

The Synergistic Analgesic Interactions Between Hydrocodone and Ibuprofen

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The practice of combining opioids with nonsteroidal antiinflammatory drugs is widespread in the clinical management of acute and chronic pain. Using the mouse radiant heat tail-flick nociception model, we observed potent analgesia with hydrocodone. In contrast, ibuprofen as a single drug was inactive in this model of moderate to severe pain, perhaps reflecting its limited analgesic potential. Despite the inactivity of ibuprofen alone in this model, the inclusion of ibuprofen with hydrocodone markedly enhanced the analgesic response. Dose-response studies revealed an 50% effective dose

for hydrocodone alone in mice of 11 mg/kg, SC. Inclusion of a fixed ibuprofen dose with the various hydrocodone doses shifted the 50% effective dose value almost seven-fold to the left to 1.6 mg/kg, SC, despite the lack of effect of ibuprofen alone in this model. Using a fixed hydrocodone:ibuprofen ratio (1:40) also revealed a marked four-fold shift to 2.6 mg/kg, SC. These findings suggest a synergistic interaction between ibuprofen and hydrocodone in a noninflammatory pain model.

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The analgesic activity of opioids has been demonstrated in multiple species, including rodents and humans. In animal studies, the analgesic actions of these drugs are readily seen using a variety of analgesic assays, including the radiant heat tail-flick assay, which is one of the earliest paradigms used to assess analgesic drugs (1,2). Opioids produce their effects by activating specific opioid receptors (3). There are three major classes of opioid receptors, each with its own ligand selectivity. Most clinical drugs work through μ (morphine-like) receptors.

Hydrocodone is a well-established μ opioid analgesic (3). Ibuprofen, a nonsteroidal antiinflammatory drug (NSAID), is widely used for mild to moderate acute and chronic pain. Unlike opioids that have no ceiling effects on their analgesic activity, NSAID analgesia does display a ceiling effect and, when given alone, has limited activity against severe pain. Indeed, NSAIDs are typically not sufficiently effective to demonstrate activity in many of the more rigorous preclinical analgesic assays, such as the radiant heat tail-flick assay.

Opioids are often used in combination with NSAIDs, and a number of products containing combinations are currently used widely in the management of pain (4). Preclinical studies have suggested interactions between NSAIDs in neuropathic and inflammatory pain models. In a model of chronic neuropathic pain, systemic ketorolac or piroxicam was found to synergize with spinal morphine (5). Interestingly, these same authors failed to identify synergy between ketorolac and morphine using a thermal paradigm, the immersion (52°C) tail-flick assay. It also is notable that these authors were not able to obtain an 50% effective dose (ED₅₀) value for ketorolac in the tail-flick assay because of its limited activity. Others have observed interactions between opioids and NSAIDs in a range of inflammatory models where the NSAIDs would be expected to be active (6-9). The objective of this study was to evaluate the hypothesis that combinations of ibuprofen and hydrocodone would show more than additive interactions in the rodent radiant heat tail-flick assay, a noninflammatory model of moderate to severe pain.

Methods

These studies have been approved by the Institutional Animal Care and Use Committee of MSKCC. Ibuprofen and hydrocodone were supplied by Abbott Laboratories (Whippany, NJ). Male Crl:CD-1(ICR)BR mice (25 g) were purchased from Charles River Laboratories (Wilmington, MA). All drugs were administered

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subcutaneously to groups of mice ($n = 10$) before evaluation in the radiant heat tail-flick assay, as previously described (10). In brief, the apparatus consists of a light beam that is focused on the tail. Below the tail is a photoelectric cell that controls a timer. When the tail is moved (i.e., flicked), the light activates the photoelectric cell and stops the timer, providing an indication of the actual latency for the animal. Each animal was tested twice at baseline and at the stated times, and the two values were averaged. Baseline tail-flick latencies typically ranged from 2 to 3 s. Analgesia was assessed quantally as a doubling or more of the baseline latency for an individual mouse (1). Analgesia is defined as the percentage of animals displaying the analgesic response. ED₅₀ values, representing the drug dose of hydrocodone required to elicit analgesia in 50% of animals, was determined from a dose-response curve using a computerized log probit analysis (11). Each assay was replicated twice, resulting in 20 mice per group overall (12-14). Preliminary testing showed a peak effect of ibuprofen on hydrocodone actions at 45 min (data not shown) and a peak effect of hydrocodone itself at 30 min. Therefore, the ibuprofen was administered 15 min before the hydrocodone, and all testing was performed 30 min after the hydrocodone. Testing with ibuprofen alone was evaluated 45 min after the administration.

