# Effect of trazodone on spontaneous pain-like behavior in the chronic constriction injury rat model

A. di Matteo[1], S. De Santi[1], A. Amato[1], B. Garrone[1], L. Durando[1]

[1]Angelini S.p.A - R&D, Angelini Research Center,Piazzale della Stazione, snc – 00071 S. Palomba – Pomezia (RM) - Italia

Chronic pain can have a significant impact on a patient's daily life and consequently, effective pain relief is highly warranted (1-2). Experiments investigating pain in human subjects have intrinsic ethical and practical difficulties; accordingly, early analgesic development relies on animal models. Innate responses against spontaneous pain are proposed to improve the predictive validity of preclinical analgesia model.

To investigate whether spontaneous pain is a useful alternative behavioral readout for assessment of analgesic efficacy, the chronic constriction injury model (CCI) was used to evaluate the effect of gabapentin, used as reference drug, and trazodone a multifunctional antidepressant drug recently reported with an antihyperalgesic activity (3), in weight-bearing (WB), activity cage, burrowing and nest construction tests.

Male Sprague Dawley rats were anaesthetized and the left common sciatic nerve was exposed at the level of the middle of the thigh and three loosely constrictive ligatures were tied around the nerve with about 1 mm spacing. Gabapentin (100 mg/kg, ip) and trazodone (10 mg/kg, po) were administered 14 days following nerve ligation. WB was determined using a rat incapacitance tester; horizontal distance moved both in the central and peripheral area and vertical rearings in activity cage were recorded; following four training sessions and the baseline burrowing performance recorded the day before the surgery, burrowing was measured by the weight of gravel remaining in a hollow tube; nest construction was assessed placing rats into the nesting cages about 1 h before the dark phase until the next morning. All procedures conformed to the guidelines of the European Community's Council for Animal Experiments.

CCI-induced neuropathic pain significantly reduced WB, spontaneous locomotor activity in the central area of the arena and vertical rearings, burrowing and nest performance. In our experimental conditions, gabapentin as well as trazodone normalized WB. Inside the central area, horizontal activity was improved by the pharmacological treatments and rearing behavior was reinstated. No difference were observed in peripheral area. Finally, in burrowing and nest construction, gabapentin and trazodone significantly reversed CCI-induced deficits.

In conclusion, our results suggest that the activities and performances measured represent an robust and reproducible measure of response to pain-like behavior. As far as trazodone effects on the spontaneous pain is concerned, data suggest that this drug could be used to improve the affective/emotional dimension of pain. Further investigations on Trazodone mechanism of action are ongoing in order to clarify its effect.

References

(1) Gore M et al. (2005). J Pain Symptom Manage; 30: 374–385.

(2) Rutten K. et al. (2014). Eur J Pain; 18: 204-212.

(3) di Matteo A. et al. (2015). 5th International Congress on Neuropathic Pain.