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

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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.

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.

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 on the concept of Loewe additivity (2). A quadratic model was used to describe the experimental response surface based on a polynomial function. The model using an electronic von Frey device (1) was fitted with generalized least squares modeling using the "gnls" function from the "nlme" library. Model selection was based on the AIC criterion.

Dose–response curves of morphine (A and B) and gabapentin (C and D). Responses expressed as AUC (A, C) were modelled using linear models for both drugs. Responses expressed as %MPE (B, D) were modelled using an Emax and a power function model for morphine and gabapentin respectively. The derived quadratic dose–response model for the combination data was:

\[ E_{\text{max,comb}} = B + \text{Slope}_1 \cdot \text{M} + \text{M} \cdot \text{Slope}_2 \cdot \text{Dose} \]

\[ \%\text{MPE,comb} = E_{\text{max,comb}} - \text{Baseline} \]

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

Results

Dose–response parameter estimates for morphine and gabapentin:

<table>
<thead>
<tr>
<th>Drug</th>
<th>AUC (g·h)</th>
<th>Slope</th>
<th>Emax (g·h·kg/mg)</th>
<th>VFC* (unitless)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>6.52 (1.37)</td>
<td>-12.56 (0.96)</td>
<td>1.88 (0.27)</td>
<td>0.09</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>6.52 (1.37)</td>
<td>-12.56 (0.96)</td>
<td>1.88 (0.27)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

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.

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.

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:

