317

Isobolographic Analysis of Interactions between Intravenous Morphine, Propacetamol, and Diclofenac in Carrageenin-injected Rats

Dominique Fletcher, M.D., Ph.D.,* Jean-Michel Benoist, M.D.,† Michèle Gautron,‡ Gisèle Guilbaud, D.Sc., M.D.‡

Background: It has been suggested that the combination of analgesic drugs may have additive or synergistic effects. In clinical practice, this might allow better analgesia and reduction of side effects.

Methods: The effects of analgesic drugs were studied in a model of acute inflammatory pain in carrageenin-injected rats using the vocalization threshold to paw pressure. A combination of three different intravenous drugs were used: morphine, diclofenac, and propacetamol, a pro-drug of acetaminophen. The dose-response curves were first obtained for each drug alone. The analgesic potencies of the combinations of morphine and diclofenac (ratios, 1:5.66 and 1:10), morphine and propacetamol (ratio, 1:250), and diclofenac and propacetamol (ratio, 1:65.7) were thereafter evaluated and compared with the effects of the drugs alone.

Results: For the two different ratios tested, synergy between diclofenac and morphine was observed only with the higher doses. Propacetamol and morphine or diclofenac and propacetamol combinations were additive for all doses tested.

Conclusions: This study found a synergy between intravenous morphine and diclofenac that is consistent with and helps explain the clinical value of this type of combination in the treatment of acute pain in humans. (Key words: Analgesia. Balanced analgesia. Carrageenin. Isobologram. Pain. Synergy.)

COMBINATIONS of analgesics from different pharmacologic classes are used frequently for postoperative analgesia.[1] The goal is to improve analgesia without enhancing the side effects of each drug. The effects

of such combination can be additive or synergistic; a synergistic response is possible when the drugs are acting through distinct mechanisms,[2] and this may allow a significant dose reduction. Both clinical[1] and basic studies[3,4] have been performed to evaluate such combinations. In animals, the isobolographic analysis offers a rigorous evaluation of the interaction between two drugs, but few studies using this analysis are available concerning postoperative analgesic drugs. The synergy between morphine and ketorolac, a nonsteroidal anti-inflammatory drug (NSAID), has been described after intrathecal injection, but this route of administration is not commonly used for postoperative analgesia.[3] Another study has evaluated the interaction between oral butorphanol and acetaminophen with the writhing test measuring ongoing pain in mice, describing synergy for a low opioid–high acetaminophen ratio and a simple additivity with high opioid–low acetaminophen ratio.[4]

Thus, although many clinical studies have described a 20–50% reduction in opioid use when NSAIDs are added,[5] the isobolographic analysis of the interaction between such drugs (morphine, acetaminophen, NSAIDs), by the intravenous route, may further support their clinical use in combination.[6] Our study evaluated three intravenous analgesic drug combinations, morphine and diclofenac, morphine and propacetamol (a water-soluble pro-drug that is converted by plasma esterases into 50% acetaminophen; it is not available in North America) and diclofenac with propacetamol. We used a model of acute inflammatory pain induced by intraplantar injection of carrageenin in rats.[7]

Materials and Methods

Animals

This study was conducted in concordance with the ethical guidelines of the Ethical Committee of the Inter-

* Département d'Anesthésie Réanimation Hôpital Bicêtre, Kremlin Bicêtre, France.

† Département de Pharmacologie, Hôpital Cochin, Paris, France.

‡ Unité de Physiopharmacologie du Système Nerveux, Paris, France.

national Association for the Study of Pain.[8] We used 184 male Sprague-Dawley rats that weighed 250–300 g at the time of experiment. They were housed in groups of three to five per cage, allowed free access to food and water with a natural day/night cycle and acclimatized to the laboratory at least 8 days before the experiments.

Nociceptive Behavioral Test

The experiments were done in a quiet room. The vocalization thresholds to paw pressure (VTPP) were measured by the same experimenter (who was unaware of the drug injected) using the Basile analgesimeter (1-mm tip diameter of the probe; Ugo Basile, Comerio, Italy). During the measurements, the animals were gently wrapped in a towel. For each rat, the VTPP thresholds expressed in grams were determined by applying increasing pressure to the right hindpaw until an audible squeak was elicited.[9] This criterion was chosen according to the previous experience of our group with this test, which represents a more integrated nociceptive behavior than paw withdrawal.[9] The cutoff value of 600 g was used to avoid injury to the paw.

Drug Preparation and Administration

Carrageenin (1% solution of lambda carrageenin in saline) was prepared 24 h before each experiment and injected in a volume of 0.2 ml subcutaneously with a 25-gauge needle into the right plantar hindpaw. The animals were not anesthetized for the injection.

Two hours after carrageenin injection, intravenous injections of analgesic drugs were performed in a vein of the tail. For all injections, the animals were placed in a plastic cylinder (20 × 30 cm) with the tail protruding through a hole at the base of the cylinder. For combinations, the drugs were not mixed in the same syringe and two intravenous injections were performed successively. Morphine (10 mg/ml; Meram Laboratory, Paris, France) and diclofenac (25 mg/ml; Voltarene; Ciba-Geigy Laboratory, Rueil Malmaison, France) were diluted with 0.1 ml saline to allow intravenous injection. Propacetamol (200 mg/ml; Pro-Dafalgan; UPSA Laboratory, Rueil Malmaison, France) was dissolved in a sodium-citrate aqueous solution. The concentration varied from 200–400 mg/ml, and the volume varied from 0.1–0.3 ml depending on the doses. Control injections were performed using vehicle of diclofenac, solvent of propacetamol, or saline.

Choice of Doses

Analgesic Drugs Administered Alone. The doses were chosen according to previous reports on the analgesic effect of morphine and propacetamol in carrageenin-injected rats,[10-12] diclofenac in rats with arthritis,[13] or carrageenin-injected rats.[14] Nine groups of animals (n = 8 for each group) received intravenous morphine (0.1, 0.5, and 1 mg/kg), diclofenac (2, 4, and 8 mg/kg), or propacetamol (100, 200, and 500 mg/kg), respectively.

