Gabapentin and Pregabalin Can Interact Synergistically with Naproxen to Produce Antihyperalgesia

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Background: Gabapentin and pregabalin are anticonvulsants with antihyperalgesic effects in animal models of neuropathic and inflammatory nociception. This study characterized the manner in which gabapentin or pregabalin interacts with naproxen to suppress thermal hyperalgesia and inflammation in the carrageenan model of peripheral inflammation.

Methods: Gabapentin, pregabalin, naproxen, or a fixed-dose ratio of gabapentin + naproxen or pregabalin + naproxen was administered orally to rats after the induction of inflammation by intraplantar injection of δ-carrageenan in one hind paw. Nociceptive thresholds were determined by the radiant heat paw-withdrawal test. Paw edema was measured by plethysmometry. Drug plasma concentrations were determined by a liquid chromatography–mass spectrometry–mass spectrometry method.

Results: Gabapentin, pregabalin, and naproxen alone reversed thermal hyperalgesia with ED₅₀ values of 19.2, 6.0, and 0.5 mg/kg, respectively. Mixtures of gabapentin + naproxen in fixed-dose ratios of 50:1, 10:1, or 1:1 interacted synergistically to reverse carrageenan-induced thermal hyperalgesia. However, 1:50 gabapentin + naproxen produced only additive effects. No combination of gabapentin + naproxen decreased paw edema in a manner greater than additive. Plasma concentrations of gabapentin and naproxen were unaltered by the addition of the other drug. The mixture of 10:1 of pregabalin + naproxen interacted synergistically to reverse thermal hyperalgesia on the inflamed hind paw, whereas mixtures of 1:1 or 1:10 produced additive effects.

Conclusions: These data suggest that gabapentin + naproxen and pregabalin + naproxen can interact synergistically or additively to reverse thermal hyperalgesia associated with peripheral inflammation. Therefore, the use of gabapentin or pregabalin in low-dose combinations with naproxen may afford therapeutic advantages for clinical treatment of persistent inflammatory pain.

Gabapentin and pregabalin are anticonvulsants that were originally developed as spasmylic agents and adjuncts for the management of generalized or partial epileptic seizures resistant to conventional therapies. However, subsequent single center and multicenter, randomized double-blind trials established that gabapentin is also effective for the management of pain of inflammatory and neuropathic origin, such as postherpetic neuralgia and painful diabetic neuropathy. Although pregabalin has not been as extensively investigated as gabapentin, recent double-blind trials determined that it is effective in the management of postoperative dental pain and painful diabetic neuropathy. In animal models of nociception, gabapentin reduces the mechanical or thermal hypersensitivity associated with models of nerve injury, incisional injury, inflammatory injury, and formalin-induced injury. Pregabalin similarly reduces the mechanical or thermal hypersensitivity associated with models of nerve injury, incisional injury, inflammatory injury, and formalin-induced injury.

The present study examined whether the oral administration of gabapentin or pregabalin in combination with the NSAID naproxen would yield more efficacious or more potent relief in an animal model in which peripheral inflammatory nociception is induced by the intraplantar injection of δ-carrageenan in the hind paw of the rat. These experiments used an isobolographic approach to examine the interaction of gabapentin and naproxen administered in four different fixed-dose combinations and the interaction of pregabalin and naproxen administered in three different fixed-dose combinations. A separate set of experiments sought to determine if a pharmacokinetic component contributed to the nature of the interaction between gabapentin and naproxen.

Materials and Methods

Experiments were conducted according to a protocol approved by the Institutional Animal Care and Use Committee of the University of Chicago where these studies were conducted. Male Sprague-Dawley rats (Sasco, Kingston, NY) weighing 250–300 g were used. Animals were housed four/cage on a 12-h light–dark cycle with free

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access to food and water. Rats were only used once and received only one dose of drug or drug combination.

