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RESEARCH ARTICLE

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Assessment of the antinociceptive and ulcerogenic activity of the tapentadol–diclofenac combination in rodents

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Abstract

The objective of the present study was to evaluate the tapentadol–diclofenac combination in three dose-ratios in the mouse acetic acid-induced visceral pain and their ulcerogenic activity on the stomachal mucous. Dose-response curves were generated for tapentadol, diclofenac, and their combination in the acetic acid-induced writhing test in mice. Moreover, the stomachs of animals were surgically removal and gastrointestinal ulcerogenic action of the combination was assessed. The isobolographic analysis, interaction index, and ANOVA were used to analyze the data. The isobolographic analysis and interaction index showed a similar antinociceptive activity for the three combinations of the analgesic mixture. Moreover, tapentadol and the proportions 1:1 or 3:1 of the analgesic combination caused a mild gastrointestinal damage. These data indicate that the systemic co-administration of tapentadol and diclofenac produced a synergistic interaction in the acetic acid-induced visceral pain test with an acceptable gastric damage profile in mice.

KEYWORDS

acetic acid-induced writhing test, antinociceptive synergistic interaction, diclofenac, gastrointestinal damage, tapentadol

1 | INTRODUCTION

Visceral pain originates from the internal thoracic, pelvic, and/or abdominal organs. It is dull, diffuse, poorly localized and characterized by hypersensitivity to pressure or distension. Visceral pain is the primary reason to seek medical attention (Kamp, Jones, Tillman, & Gebhart, 2003). Epidemiological data show that 5–25% of patients present chronic abdominal pain (El-Matary, Spray, & Sandhu, 2004), despite this large numbers of patients with chronic visceral pain the clinical management of these patients is largely inadequate (Patrizi, Freedman, Pascual-Leone, & Fregni, 2016). Consequently, it is crucial to explore novel therapeutic options to relieve this type of pain.

The association of two (or more) analgesic agents can produce an increase in the antinociceptive activity as well as a reduction in the amount or severity of the adverse effects compared to either drug alone (Ortiz et al., 2016). The use of drug combinations acting at different levels of the nervous system can enhance antinociception and allows lower doses to be used, which may decrease the side effects. Hence, the use of analgesic combinations may improve pain relief and safety profile, and in consequence, the clinical outcome (Raffa, 2001).

Tapentadol is an opioid analgesic effective in multiple pain conditions (Hale, Upmalis, Okamoto, Lange, & Rauschkolb, 2009; Lange et al., 2010; Riemsma et al., 2011; Wade & Spruill, 2009). It acts by binding to μ-opioid receptors and by inhibiting the noradrenaline reuptake (Falk, Patel, Heegaard, Mercadante, & Dickenson, 2015). As a consequence of these effects, tapentadol presents several adverse effects on the nervous and gastrointestinal systems (Isiordia-Espinoza, Pozos-Guillén, & Aragon-Martinez, 2014). Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) effective for the relief of post-surgical and

inflammatory pain (Patrono & Rocca, 2009) acting via nonselective inhibition of the cyclooxygenases (COXs), COX-1 and COX-2 (Pountos, Georgouli, Bird, & Giannoudis, 2011). Patients taking this drug have showed several adverse reactions of which the gastrointestinal injury is of great interest (Ortiz, 2017; Ortiz et al., 2016). The opioid-sparing effects of NSAIDs can lead to a reduction in opioid-related adverse effects, in particular of nausea, vomiting, and sedation (Elia, Lysakowski, & Tramèr, 2005; McDaid et al., 2010). In contrast, the reduction of gastrointestinal side effects by opioids has been less explored.

The purpose of the present study was to evaluate the antinociceptive effect and gastric damage of tapentadol alone and combined with diclofenac in the acetic acid-induced visceral pain in mice.

2 | MATERIALS AND METHODS

2.1 | Animals

Male CD-1 mice (8–10 weeks old; 20–25 g) were used. Animals were maintained at 22°C with a 12-hr light–dark cycle and fed standard laboratory diet and water *ad libitum*. All experiments were carried out in agreement with the Guidelines on Ethical Standards for Investigation of Experimental Pain in Animals (Zimmerman, 1983). The experimental protocol was approved by our Institutional Ethics Committee.

