SCREENING FOR ANALGESIC ACTIVITY USINGA PANEL OF BEHAVIORAL PAIN MODELS:POTENTIAL UTILITY IN COMBINATION STUDIES TO ASSESS SYNERGY

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SCREENING FOR ANALGESIC ACTIVITY USING A PANEL OF BEHAVIORAL PAIN MODELS: POTENTIAL UTILITY IN COMBINATION STUDIES TO ASSESS SYNERGY

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Introduction

We have previously shown that **ALGOGram™**, our preclinical behavioral pain panel, can provide a rapid and predictive evaluation of various reference drugs commonly used in clinical pain practice (see poster communications at SfN 2015 [1] and IASP 2016 [2]). In this sense, **ALGOGram™** appears to be a valuable screening tool for a broad range of analgesic activity when used in a signal detection exercise.

In order to investigate the level of sensitivity of our *in vivo* screening tool, we have utilized it to explore the possible synergistic effect of a combination of Morphine and Acetaminophen. As a follow-up to the panel results, the most relevant effect observed in a given pain area was then investigated in a fully powered study to confirm the signal detection provided by **ALGOGram™** .

Materials and Methods

ALGOGram™ is based on a battery of 11 validated animal models/ tests spanning a broad range of pain areas including acute and tonic pain, neuropathic pain, inflammatory pain, post-operative pain and visceral pain. Compounds (Morphine 0.3mg/Kg, s.c and Acetaminophen 100mg/Kg, *p.o.*) were evaluated alone or in combination in the pain models and tests listed below.

Models: CCI, oxaliplatin, carrageenan, kaolin, incision and TNBS.

Tests: paw pressure, electronic Von Frey, colonic distension, tail flick, writhing and formalin.

Modified Irwin grid: the behavioral and acute toxicity was also evaluated.

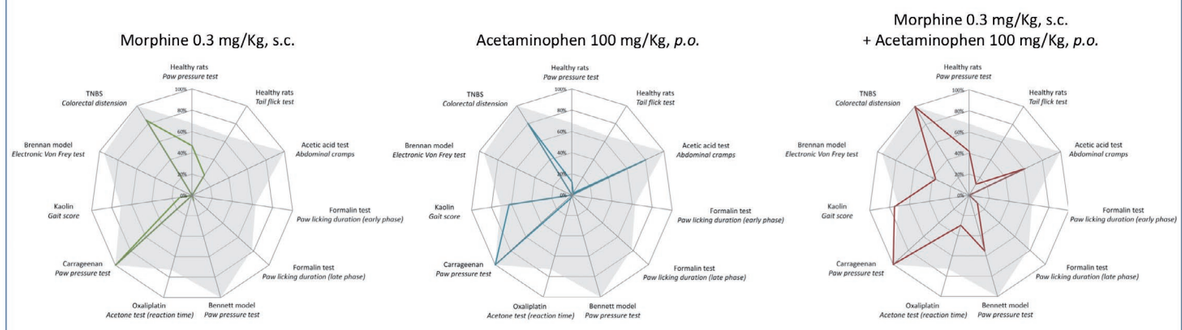
Results are expressed for each group as the percentage of activity calculated from the mean value of the vehicle-treated animals from our 10 year-historical database.

Fully powered study (Brennan model) (Figure 2) [3]:

Surgery: Under gas anaesthesia, the plantar aspect of the hindpaw was exposed and a 1-cm longitudinal incision was made using a surgical blade, through skin and fascia. The plantaris muscle was elevated and incised longitudinally whereas the insertions remained intact. After haemostasis, the skin was stitched up with two sutures and animals were allowed to recover in their cages.

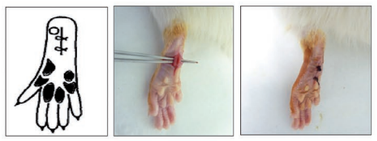
Test: Static mechanical allodynia was assessed using the electronic Von Frey test 24h post-surgery / 30 min post-administration.

***Figure 1:* Radar representations of the effects of a single administration of Morphine, Acetaminophen and the combination of Morphine-Acetaminophen in ALGOGram™**



Compounds were given as a single administration to Sprague-Dawley male rats and tests were carried out 30 min after dosing.
n=4 rats / model & test

***Figure 2:* Incisional pain model: surgery and test**



Tactile allodynia was induced by incision in the plantar aspect of the hindpaw in anaesthetized rats (Brennan *et al.*, 1996) [3].

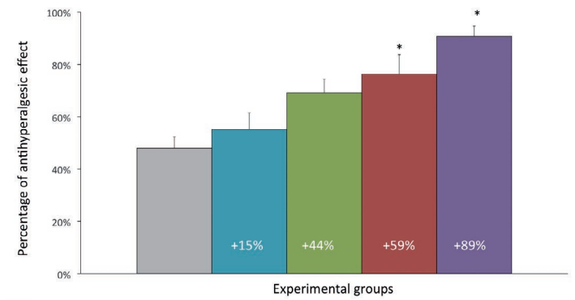
Electronic Von Frey test:

- Progressive increasing force applied to the plantar surface of each hindpaw

- Thresholds determined as the pressure (g) required to elicit paw withdrawal.

Statistical analysis:
Tuckey's test after significant Kruskal Wallis ANOVA on ranks
(SigmaStat software version 3.5 (SPSS Science Software, Erkrath, Germany)

***Figure 3:* Effects of a single administration of Morphine, Acetaminophen and the combination of Morphine-Acetaminophen in a fully powered study (incisional pain in rats)**



1% Methylcellulose, *p.o.*
Acetaminophen 100 mg/Kg, *p.o.*
Morphine 0.3 mg/Kg, s.c.
Acetaminophen 100 mg/Kg, *p.o.*, + Morphine 0.3 mg/Kg, s.c.
Morphine 3 mg/Kg, s.c.

n=10 rats / experimental group

*: p<0.05 as compared to the vehicle-treated group, Tuckey's test after significant Kruskal Wallis ANOVA on ranks
Percentage of variation are expressed as increase (+) as compared to the vehicle-treated group.

Results

Used at sub-threshold doses as determined in previous fully-powered studies, Morphine (0.3mg/Kg, s.c.) and Acetaminophen (100mg/Kg, *p.o.*) did not show activity in most of the different somatic pain models. In contrast, animals co-administered with both subactive doses of Morphine and Acetaminophen exhibited significant pain relief in both post-operative and neuropathic pain (CCI) models, confirming results published in the literature (Figure 1). Interestingly, when a promising signal observed in a given pain area (*i.e.* post operative pain) was followed in a second step by the corresponding fully powered study (*i.e.* Brennan model), the pain relief induced by the combination was confirmed (Figure 3).

Conclusion

ALGOGram™ provides a rapid, cost-effective and predictive evaluation of investigational chemical entities in 11 different pain models/tests, enabling their prioritization for fully powered studies.

In this study, we have challenged our *in vivo* screening tool and shown that it is enough sensitive to detect a synergistic effect, using the well-known combination of Morphine and Acetaminophen.

Bibliography

[1] Darbaky & Diop, 2015 Poster # 705.02 - 45th Annual meeting of Society for Neuroscience
[2] Darbaky *et al.*, 2016 Poster # 285 - 16th World Congress on Pain
[3] Brennan *et al.*, Pain, 1996 (64):493-501

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