**Drugs**

λ-Carrageenan (lot no. 117H0380 and 118H0665) and naproxen (lot no. 76H0435) were purchased from Sigma Chemical Company (St. Louis, MO). Gabapentin (Neurontin, 1-[aminomethyl] cyclohexanacetic acid; lot no. 38 and N) and pregabalin (S(+)-3-isobutylgaba; lot no. G) were provided by Parke Davis Pharmaceuticals (Ann Arbor, MI). All drugs were dissolved in 0.9% saline solution.

**Nociceptive Testing**

Thermal nociceptive thresholds were determined for both hind paws using a radiant heat device as described previously. Briefly, the rat was placed in a clear box resting on an elevated glass plate that was maintained at 25°C. A beam of light was positioned under either hind paw, and the time for the rat to remove the paw from the thermal stimulus was recorded as the paw withdrawal latency (PWL). The intensity of the stimulus was set to produce a PWL between 8 and 12 s in a naive rat. If the rat did not withdraw its paw from the stimulus by 20 s, the test was terminated, and the rat was assigned this cut-off value.

The rats were acclimated in the testing room for 1 h and the testing chamber for 30 min before testing. After determination of the baseline PWL, 100 μl of a 1% solution of λ-carrageenan was injected into the plantar surface of one hind paw. Baseline PWLs were determined 2.5 h later to confirm the presence of thermal hyperalgesia. Vehicle, gabapentin (3.0–300.0 mg/kg), naproxen (0.1–30.0 mg/kg), pregabalin (3.0–30.0 mg/kg), or a mixture of gabapentin and naproxen (0.001–300.0 mg/kg total dose) or pregabalin and naproxen (0.1–30.0 mg/kg total dose) was then administered via gavage in a volume of 2 ml/kg body weight. Response latencies for the ipsilateral and contralateral hind paw were determined again 30, 60, 90, and 120 min after drug administration. Gabapentin and naproxen were administered in fixed-dose ratios of 50:1, 10:1, 1:1, and 1:50 based on mass units. Pregabalin and naproxen were administered in fixed-dose ratios of 10:1, 1:1, and 1:10. These fixed-dose ratios were chosen to bracket a range that included the ratio of the ED50 values of each drug and the reciprocal of that ratio. The timing of drug administration was based on earlier findings that the thermal hyperalgesia induced by carrageenan was maximal at 2.5 h and remained stable for at least another 2 h.

**Measurement of Peripheral Edema**

Paw volume was determined by plethysmometry (Ugo Basile, Comerio, Italy) before the injection of carrageen, 2.5 h after the injection of carrageenan (just before the injection of drug), and then again 2 h after drug administration.

**Measurement of Plasma Drug Concentration**

After the measurement of paw volume, the rats were deeply anesthetized with halothane, and 1.5 ml blood samples were obtained by cardiac puncture. Blood samples were stored at –80°C until further processing. Aliquots (50 μl) of plasma samples or the prepared calibration standards in plasma were mixed with 250 μl of internal standard solution in methanol (300 ng/ml). The mixture was vortex-mixed and then centrifuged at 4,000 rpm. Aliquots (50 μl) of the supernatant were mixed with 50 μl of water for analysis by liquid chromatography–mass spectroscopy–mass spectroscopy methods. Liquid chromatography and mass spectrometry assays were performed on a PE Series 200 LC pump and autosampler with a Micromass Quattro II triple-quadrupole mass spectrometer. For gabapentin and the internal standard pregabalin, spectra were acquired in positive ionization electrospray multiple reaction monitoring mode. Chromatographic separation was achieved by using a column of Keystone AQ 2 mm × 100 mm × 5 μm during isocratic conditions. The mobile phase was methanol:water (50:50 v/v) at a flow rate of 0.22 ml/min. The injection volume was 2 μl. For naproxen and its internal standard naphthoxyacetic acid, spectra were acquired in negative ionization mode. The HPLC column was a YMC basic 2 mm × 50 mm × 3 μm. The mobile phase consisted of acetonitrile–methanol–0.02% ammonium hydroxide with 10 mM ammonium acetate 20/20/40 (v/v/v) at a flow rate of 0.22 ml/min. The sample injection volume was 3 μl. The minimal quantitation limit was 0.01 μg/ml for gabapentin and naproxen; linearity was demonstrated up to 100 μg/ml. No measurements of the plasma concentration of pregabalin in the presence of naproxen were made.

