Use of intravenous patient-controlled analgesia for the
documentation of synergy between tramadol and metamizol

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The quantification of the synergistic interactions (beneficial and adverse) of analgesic drug combinations in humans has been elusive. We propose a new procedure based on analgesic requirements (i.v.-PCA) and pain intensity (VAS-PI). One hundred and one post-hysterectomy patients received at the time of analgesia request (TAR) tramadol (100 mg, group I) or metamizol (1.2 g, group II) alone, or combined in 1:1 (III), 1:0.3 (IV) or 1:3 ratio (V). After 15 min, they received the same treatment by PCA. VAS-PI, analgesic consumption and adverse effects were assessed at TAR, and periodically for 24 h. Data were analysed using interaction indexes and isobolograms. All treatments produced equivalent VAS-PI, per cent efficacy and adverse effects. When drugs were combined in a 1:1 ratio, synergy was present for the analgesic and adverse effects; all other treatments were additive.


Keywords: pain, postoperative; analgesic, interaction (drugs), measurement, pain

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Drug combinations are used widely in the treatment of acute and chronic pain, and constitute the basis for multimodal or balanced analgesia.1 2 The rationale for the use of drug combinations is to obtain effective analgesia while decreasing the incidence and severity of side effects. When two or more drugs are administered simultaneously, their various pharmacological effects can be manifested independently and, in this instance, no interaction occurs (i.e. additive effects). However, observed effects may be different (of greater or lesser intensity) from those expected, and synergy or antagonism is said to occur. In order to establish a clinically relevant drug combination, the interaction of drugs with respect to both beneficial and adverse effects should be estimated.

One conventional means of evaluating drug interactions involves establishing the dose–response relationship of each drug individually and when combined in fixed dose ratios. From these experiments, isobolograms can be constructed which compare the doses of the drugs individually and in combination. The isobologram demonstrates the type of interaction in a manner that allows statistical evaluation.3 Unfortunately, this experimental strategy is difficult to perform in humans, especially when evaluating analgesic drugs. In such studies, technical and ethical considerations make it difficult to establish reproducible dose–response relationships.4

In the present investigation, we evaluated drug interaction based on analgesic requirements determined by i.v. patient-controlled analgesia (PCA).5 6 Our working hypothesis was that patients would self-administer or ‘titrate’ the analgesics to a consistent and satisfactory level of effect, regardless of the drug or drug combination used. Thus, the main purpose of our study was to evaluate a new protocol for the assessment and quantification of analgesic drug interactions in humans. A secondary goal was to investigate a possible interaction between tramadol and metamizol. These drugs were selected on the basis of their different mechanisms of action and similar duration.7 8 Equianalgesic doses were used based on a potency ratio of 1:12.6

Methods

Experimental design
One hundred and one ASA I–II patients (age 18–70) scheduled for total abdominal hysterectomy (TAH) under general anaesthesia were included in the study. The protocol was approved by the Ethical Committee of our Institution, and all patients gave informed consent. Patients were visited
the night before surgery and the use of PCA for post-
operative pain relief was explained. Those who were unable to
understand the PCA technique, those with morbid obesity and/or history of allergies to analgesic drugs were excluded from
the study.

During the preoperative visit, patients were randomized
using a numerical table into five groups of about 20 patients
each (designated as groups I–V). The patients and investiga-
tors were unaware of the analgesic drug/s that would be
used for each patient during the study.

All patients were premedicated with sublingual diazepam
10 mg administered 1 h before surgery. On arrival in the
operating room, ECG, non-invasive arterial pressure, heart
rate and Spo₂ were monitored. An 18-gauge catheter was
placed in the non-dominant hand and used for fluid
administration intraoperatively, and for PCA in the post-
operative period. A second 18-G catheter was placed in the
other hand for the administration of anaesthetic drugs; this
catheter was removed upon discharge from the recovery
room.

Induction of anaesthesia was accomplished with fentanyl,
midazolam, thiopental and atracurium. After tracheal
intubation, mechanical ventilation was initiated and a 50%
mixture of O₂/N₂O administered throughout surgery. Anaesthesia was maintained with a constant infusion of
fentanyl 4 μg kg⁻¹ h⁻¹ and supplemental isoflurane in the
concentrations required to maintain an adequate depth of
anaesthesia (mean arterial pressure (MAP) and heart rate
(HR) within 20% range of preoperative values). Inspired
and expired isoflurane concentrations were monitored at
90–120-s intervals by mass spectrometry. Muscle relaxation
was obtained with an infusion of atracurium and monitored
with a nerve stimulator. The infusions of fentanyl and
atracurium were ceased ~20–25 min before the end of
surgery and residual muscle relaxation was reversed with
neostigmine and atropine. All patients were extubated in the
operating room.