Analgesic Drug Combinations. The drugs were administered in combination at a fixed ratio. Table 1 lists the different doses and ratios. Because equianalgesia or other criteria to choose the ratio are not recommended in the literature and although kinetics of elimination of each component may be different in rats, we chose ratios similar to those used for postoperative analgesia. For example, the ratios of morphine and diclofenac (1:5.66 and 1:10) were chosen because the usual dose of intravenous morphine (0.1 mg/kg) for postoperative analgesia represents a ratio of 1:7.5 with the usual dose of intravenous diclofenac (0.75 mg/kg).

Expression of the Results

Time Course of the Analgesic Responses. For each animal, the VTPP was measured before and then 2 h after carrageenin injection, with this last measure chosen as a control value ($VTPP_{t=0}$). After this last test, the analgesic drug was injected and the time course of its effect was evaluated by repeating the measure of the VTPP every 10 min until return to control value (see examples in figure 1).

The variation of the threshold at time t ($VTPP_t$–$VTPP_{t=0}$) was expressed as a percentage of the control value using the percentage ratio:

$$\frac{(VTPP_t - VTPP_{t=0}) \times 100}{VTPP_{t=0}}$$

The percentage ratios were calculated for each time point. Then three parameters were used to characterize the analgesic response. (1) The peak amplitude was defined by the percentage ratio value measured 20 min after the drug injection. This delay corresponds approximately to the latency of the maximal effect for the three drugs. (2) The whole duration of the response was defined as the time until the return to baseline confirmed through two successive tests at 10-min inter-

MORPHINE, PROPACETAMOL, AND DICLOFENAC IN CARRAGEENIN-INJECTED RATS

Table 1. Doses and Ratios Used for Drug Combination

Drug Combination Drug 1/Drug 2	n	Ratio Drug 1:Drug 2	Dose (mg · kg⁻¹)		
			Drug 1	Drug 2	Combination
Morphine/diclofenac	8	1:5.66	0.25	1.41	1.66
	6		0.33	1.87	2.2
	7		0.5	2.83	3.33
Morphine/diclofenac	8	1:10	0.09	0.91	1
	8		0.27	2.73	3
	8		0.36	3.64	4
Morphine/propacetamol	8	1:250	0.2	49.8	50
	8		0.4	99.6	100
	7		0.6	149.4	150
Diclofenac/propacetamol	8	1:65.7	1.05	68.95	70
	8		2.25	147.75	150
	8		3.75	246.25	250

vals. (3) The area under the curve (AUC) evaluated the overall effect. The AUC was calculated using the surface of trapeziums, by summing the percentage ratio values measured every 10 min after injection, until back to the baseline. This total value is proportional to the AUC because the intervals between the successive tests are similar.

Dose–Response Curves. Dose-response curves were built for each of the three parameters previously defined: peak amplitude, duration of the analgesic effect, and AUC. In figures 2, 3, and 4, the mean values of AUC ($\pm$ SEM) are plotted on the same graph against

the doses of each single drug and of their combination to facilitate the comparison of equianalgesic doses.

Analysis of Drug Interaction

To characterize the interaction between intravenous morphine, diclofenac, and propacetamol, an isobolo-
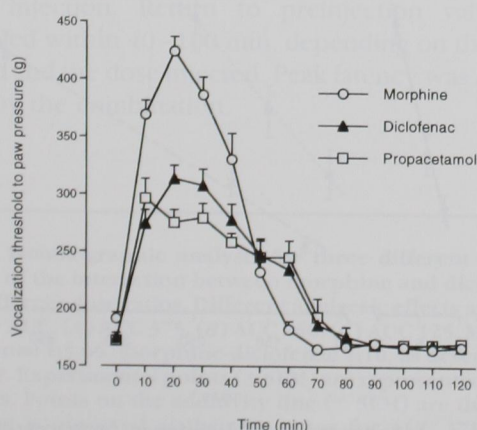