**Statistical Analysis**

A two-way analysis of variance for repeated measures was used to compare the effects of gabapentin, naproxen, pregabalin, and the combinations of these drugs with those of the vehicle control. The Newman-Keuls test was used for post hoc comparisons among the individual group means. Dose–response relationships for gabapentin, naproxen, pregabalin, and the mixtures of gabapentin with naproxen and pregabalin with naproxen were determined using the PWLs obtained 120 min after drug administration at the time of peak effect. For concurrent administration, the dose was expressed as the total dose in mass units of gabapentin and naproxen, or pregabalin and naproxen. The ED50 value was defined as the dose that produced one half the maximum possible increase in PWL. This value corresponded to 7.0 s. Fieller theorem was used to determine the 95% CI.
To determine the nature of the interaction, the experimentally derived dose–response relationship for the total dose of gabapentin and naproxen was compared with its theoretical dose–additive relationship by standard parallel line assay methods. Because the slopes of the dose–effect curves for pregabalin and naproxen differed, standard parallel line assays could not be used to compare the slopes and intercepts of the experimental mixture and the theoretical dose additive line. Rather, the experimentally derived ED$_{50}$ value was compared with the theoretical dose–additive value at a specified level of effect, in this case an increase in PWL to 7.0 s. For conventional graphic presentation, isobolograms of the theoretical dose–additive values for the combinations and the experimentally derived ED$_{50}$ values of the various drug combinations were also constructed.

Mean baseline paw volume ranged from 1.5 to 1.6 ml among the different treatment groups. When measured 2.5 h after the injection of carrageenan, mean paw volume ranged from 2.5 to 3.0 ml among the different treatment groups. Drug effects were expressed as a difference score in which the paw volume measured 2 h after administration of the drug was subtracted from that determined immediately before (i.e., 2.5 h after carrageenan). Negative values, therefore, represent a reduction in inflammation. A one-way analysis of variance and Newman–Keuls test were used to compare the difference scores between treatment groups.

**Results**

*Effect of Gabapentin, Pregabalin, and Naproxen Administered Alone*

Administration *via* gavage of 3.0–300.0 mg/kg gabapentin after the induction of inflammation produced a time- and dose-dependent increase in PWL of the ipsilateral hind paw (fig. 1A). The peak effect consistently occurred within 120 min. Response latencies of the contralateral, noninflamed hind paw were unaffected (data not shown). The ED$_{50}$ value (and 95% CL) for gabapentin given *via* gavage was 19.2 mg/kg (range, 5.5–43.1 mg/kg).

Administration *via* gavage of 3.0–30.0 mg/kg pregabalin after the induction of inflammation also produced a time- and dose-dependent increase in PWL of the ipsilateral hind paw (fig. 1B). The ED$_{50}$ value (and 95% CL) for pregabalin given *via* gavage was 6.0 mg/kg (range, 2.3–10.2 mg/kg). Unlike gabapentin, pregabalin increased the PWL of contralateral hind paw. However, this modest effect was observed only 90–120 min after administration of the 10 mg/kg (to 12.7 ± 0.7 s) or 30 mg/kg (to 14.0 ± 1.0 s) doses.

Administration *via* gavage of 0.1–30.0 mg/kg naproxen after the induction of inflammation produced a time- and dose-dependent increase in PWL of the ipsilateral (fig. 1C) but not the contralateral, noninflamed hind paw (data not shown).

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shown). As with gabapentin and pregabalin, the peak effect of naproxen consistently occurred within 120 min. The ED50 value (and 95% CL) for naproxen given via gavage was 0.48 mg/kg (range, 0.05–1.38 mg/kg).

The dose–response relationships determined 2 h after administration of gabapentin, pregabalin, or naproxen for the ipsilateral hind paw are illustrated in figures 2 and 3.