Patients were transported to the recovery room where
they were monitored in the standard manner. Time of first
request for analgesia was noted (TAR), and the intensity of
pain evaluated at rest, using a 0–10 visual analogue scale
(VAS-PI).

At the TAR, a loading dose (10 ml) of one of the five
analgesic treatments was administered i.v. The study groups
and the corresponding drug mixtures included in the cassette
or reservoir of the PCA pump are shown in Table 1. Thus, in
group I, the PCA reservoir contained only tramadol at a
concentration of 10 mg ml⁻¹; group II had only metamizol at
a concentration of 120 mg ml⁻¹. The reservoir in group III
contained a mixture of tramadol–metamizol combined at a
1:1 potency ratio (1:12 mg), that is tramadol 5 mg combined
with metamizol 60 mg. Group IV received a combination of
drugs at a ratio of 1:0.3 (i.e. 75:25); thus tramadol 7.5 mg
plus metamizol 30 mg were combined. Group V received
the same drugs combined at a 1:3 ratio (25:75), that is
tramadol 2.5 mg plus metamizol 90 mg.

Fifteen minutes after the loading dose, VAS-PI was
reassessed. At this time, PCA was initiated with the same
analgesic ratio as the loading dose. The PCA administered
boluses of 2 ml, with a lockout interval of 15 min and a
maximal volume of 50 ml in 24 h. No baseline drug infusion
was administered. The pumps (Pharmacia, Deltec 5800R) registered the number of boluses requested and the number
delivered.

VAS-PI, pain relief and the doses of analgesics delivered
were assessed at the following time-points after TAR:
15 min, and 1, 2, 4, 8, 12, 20 and 24 h. During the first hour,
patients received a loading dose plus any drug self-
administered by PCA during the following 45 min. Patients
requesting additional analgesia at any time during
the first 24 postoperative hours were rescued with i.v.
morphine. In those patients, the PCA was discontinued and
they were excluded from the study.

At each time of evaluation, patients were monitored for
the occurrence of adverse effects: nausea, vomiting,
sedation, pruritus, headache and pain on the site of injection.
Sedation was evaluated using the Ramsay scale (graded
1–6)⁹ and considered present when the value was ≥3.
Treatment for nausea and vomiting was i.v. metoclopra-
mide, and for pruritus was diphenidramine.

**Data analysis**

Evaluation of the efficiency of the treatment (per cent pain
relief) at the different time-points was performed according
the following equation: VAS-PI at TAR (pain intensity
before treatment) minus VAS-PI at a given time-point (pain
intensity after treatment) divided by VAS-PI at the TAR
(before treatment), multiplied by 100.

<table>
<thead>
<tr>
<th>Group</th>
<th>Ratio TR:MTZ</th>
<th>Concentration TR:MTZ (mg ml⁻¹)</th>
<th>Number of patients/group</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1:0</td>
<td>10:0</td>
<td>21</td>
</tr>
<tr>
<td>II</td>
<td>0:1</td>
<td>0:12</td>
<td>21</td>
</tr>
<tr>
<td>III</td>
<td>1:1</td>
<td>5:60</td>
<td>20</td>
</tr>
<tr>
<td>IV</td>
<td>1:0.3</td>
<td>7:50</td>
<td>19</td>
</tr>
<tr>
<td>V</td>
<td>1:3</td>
<td>2:5:90</td>
<td>20</td>
</tr>
</tbody>
</table>
Table 2  Patient characteristics and TAR. Results are mean values (SEM) (age, range)