2.2 | Drugs

Commercial tablets of tapentadol (Palexia 50 mg) were acquired from Grünenthal de Mexico (Mexico City), while diclofenac sodium was obtained from Sigma (St. Louis, MO). These drugs were dissolved in sterile saline before their administration to animals.

2.3 | Acetic acid-induced writhing model

Animals were administered with 10 mL/kg of 1% acetic acid ip previously described (Vinegar, Truax, & Selph, 1976; Zapata-Morales et al., 2016). A characteristic writhing (a contraction of the abdominal muscle together with a stretching of the hind limbs) occurred and the animals were immediately placed in observation chambers, and the number of writhing episodes in a 5 min-period were recorded over the next 30 min. A reduction of the number of writhing episodes in the 30 min period was considered as antinociception. Each mouse was sacrificed in a CO_2 chamber at the end of the behavioral assay.

2.4 | Experimental design

Sterile saline solution (control group, i.p.), tapentadol (5.62, 10, 17.78, or 31.62 mg/kg, i.p.), or diclofenac (17.78, 31.62, 56.23, or 74.98 mg/kg, i.p.) were administered 15 min before the acetic acid injection. The percent antinociception was calculated according to the following equation: [(vehicle-post compound)/vehicle] × 100. Dose-response curves were used to calculate the dose resulting in 50% of the effect (ED_{50} value) of each individual agent. These ED_{50} values were used to determine the experimental combinations in three different fixed ratios (1:1, 3:1, and 1:3). Each combination was evaluated in four different animal groups.

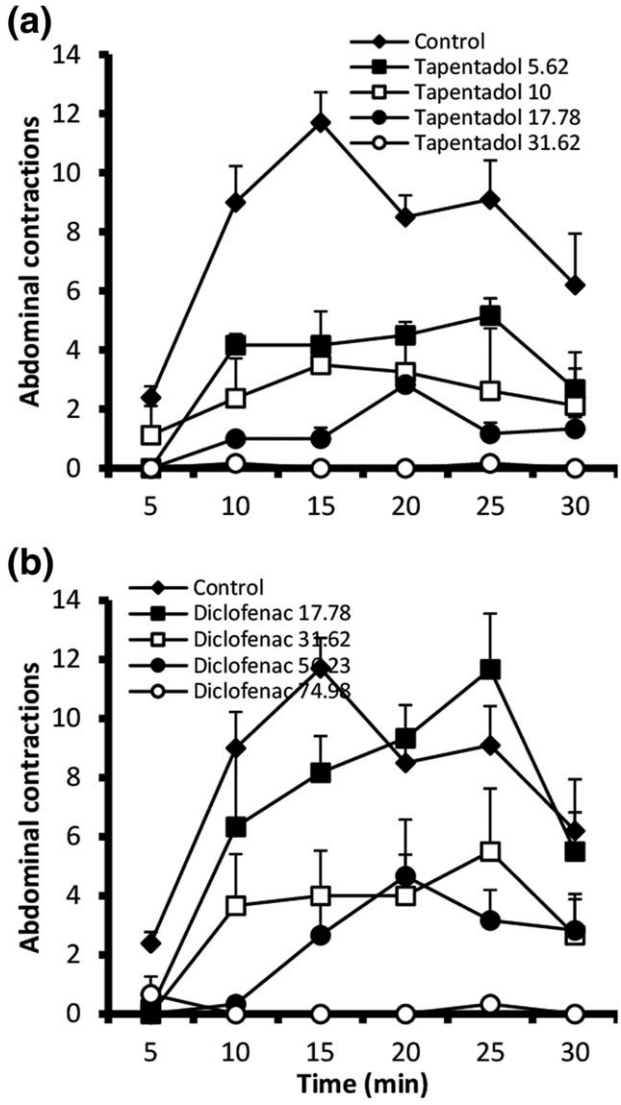

FIGURE 1 Time-courses of the antinociceptive activity of tapentadol (a) and diclofenac (b) in the acetic acid-induced visceral pain test. Data are means ± *SEM* at least for six animals