**Effect of Gabapentin Administered in Combination with Naproxen**

Figure 2 also illustrates the experimentally derived dose–response relationship for each fixed-dose combination of gabapentin and naproxen determined 2 h after drug administration and the corresponding theoretical additive–dose response relationship constructed for that fixed-dose combination. Each combination produced significant reversal of the carrageenan-induced hyperalgesia. The time course of the antihyperalgesic effect was similar for each fixed-dose ratio and was maximal within 120 min after oral administration (data not shown). No combination of gabapentin and naproxen had an antinociceptive effect on the contralateral, uninjured hind paw (data not shown).

For the 50:1 fixed-dose ratio (gabapentin:naproxen), which approximated the ratio of ED50 values of the drugs administered alone, total doses of 10 mg/kg or higher significantly increased PWL of the inflamed hind paw. The dose–response relationship for the combination was situated 14-fold to the left of the theoretical dose–additive line (fig. 2A) and was significantly different from the dose–additive line, consistent with a synergistic interaction (table 1). For the 10:1 fixed-dose ratio (gabapentin:naproxen), total doses of 1 mg/kg or higher significantly increased PWL of the inflamed hind paw. The dose–response relationship for the combination was situated about fivefold to the left of the theoretical dose–additive line (P < 0.05). For the 1:1 fixed-dose ratio (gaba-
pentin:naproxen), total doses of 0.01 mg/kg or higher significantly increased PWL of the inflamed hind paw. The dose-response relationship for very low doses of the combination was situated about 1,500-fold to the left of the theoretical dose-additive line (fig. 2C) and was significantly different from the dose-additive line, consistent with a synergistic interaction (table 1). This enhancement was restricted to changes in the potency of the drugs, not their maximum efficacy. Thus, administration of a total dose of 10 mg/kg of the 1:1 dose ratio produced no further increase in PWL than did the 0.1 mg/kg total dose, which was sufficient to completely reverse the thermal hyperalgesia (fig. 2C). For the 1:50 fixed-dose ratio (gabapentin:naproxen), total doses of 0.1 mg/kg or higher significantly increased PWL of the inflamed hind paw. Although the experimentally derived dose-response relationship was situated threefold to the left of the theoretical dose-response relationship (fig. 2D), statistical comparison of the regression lines and their variances indicated that they did not differ significantly. These conclusions are supported by examination of the isobologram (fig. 4). Isobolographic analysis conducted using the 50:1, 10:1, and 1:1 (gabapentin:naproxen) ratios revealed a synergistic interaction between the two drugs, whereas analysis of the 1:50 (gabapentin:naproxen) ratio revealed only an additive interaction.

**Effect of Pregabalin Administered in Combination with Naproxen**

Figure 3 illustrates the experimentally derived dose-response relationships for the concurrent administration of each fixed-dose ratio of pregabalin and naproxen and the theoretical additive dose-response relationship constructed for that dose ratio. Each combination produced significant reversal of the carrageenan-induced hyperalgesia. The time course of the antihyperalgesic effect was similar for each fixed-dose ratio and was maximal within 120 min after oral administration (data not shown). No antinociceptive effect of any combination was observed on the contralateral, uninjured hind paw (data not shown).

For the 10:1 fixed-dose ratio (pregabalin:naproxen), total doses of 0.1 mg/kg or higher significantly increased PWL of the inflamed hind paw. The experimentally derived ED50 value was 6.5-fold less than the ED50 value predicted for an additive interaction of this mixture at the specified level of effect (i.e., an increase in PWL to 7.0 s), indicating that pregabalin and naproxen interacted in a synergistic manner in this dose ratio (table 1). Because the dose-effect curves for pregabalin, naproxen, and their mixtures were not parallel, additional comparisons were made between the experimentally derived doses and the theoretical additive doses at criterion latencies of 6 or 8 s. These comparisons yielded the same conclusion. However, at response latencies greater than 9 s, the interac-