<table>
<thead>
<tr>
<th>Group</th>
<th>I (1:0)</th>
<th>II (0:1)</th>
<th>III (1:1)</th>
<th>IV (1:0.3)</th>
<th>V (1:3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>44.8 (37–53)</td>
<td>46.9 (35–60)</td>
<td>48.5 (41–60)</td>
<td>46.9 (34–70)</td>
<td>47.4 (36–62)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66.7 (2.9)</td>
<td>64.5 (2.8)</td>
<td>68.7 (2.6)</td>
<td>66.0 (1.7)</td>
<td>69.2 (2.6)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>157 (0.9)</td>
<td>156 (1.5)</td>
<td>156 (1.6)</td>
<td>157 (1.2)</td>
<td>155 (1.4)</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>107 (6)</td>
<td>97 (7)</td>
<td>103 (6)</td>
<td>103 (6)</td>
<td>111 (7)</td>
</tr>
<tr>
<td>TAR (min)</td>
<td>54.3 (8.6)</td>
<td>44.2 (7.2)</td>
<td>50.3 (6.8)</td>
<td>52.4 (6.0)</td>
<td>45.3 (5.9)</td>
</tr>
</tbody>
</table>

This calculation permits the distribution of patients into two groups: those that had an improvement of their pain equal or above 50%, and those that benefited to a lesser degree (<50% improvement). Thus, the efficacy of the treatment will be expressed as the number of patients in each group that experienced a 50% or greater pain relief.

**Analysis of the interaction**

The cumulative doses consumed at each time-point were used to calculate interaction indexes and for constructing isobols; the calculation was possible because all drug combinations produced equivalent responses (VAS-PI) at each time of evaluation. For efficacy and adverse effects, dose–response relationships were obtained by plotting cumulative doses against efficacy and incidence of adverse effects, and the EDₐ₀ determined according to the method of Litchfield and Wilcoxon. These values were then used to calculate interaction indexes. Interaction indexes (INT-I) permit a mathematical analysis of the nature of drug interactions and are obtained utilizing the following relationship:

\[ \frac{d_A}{D_A} + \frac{d_B}{D_B} = 1 \]

\( D_A \) and \( D_B \) are the doses of the drugs when used alone, while \( d_A \) and \( d_B \) are the doses of the same drugs when used in combination; in each case all producing the same response. Interaction indexes greater or lower than 1 demonstrate interactions that are less or more than additive, respectively. Statistical analysis (Student’s t-test) of the interaction indexes was performed comparing the experimentally observed doses with those expected to occur had no interaction been present.

**Construction of isobols**

Isobols are graphic representations of equally effective doses of two or more agents. The mean (SEM) doses of each drug that produces a given response are plotted on the axes of the graph. A zero interaction line (isobol) connects these isoeffective doses in the axis; lines connecting the upper and lower values of the SEM in the axis indicate the error of the isobol line. Doses of drug combinations producing the same effect are then plotted. Points falling on the diagonal line represent zero interaction (additivity), while those located above and below are antagonistic and synergistic, respectively. Mean and SEM were calculated for all the doses plotted, and points were considered to differ significantly if their SEMs did not overlap. In our study, isobs were constructed with doses of the drugs (individually and in combination) associated with the same pain intensity.

**Statistical evaluation**

Statistical calculations were performed as described by Tallarida and Murray. Data are expressed as mean (SEM) or 95% confidence limits (CL). One-way analysis of variance (ANOVA) or chi-squared tests were used for comparison of the data.

**Results**

Patient characteristics, duration of surgery and TAR for each group are shown in Table 2. There were no significant differences.

Figure 1 illustrates mean pain intensity as a function of time for each of the five treatment groups. Pain intensity at the TAR (zero time-point) varied from 7.2 to 8.0. There were no significant differences (ANOVA). The decline in VAS-PI with time was found to be exponential with rate constants \( k \) that did not differ significantly between groups (\( k \) values ranging from –0.39 to –0.68). All groups exhibited a rapid fall in VAS-PI over the first 2 h, and a slow decline thereafter. A test for parallelism of the two segments of the graphs (represented by time-points 0–2 h and 4–24 h) demonstrated that, for each component, the slopes did not differ significantly between treatment groups (mean values 0.40 and 0.07, respectively). The similarity in the slopes of the lines representing the different treatments demonstrates that each provided a similar VAS-PI throughout the duration of the study.

The consistency of the VAS-PI at each time-point supports our assumption that patients would self-administer analgesics to a uniform end point. This similarity allows us to perform a null-point evaluation of the doses of the drugs and their interaction at the same VAS-PI. Thus, differences in the doses (not changes in response) of each drug individually or in combination will be the variable used to evaluate drug interactions.

