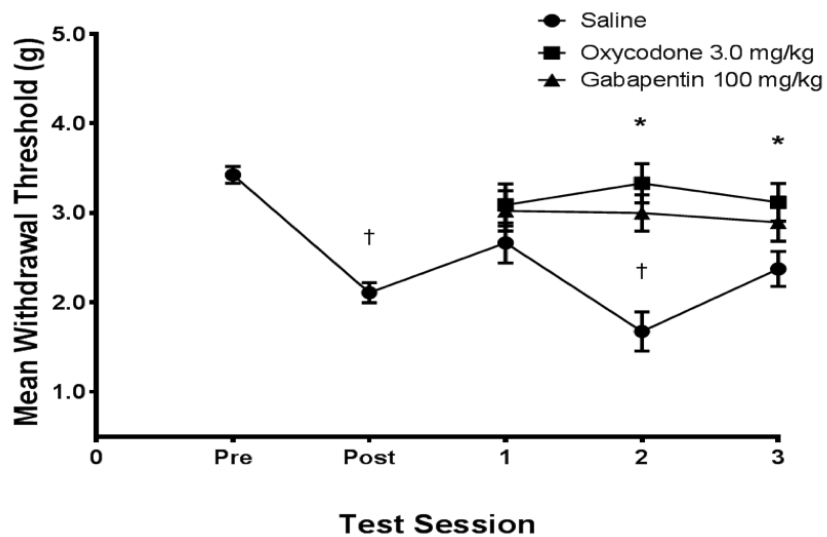


FIGURE 1. eVF: Cisplatin produced significant allodynia (†) that was significantly attenuated (*) by both oxycodone and gabapentin on test sessions 2 and 3 ($p < 0.005$).

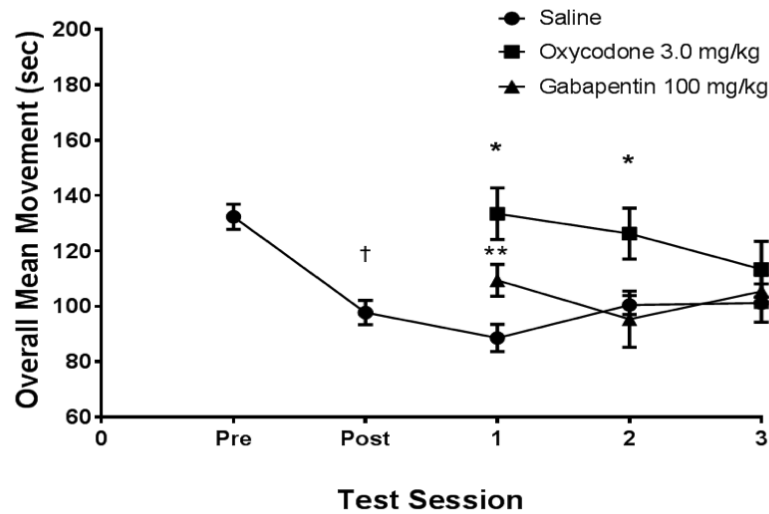


FIGURE 2. Arena-Movement: Cisplatin produced significant decrease in movement (†) that was significantly attenuated (*) by oxycodone and (**) gabapentin on test session 1 but only by oxycodone on test session 2 (p s < 0.005).

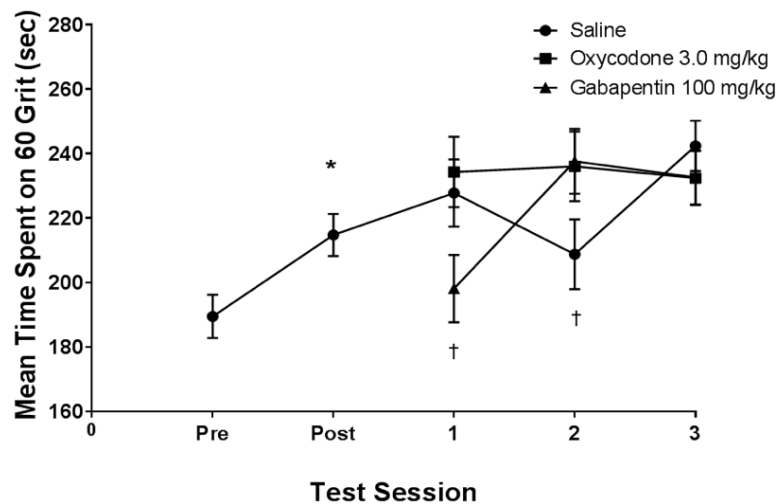


FIGURE 3. Arena-Time on ½ Field: Cisplatin produced a significant increase in spent time in the 60-grit ½ field (*) that was significantly attenuated (†) only by gabapentin on test session 1 (p s < 0.005).

DISCUSSION & CONCLUSION

In clinical populations, CIN is effectively treated with oxycodone but not gabapentin. This research found that evoked responses from eVF were sensitive to oxycodone and gabapentin in attenuating allodynia induced by CIN and, thus, susceptible to false positives. The novel tactile arena was most sensitive to oxycodone and only modestly sensitive to gabapentin on movement and only sensitive to gabapentin on time in ½ field. This tactile arena using changes in movement may provide a more translationally relevant measure of allodynia than eVF. These findings suggest this novel apparatus may be useful in identifying novel analgesic pharmacotherapies in oncology settings.

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