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**Fig. 3.** Dose–response relationships for pregabalin (open diamond, solid line), naproxen (open square, solid line), and the combination of the pregabalin and naproxen (filled-in circle, solid line). The slope of the dose–response curve for pregabalin is significantly steeper than that of naproxen. Therefore, the theoretical dose–additive line (dashed line) for the total dose of pregabalin and naproxen at each fixed-dose combination was constructed as described by Tallarida19 (A) The dose of the 10:1 pregabalin:naproxen (P:N) combination required to achieve the specified level of effect (i.e., an increase in PWL to 7.0 s) is significantly less than the theoretical dose–additive point (P < 0.05). In contrast, the doses of the 1:1 pregabalin:naproxen combination (B) or the 1:10 pregabalin:naproxen combination required to increase PWL to 7.0 s do not differ from their respective theoretical dose–additive points (P > 0.05, both combinations). Symbols represent the mean ± SEM response latencies from 7–16 rats.
tion became additive. For the 1:1 fixed-dose ratio (pregabalin:naproxen), total doses of 1.0 mg/kg or higher administered concurrently significantly increased PWL of the inflamed hind paw. The ED$_{50}$ value for the 1:1 mixture did not differ from the ED$_{50}$ value predicted for an additive interaction of this mixture (table 1), indicating that pregabalin and naproxen interacted in an additive manner in this ratio. The same conclusion was reached for comparison of the experimentally derived dose with the theoretical additive dose at other criterion values of 6, 8, or 9 s. For the 1:10 fixed-dose ratio (pregabalin:naproxen), total doses of 1.0 mg/kg or higher administered concurrently significantly increased PWL of the inflamed hind paw. The ED$_{50}$ value for the 1:10 mixture was approximately the same as the ED$_{50}$ value predicted for an additive interaction of this mixture (table 1), indicating that pregabalin and naproxen interacted in an additive manner. A comparison of the experimentally derived doses with the theoretical additive doses at other criterion values of 6, 8, or 9 s yielded the same conclusion. These findings are supported by examination of the isobologram (fig. 5). Isobolographic analysis of the 10:1 (pregabalin:naproxen) ratio revealed a synergistic interaction between the two drugs, whereas analysis of the 1:10 and 1:1 (pregabalin:naproxen) ratios revealed only an additive interaction. Although the ED$_{50}$ value of the 1:10 (pregabalin:naproxen) ratio is above and to the right of the dose-additive line on the isobologram, it resides within the standard error of that line and therefore does not differ from additivity.

**Effects of Gabapentin, Pregabalin, and Naproxen Alone and in Combination on Paw Volume**

Naproxen alone at 30 mg/kg decreased paw volume by 0.35 ml (a 12% decrease) as compared with saline vehicle (fig. 6A). Lower doses of naproxen were ineffective (data not shown). Gabapentin at a dose as high as 300 mg/kg was without significant effect. The highest doses of the 50:1, 10:1, 1:1, and 1:50 fixed-dose combinations of gabapentin and naproxen also caused no significant decrease in paw volume (fig. 6A). It should be noted that the amount of naproxen contained within even the highest doses of any of the fixed-dose ratios did not exceed 10 mg/kg and that the effects of the mixtures did not exceed the effects produced by this dose of naproxen alone (data not shown). Thus, it would appear that the synergistic interaction of gabapentin and naproxen does not extend to inflammation. Pregabalin alone at 30 mg/kg had no significant effect on paw volume. No combination of pregabalin and naproxen caused a significant decrease in paw volume even at the highest doses administered (fig. 6B).

