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Short communication

Non-steroidal anti-inflammatory drugs antagonise the constipating effects of tramadol

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Abstract

We report an antagonistic interaction between tramadol and non-steroidal anti-inflammatory drugs (NSAIDs), on gastrointestinal transit in rats. Transit was evaluated with charcoal and results are expressed as %inhibition. Tramadol and morphine had ED_{50}s of 120.70 ± 9.54 and 3.20 ± 0.26 mg/kg, respectively, while metamizol (85 mg/kg), paracetamol (100 mg/kg) or ibuprofen (50 mg/kg) had no effect. All combinations of tramadol plus an NSAID, resulted in a rightward, non-parallel shift of the curves, which showed (two-way analysis of variance, ANOVA) significant differences from tramadol alone for the dose ($P<0.0001$), the drug ($P<0.0001$) and their interaction ($P<0.0001$), demonstrating antagonism. No interaction was present for morphine plus NSAIDs. The results demonstrate that NSAIDs antagonise the constipating effects of tramadol in rats, a fact that could have clinical relevance when combinations of these drugs are used in pain management in humans.

Keywords: Tramadol; Non-steroidal anti-inflammatory drug (NSAID); Antagonism; Interaction; Gastrointestinal transit

1. Introduction

Drug combinations are commonly used in pain management during multimodal analgesia (Kehlet et al., 1999), with the aim of enhancing/maintaining analgesia, and reducing adverse effects. When two or more drugs are given simultaneously, their pharmacological effects (beneficial and adverse) can be additive, or an interaction (synergy, antagonism) may occur. Synergy has been demonstrated for analgesia with different drug combinations both in humans (Montes et al., 2000) and in animal models (Poveda et al., 2003); however, the type of interaction regarding adverse effects is generally unknown. Ileus/constipation is a common adverse effect of opioids, while non-steroidal anti-inflammatory drugs (NSAIDs) do not appear to decrease transit; thus the simultaneous administration of morphine plus metamizol did not alter the constipating effects of the opioid (Hernández-Delgadillo et al., 2002). Tramadol is a μ-opioid receptor agonist that increases serotonin and noradrenaline levels in the central nervous system (CNS) and induces less constipation than morphine (Desmeules, 2000). NSAIDs as a group produce analgesia by blocking the cyclooxigenase isoenzymes, but other mechanisms implicating serotonin and noradrenaline descending inhibitory pathways have been suggested (Bjorkman, 1995). The possible similarities in the mechanisms of action of these drugs could partially explain analgesic synergy. In the present investigation, we hypothesised that synergy could also be present for constipation, and thus we investigated the effects of the combination of tramadol with NSAIDs on the inhibition of gastrointestinal transit in rats.

2. Material and methods

2.1. Animals

The Institutional Committee on Animal Use and Care approved the protocol. Male Sprague–Dawley rats (150–

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170 g) housed under controlled standard conditions (12 h dark/light cycle, 22 °C temperature and 66% humidity) was used in the study. Animals were acclimated to the housing conditions for at least 1 week before use. All experiments were conducted between 9 and 15 h.

2.2. Drugs

Morphine chlorhydrate (Alcaliber, Madrid, Spain); tramadol chlorhydrate (Grünenthal, Spain); metamizol magnesium (Boehringer Ingelheim, Spain); ibuprofen and paracetamol (Sigma, USA) were used. Drugs and their combinations were prepared in 0.9% NaCl, except for paracetamol, which was dissolved in ethanol 0.5 M. All drugs were given subcutaneously (s.c.) in a final volume of 3.3 ml/kg, 30 min before charcoal. Control animals received s.c. saline.

2.3. Evaluation of gastrointestinal transit

Gastrointestinal transit was evaluated according to procedures used by our group in mice (Puig et al., 2000). After fasting for 18 h gastrointestinal transit was evaluated 25 min after the intragastric administration of a charcoal meal (2 ml of a suspension of 10% vegetable charcoal in 5% gum acacia). After sacrifice, the small intestine was separated from the omentum, and the length of intestine from the pyloric sphincter to the ileocecal junction, and the distance travelled by the charcoal were recorded. For each animal, gastrointestinal transit was calculated as the percentage of the distance travelled by the marker relative the total length of the small intestine. The inhibitory effects of drugs on gastrointestinal transit are expressed as %inhibition of gastrointestinal transit (test transit) when compared with the gastrointestinal transit in vehicle-treated rats.

$$\%\,\text{inhibition} = \frac{(\text{transit vehicle} - \text{transit test})}{(\text{transit vehicle})} \times 100.$$

2.4. Experiments performed

Dose–response relationships were first established for tramadol and morphine individually, and the median effective doses (ED_{50}s), determined. This was defined as the dose of a drug or a combination that produced a 50% inhibition of gastrointestinal transit. The inhibitory effects of metamizol (85 mg/kg), paracetamol (100 mg/kg) and ibuprofen (50 mg/kg), each one individually, on the inhibition of gastrointestinal transit were also tested ($n = 6–8$ animals per group). Next we obtained dose–response curves to tramadol in the presence of a fixed dose of each one of the NSAIDs, at the doses previously tested. The doses were selected on the basis of their antinociceptive efficacy in different rat models of acute inflammatory pain (Poveda et al., 2003; Alloui et al., 2002; Lichtenberger et al., 2001). A dose–response curve for morphine in the presence of metamizol (85 mg/kg) was also carried out. In addition, we tested the inhibitory effects of the ED_{50} of morphine (3.2 mg/kg) in the presence of paracetamol (100 mg/kg) or ibuprofen (50 mg/kg), using 6–8 animals per group.