2.5 | Ulcerogenic effect

Mice were fasted for 18 hr before the experiment, with free access to water. Mice were divided into seven treatment groups ($n = 8$, each group). Animals received the following treatments orally: (a) vehicle (saline solution), (b) 0.2 mL ethanol (EtOH) to induce gastric ulceration, (c) tapentadol 31.62 mg/kg, (d) diclofenac 74.98 mg/kg, (e) tapentadol 5.8 mg/kg and diclofenac 16.4 mg/kg (1:1 ratio), (f) tapentadol 3.9 mg/kg and diclofenac 32 mg/kg (3:1 proportion), and (g) tapentadol 19 mg/kg and diclofenac 49 mg/kg (1:3 ratio). After 6 hr of treatment, mice were sacrificed and their stomachs removed and placed in 50 mM phosphate buffer (pH 7.4) at 4°C for 5 min,

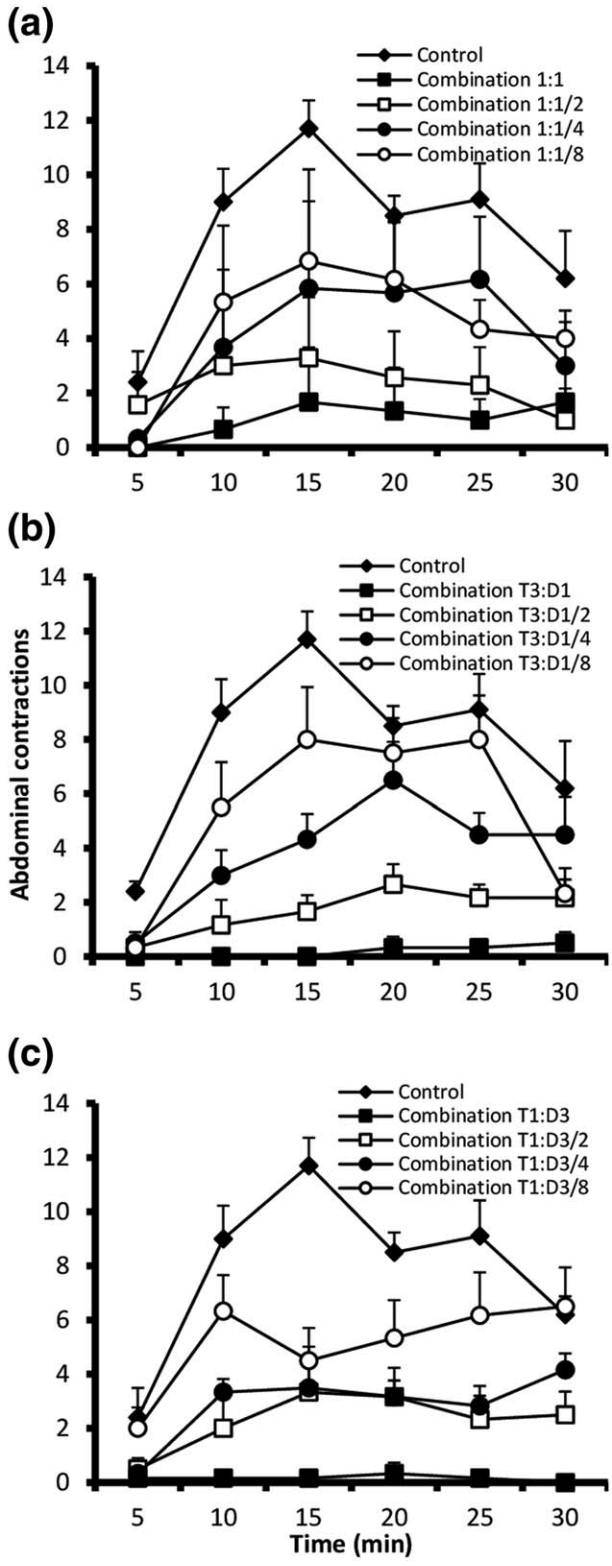

FIGURE 2 Time-curves of the antinociceptive effect of the three ratios of the tapentadol–diclofenac combination in the acetic acid-induced visceral pain test. Data are means ± *SEM* at least for six animals