Fig. 1. Time course of the effect on the VTPP of the highest doses of the three analgesic drugs alone. Values are expressed as means $\pm$ SEM. Morphine: the group (n = 8) receiving 1 mg/kg intravenous morphine. Diclofenac: the group (n = 8) receiving 8 mg/kg intravenous diclofenac. Propacetamol: the group (n = 8) receiving 500 mg/kg intravenous propacetamol.
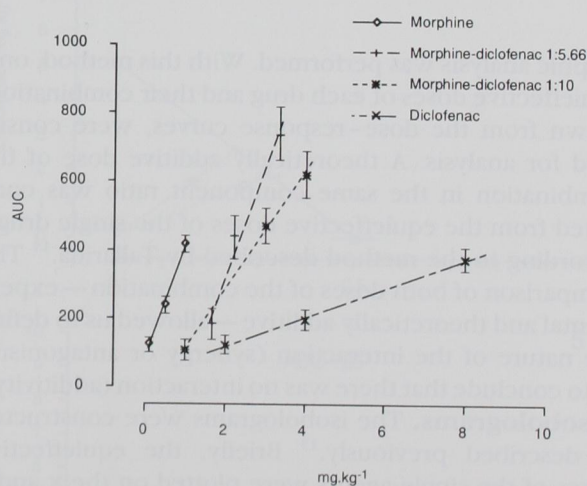
Fig. 2. Dose–response curves of morphine, diclofenac, and morphine-diclofenac combinations at two different dose ratios. Values are expressed as means $\pm$ SEM. Morphine: the groups (n = 8 in each) receiving intravenous morphine (0.1, 0.5, 1 mg/kg; r = 0.85). Diclofenac: the groups (n = 8 in each) receiving intravenous diclofenac (2, 4, 8 mg/kg; r = 0.82). Morphine-diclofenac 1:5.66: the groups receiving the intravenous morphine-diclofenac combination (total combination dose of 1.67, 2.2, 3.33 mg/kg¹; n = 8, 7, 6, respectively; r = 0.84). Morphine-diclofenac 1:10: the groups (n = 8 in each) receiving intravenous morphine-diclofenac combination (total combination dose of 1, 3, 4 mg/kg; r = 0.85).
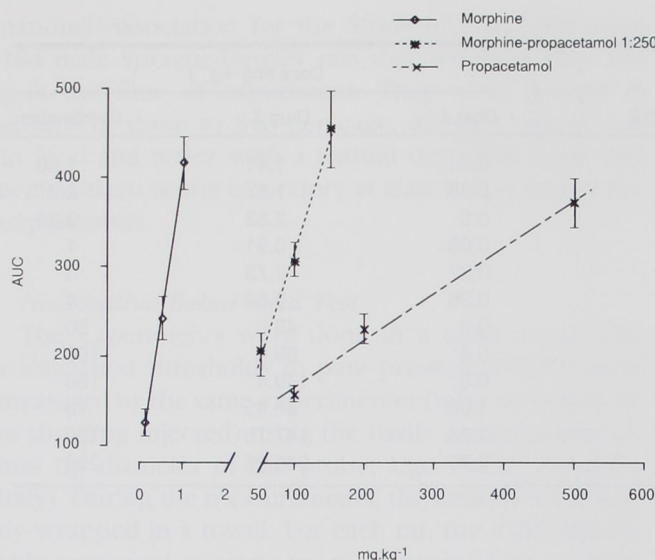
Fig. 3. Dose–response curves of morphine, propacetamol, and morphine-propacetamol combination. Values are expressed as means ± SEM. Morphine: the group described in figure 2. Propacetamol: the groups (n = 8 in each) receiving intravenous propacetamol (100, 200, 500 mg/kg; r = 0.87). Morphine-propacetamol 1:250: the groups receiving the intravenous morphine-propacetamol combination (total combination dose of 50, 100, 150 mg/kg; n = 8, 8, and 7, respectively; r = 0.81).

graphic analysis was performed. With this method, only equieffective doses of each drug and their combination, drawn from the dose–response curves, were considered for analysis. A theoretically additive dose of the combination in the same component ratio was computed from the equieffective doses of the single drugs, according to the method described by Tallarida.[15] The comparison of both doses of the combination — experimental and theoretically additive — allowed us to define the nature of the interaction (synergy or antagonism) or to conclude that there was no interaction (additivity).

Isobolograms. The isobolograms were constructed as described previously.[15] Briefly, the equieffective doses of the single agents were plotted on the x and y axes as the amounts of each component in combination (experimental and theoretically additive doses). The isobolograms were displayed using only the parameter AUC. Three different values of AUC were used for each analysis: AUC 125, 250, and 375 for morphine-diclofenac combination and AUC 125, 250, and 350 for morphine-propacetamol and diclofenac-propacetamol combinations. To limit the extrapolation and interpolation of dose–response curves, these effects were chosen to

be as close as possible to the mean values of the analgesic effect calculated for each dose of the drugs and their combination.

Evaluation of the Magnitude of the Interaction. To describe the magnitude of the interaction, a total fraction value was calculated using the equieffective doses of drug 1, drug 2, and their combination:

$$\frac{\text{dose of drug 1 in combination}}{\text{dose of drug 1 given alone}}$$

$$+ \frac{\text{dose of drug 2 in combination}}{\text{dose of drug 2 given alone}}$$

This total fraction value measures the divergence between the experimental dose of the combination and the theoretical, equieffective additive dose.[3,16]

Values near 1 indicate additivity; values less than 1 imply a synergistic interaction; and values greater than 1 indicate an antagonistic interaction. The total fraction value was computed for AUC, peak amplitude, and duration of analgesic effect.

Statistical Analysis

The dose–response lines were fitted using least-squares linear regression analysis. The confidence inter-
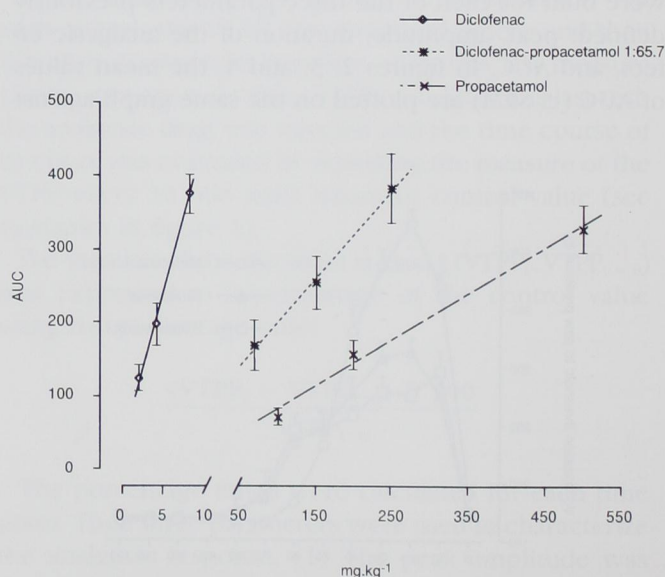

Fig. 4. Dose–response curves of diclofenac, propacetamol, and the diclofenac-propacetamol combination. Values are expressed as means ± SEM. Diclofenac, Propacetamol: groups described in figures 2 and 3. Diclofenac-propacetamol 1:65.7: the groups (n = 8 in each) receiving the intravenous diclofenac-propacetamol combination (total combination dose of 70, 150, 250 mg/kg; r = 0.68).

vals of equieffective doses (experimental and theoretically additive) were calculated according to the method of Tallarida[15] and compared using Student's *t* test. Probability values less than 0.05 were considered significant.

