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Research report

Selective potentiation of opioid analgesia by nonsteroidal anti-inflammatory drugs

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Abstract

Opioids are often used in conjunction with nonsteroidal anti-inflammatory drugs (NSAIDs) in the treatment of moderate to severe pain. In this study we have examined interactions between these two classes of drugs. NSAIDs are inactive in the radiant heat tail-flick test, an assay of moderate to severe pain in which opioids are effective. In this assay, ibuprofen potentiated the analgesic actions of hydrocodone and oxycodone, shifting their ED_{50} values by 2.5-fold and 4.6-fold despite its inactivity when given alone. These opioid/NSAID interactions were dependent upon both the opioid and the NSAID. Neither aspirin nor ketorolac influenced hydrocodone actions in this model and ibuprofen did not potentiate fentanyl or morphine analgesia. Together, these studies demonstrate potent interactions between selected combinations of opioids and NSAIDS and may help explain the clinical utility of combinations. However, the findings also illustrate differences between the drugs within each class.

Theme: Sensory systems
Topic: Pain modulation: pharmacology

Keywords: Opioid; Nonsteroidal anti-inflammatory drugs; Analgesia; Synergy

1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) comprise a group of agents that possess antipyretic, analgesic, and anti-inflammatory properties. There is substantial evidence that NSAID-induced analgesia is due to the inhibition of cyclooxygenase enzymes (COX-1 and COX-2), with a resultant decrease in prostaglandin synthesis, a potent inflammatory mediator [40]. Most NSAIDs are nonselective [40]. Selective COX-2 inhibitors, such as celecoxib and rofecoxib, may be associated with fewer adverse effects, in particular gastrointestinal toxicity [6,24]. NSAIDs have limited use in the management of moderate to severe pain due to a ceiling effect on their analgesic activity. This is consistent with their limited activity in many of the preclinical analgesic assays, which are predictors of strong analgesics, such as the radiant heat tail-flick assay. Opiate agonists, on the other hand, are powerful analgesics with no ceiling effects, but their utility is limited by adverse side effects.

Opioids are often used in combination with NSAIDs and a number of combination products are currently widely used in pain management [41,43]. The intent of the combination approach is to utilize agents with different mechanisms of action and thereby enhance analgesic activity with fewer side effects. In clinical studies, NSAIDs lower postoperative opiate use by 20–50%, despite their limited utility alone [1,7,8,13,17,19,23,29]. There is some evidence for synergy between opioids and NSAIDS in animal models of neuropathic and inflammatory pain [14,15,22,25,27,28,46].

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Recently, we demonstrated synergistic interactions between ibuprofen and hydrocodone in a thermal model, the radiant heat tail-flick assay [20]. The objective of the current study was to assess potential interactions in a model of moderate to severe pain, the radiant heat tail-flick assay, and evaluate whether or not NSAID/opiate interactions reflected general drug interactions or whether they were restricted to specific drugs within each class.

2. Materials and methods

All in vivo studies were carried out in accordance with the Declaration of Helsinki and with the Guide for Care and Use of Laboratory Animals, as adopted and promulgated by the National Institutes of Health. Male Crl:CD-1® (ICR) BR mice (20–25 g) were purchased from Charles River Laboratories (Raleigh, NC) and were housed in a 12:12-h light–dark cycle temperature-controlled room with food and water freely available. Drugs were obtained from the Research Technology Branch of the National Institute on Drug Abuse (Rockville, MD) and from Sigma (St. Louis, MO, USA).

2.1. Radiant heat tail-flick assay

Antinociception, referred to as "analgesia", was assessed in the radiant heat tail-flick test using groups of mice, as previously described [12,38,39]. Baseline latencies typically ranged between 2 and 3 s. Analgesia was defined quantally as the doubling or greater of the baseline latency for each mouse [38,39,45]. The use of quantal analysis goes back to the original studies of D'Amour and Smith [12,26]. Results analyzed quantally corresponded closely to those analyzed using graded responses (data not shown). Drugs were tested at peak analgesic effect, which corresponded to 30 min after the opioid and 45 min after the NSAID. All assays utilized groups of 10 mice and were replicated at least twice, yielding total groups of at least 20 mice for each point. ED_{50} values and 95% confidence limits were calculated by computerized probit analysis with the aid of Pharm Tools Pro (The McCary Group, Elkins Park, PA).