For all dose–response curves, six to eight rats were tested per dose, and five points used to define each curve; with this data we could generate 6–8 dose–response curves for each experimental protocol used in the study.

2.5. Data analysis

The antitransit effects of the individual drugs and their combinations are expressed as %inhibition of gastrointestinal transit. The EDs at the different levels of effect were calculated by linear regression analysis, according to Tallarida (2001). The effects of the NSAIDs on the inhibition of gastrointestinal transit when compared to control (non-treated animals), was established by one-way analysis of variance (ANOVA).

In the fixed-dose experiments, the dose–response curves to tramadol or morphine alone were compared with the dose–response curves to each opioid in the presence of a fixed dose of an NSAID (metamizol, paracetamol or ibuprofen). For each treatment, if the log dose–response curve for the combination shows a shift to the right, and the effect produced by each dose of tramadol alone is greater than the effect obtained with the combination (Student's *t*-test), an antagonism is present. The type of interaction was also assessed by two-way ANOVA that determines the presence of statistical differences between two groups. The groups compared were the log dose–response curve of tramadol or morphine alone, and the log dose–response to each opioid in the presence of a fixed dose of an NSAID. For the two-way ANOVA, the two factors evaluated were: the drugs (opioid alone and opioid + one NSAID) and the doses used to obtain the dose–response curves. The effect of the drugs, the dose, and their interaction was determined (Miaskowski et al., 1992). If all factors (drugs, dose and interaction) are significantly different, the analysis shows that the effect of the combination differs from additivity. However, if the interaction is not statistically significant, the effects are considered additive. This method is not applicable when dose–response curves are parallel because ANOVA cannot discriminate parallel-additive from parallel-synergistic or antagonistic interactions (Tallarida, 1992).

3. Results

In control animals ($n = 40$) percent gastrointestinal transit was 55.4 ± 0.75. The variability of the test expressed as

percent of the coefficient of variability was 8.53% (% CV = S.D./mean × 100).

3.1. Effects of the individual drugs on gastrointestinal transit

Tramadol and morphine each induced a dose-related inhibition of gastrointestinal transit with Emax values of 60% and 88%, respectively. The slopes of the curves were not significantly different. From each curve, calculated EDs were: $ED_{20} = 48.67 \pm 3.28$ and $ED_{50} = 120.70 \pm 9.54$ mg/kg for tramadol, and for morphine $ED_{20} = 1.07 \pm 0.12$, $ED_{50} = 3.20 \pm 0.26$ and $ED_{80} = 9.61 \pm 1.29$ mg/kg. Thus on the basis of their ED_{50}s, morphine is approximately 40 times more potent than tramadol on the inhibition of gastrointestinal transit.

The s.c. administration of metamizol (85 mg/kg), paracetamol (100 mg/kg) or ibuprofen (50 mg/kg) alone, did not alter gastrointestinal transit when compared to control animals (one-way ANOVA). The actual values were: $55.4 \pm 0.75\%$, $54.0 \pm 2.24\%$, $52.4 \pm 1.28\%$ and $53.5 \pm 1.58\%$ for control, metamizol, paracetamol and ibuprofen treated animals, respectively. Higher doses of the drugs (twofold) also failed to induce an inhibitory effect on gastrointestinal transit.

3.2. Antitransit effect of the combinations

The three combinations of tramadol plus an NSAID, resulted in non-parallel dose–response curves that were shifted to the right (Fig. 1). When the tramadol dose–response curve was compared with each one of the tramadol + NSAID combinations (two-way ANOVA), statistically significant differences were obtained for the dose ($P < 0.0001$), the drug ($P < 0.0001$) and their interaction ($P < 0.0001$), demonstrating the presence of an interaction. The effects produced by each dose of tramadol alone were also compared with the corresponding doses of each drug combination (Student's *t*-test); the results demonstrated significant differences ($P < 0.05$) between the inhibitory effect of tramadol and each one of the combinations (tramadol plus metamizol, paracetamol or ibuprofen) at levels of effect above 30%. Thus the three NSAIDs evaluated at fixed doses, were able to antagonise the antitransit effects of tramadol.