Results

Time Course of Responses and Dose–Response Relations

Individual Drug Responses. The three doses of morphine (0.1, 0.5, and 1 mg/kg), diclofenac (2, 4, and 8 mg/kg), and propacetamol (100, 250, and 500 mg/kg) produce a significant elevation of the VTPP. The time course of the VTPP for the highest dose of each drug is shown on figure 1. For each drug, the peak of VTPP is reached at 10 or 20 min after intravenous injection, and the return to control value is achieved within 40–80 min depending on the drug and the dose injected. The AUCs for all three drugs were clearly dose dependent (figs. 2–4). The best correlation is obtained by linear regression in the range of doses administered (coefficients greater than 0.80).

In carrageenin-injected rats, saline (n = 8), vehicle of diclofenac (n = 4), and solvent of propacetamol (n = 4) did not influence the VTPP compared with animals injected with carrageenin alone (n = 8), excluding the possible bias caused by nonspecific effects of the injection itself or the solvents.

Analgesic Drug Combination Responses. The peak of VTPP was reached 10 or 20 min after intravenous injection. Return to preinjection values was achieved within 40–100 min, depending on the combination and the dose injected. Peak latency was not modified by the combination.

The AUCs for all drug combinations were clearly dose-dependent (figs. 2–4). The best correlation is obtained by linear regression in the range of doses administered (coefficients being higher than 0.80 except for the com-
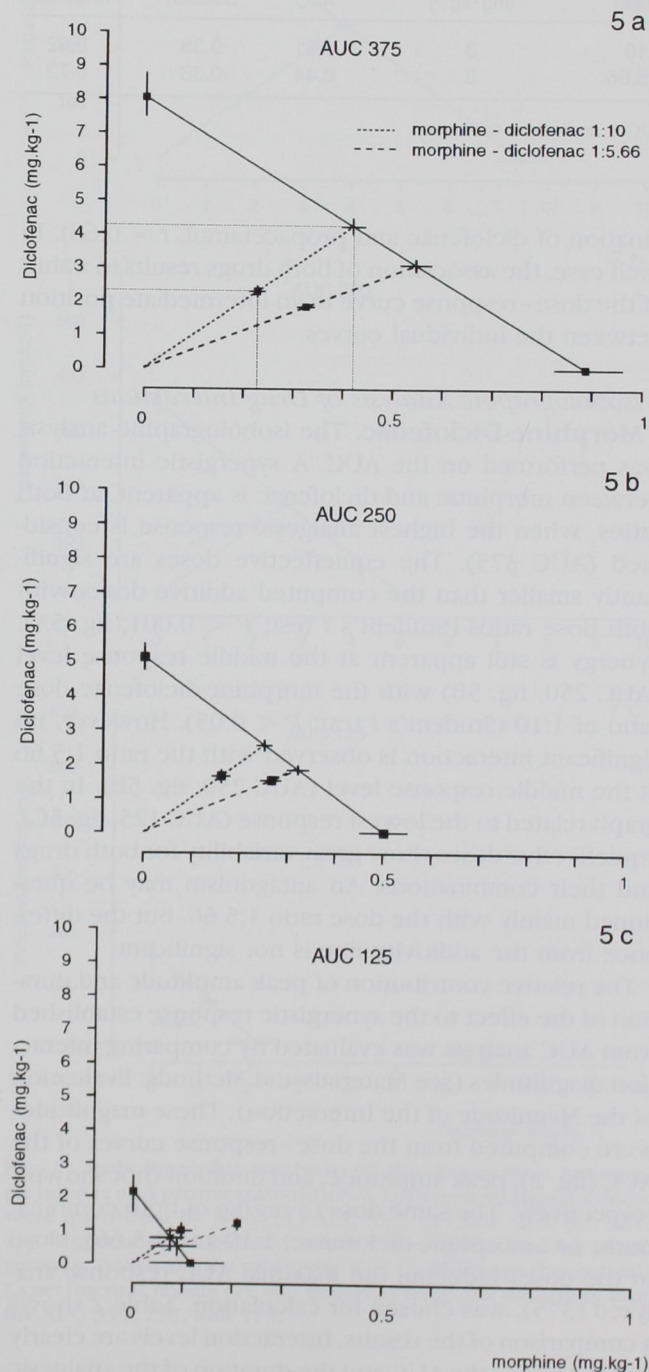
Fig. 5. Isobolographic analysis for three different analgesic effects of the interaction between morphine and diclofenac at two different dose ratios. Different analgesic effects are quantified by AUC. (*A*) AUC 375. (*B*) AUC 250. (*C*) AUC 125. Morphine-diclofenac 1:5.66, morphine-diclofenac 1:10, as described previously. Experimental points (± SEM) are represented by black squares. Points on the additivity line (± SEM) are theoretical. Synergy is observed at the two ratios for AUC 375 (*A*; *P* < 0.001) and only at ratio 1:10 for AUC 250 (*B*; *P* < 0.05). Experimental points are not different from the additivity line for AUC 125 (*C*). A graphic explanation (dotted line) for *A* shows that the experimental doses of each component of the combination morphine-diclofenac (ratio, 1:10) are reduced compared with the theoretical additive doses.

Table 2. Comparison of Synergistic Interaction Magnitude for the Morphine/Diclofenac Combination When Assessed on AUC, Duration, or Peak Amplitude of the Analgesic Effect

Dose Ratio	Combination Dose (mg · kg⁻¹)	Magnitude of the Interaction Evaluated on:		
		AUC	Duration	Peak Amplitude
1:10	3	0.51	0.38	0.82
1:5.66	3	0.44	0.36	0.72

AUC = area under the curve.

bination of diclofenac and propacetamol, r = 0.68). In each case, the association of both drugs results in a shift of the dose–response curve to an intermediate position between the individual curves.

