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A Two Part, Randomised, Double-blind, Placebo-controlled, Four-way Cross-over, Single Dose Study To Pharmacologically Validate A Pain Model Battery Suitable For Early Phase Clinical Drug Development

P Okkerse, J Hay, G van Amerongen, M de Kam, G Groeneveld. Centre for Human Drug Research, Leiden, The Netherlands

Introduction: Pharmaceutical science continues to search for suitable biomarkers that can assist in predicting the therapeutic potential of analgesic medication and its efficacy in the target population. No single experimental model can replicate the complex nature of clinical pain. Although a single experimental pain model can be used to demonstrate the pharmacological mechanism of action of a compound, one single model can not reliably mimic clinical pain. The aim of this study was to investigate the ability of a battery of pain models to detect analgesic properties of commonly used analgesics in healthy subjects. This was the first time that an integrated battery of experimental pain models was executed in combination with the administration of different analgesic drugs.

Methods: The test battery consists of a sequence of tests eliciting cutaneous electrical-, mechanical (pneumatic)-, and thermal (cold pressor)-pain, and measuring pain detection threshold (PDT), pain tolerance thresholds (PTT) and area under the VAS-time curve (AUC). Furthermore, the battery included the UVB model to measure hyperalgesia, comparing heat pain detection thresholds in UVB exposed skin compared to normal skin, the thermal grill illusion and a paradigm to measure conditioned pain modulation (CPM). In part I of the study, subjects received fentanyl 50 µg/kg, phenytoin 300 mg, (s)-ketamine 10 mg or placebo (sodium chloride 0.9%) as an intravenous infusion over 30 minutes. In part II, subjects were administered imipramine 100 mg, pregabalin 300 mg, ibuprofen 600 mg or placebo capsules as a single oral dose. Following a training session, pain test measurements were performed at baseline (twice), 0.5, 1, 2, 3, 4, 6, 8 and 10 hours. In each part, subjects received all four treatments. Pharmacodynamic outcome variables were analysed using a mixed model analysis of variance.

Results: 22 healthy subjects participated in part I and 17 in part II. 16 subjects completed all treatments periods in part I and 16 in part II (8 females in each part). The PTT for electrical stimulation was increased compared to placebo for (s)-ketamine (+10.1%, p=0.044), phenytoin (+8.5%, p=0.019), and pregabalin (+10.8%, p=0.012). The PTT for mechanical pain was increased by pregabalin (+14.1%, p=0.005). The cold pressor PTT was increased by fentanyl (+17.1%, p=0.023) and pregabalin (+46.4%, p=<.0001). Normal skin heat PDT was increased by (s)-ketamine (+3.3%, p=0.004), fentanyl (+2.8%, p=0.002) and pregabalin (+4.1%, p=0.005). UVB treated skin PDT was increased by fentanyl (+2.6%, p=0.0006) and ibuprofen (+4.0%, p=0.0006). Thermal grill unpleasantness AUC decreased after administration of fentanyl (-34.3, p=0.011). No differences in conditioned pain modulation were observed. Adverse events reported in the study were all mild or moderate in severity and in line with their known pharmacological profile.

Conclusion: This validation study shows that the battery of pain models is able to detect changes in pain detection and pain tolerance thresholds after administration of different classes of analgesic compounds in healthy male and female subjects. The analgesic compounds all showed a unique profile in their effects on the pain tasks administered. These profiles were in most cases compatible with the expected pharmacology. This battery of pain models can be used to benchmark analgesic properties of new drugs against established analgesics in early phase clinical studies in healthy subjects.