3. Results

The first objective of the current study was to characterize the interactions between combinations of nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids in the radiant heat tail-flick assay, a model of moderate to severe pain that correlates well to the clinical situation in which the combination is most commonly used. In this assay, ibuprofen alone was inactive at doses up to 200 mg/kg sc, the highest dose that could be tested due to toxicity [21]. Similarly, doses of a variety of other NSAID drugs given alone also were without effect in the radiant heat tail-flick assay, including aspirin and ketorolac at doses up to 500 mg/kg and naproxen at a dose as high as 200 mg/kg (data not shown). Higher doses of these drugs could not be examined due to toxicity.

We next examined possible interactions between the NSAIDs and hydrocodone in which increasing doses of NSAIDs were administered with a fixed low dose of hydrocodone in the tail-flick assay (Fig. 1). Hydrocodone alone gave a very low response, 13%. Both ibuprofen and naproxen significantly increased the analgesic response of hydrocodone in a dose–dependent manner. Doses of the NSAIDs greater than 200 mg/kg sc could not be examined due to toxicity, so that it is not clear whether or not greater effects would be seen if the ibuprofen or naproxen dose could have been increased further. In contrast, neither ketorolac nor aspirin significantly enhanced hydrocodone analgesia at any of the doses examined, clearly differentiating the ability of various NSAIDs to interact with opioids.

To more fully define the ibuprofen/hydrocodone interaction, we determined the ED_{50} values of hydrocodone alone and with various ibuprofen doses (Table 1). Although the lowest ibuprofen doses did not significantly alter the ED_{50}, we observed an enhanced analgesic response (Fig. 1). The highest dose (200 mg/kg sc) of ibuprofen significantly shifted the hydrocodone ED_{50} by 2.5-fold. Neither aspirin nor ketorolac at the high dose (200 mg/kg) significantly shifted the hydrocodone ED_{50} (Table 2), consistent with their inactivity with the fixed dose hydrocodone seen earlier (Fig. 1). However, naproxen was even more effective than ibuprofen, shifting the hydrocodone dose–response curve 4.6-fold. Thus, the interactions of these drugs with hydrocodone were markedly dependent upon which NSAID was examined.

To determine whether ibuprofen showed a similar potentiation of other opioids, we next examined the combination of ibuprofen with a series of opiates, including fentanyl, oxycodone, methadone, morphine, and levorphanol (Table 3).

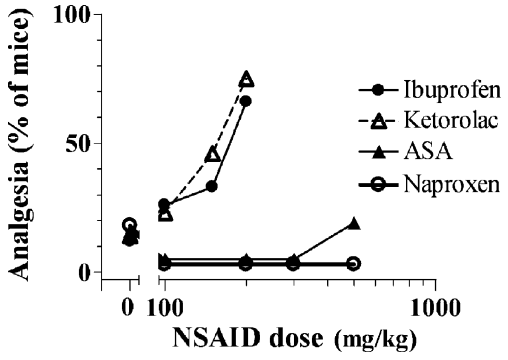

Fig. 1. Hydrocodone analgesia alone and in combination with NSAIDs. Mice were administered hydrocodone at a fixed dose (2.5 mg/kg sc) in combination with the indicated dose of NSAID ($n \geq 24$) and tested in the tail-flick assay. Hydrocodone alone ($n = 90$) gave a response of 13%. Ibuprofen and naproxen both significantly increased the analgesic response of hydrocodone despite their inactivity alone ($P < 0.05$). Ketorolac and aspirin were without significant effect at all doses examined.