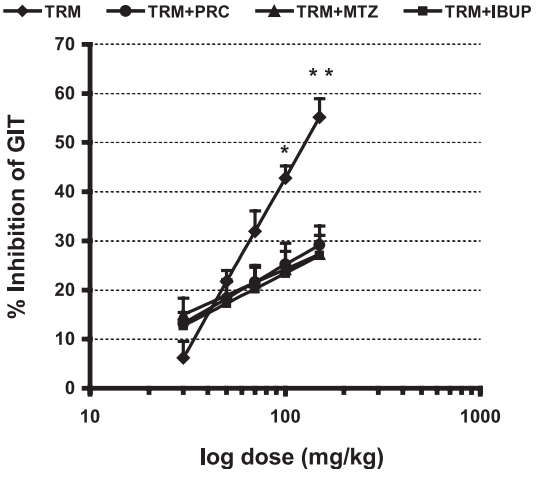

Fig. 1. Log dose–response curves for tramadol alone (TRM) (diamonds) and combined with metamizol (MTZ) (triangles), paracetamol (PRC) (circles) or ibuprofen (IBUP) (squares), on the inhibition of gastrointestinal transit. Each point represents the mean values and vertical bars indicate the S.E.M. Six to eight animals were tested per dose, and five points used to define each curve; with this data we could generate 6–8 dose–response curves for each treatment, that were used to obtain the mean values. An (*) and (**) indicates a $P < 0.05$ and $P < 0.01$, respectively, when compared to each one of the drug combinations.

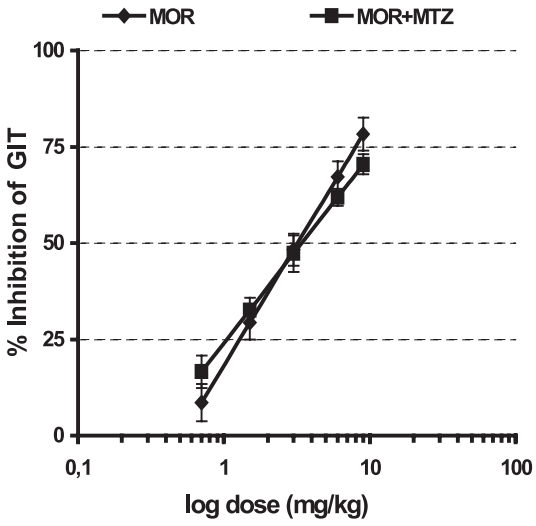

Fig. 2. Log dose–response curves for morphine alone (MOR) (diamonds) and combined with metamizol (MTZ) (squares), on the inhibition of gastrointestinal transit. Each point represents the mean values and vertical bars indicate the S.E.M. Six to eight rats were tested per dose, and five points used to define each curve; with this data we could generate 6–8 dose–response curves for each treatment, which were used to obtain the mean values.

We also obtained a morphine dose–response curve in the presence of a fixed dose of metamizol (85 mg/kg) and compared the effects with those of morphine alone. The resulting curves were parallel and practically identical (Fig. 2), demonstrating that metamizol does not alter the effects of morphine on the inhibition of gastrointestinal transit. On the basis of these results, and in order to avoid unnecessary use of animals, we tested the ED_{50} of morphine (3.2 mg/kg) in the presence of paracetamol (100 mg/kg) or ibuprofen (50 mg/kg). No significant differences could be established between the effect of the ED_{50} of morphine alone ($50 \pm 4.5\%$) and those of morphine plus metamizol ($49.9 \pm 4.3\%$), paracetamol ($42.4 \pm 3.3\%$) or ibuprofen ($42.3 \pm 4.3\%$) (Student's *t*-test). Thus no interaction between morphine and NSAIDs

on the inhibition of gastrointestinal transit could be demonstrated.

4. Discussion

The paper illustrates an antagonistic interaction between tramadol and NSAIDs on the inhibition on gastrointestinal transit. This antagonism seems to be drug specific for tramadol since the effect of morphine is not altered by the simultaneous administration of NSAIDs.

The interaction could have clinical relevance, since tramadol is widely used in the treatment of acute and chronic pains, and often combined with NSAIDs. Although the constipating effects in humans are clearly less marked with tramadol than with other opioids such as morphine, ileum/constipation still occurs during tramadol administration. We have recently reported synergy for the antinociceptive effects of tramadol and metamizol both in humans (Montes et al., 2000) and in a model of visceral pain in rats (Poveda et al., 2003). If the antagonist effects on gastrointestinal transit can be demonstrated in humans, tramadol related ileus/constipation could be avoided by combining this drug with NSAIDs in the management of pain.

Regarding likely mechanisms implicated in the interaction, it is possible that drug-induced central (CNS) or peripheral release of serotonin may be implicated in the antagonism. Intestinal function is regulated by the central and peripheral nervous systems as well as by local (intestinal) mechanisms (Hansen, 2003). Tramadol produces constipation by activation of μ-opioid receptors and possibly by increasing noradrenaline levels; the increase in serotonin levels could partially counteract this effect and thus explain the lower constipating effects of tramadol. Moreover, all the NSAIDs used in the study have been postulated to activate descending inhibitor pathways that release serotonin in the spinal cord (Bjorkman, 1995). It is possible that increased levels of serotonin in the nervous system and/or in the gut could increase gastrointestinal transit, and thus antagonise the μ-opioid and/or noradrenaline induced constipation induced by tramadol. However, further experiments will be necessary to substantiate this hypothesis.

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