

Response Surface Analysis of Synergistic Interactions of Morphine and Gabapentin in a Rat Model of Postoperative Pain

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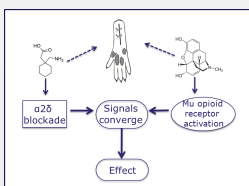
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Introduction

Even though morphine is the “gold standard” for postoperative pain management, its use is often hampered due to the development of severe adverse effects. Simultaneous treatment with opioids and non-opioid analgesics may lead to a synergy of increased analgesic effect, meaning that lower doses of both drugs can be used with a subsequent lower occurrence of adverse effects.

Methods

The pharmacodynamic effects of morphine (1, 1.5*, 3, 5*, 7 and 10* mg/kg), gabapentin (10, 30 and 100 mg/kg) or their combination (9 combinations of the above doses) after single s.c. administration were evaluated in a rat plantar incision model using an electronic von Frey device (1). The area under the response curve (AUC**) and the percentage of maximum possible effect (%MPE***) were used for the evaluation of the antihyperalgesic effects of the drugs. Identification of synergistic interactions was based on three-dimensional response surface analyses based on the concept of Loewe additivity (2). A quadratic model was used to describe the experimental response surface based on a polynomial function. Modeling of the pharmacodynamic data was performed using R (3). All models were fitted with generalized least squares modeling using the “gnls” function from the “nlme” library. Model selection was based on the AIC criterion.



Loewe Additivity Models

AUC

$$E_{addM,G} = Base + Slope_M \cdot M + Slope_G \cdot Dose_G + \left(\frac{Slope_G \cdot Dose_G}{Slope_M} \right) M$$

%MPE

$$E_{addM,G} = \frac{E_{maxM} \cdot M^m}{M^m + D_{50M}^m}$$

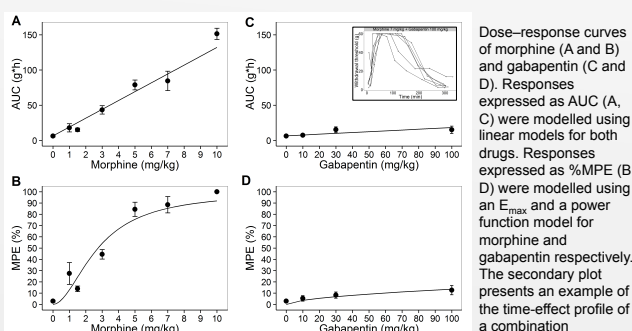
$$M = Dose_M + \frac{D_{50M} \cdot (Slope_G \cdot Dose_G)^{1/m}}{(E_{maxM} - Slope_G \cdot Dose_G)^{1/m}}$$

* Not combined with Gabapentin

** AUC was estimated based on the trapezoidal rule (0–t_{last}) for the entire observation period (300 min)

*** %MPE = (postdose threshold – predose threshold) / (cutoff value – predose threshold) * 100%

Results



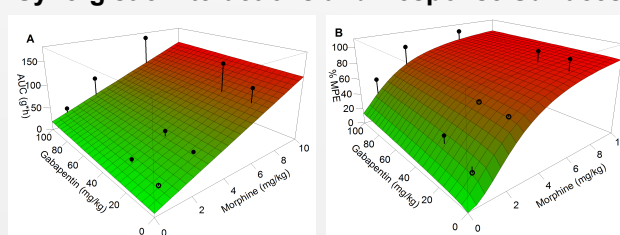
Dose response parameter estimates for morphine and gabapentin
*VFC: Variance function Coefficient

	Morphine	Gabapentin
AUC (g·h)		
Baseline (g·h)	6.52 (1.37)	6.52 (1.37)
Slope (g·h·kg/mg)	12.56 (0.96)	0.12 (0.04)
VFC* (unitless)	0.59	0.59
%MPE		
E _{max} (%)	100 (fixed)	-
D ₅₀ (mg/kg)	2.75 (0.24)	-
Hill (unitless)	1.88 (0.27)	0.57 (0.08)
Slope (kg/mg)	-	1 (fixed)
VFC* (unitless)	0.09	0.09

Aim

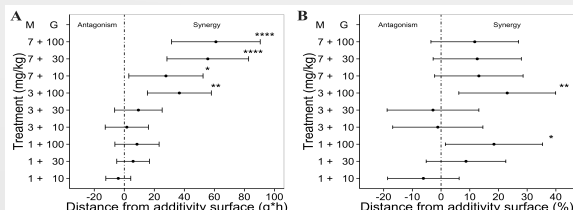
The aim of this study was to assess the interaction of morphine and gabapentin in a wide range of dose combinations and investigate whether co-administration can lead to synergistic effects in a preclinical model of postoperative pain.

Synergistic Interactions and Response Surfaces



Loewe additivity predicted surfaces and observed effects for all combinations of morphine and gabapentin. The surfaces represent the theoretical additive effect of the two drugs and were constructed based on the individual dose response curves. Superimposed points represent the mean values of observed effects for experimental drug combinations.

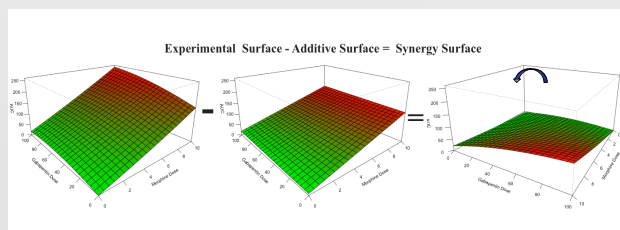
(A) Surface based on the AUC values. (B) Surface based on the %MPE values.



Mean and 95% confidence intervals of the distance of the observed effects from the theoretical additive response. Significant deviation from Loewe additivity surface is an indication of synergism whereas not significant deviation is an indication of additivity.

(A) Distance of experimental AUC from the theoretical Loewe response surface.

(B) Distance of experimental %MPE from the theoretical Loewe response surface.



$$E_{syn} = 0.03 + 0.79 \cdot Dose_M + 0.05 \cdot Dose_G + 0.005 \cdot Dose_M \cdot Dose_G + 0.01 \cdot Dose_M^2 - 0.0003 \cdot Dose_G^2$$

Conclusion

- Combination of morphine and gabapentin resulted in dose-dependent synergistic antihyperalgesic effects in a preclinical model of postoperative pain.
- These results may encourage future clinical studies that will aim to clarify whether the synergistic interaction is present in post-operative pain in humans.
- Use of alternative preclinical pain models could provide additional insight on the relevance of the combination in the clinic.

References:

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