The time to analgesia request (TAR) and the VAS-PI at that time did not differ significantly between the treatment groups. Fifteen minutes after the loading dose, VAS-PI was found to vary between 4.5 and 5.8 (Fig. 1). Analysis of
Fig 1 Mean VAS-PI values for each of the indicated times of evaluation. VAS-PI values obtained from each group were compared with the other treatments at every time-point (ANOVA). No significant differences were observed.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>III (1:1)</th>
<th>IV (1:0.3)</th>
<th>V (1:3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Synergy (0.79*)</td>
<td>Additive (0.94)</td>
<td>Additive (0.92)</td>
</tr>
<tr>
<td>8</td>
<td>Synergy (0.74**)</td>
<td>Additive (0.93)</td>
<td>Additive (0.97)</td>
</tr>
<tr>
<td>12</td>
<td>Synergy (0.71*)</td>
<td>Additive (0.88)</td>
<td>Additive (0.93)</td>
</tr>
<tr>
<td>20</td>
<td>Synergy (0.73**)</td>
<td>Additive (0.89)</td>
<td>Additive (0.97)</td>
</tr>
<tr>
<td>24</td>
<td>Synergy (0.73**)</td>
<td>Additive (0.93)</td>
<td>Additive (0.93)</td>
</tr>
</tbody>
</table>

The variance of VAS-PI and of the per cent pain relief failed to reveal any significant differences. Mean per cent pain relief was 32.7% demonstrating that the loading doses produced similar but clinically insufficient pain relief. PCA was initiated 15 min after the loading dose, and VAS-PI assessed 1, 2, 4, 8, 12, 20 and 24 h afterwards. At each time-point, all treatments produced equivalent degrees of per cent pain relief. Pain relief increased over time, and starting at 2 h, all patients experienced at least 50% pain relief (54–88% range) for the duration of the study.

Efficacy was defined as the proportion of patients who experienced a 50% or greater degree of pain relief. In all treatment groups, efficacy was fully established by 2 h and continued throughout the study. Furthermore, there were no differences in efficacy between groups at any of the time-points (chi-squared test). A total of 14 patients were excluded from the study at 20 and 24 h. In three of these cases, patients required rescue analgesia after utilizing all the medication in the cassette; in 10 additional cases, patients elected not to continue with the study because of low pain intensity and the discomfort created by the i.v. line. For one patient, there was mechanical pump malfunction. All patient exclusions occurred after 20 and 24 h of treatment. The incidence of subject exclusion in the different groups did not differ significantly (Student’s t-test; *P<0.05 and **P<0.001).

At each time of evaluation, the cumulative volumes that were dispensed by the pump were recorded and converted into dose in mg. For groups III–V, the dose of each drug in the mixture was calculated (Table 1). The data were then analysed as cumulative dose and as milligrams per hour.

**Analysis of drug interactions**
The data show that all PCA treatments were equally effective in reducing pain. Drug interactions were evaluated using: (i) per cent pain relief at each time-point; and (ii) 50% efficacy. Because treatments produced equivalent effects, the results could be calculated arithmetically using interaction indexes, and graphically with isobolograms.

**Per cent pain relief**
Statistical evaluation of per cent pain relief revealed that when the drugs were used in a 1 : 1 combination (group III),
a synergistic interaction occurred at 4 h and all subsequent 
time-points. The interaction indexes in this group varied 
from 0.79 to 0.71 (P<0.05 when compared with an index of 
1). None of the other combinations (1:0.3 and 1:3, groups IV 
and V, respectively) were significantly different from 
additivity (Table 3).

Isobols were constructed showing the doses of drug 
combinations in groups III–V required to produce the same 
degree of analgesia (VAS-PI range 2.4–2.7) at the 8 h time-
point. This time was selected as being representative of the 
time-points at which VAS-PI was most stable in the second 
segment of the curve (Fig. 1). The isobologram (Fig. 2) 
demonstrates synergy for the 1:1 combination, while no 
interaction was observed for the 1:0.3 and 1:3 drug ratios 
(additivity).

Efficacy of the treatments
The tramadol–metamizol interaction was also analysed 
utilizing cumulative doses of the drugs and the fraction 
of individuals with 50% pain relief (50% efficacy). From the 
quantal dose–response curves, we determined the doses at 
which half of the patients achieved this level of response 
(ED50), and the values used to calculate the interaction 
indexes. The CL of the ED50 of each drug alone were 
compared with those of the drugs used in combination; if the 
95% CL did not overlap the values were considered to be 
significantly different. The results (Table 4) also demon-
strated statistically significant synergy in patients in group 
III (1:1 ratio) and no interaction with the other groups.