**Plasma Concentrations of Gabapentin and Naproxen Alone and in Combination**

In rats that received naproxen alone or gabapentin alone, the plasma concentration of each drug increased with dose in an orderly manner. The plasma concentration curves for naproxen determined for each of the four different combinations of gabapentin and naproxen were superimposed on that of naproxen alone (fig. 7A). Statistical estimates of the dose of naproxen needed to yield a plasma concentration of 1 µg/ml did not differ among any of the treatment groups (table 2). Thus, the additional presence of gabapentin did not alter the plasma concentrations of naproxen. In general, the plasma concentration curves for gabapentin determined for each of the four different combinations of gabapentin and naproxen did not differ from that determined for gabapentin alone (fig. 7B). However, for the 50:1 dose ratio, there was a small increase in the estimated dose of
of the dose ratio administered. A consistent finding was that gabapentin and naproxen interact in a synergistic manner to produce antihyperalgesia when gabapentin is in equal proportion or the predominant component of the drug mixture. The interaction changed to additive when naproxen was the predominant component. Pregabalin also was found to interact in a synergistic manner with naproxen when it was the predominant component of the drug mixture. However, unlike gabapentin, this interaction became additive when pregabalin was in equal proportion or the lesser component. The mechanism responsible for the synergistic interactions of gabapentin with naproxen is unlikely to be pharmacokinetic because measurements of the plasma concentrations of each drug demonstrated that each did not significantly alter the levels of the other.

Mechanism of Action of Gabapentin, Pregabalin, and Naproxen

An understanding of the sites and mechanisms that mediate the effect of these drugs alone is a useful pre-

Discussion

This study used an isobolographic approach to characterize the nature of the interaction of gabapentin or pregabalin with naproxen in an animal model of inflammatory pain. Carrageenan-induced thermal hyperalgesia is a well-established behavioral correlate that reflects the induction of central sensitization of spinal cord neurons as a result of the repetitive activation of primary afferent neurons that are themselves sensitized as a consequence of peripheral inflammation. This study examined a range of different fixed-dose ratios because the nature of the pharmacologic interaction can differ as a function of the dose ratio administered. A consistent finding was that gabapentin and naproxen interact in a synergistic manner to produce antihyperalgesia when gabapentin is in equal proportion or the predominant component of the drug mixture. The interaction changed to additive when naproxen was the predominant component. Pregabalin also was found to interact in a synergistic manner with naproxen when it was the predominant component of the drug mixture. However, unlike gabapentin, this interaction became additive when pregabalin was in equal proportion or the lesser component. The mechanism responsible for the synergistic interactions of gabapentin with naproxen is unlikely to be pharmacokinetic because measurements of the plasma concentrations of each drug demonstrated that each did not significantly alter the levels of the other.

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lude to any discussion of the mechanisms that may subserve their synergistic or additive interaction.

Studies of the sites at which gabapentin and pregabalin may act to produce antihyperalgesia have identified the spinal cord as an important locus. Support for a spinal site of action is provided by several electrophysiologic,22 behavioral,8,10,25,24 and anatomic11 investigations. Although a peripheral site of action also has been suggested,25 efficacy by this route may depend on the measure of nociception and the relative time of drug administration.8

Fig. 6. Paw volumes of the ipsilateral hind paw after the administration of the drugs alone or in combination. The effect of the highest dose of each individual drug or combination is illustrated with the dose indicated in parentheses. Difference scores were calculated for each animal by subtracting the paw volume obtained 2 h after the administration of the drug from the baseline paw volume obtained 2.5 h after the induction of inflammation with carrageenan. Therefore, negative values represent a decrease in inflammation. Asterisks indicate values that are significantly different from values in rats in saline-treated rats; *P < 0.05. Bars represent the mean ± SEM of 8–16 rats. G:N = gabapentin:naproxen; P:N = pregabalin:naproxen.