Results

First, we examined the activity of ibuprofen alone. Ibuprofen at 50, 100, and 200 mg/kg, SC, ($n = 20$ at each dose) was inactive in the radiant heat tail-flick assay (data not shown). Latencies after the drug were indistinguishable from those at baseline. Larger ibuprofen doses could not be assessed because of severe toxicity. To determine whether there were any interactions between ibuprofen and hydrocodone, we administered a single dose of either drug alone or in combination (Fig. 1). As anticipated, ibuprofen alone had no observable effect. However, it significantly enhanced the analgesia from a single dose of hydrocodone (5 mg/kg; $P < 0.001$; Fisher's exact test).

Dose-response studies confirmed this interaction (Fig. 2; Table 1). Hydrocodone alone was effective in the assay, yielding an ED₅₀ value of 11 mg/kg, SC. Interactions were assessed using two different combination paradigms. In one, we maintained a fixed dose of ibuprofen with increasing doses of hydrocodone. In the other, we used a fixed ratio of the drugs. In this second approach, the doses of ibuprofen were smaller than in the fixed ratio study, with the exception of the largest ratio dose tested, which was the same. Despite the inactivity of ibuprofen alone, the combination of a fixed ibuprofen dose (200 mg/kg, SC) markedly enhanced its analgesic activity, shifting the dose-response curve for hydrocodone close to seven-fold to the left (Fig. 2; Table 1).

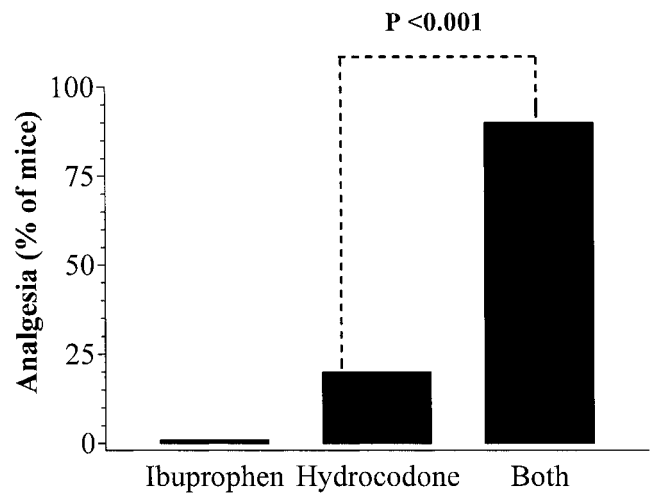


Figure 1. Effects of the combination of hydrocodone and ibuprofen. Groups of mice ($n = 20$) received SC either ibuprofen or hydrocodone alone. Another group of mice ($n = 20$) received a fixed dose of ibuprofen (200 mg/kg, SC) 15 min before the hydrocodone administration (5 mg/kg). Analgesia was assessed 30 min after the hydrocodone injection.

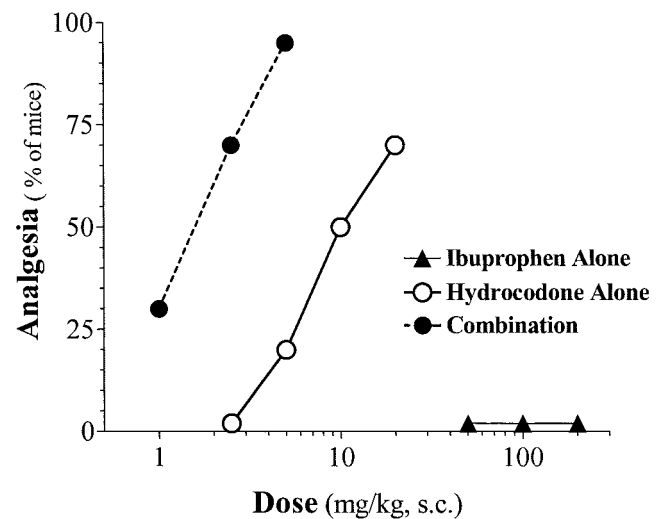


Figure 2. Dose-response study of hydrocodone alone and in combination with ibuprofen. Groups of mice ($n = 20$) received either hydrocodone alone ($n = 20$) or in combination with a fixed dose of ibuprofen (200 mg/kg, SC) given 15 min earlier. Analgesia was assessed 30 min after the hydrocodone.