Adverse effects
At each time of evaluation patients were monitored for the 
occurrence of adverse effects: nausea, vomiting, sedation, 
pruritus, headache and pain on the site of injection. Nausea 
and vomiting were the most prevalent followed by sedation; 
the others were not analysed because they occurred 
infrequently.

We expressed these data quantally, and for each treatment 
group the results were analysed to determine: (i) the total 
number of adverse effects (global incidence) associated 
with each treatment; (ii) the number of patients with one or 
more adverse effects; and (iii) the time at which adverse 
effects occurred. The relatively low incidence of each one of 
the adverse effects precluded their separate or individual 
evaluation, and thus the results were analysed globally.

Forty-seven per cent of the patients reported one or more 
adverse effect (average 1–2) with a total of 71 events 
reported during the 24 h of observation. Neither the total 
number of adverse effects nor the number of patients 
experiencing them differed significantly between the treat-
ment groups (chi-squared test). When adverse effects were 
present, they occurred most often at 4 and 8 h (27% each), 
and during the first hour (20%).

An analysis of the incidence of adverse effects indicated 
that the overall incidence of these events tended to decline 
as the concentration of metamizol in the mixture increased 
correlation coefficient 0.64, P<0.05). The ED50 values for 
adverse events were obtained and used for the calculation of 
the interaction indexes (Table 4). Synergy was demon-
strated in group III (1:1 mixture), while no significant 
interaction occurred in the other groups (additivity). The 
results demonstrate that when drugs are used in a 1:1 
combination (group III) a synergistic interaction is present.

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**Table 4** Type of interaction of the combinations of tramadol and metamizol, for efficacy and adverse effects at the ED50 values. Mean ED50 values (95% 
CL) expressed in total mg were obtained from quantal dose–response curves in which efficacy and incidence of adverse effects are plotted against the 
cumulative doses. INT-I: interaction indexes. *P<0.05, NS (not significant when compared with additivity)

<table>
<thead>
<tr>
<th>Group</th>
<th>III (1:1)</th>
<th>IV (1:0.3)</th>
<th>V (1:3)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ED50</td>
<td>601 (448–807)</td>
<td>586 (478–719)</td>
<td>1417 (1121–1793)</td>
</tr>
<tr>
<td>Interaction</td>
<td>Synergy</td>
<td>Additive</td>
<td>Additive</td>
</tr>
<tr>
<td>INT-I</td>
<td>0.60*</td>
<td>1.10 (NS)</td>
<td>0.98 (NS)</td>
</tr>
<tr>
<td><strong>Adverse effects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ED50</td>
<td>1649 (1425–1905)</td>
<td>1355 (1103–1663)</td>
<td>5867 (4054–8489)</td>
</tr>
<tr>
<td>Interaction</td>
<td>Synergy</td>
<td>Additive</td>
<td>Additive</td>
</tr>
<tr>
<td>INT-I</td>
<td>0.62*</td>
<td>1.07 (NS)</td>
<td>1.3 (NS)</td>
</tr>
</tbody>
</table>
both for beneficial and undesirable effects; a comparison of the ED$_{50}$ values reveals a therapeutic index of 2.7.

**Discussion**

The present study shows that the interaction between tramadol and metamizol is synergistic when the drugs are combined in a 1:1 potency ratio, and that both beneficial and adverse effects demonstrate the same type of interaction. We have utilized i.v. PCA as a means of evaluating the analgesic requirements needed to relieve postoperative pain. The drugs were selected because they are routinely used for the treatment of postoperative pain in our institution, their potency ratio is well established, and they have a similar onset and duration of action. Evaluation of drug interactions using PCA is not applicable to drugs with significantly different pharmacokinetic values.

PCA-based analgesic consumption is not a very precise method determining degree of analgesia, but it is the only available method to determine objectively drug requirements. However, pain intensity was estimated by a VAS scale, a method which is widely accepted.