Isobolographic Analysis of Drug Interactions

Morphine-Diclofenac. The isobolographic analysis was performed on the AUC. A synergistic interaction between morphine and diclofenac is apparent, at both ratios, when the highest analgesic response is considered (AUC 375). The equieffective doses are significantly smaller than the computed additive doses with both dose ratios (Student's *t* test; $P < 0.001$; fig. 5A). Synergy is still apparent at the middle response level (AUC 250; fig. 5B) with the morphine-diclofenac dose ratio of 1:10 (Student's *t* test; $P < 0.05$). However, no significant interaction is observed with the ratio 1:5.66 at the middle response level (AUC 250; fig. 5B). In the graph related to the lowest response (AUC 125; fig. 5C), equieffective doses show great variability for both drugs and their combinations. An antagonism may be questioned mainly with the dose ratio 1:5.66, but the difference from the additivity line is not significant.

The relative contribution of peak amplitude and duration of the effect to the synergistic response established from AUC analysis was evaluated by comparing interaction magnitudes (see Materials and Methods: Evaluation of the Magnitude of the Interaction). These magnitudes were computed from the dose–response curves of the AUC (fig. 2), peak amplitude, and duration (not shown), respectively. The same dose (3 mg/kg of both combinations; *i.e.*, morphine-diclofenac, 1:10 and 1:5.66), close to the doses inducing the maximal AUC response analyzed (375), was chosen for calculation. Table 2 shows a comparison of the results. Interaction levels are clearly less than 1 for the AUC and the duration of the analgesic

effect, revealing a strong synergistic interaction. A synergistic interaction is also present for the peak amplitude, measured 20 min after drug injection, although to a lesser extent.

Morphine-Propacetamol. No significant difference from additivity was noted for the three response levels considered (AUC 350, 250, and 125; fig. 6A–C). As previously observed with the morphine-diclofenac combination, a trend to antagonism is possible for AUC 125 (fig. 6C); the doses of morphine calculated for this effect and shown in figure 5C and 6C are in the same range (0.21 and 0.22 mg/kg in the combinations with diclofenac and propacetamol, respectively).

Propacetamol-Diclofenac. The isobolograms presented in figures 7A–C reveal no significant difference compared with the additivity line (AUC 350, 250, and 125).

Discussion

This study describes a synergy between intravenous diclofenac and morphine at two different dose ratios in carrageenin-injected rats. On the other hand, only additivity was observed when propacetamol was associated with morphine or diclofenac.

The carrageenin injection produces acute, localized inflammation, which results in mechanical allodynia and edema with a well-defined time course.[7] The respective responses to NSAIDs[13] and opiates,[10] which are clearly enhanced during an allodynic state, may differ in this model of acute inflammatory pain and in the conditions of postoperative pain. Our test, the vocalization to paw pressure, evaluates pain behaviors provoked by a standardized pressure, and this can be compared with stimulus-evoked pain in the postoperative period (*e.g.*, pain with cough or ambulation). However, ongoing pain is not evaluated in this experiment, although it represents a significant part of postoperative pain. Therefore, our results may not be extrapolated to an ongoing pain situation because, as previously observed,[17] the test used to evaluate the analgesic effect may influence the result of interaction analysis.

The synergy between diclofenac and morphine has been shown at two different dose ratios, and this is important because some reports have stated that the type of interaction between two analgesic drugs depends on the dose ratio.[15] Synergy seemed to be dose related. In fact, synergy was intense for both ratios at

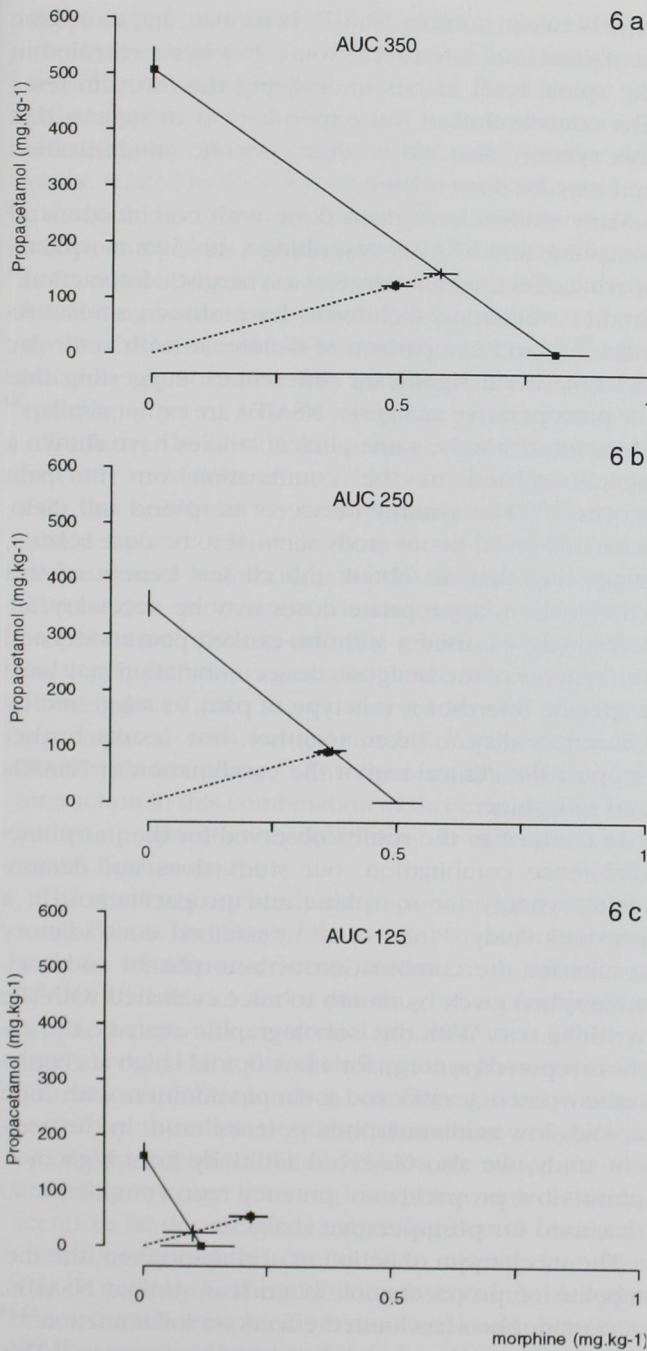MORPHINE, PROPACETAMOL, AND DICLOFENAC IN CARRAGEENIN-INJECTED RATS

Fig. 6. Isobolographic analysis for three different analgesic effects of interaction between morphine and propacetamol at the 1:250 ratio. Different analgesic effects are quantified by AUC. (*A*) AUC 350. (*B*) AUC 250. (*C*) AUC 125. Experimental points (± SEM) are represented by a black square. Points on the additivity line (± SEM) are theoretical. Experimental points are not different from the additivity line for AUC 350, 250, and 125.