We also examined the combination of ibuprofen with hydrocodone using a fixed ratio of ibuprofen:hydrocodone (40:1). Again, the inclusion of ibuprofen significantly enhanced the analgesic activity of the hydrocodone, shifting the dose-response curve over four-fold to the left (Table 1). The largest ratio dose of hydrocodone tested in this study was 5 mg/kg with 200 mg/kg of ibuprofen. The other doses consisted of proportionally smaller ibuprofen doses. The shift in the fixed ratio study was somewhat smaller than with the fixed ibuprofen dose. Presumably, this reflects the

Table 1. Fifty-Percent Effective Dose (ED₅₀) Values of Hydrocodone Alone and in Combination with Ibuprofen

Drug(s)	ED ₅₀ value (mg/kg, SC)	95% CL	Ratio
Hydrocodone alone	11	(8, 16)	
Hydrocodone/ibuprofen combination			
Fixed dose	1.6	(1.0, 2.1)	6.9
Fixed ratio	2.6	(1.8, 3.6)	4.2

Groups of mice ($n = 20$) received 3 doses of hydrocodone alone (2.5, 5, 10, and 20 mg/kg, SC) or hydrocodone (1, 2.5, and 5 mg/kg, SC) in combination with ibuprofen. One combination group received the same fixed dose of ibuprofen (200 mg/kg, SC) with each hydrocodone dose. Another combination group received a fixed ratio (40:1) of ibuprofen:hydrocodone. Results are presented as ED₅₀ values with 95% confidence limits (95% CL). The ratios of the combinations compared with hydrocodone alone are also given.

smaller ibuprofen doses used at the smaller doses of hydrocodone in the ratio study. Thus, at the smaller doses of hydrocodone, there is dose-dependent enhancement of analgesia by ibuprofen.

Discussion

Although ibuprofen is used for a wide range of pain intensities, hydrocodone is usually reserved for moderate to severe pain. Yet, the combination of hydrocodone and ibuprofen is commercially available as a combination and is widely used. The radiant heat tail flick is an excellent predictor for activity against moderate and severe pain (1). Interactions between opioids and NSAIDs have been reported previously in models of neuropathic (5) and inflammatory pain (6–9), but efforts to show interactions in a thermal tail-flick assay failed (5). The current study finds synergistic interactions between hydrocodone and ibuprofen in the radiant heat tail-flick assay, a noninflammatory model of moderate to severe pain, suggesting that it would be an appropriate model to assess the overall utility of the combination in a range of clinical settings.

As anticipated, hydrocodone alone was an effective analgesic in the radiant heat tail-flick assay. In contrast, ibuprofen alone was inactive in this model of nociception at all doses tested, including 200 mg/kg, the largest dose used in the combination studies. Larger ibuprofen doses could not be used because of severe toxicity. Yet, the inclusion of ibuprofen with hydrocodone significantly enhanced the potency of the combination. This was readily seen at a single dose of the two drugs, as well in dose-response curves using two different types of combinations. A fixed dose of ibuprofen (200 mg/kg, SC) shifted the hydrocodone dose-response curve almost seven-fold ($P < 0.05$). Additional studies looking at a fixed ratio of the two drugs also elicited a significant four-fold increase in activity ($P < 0.05$). The fixed ratio study combined hydrocodone with far smaller doses of ibuprofen than those used in the fixed dose study and

still potentiated the analgesic actions. Thus, smaller ibuprofen doses also potentiated hydrocodone actions.

These findings strongly suggest a synergistic interaction between the two drugs in a noninflammatory model. Because ibuprofen alone is inactive at doses as large as 200 mg/kg, SC, the enhanced analgesia of the combination represents more than additive effects. Classical isobolographic analysis cannot be used in this situation because ibuprofen does not have an ED₅₀ value in the assay. Its ability to significantly enhance the activity of hydrocodone despite its own inactivity in the assay strongly implies the presence of synergy between the two drugs. The presence of these interactions in a pain model of moderate to severe pain in which ibuprofen alone was ineffective may suggest the utility of these combinations in clinical pain states where NSAIDs alone are insufficient. It will be interesting to see whether these synergistic interactions can be discerned clinically in future trials. It also will be interesting to see whether these interactions can be extended to other NSAIDs and opioids.

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