Fig. 7. Plasma concentrations of naproxen (A) or gabapentin (B) after administration via gavage of the drug alone or in combination. Symbols represent the mean ± SE of determinations in 8–16 rats. The doses on the abscissa represent the actual dose of naproxen (N) or gabapentin (G) administered alone or in the mixture. Only the plasma concentration of gabapentin for the highest dose of the 1:50 gabapentin:naproxen (G:N) mixture is illustrated because lower doses yielded plasma concentrations below the limit of detection of this assay method.
Gabapentin and pregabalin were originally designed as structural analogs of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). However, neither drug is an agonist at GABA_A or GABA_B receptors, and neither drug acutely alters GABA uptake. It is likely that their antihyperalgesic effects result from an action at the α_2β_1 subunits of voltage-dependent Ca^{2+} channels (VDCC) for which gabapentin has substantial affinity and which are upregulated in the dorsal root ganglia and spinal cord after peripheral nerve injury. The N- and P/Q-types of VDCC are implicated in the development of enhanced pain states after the induction of inflammation. Initial studies of the effect of gabapentin on neuronal Ca^{2+} currents evoked by voltage steps yielded disparate conclusions. The inhibition of N- and P/Q-type Ca^{2+} channel activity was only modest, and the effect on the L-type channel was not consistent. However, subsequent studies of dorsal root ganglion neurons indicated that gabapentin reduced whole cell Ca^{2+} currents most effectively when test pulses were preceded by depolarization or activation of protein kinase A. Further, gabapentin decreased Ca^{2+} currents in a larger proportion of dorsal root ganglion neurons obtained from rats with chronic constriction or sham surgery of the sciatic nerve compared with unoperated rats. Enhanced excitability and sustained membrane depolarization are hallmarks of injury-induced central sensitization of spinal cord neurons. Such a condition-selective action of gabapentin may explain the ability of these drugs to alleviate the allodynia and hyperalgesia produced by inflammatory injury (seen in this study and others) or neuropathic injury and their lack of efficacy in models of nonrepetitive, acute noxious stimulation. Gabapentin may also produce antihyperalgesia by its ability to decrease glutamatergic transmission in the spinal cord presumably by inhibition of presynaptic VDCC. Therefore, gabapentin and pregabalin may inhibit central sensitization and its behavioral correlate of thermal hyperalgesia through an action at VDCC that results in a direct postsynaptic inhibition of Ca^{2+} influx or a presynaptic inhibition of Ca^{2+} influx that decreases excitatory amino acid neurotransmission and its sequelae.

Nonselective NSAIDs, such as naproxen, inhibit cyclooxygenase I and II enzymes and thereby decrease the production of prostaglandin E_2 (PGE_2). Several studies have highlighted the importance of a peripheral site of action for NSAIDs. Administration of PGE_2 directly into the hind paw produces edema and hyperalgesia. Systemic administration of monoclonal antibodies to PGE_2 decreases carrageenan-induced paw edema and hyperalgesia. Systemically administered NSAIDs reduce inflammation and hyperalgesia, and inhibit the expression of c-Fos by spinal cord dorsal horn neurons. This latter effect suggests that NSAIDs attenuate hyperalgesia by their ability to decrease nociceptive drive by primary afferents onto dorsal horn neurons. More recent studies have highlighted a central component of NSAID action. In the spinal cord, PGE_2 can act presynaptically to increase the release of glutamate from primary afferent C-fibers and postsynaptically to directly excite dorsal horn neurons by activation of nonselective cation currents. Both effects would promote the development and maintenance of central sensitization and enhanced pain states. Intrathecal administration of NSAIDs prevents the development of hyperalgesia and inhibits the release of PGE_2. Taken together, these findings indicate that NSAIDs act centrally and peripherally through an inhibition of PGE_2 synthesis to produce antihyperalgesia and reduce inflammation.

**Mechanisms by which Gabapentin and Pregabalin May Interact with Naproxen**

As just described, the sites at which gabapentin and pregabalin act to produce antihyperalgesia (predominantly the spinal cord) and the sites at which naproxen acts (spinal cord and periphery) appear to be complementary. Further, the mechanisms by which these two classes of compounds act to suppress pain transmission differ (inhibition of VDCC vs. inhibition of cyclooxygenase). This profile could be the basis for a synergistic interaction of these compounds. Central sensitization and the behavioral correlate induced by peripheral inflammation are mediated in part by an action of glutamate at NMDA receptors, which results in an influx of Ca^{2+}, increased neuronal excitability, and the eventual upregulation of prostaglandins. Gabapentin and pregabalin may decrease Ca^{2+} influx by several mechanisms, including presynaptic inhibition of glutamate release via Ca^{2+} channel inhibition and postsynaptic inhibition of VDCC on dorsal horn neurons. Naproxen may synergize with these effects through its inhibition of PGE_2 synthesis, which would cause presynaptic neurons to release less glutamate and thereby reduce the excitability of postsynaptic dorsal horn neurons. Thus, there