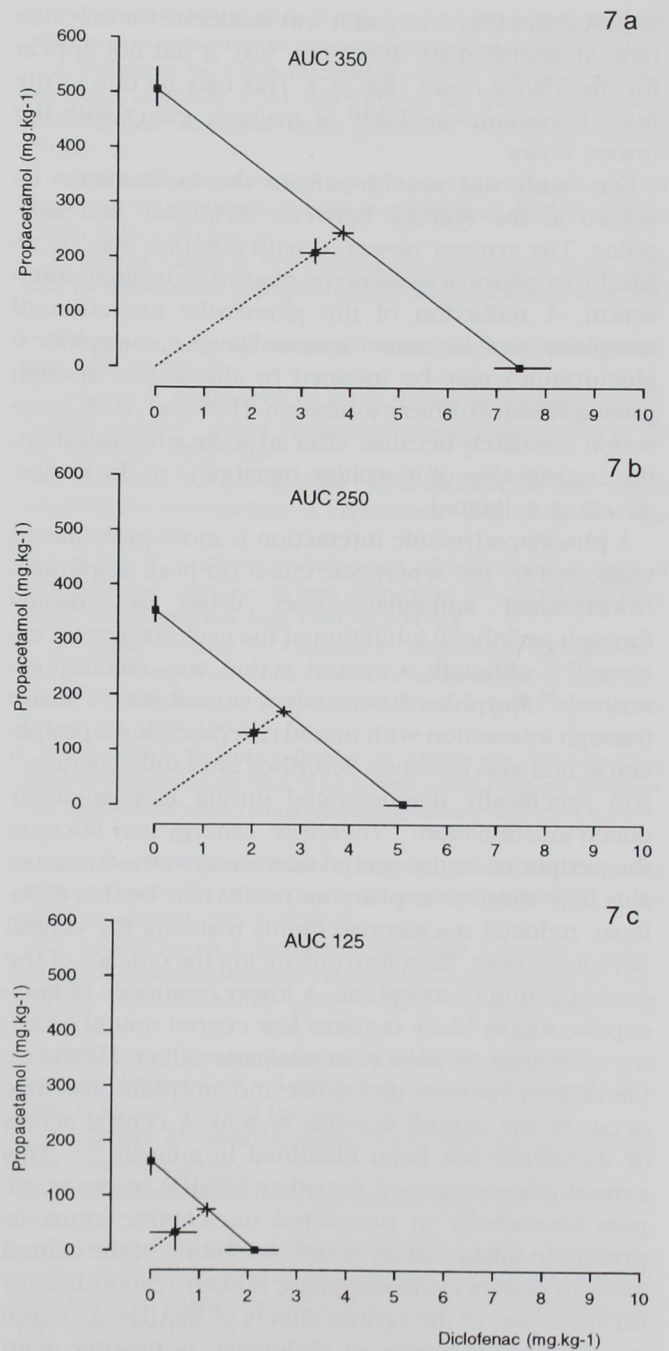Fig. 7. Isobolographic analysis of the interaction between diclofenac and propacetamol 1:65.7. Different analgesic effects were quantified by AUC. (*A*) AUC 350. (*B*) AUC 250. (*C*) AUC 125. Experimental points (± SEM) are represented by black squares. Points on the additivity line (± SEM) are theoretical. Experimental points are not different from the additivity line for AUC 350, 250, and 125.

largest doses (fig. 5A), and it was moderate for only one ratio at intermediate doses (fig. 5B). It did not appear for the lowest doses (fig. 5C). This may be due to the more important variability of analgesic effect with the lowest doses.

Our study did not investigate the mechanisms involved in the synergy between diclofenac and morphine. The synergy observed with duration may be related to a pharmacokinetic or pharmacodynamic interaction. A reduction of the glomerular excretion of morphine and its active metabolite (*i.e.*, morphine-6 glucuronide) may be induced by diclofenac through prostaglandin synthesis inhibition. However, such interaction is unlikely because, after an acute administration, the contribution of morphine metabolite to the analgesic effect is limited.

A pharmacodynamic interaction is more probable, as suggested by the synergistic effect on peak amplitude. Nonsteroidal anti-inflammatory drugs act mainly through peripheral inhibition of the cyclooxygenase enzyme,[18,19] although a central action was recently described.[20] Morphine has mainly a central site of action through interaction with opioid receptors, but a peripheral action also has been described after inflammation[21] and specifically demonstrated during carrageenin-induced inflammation.[10] Therefore, synergy may occur in the peripheral or the central nervous systems. A reasonable hypothesis to explain our results may be that diclofenac reduced nociceptive inputs reaching the central nervous system, therefore enhancing the efficacy of the central action of morphine. A lower frequency of nociceptive inputs likely requires less central opioid receptor activation to induce an analgesic effect. However, interaction between diclofenac and morphine also may occur in the central nervous system. A central action of diclofenac has been identified in animals.[22,23] This central effect observed for other NSAIDs seems to appear secondarily to protracted nociceptive input, as present in inflammatory pain.[24] Inhibition of the central nervous system cyclooxygenase is likely responsible for the most part of the central effects of NSAIDs. A central synergistic interaction of diclofenac is possible with drugs acting through a clearly different cellular site,[2] such as opioid receptor agonist, even though further interferences with common biochemical systems including serotoninergic,[12,25] endomorphinic,[23,26] and nitric oxide mediation,[25] may be involved in the final response. Our integrated test, VTPP, does not give any information on the level of interaction. However, a synergy between another NSAID, ketorolac, and morphine combined *via* intrathecal route has been revealed at the spinal level in rats undergoing the formalin test.[3] The contribution of our experiment is to suggest that this synergy also exists after systemic administration and may be dose related.