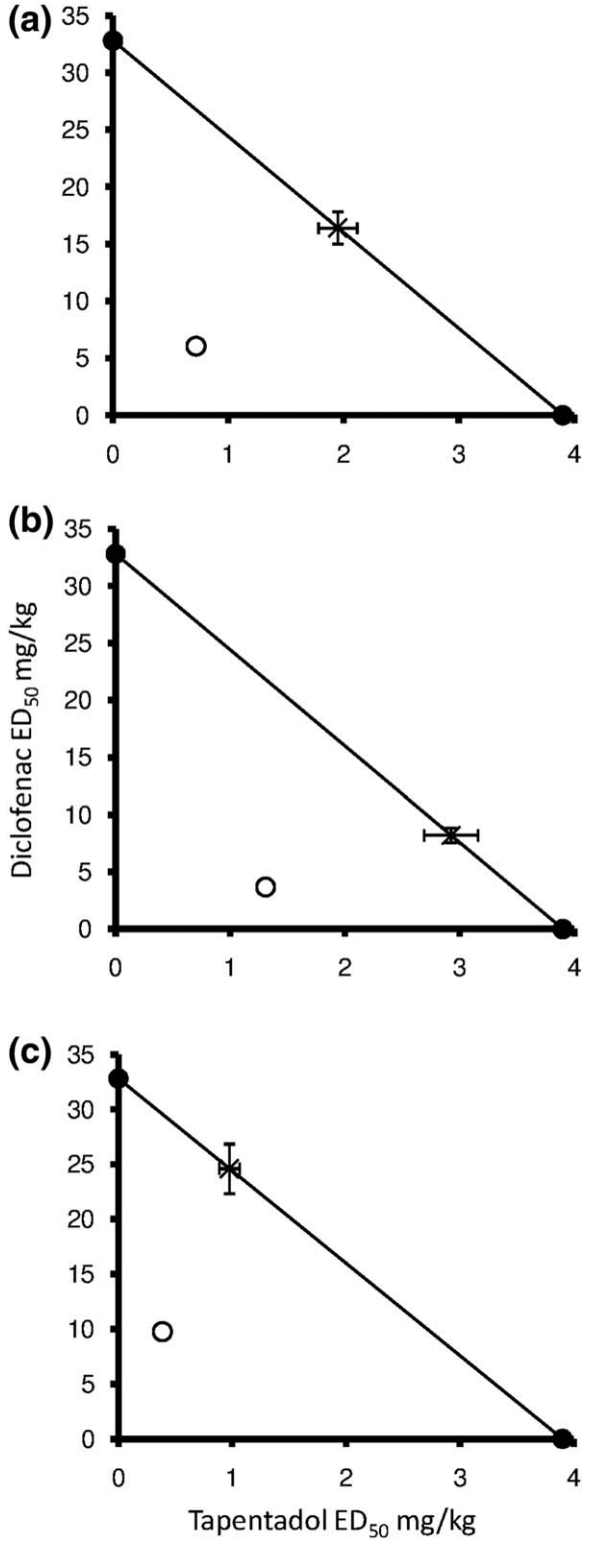

FIGURE 3 Isobolograms describing the synergistic interaction of the tapentadol–diclofenac combination in the acetic acid-induced visceral pain model [1:1 (a), 3:1 (b), and 1:3 (c) ratios]. Horizontal and vertical bars indicate *SEM*. The oblique line that connects the individual ED_{50} values in each combination (•) is the theoretical additive line. The point in this line is the theoretical additive point (Z_{add}, ■) calculated from the individual drug ED_{50} values. In all cases, the experimental ED_{50} values (Z_{exp}, ○) lie far below the additive lines indicating synergistic antinociceptive activity

inflated with 2 mL of 2% formalin and placed in 2% formalin to fix both the inner and outer layers. The stomachs were opened along the greater curvature, crushed and sandwiched between two

TABLE 1 Theoretical (Z_{add}) and experimental (Z_{exp}) ED_{50} values and interaction index for the different ratios of the mixture of tapentadol and diclofenac

	Combinations		
	T1:D1	T3:D1	T1:D3
Z_{add} (mg/kg)	18.36 ± 1.58	11.13 ± 0.89	25.59 ± 2.34
Z_{exp} (mg/kg)	6.77 ± 0.04*	4.98 ± 0.12*	10.16 ± 0.58*
Interaction Index	0.36	0.44	0.39

T: Tapentadol; D: Diclofenac.
Values are means ± *SEM*.
*$p < .05$ Z_{add} versus Z_{exp}, by the Student's *t*-test.

microscope slides. The stomachs were scanned and the captured image was analyzed to quantify the ulcer area (mm^2) using the processing and analysis program, Scion Image for Windows, Release Beta 4.0.2. (Khan, 2004).