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**Table 2. Estimated Dose and 95% Confidence Limits of Gabapentin or Naproxen to Yield a 1 μg/ml Plasma Concentration When Administered Alone or in a Fixed-dose Combination with the Other Drug**

<table>
<thead>
<tr>
<th>Fixed-dose Ratio of Gabapentin to Naproxen</th>
<th>Gabapentin (mg/kg intragastric)</th>
<th>Naproxen (mg/kg intragastric)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alone</td>
<td>1.34 (1.10–1.60)</td>
<td>0.32 (0.29–0.35)</td>
</tr>
<tr>
<td>50:1</td>
<td>2.37 (2.09–2.62)</td>
<td>0.41 (0.34–0.51)</td>
</tr>
<tr>
<td>10:1</td>
<td>2.4 (1.37–4.09)</td>
<td>0.32 (0.16–0.61)</td>
</tr>
<tr>
<td>1:1</td>
<td>1.81 (1.20–2.97)</td>
<td>0.30 (0.21–0.46)</td>
</tr>
<tr>
<td>1:50</td>
<td>ND</td>
<td>0.29 (0.24–0.33)</td>
</tr>
</tbody>
</table>

*P < 0.05 compared to gabapentin alone.

ND = not determined because only the highest dose in this treatment group yielded consistently quantifiable plasma concentrations of gabapentin.
is a basis for a synergistic interaction of these drugs within the spinal cord.

Intrathecally administered NSAIDs block the development of hyperalgesia when given before the induction of inflammation but are ineffective when administered after the development peripheral inflammation, suggesting that spinal PGE2 is responsible for the development but not the maintenance of hyperalgesia. However, when systemically administered, NSAIDs are able to alleviate hyperalgesia after the development of inflammation. Thus, it is possible that the effects of NSAIDs during the maintenance phase of hyperalgesia may be preferentially mediated by a peripheral site of action. With conditions of an established inflammatory hyperalgesia, as in this study, synergism may occur because the predominant action of gabapentin or pregabalin is exerted centrally in the spinal cord, whereas naproxen acts predominantly in the periphery to decrease inflammation and excitatory drive to the spinal cord. Just as synergism can occur between two distinct sites in the spinal cord (vide supra), it may also occur between two disparate anatomic sites that converge to have the same functional outcome.

Ibuprofen and gabapentin were recently reported to interact in an additive manner to suppress pain behaviors in the formalin test. Aside from the use of a different NSAID, numerous differences in the design of these two studies may underlie the disparate results. First, the use of a single fixed-dose ratio does not permit full characterization of a complex pharmacologic interaction. Second, the formalin and carrageenan models differ in terms of the stimulus intensity and time course, the type of behavioral measures made, and possibly in the mechanisms of hyperalgesia (this study) and spontaneous pain behaviors (formalin test). Several studies have demonstrated that the nature of the pharmacologic interaction of two compounds will depend on the test measure and the intensity of that measure. Finally, the former study administered the compounds before the induction of the injury, whereas in the present study, the compounds were given after the development of hyperalgesia. Pretreatment can prevent the development of central sensitization. It is possible that the synergism of gabapentin or pregabalin with naproxen may only be present during conditions in which central sensitization has previously been induced and in which the activity of primary afferents and dorsal horn neurons has been greatly enhanced.

Summary and Implications

The synergistic interactions of gabapentin or pregabalin with naproxen are reflected as an increase in potency rather than an increase in efficacy. Therefore, the principal advantage of this mixture lies in the ability to administer very low doses of each drug in combination to achieve significant reductions in thermal hyperalgesia.

The development of a low-dose combination could afford an important therapeutic advantage for the management of chronic pain, particularly among the elderly population at heightened risk for the adverse renal and gastrointestinal effects of NSAIDs. These results suggest that combination therapies based on mixtures of gabapentin or pregabalin with NSAIDs like naproxen could be an effective approach to the relief of pain of inflammatory origin.

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References


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