The single use of the VAS-PI at rest for the evaluation of pain relief is a relative weakness of our study. In our original protocol, pain relief was also assessed by the nursing staff according to a four-point categorical scale. However, data collection was irregular and unreliable, thus precluding its use in the statistical evaluation. Similarly we were unable to use the number of boluses requested/delivered by the PCA pump each hour as a measure of the adequacy of the treatments. The data demonstrated considerable variability mainly in the number of requests per hour, while the number of boluses delivered/hour was more uniform; an analysis of variance failed to detect significant differences in either value.

The VAS-PI at the TAR was similar in all groups, and was used as the reference point for further calculations (per cent pain relief, per cent efficacy). Patients in each group titrated themselves to a comparable VAS-PI throughout the study, thus confirming our working hypotheses and validating the method of analysis. Our results are consistent with those previously reported that patients do not self-administer analgesics to a complete elimination of pain, but rather to a VAS-PI value <3, a value that reflects a low to moderate pain intensity.

In all patients, the loading doses by themselves failed to provide a satisfactory degree of analgesia (mean VAS-PI of 5.1). We think that this inadequacy was related to the high level of pain at the time of administration, a situation which would not occur in a clinical setting where analgesics are usually administered before experiencing severe pain. Consequently, in the present study, higher loading doses would have been appropriate.

During PCA, the VAS-PI declined rapidly, reaching a steady-state by about 2–4 h. When analysing the curves we were able to demonstrate that all treatment regimes followed a similar pattern of decline over time. The importance of these data is that, regardless of the regimen to which patients were assigned, all had a similar VAS-PI at each time of evaluation. This fact enabled the comparison of the doses of each drug (alone or in combination) needed to produce equivalent VAS-PIs. Figure 1 also shows that, at 1 and 2 h, patients were experiencing moderate pain (VAS-PI about 4) despite the possibility of self-administering additional medication, as at this time(s) the maximal doses allowed by the protocol were not exhausted. We are not able to explain this observation although the decrease in pain intensity (from severe to moderate) may have produced a subjective sensation of relief that made additional request(s) unnecessary.

We defined efficacy as the proportion of patients who experienced a 50% or greater degree of pain relief, when compared with the VAS-PI at the TAR. However, because pain relief decreases gradually during the postoperative period, the calculated effect of the drugs includes the spontaneous decrease in pain intensity that is not drug related. Because VAS-PI at the TAR was unusually high (about 8), the calculated 50% efficacy does not necessarily reflect adequate analgesia, but the value was used as an additional method to assess and compare the effects. Regardless of the way in which the data were presented, all treatment regimens produced comparable results. The similarity of effects at each time-point permitted us to compare the doses of individual agents and their combination/s needed to produce equivalent results (i.e. VAS-PI, per cent relief, per cent efficacy).

Our data also show that per cent pain relief increased over time. Similarly, hourly drug usage also decreased up to 20 h. These data suggest a substantial decrease in pain intensity after 4 h, a fact that probably deserves further evaluation. The progressive decrease in VAS-PI (Fig. 1) together with the decline in the doses of the drugs self-administered shows that postoperative pain spontaneously diminished during the first 24 h. If pain remained constant, drug utilization would be expected to increase or remain high in order to reduce the VAS-PI to acceptable levels.

For the analysis of the interaction between tramadol and metamizol we used mathematical (combination indexes) and graphic (isobolograms) methods of evaluation. Both methods require that individual drugs and their combination produce the same level of response. When the drugs were used in a 1:1 ratio, synergy was demonstrated from 4 h onwards for the VAS-PI data. Similarly synergy was detected only in the same group for efficacy. Other treatment groups using 1:0.3 and 1:3 drug combinations were found to be additive. As with most other drug combinations, the mechanism/s involved in the change in the type of interaction when using different drug ratios are unknown. The evaluation of dose–response curves for adverse effects likewise demonstrated synergy when the drugs were used in a 1:1 combination. A comparison of the ED$_{50}$ values (Table 4) for efficacy and adverse effects for
the 1:1 combination reveals a therapeutic index of 2.7, indicating that the combination may be of therapeutic value. However, due to the number of patients and groups evaluated, and the incidence of adverse effects, these could only be evaluated globally and the results are not specific for nausea, vomiting or sedation. A larger number of patients using the same protocol would have to be evaluated in order to be able to demonstrate that each one of the adverse effects observed in the study is (or is not) dose dependent. Thus, the results show that when beneficial and pooled adverse effects were evaluated, tramadol and metamizol interact synergistically when combined in a 1:1 ratio.

Acknowledgements
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