Many studies have been done with combinations of morphine and NSAIDs describing a 20–50% morphine-sparing effect, which suggests a synergistic interaction.[5] Studies evaluating diclofenac have shown similar results,[27–29] and comparison of diclofenac with ketorolac did not reveal significant differences, suggesting that for postoperative analgesia, NSAIDs are rather similar.[30] More interestingly, some clinical studies have shown a benefit related to the combination on the pain scores.[31,32] The synergy between morphine and diclofenac observed in our study seemed to be dose related, suggesting that, to obtain the clinical benefit of this combination, appropriate doses may be necessary. Interestingly we used a stimulus-evoked pain model and the synergy of the analgesic drug combination may have a specific interest for this type of pain, as suggested by clinical studies.[31] Taken together, our results further support the clinical use of the combination of NSAIDs and morphine.

In contrast to the results observed for the morphine-diclofenac combination, our study does not demonstrate synergy for morphine and propacetamol. In a previous study, Pircio *et al.*[4] described contradictory results for the combination of butorphanol and acetaminophen given by mouth to mice evaluated with the writing test. With the isobolographic analysis, the authors reported synergy for a low opioid–high acetaminophen potency ratio and a simple addition with high opioid–low acetaminophen potency ratio. In the present study, we also observed additivity for a high morphine–low propacetamol potency ratio comparable to that used for postoperative analgesia.

The mechanism of action of acetaminophen, the metabolite of propacetamol, is unclear. Unlike NSAIDs, acetaminophen has limited effects on inflammation[12,33] and on the activity of peripheral cyclooxygenase.[34] This relative lack of peripheral effect of acetaminophen may underline *a contrario* the role of reducing afferent nociceptive inputs in the morphine-diclofenac synergy. Several basic and clinical studies strongly favor a direct action of acetaminophen in the central nervous system.[35,36] Biochemical mechanisms of this action may include inhibition of central cyclooxygenase[35] and bind-

ing of oxygen free radicals.[37] In addition, as for NSAIDs, interferences with the serotoninergic descending pathway,[12,38] or nitric oxide synthesis, have been proposed.[25] The lack of synergistic interaction between morphine and propacetamol is debatable[4] and cannot yet be related to these hypothetical mechanisms of central action. Furthermore, the simple additivity observed in this study does not preclude the clinical interest of such combinations. In fact, this combination may be interesting because propacetamol has much less toxicity than NSAIDs, and a clinical study evaluating the combination of morphine and propacetamol described a sparring effect of 35% on morphine consumption.[39]

Similarly, the diclofenac-propacetamol combination had only an additive effect. This combination may, however, be beneficial for postoperative analgesia as suggested by a recent evaluation of the combination of propacetamol and another NSAID, ketoprofen. In fact, after lumbar spine surgery, intravenous ketoprofen and propacetamol (50 mg and 2 g given every 6 h for 2 days, respectively) associated with intravenous morphine reduced pain scores at rest and with movement as compared with ketoprofen or propacetamol used alone with morphine.[40] The rigorous evaluation of the interaction in this combination of three drugs (i.e., ketoprofen, propacetamol, morphine) is difficult but deserves further study.

The results of our study are important for several reasons. This is the first study to offer an isobolographic analysis of the interaction between morphine, an NSAID, diclofenac, and a pro-drug of acetaminophen, propacetamol, after systemic administration. The synergy observed, for the diclofenac-morphine combination, at two different ratios, confirmed what was suggested by the clinical studies describing a significant opioid-sparing effect when NSAIDs are added. In addition, this synergy between morphine and diclofenac seems to be dose-related, suggesting that to obtain the clinical benefit of this combination, appropriate doses may be necessary. The additivity observed in this experiment for the morphine-propacetamol and diclofenac-propacetamol combinations does not preclude their clinical use but suggest that the clinical benefit of these combinations may be more limited.

References

1. Kehlet H, Dahl JB: The value of "multimodal" or "balanced analgesia" in postoperative treatment. Anesth Analg 1993; 77:1048–56

2. Unkelbach HD, Pöch G: Comparison of independence and additivity in drug combinations. Arzneim Forsch Drug Res 1988; 38:1–6

3. Malmberg AB, Yaksh TL: Pharmacology of the spinal action of ketorolac, morphine, ST-91, and L-PIA on the formalin test and an isobolographic analysis of NSAID interaction. ANESTHESIOLOGY 1993; 79:270–81

4. Pircio AW, Buyniski JP, Roebel LE: Pharmacological effects of a combination of butorphanol and acetaminophen. Arch Int Pharmacodyn 1978; 235:116–23

5. Dahl JB, Kehlet H: Non-steroidal anti-inflammatory drugs: rationale for use in severe postoperative pain. Br J Anaesth 1991; 66:703–12

6. Eisenach J: Aspirin, the miracle drug. Spinally too? ANESTHESIOLOGY 1993; 79:211–3

7. Kayser V, Guilbaud G: Local and remote modifications of nociceptive sensitivity during carrageenin-induced inflammation in the rat. Pain 1987; 28:99–108

8. Committee for Research and Ethical Issues of the IASP: Ethical standards for investigations of experimental pain in animals. Pain 1983; 16:109–10

9. Kayser V, Guilbaud G: Differential effects of various doses of morphine and naloxone on two nociceptive test thresholds in arthritic and normal rats. Pain 1990; 41:353–63