2.6 | Statistical analysis

Antinociceptive and ulcerogenic activities for all experimental treatments were analyzed by one-way analysis of variance followed by the Student–Newman–Keuls test. Isobolographic analysis and interaction index were used for evaluating the antinociceptive interaction between tapentadol and diclofenac according to Tallarida (2002). *p* Values less than .05 were considered significant.

3 | RESULTS

3.1 | Antinociceptive activity

Tapentadol and diclofenac dose-dependently decreased acetic acid-induced nociception (Figure 1a,b). The antinociceptive effects of diclofenac were 12, 58, 71, and 98%, and for tapentadol were 56, 75, 84, and 96%. The three fixed dose ratios of the tapentadol–diclofenac combination dose-dependently diminished the pain behavior across the 30 min of the writhing test. The antinociception values of the 1:1 ratio of the tapentadol–diclofenac combination were 43, 47, 86, and 87%. The percentages of the 3:1 combination were 33, 50, 78, and 97%; while that for the 1:3 ratio were 34, 63, 71, and 97%. The time-courses of antinociceptive effect of the three proportions of the mixture are show in the Figure 2a–c.

3.2 | Isobolographic analysis

Isobolographic analysis of the co-administration of tapentadol and diclofenac showed an increased antinociceptive effect employing low doses of each drug in comparison with the action of the individual drugs. Thus, the experimental ED_{50} value of all combinations was below the additivity line indicating a synergistic interaction of the three dose ratios of the drug combination (Figure 3a–c).

3.3 | Interaction index

Both interaction index and isobolographic analysis showed similar results for all proportions of the mixture confirming a synergism in the inhibitory activity of the nociceptive behavior (Table 1).

3.4 | Ulcerogenic effect

EtOH produced significant mucosal damage (ulcers) of the mice as did diclofenac. In contrast, tapentadol alone as well as the 1:1 and 3:1 ratios of the combination produced mild gastric damage. The 1:3 the combination produced less gastric damage than diclofenac alone or EtOH but more than the 1:1 and 3:1 combination ratios (Figure 4a,b).

4 | DISCUSSION

The present study shows that the systemic administration of tapentadol produces a dose-dependent antinociceptive effect in a mouse

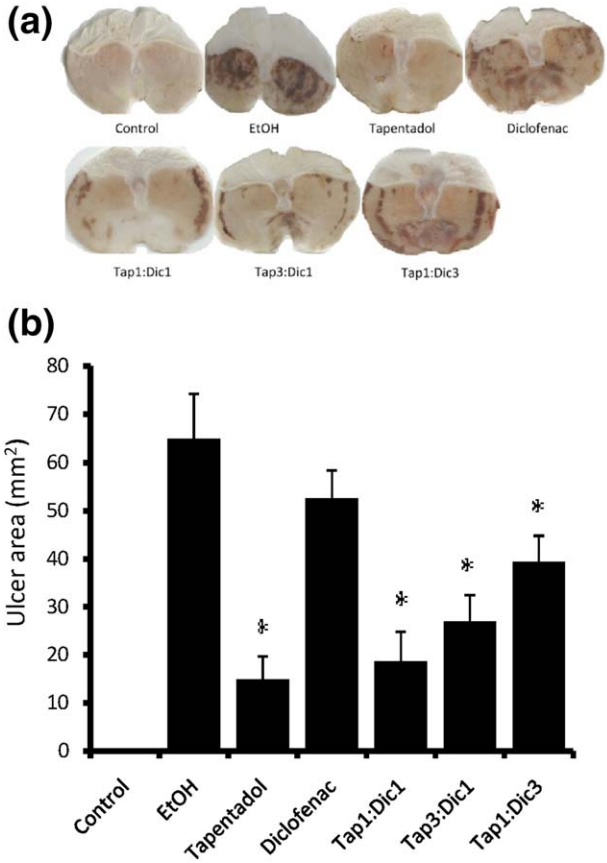

FIGURE 4 Graph showing the gastric effect of the highest doses of each treatment. All treatments were compared with ethanol (EtOH). The tapentadol slightly affected the stomach of the animals. However, diclofenac showed a high ulcerogenic activity similar to the effect of EtOH. The gastric action of the three combinations showed a dose-dependent effect of diclofenac in the combination. *Significantly different from EtOH-control group ($p < .05$) using ANOVA followed by the Student–Newman–Keuls test [Color figure can be viewed at wileyonlinelibrary.com]

