ALGOGRAM™: A NEW TOOL TO EVALUATE DRUGS IN DIFFERENT PAIN AREAS

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ALGOGram™ : A NEW RESEARCH TOOL TO EVALUATE DRUGS IN MULTIPLE PAIN AREAS

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Introduction :

To evaluate the efficacy of exploratory compounds in different pain areas, various classical preclinical models are routinely used. For early drug discovery purposes, however, the full characterization package can be long and significantly expensive.

Aim of investigation :

To address this issue, we have developed an innovative screening tool, **ALGOGram™**, a panel of behavioral pain models each validated with the most clinically relevant drugs.

Material and Methods :

ALGOGram™ is a battery of 11 validated animal models/ tests spanning a broad range of pain. The concept is an assessment of efficacy based on a group size of n=4 rats/ model/test, thus providing a general pharmacological profile while reducing costs; assays/tests are run in parallel, thus minimizing timelines.

Drugs : To pharmacologically validate **ALGOGram™**, various reference drugs classically used in clinical pain practice (morphine, gabapentin, buprenorphine, tramadol, acetaminophen and diclofenac) were evaluated in the 11 pain models / tests.

Results are expressed for each group as a percentage of activity for each model/test calculated from the mean value of the vehicle-treated animals from our 9 year-historical database.

Statistics : To statistically validate **ALGOGram™**, Confidence Interval (CI) was calculated for each model/test and a simulation of 1000 random samples (n=4) from the historical database was generated to challenge the strength of **ALGOGram™**.

$$CI = Mean \pm 1.96 \times \frac{\text{Standard deviation}}{\sqrt{n}}$$

Figure 1 : Radar representation of the effect of a single administration of known analgesics in ALGOGram™

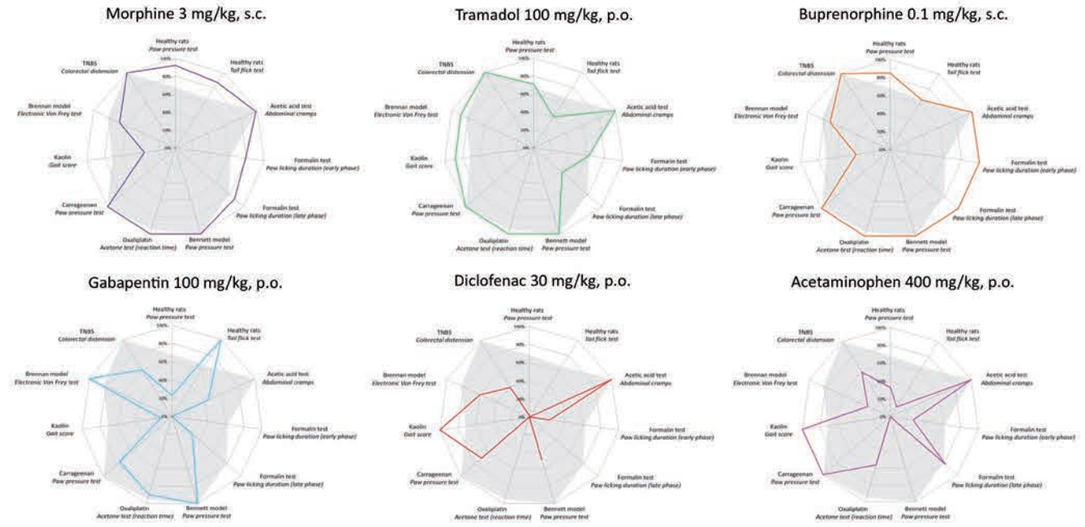
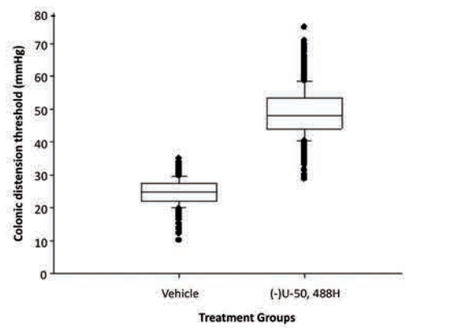


Table 1 : Models and tests used in ALGOGram™

Pain area	Model-test	Reference ID	Risk
Acute & Tonic pain	Healthy rats *Paw pressure test*	Morphine 4mg/kg s.c.	3%
	Healthy rats *Tail flick test*	Morphine 4mg/kg s.c.	6%
	Acetic acid test *Abdominal cramps*	(-) U50, 488 H 3mg/kg s.c.	0%
	Formalin test *Paw licking duration (early phase)*	Morphine 4mg/kg s.c.	19%
	Formalin test *Paw licking duration (late phase)*	Morphine 4mg/kg s.c.	10%
Neuropathic pain	Bennett model *Paw pressure test*	Morphine 3mg/kg s.c.	4%
	Oxaliplatin *Acetone test (reaction time)*	Gabapentin 100mg/kg, p.o.	3%
Inflammatory pain	Carrageenan Paw pressure test	Indomethacin 30mg/kg, p.o.	8%
	Kaolin *Gait score*	Indomethacin 10mg/kg, p.o.	6%
Post-operative pain	Brennan model *Electronic Von Frey test*	Morphine 4mg/kg s.c.	0%
Visceral pain	TNBS *Colorectal distension*	(-) U50, 488 H 3mg/kg s.c.	20%

Figure 2 : Simulation of 1000 random samples (n=4) for vehicle- and (-)U-50,488H-treated groups in the TNBS model



Results :

Buprenorphine, morphine and tramadol were active in all 11 different pain models. In contrast, gabapentin was active in several hypersensitive pain models, and diclofenac and acetaminophen displayed antinociceptive properties in some inflammatory pain models. Importantly, analgesic profiles obtained with n=4 animals in **ALGOGram™** were in line with those generated in various and repeated fully-powered studies performed in-house as well as those described in the literature.

Our statistical analysis, based on the historical database, demonstrates that the risk of being outside of the CI ranged between 0% and 20%. Considering the TNBS model, in which the largest CI emerged (20%), the distribution of vehicle-treated and positive reference–treated populations still remain distinct.

Conclusion :

ALGOGram™ provides a rapid and predictive evaluation of investigational compounds in 11 different pain models/tests, enabling their prioritization for fully-powered studies. Shortened timelines and reduced costs are possible due to small group sizes that are run in parallel. In summary, **ALGOGram™** may prove to be useful in a signal detection exercise for a broad range of potential analgesic activity.

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