10. Kayser V, Chen YL, Guilbaud G: Behavioural evidence for a peripheral component in the enhanced antinociceptive effect of a low dose of systemic morphine in carrageenin-induced hyperalgesic rats. Br Res 1991; 560:237–44

11. Honoré P, Buritova J, Besson JM: Aspirin and acetaminophen reduced both Fos expression in rat lumbar spinal cord and inflammatory signs produced by carrageenin inflammation. Pain 1995; 63:365–75

12. Pelissier T, Alloui A, Paeile C, Eschalier A: Evidence of a central antinociceptive effect of paracetamol involving spinal $5HT_3$ receptors. NeuroReport 1995; 6:1546–8

13. Attal N, Kayser V, Eschalier A, Benoist JM, Guilbaud G: Behavioural and electrophysiological evidence for analgesic effect of a non-steroidal anti-inflammatory agent, sodium diclofenac. Pain 1988; 35:341–8

14. Buritova J, Honoré P, Chapman V, Besson JM: Concurrent reduction of inflammation and spinal Fos-LI neurons by systemic diclofenac in the rat. Neurosci Lett 1995; 188:175–8

15. Tallarida RJ: Statistical analysis of drug combinations for synergism. Pain 1992; 49:93–7

16. Berenbaum MC: What is synergy? Pharmacol Rev 1989; 41:93–141

17. Ossipov MH, Harris S, Lloyd P, Messineo E: An isobolographic analysis of the antinociceptive effect of systemically and intrathecally administered combinations of clonidine and opiates. J Exp Pharmacol Ther 1990; 255:1107–16

18. Ferreira SH, Moncada S, Vane JR: Prostaglandin and the mechanism of analgesia produced by aspirin-like drugs. Br J Pharmacol 1973; 49:86–97

19. Vane JR: Inhibition of prostaglandin synthesis as a mechanism of action of aspirin-like drugs. Nature New Biol 1971; 231:232–5

20. Mc Cormack K: Non-steroidal anti-inflammatory drugs and spinal nociceptive processing. Pain 1994; 59:9–43

21. Stein C: The control of pain in peripheral tissue by opioids. N Engl J Med 1995; 332:685–90

22. Jurna I, Brune K: Central effect of the non-steroid anti-inflammatory agents, indometacin, ibuprofen, and diclofenac, determined in C fibre evoked activity in single neurones of the rat thalamus. Pain 1990; 41:71–80

23. Björkman R, Hedner J, Hedner T, Henning M: Central naloxone-reversible antinociception by diclofenac in rat. Naunyn-Schmiedeberg's Arch Pharmacol 1990; 342:171–6

24. Malmberg AB, Yaksh TL: Hyperalgesia mediated by spinal glutamate or substance P receptor blocked by spinal cyclooxygenase inhibition. Science 1992; 257:1276–9

25. Björkman R: Central antinociceptive effects of non-steroidal anti-inflammatory drugs and paracetamol. Acta Anaesth Scand 1995; 103(Suppl):1–44

26. Vescosi P, Passeri M, Gerra G, Grossi E: Naloxone inhibits the early phase of diclofenac analgesia in man. Pain Clinic 1987; 19:151–5

27. Perttunen K, Kalso E, Heinonen J, Salo J: Intravenous diclofenac in postthoracotomy pain. Br J Anaesth 1992; 68:474–80

28. Hodsman NBA, Burns J, Blyth A, Kenny GNC, Mc Ardle CS, Rotman H: The morphine sparing effects of diclofenac sodium following abdominal surgery. Anaesthesia 1987; 42:1005–8

29. Laitinen J, Nuutinen L: Intravenous diclofenac coupled with PCA fentanyl for pain relief after total hip replacement. ANESTHESIOLOGY 1992; 76:194–8

30. Morrow BC, Bunting H, Milligan KR: A comparison of diclofenac and ketorolac for postoperative anagesia following day-case arthroscopy of the knee joint. Anaesthesia 1993; 48:585–7

31. Grass JA, Sakima NT, Valley M, Fischer K, Jackson C, Walsh P, Bourke DL: Assessment of ketorolac as an adjuvant to fentanyl patient-controlled epidural analgesia after radical retropubic prostatectomy. ANESTHESIOLOGY 1993; 78:642–58

32. Etches RC, Warriner CB, Badner Neal: Continuous intravenous administration of ketorolac reduces pain and morphine consumption after total hip or knee arthroplasty. Anesth Analg 1995; 81:1175–80

33. Skjelbred P, Lökken P, Skoglund LA: Postoperative administration of acetaminophen to reduce swelling and other inflammatory events. Curr Ther Res 1984; 35:377–85

34. Flower RJ, Vane JR: Inhibition of prostaglandin synthetase in brain explains the anti(4-acetamidophenol)-pyretic activity of paracetamol (4-aminodophenol). Nature 1972; 240:410–1

35. Ferreira SH, Lorenzetti BB, Correa FMA: Central and peripheral antialgesic action of aspirin-like drugs. Eur J Pharmacol 1978; 53:39–48

36. Piletta P, Porchet HC, Dayer P: Central analgesic effect of acetaminophen but not of aspirin. Clin Pharmacol Ther 1991; 49:350–4

37. Lands WEM: Mechanisms of action of anti-inflammatory drugs. Adv Drug Res 1985; 14:147–63

38. Tjolsen A, Lund A, Hole K: Antinociceptive effect of paracetamol in rats is partly dependent on spinal serotoninergic systems. Europ J Pharmacol 1991; 193:193–201

39. Delbos A, Boccard E: The morphine sparring effect of propacetamol in orthopedic postoperative pain. J Pain Symptom Manag 1995; 10(4):279–90

40. Fletcher D, Nègre I, Barbin C, François A, Carreres C, Falgueirettes C, Barboteu A, Samii K: Postoperative analgesia with intravenous propacetamol and ketoprofen combination after disc surgery. Can J Anaesth 1997 (In press)