model of visceral pain in agreement with other reports (Bujalska-Zadrożny, Wolińska, Gąsińska, & Nagraba, 2015; Christoph, De Vry, Schiene, Tallarida, & Tzschentke, 2011; Ono et al., 2014; Schiene, De Vry, & Tzschentke, 2011) that included the acetic acid-induced writhing test (Zapata-Morales et al., 2016). Likewise, systemic diclofenac showed a dose-dependent antinociceptive action in the acetic acid-induced visceral pain assay in mice again in agreement with other reports (León-Reyes, Castañeda-Hernández, & Ortiz, 2009; Ortiz, 2013; Ortiz et al., 2002), that included the writhing test (Goh et al., 2014).

The isobolographic analysis revealed an antinociceptive synergism between tapentadol and diclofenac for the three ratios assayed in the acetic acid-induced writhing test in mice. However, the 3:1 proportion of the tapentadol–diclofenac combination required lower doses of both compounds to produce its synergic effect. This proportion produced a similar pattern of gastric damage than tapentadol alone suggesting that lower doses of the compounds still produce maximal antinociceptive effects with an improved side profile. To our knowledge, this the first study reporting the synergism between tapentadol and diclofenac in visceral pain. Previously, our group reported the synergic interaction between tapentadol and ketorolac in acetic acid-induced nociception (Zapata-Morales et al., 2016). However, the potentiation observed for the tapentadol–ketorolac combination was lower than the observed in the present study. Thus, our data suggest that tapentadol is able to potentiate the antinociceptive effect of at least 2 NSAIDs (diclofenac and ketorolac) in the acetic acid-induced writhing test in mice. Our results agree with the general evidence showing a synergistic interaction between drugs that act through different mechanisms of action (Berenbaum, 1989; Chou, 2006). The main mechanisms of action of tapentadol are stimulation of μ-opioid receptors and inhibition of norepinehrine reuptake (Schröder, Vry, Tzschentke, Jahnel, & Christoph, 2010). In contrast, diclofenac produces its antinociceptive effect via COX inhibition (Dorta et al., 2000; Hsu, Chu, Li, & Liu, 2008; Mard et al., 2016; Morsy & Fouad, 2008;Mózsik, 2014; Yanaka et al., 2007). The antinociceptive effects of diclofenac may also involve opioid receptors (Björkman, Hedner, Hedner, & Henning, 2008; Silva, Castor, Navarro, Romero, & Duarte, 2016), α_1-, α_{2C}-, and β-adrenoceptors (Silva, Miranda e Castor, Souza, Duarte, & Romero, 2015) and the NO-cyclic GMP-K^+ channel pathway (Ortiz, Granados-Soto, & Castañeda-Hernández, 2003; Ortiz et al., 2002) any of which may have a key role in the antinociceptive synergism observed in the present study.

One of the main side effects of NSAIDs use is gastric ulceration (Hsu et al., 2008; Mard et al., 2016; Morsy & Fouad, 2008; Ortiz, 2017; Ortiz et al., 2016). In this study, we assessed the gastric damage induced by the tested drugs. As expected, ethanol produced gastric damage (Siegmund, Haas, Schneider, & Singer, 2003; Szabo, Trier, Brown, & Schnoor, 1985). Diclofenac (74.98 mg/kg) produced gastric damage of similar magnitude to ethanol as previously reported in rodents (Hsu et al., 2008; Ortiz, 2017; Ortiz et al., 2016) and humans (Dorta et al., 2000; Mózsik, 2014; Yanaka et al., 2007). Tapentadol produced only mild gastric damage. Of note, the tapentadol–diclofenac 1:1 and 3:1 combinations also produced mild gastric damage. However, the tapentadol–diclofenac 1:3 combination produced more gastric damage than either tapentadol alone or the tapentadol–diclofenac 1:1 and 3:1 combinations. Use of these lower doses of diclofenac may explain the reduced gastric damage observed with the tapentadol–diclofenac 1:1 and 3:1 proportions.

In conclusion, our data indicate that systemic co-administration of tapentadol and diclofenac produce an antinociceptive synergistic interaction in the acetic acid-induced visceral pain test with an acceptable profile of gastric damage in mice.

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