

Analgesic Synergy between Topical Lidocaine and Topical Opioids¹

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ABSTRACT

Topical drugs avoid many of the problematic side effects of systemic agents. Immersion of the tail of a mouse into a solution of dimethyl sulfoxide (DMSO)-containing morphine produces a dose-dependent, naloxone-sensitive, analgesia (ED₅₀ 6.1 mM; CL 4.3, 8.4) limited to the portion of the tail exposed to the drug. DMSO alone in this paradigm had no analgesic activity. Like morphine, the opioids levorphanol (ED₅₀ 5.0 mM; CL 3.8, 7.8) and buprenorphine (ED₅₀ 1.1 mM; CL 0.7, 1.5) were effective topical analgesics. Lidocaine also was active in the tail-flick assay (ED₅₀ 2.5 mM; CL 2.0, 3.4), with a potency

greater than morphine. As expected, the free base of lidocaine was more potent than its salt. Combinations of a low dose of lidocaine with a low dose of an opioid yielded significantly greater than additive effects for all opioids tested. Isobolographic analysis confirmed the presence of synergy between lidocaine and morphine, levorphanol and buprenorphine. These studies demonstrate a potent interaction peripherally between opioids and a local anesthetic and offer potential advantages in the clinical management of pain.

Topical treatments offer many advantages over systemic drugs. By limiting the exposure of a drug to the periphery, central side effects can be markedly reduced. For opioids, this might decrease limiting side effects, such as sedation, respiratory depression, and nausea. Further limiting the drug to the actual site of action has even more advantages, by avoiding peripherally mediated side effects, such as constipation. In earlier studies, we demonstrated the activity of topical morphine in the radiant heat tail-flick assay after immersion in a dimethyl sulfoxide (DMSO) solution (Kolesnikov and Pasternak, 1999a). The analgesic actions seen with topical morphine were limited to the region of the tail exposed to the drug. DMSO alone was inactive in this paradigm. Other opioid ligands acting through kappa and delta receptors have activity peripherally in the radiant heat tail-flick assay as well (Kolesnikov et al., 1996a; Kolesnikov and Pasternak, 1999b). Thus, topical opioids might be useful in pain control.

Synergy is important in opioid action. First described between supraspinal and spinal sites (Yeung and Rudy, 1980), it has also been described between brainstem nuclei (Rossi et

al., 1993) and between peripheral and central sites (Kolesnikov et al., 1996b). Synergy has been observed between opioids of different classes (Horan et al., 1992; Adams et al., 1993; Rossi et al., 1994; He and Lee, 1998).

Opioid actions also can be modulated by nonopioid classes of drugs. For example, opioid tolerance can be prevented or reversed by *N*-methyl-D-aspartate (NMDA) antagonists (Tujillo and Akil, 1991; Ben-Eliyahu et al., 1992; Tiseo and Inturrisi, 1993; Elliott et al., 1994) and nitric oxide synthase inhibitors (Kolesnikov et al., 1992, 1993). Unfortunately, NMDA antagonists have proven difficult to use systemically due to their profound psychomimetic and dysphoric actions. These problems might be avoided by a topical approach. We were able to demonstrate in our topical paradigm that the combination of an NMDA antagonist with an opioid blocked tolerance to the opioid (Kolesnikov and Pasternak, 1999c). This activity of NMDA antagonists topically presumably would avoid the limiting side effects that preclude their use systemically.

Lidocaine, a local anesthetic, is active topically, by blocking sodium channels, a mechanism distinct from the opioids (Woodsley and Funck-Brentano, 1988). Clinical studies have shown advantages to the combination of intrathecal lidocaine and opioids (Atanassoff et al., 1997; Saito et al., 1998a,b), leading us to question whether similar advantages might be seen topically. We therefore have examined the activity of topical lidocaine in the tail-flick assay alone and in combination with a number of opioids.

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ABBREVIATIONS: DMSO, dimethyl sulfoxide; NMDA, *N*-methyl-D-aspartate; CL, confidence limits.

Materials and Methods

Male Crl:CD-1(ICR)BR mice (25–30 g; Charles River Breeding Laboratory, Bloomington, MA) were maintained on a 12-h light/dark cycle with food and water available ad libitum. Mice were housed in groups of five until testing. Opioids were generously provided by the Research Technology Branch of the National Institute on Drug Abuse (Rockville, MD). Lidocaine was purchased from Sigma Chemical Co. (St. Louis, MO). Lidocaine base was used in all experiments unless indicated otherwise.

Topical Administration. Drugs were administered topically and analgesia assessed as previously described (Kolesnikov and Pasternak, 1999a). In this procedure, the distal portion of the tail (2–3 cm) is immersed in a DMSO solution containing the indicated drugs for the stated time, typically 2 min (Kolesnikov and Pasternak, 1999a). Prior studies have documented that DMSO alone has no effect when tested in this manner in the radiant heat tail-flick assay (Kolesnikov and Pasternak, 1999a). Furthermore, DMSO provides an effective way of solubilizing a wide range of drugs and facilitating their transport through the skin. The onset of analgesia is rapid, with peak effects seen immediately after the removal of the tail from the treatment solution. Therefore, we tested animals immediately after termination of topical administration.

Radiant Heat Tail-Flick Test. Testing was performed on the portion of the tail immersed in the treatment solution, because the analgesic actions of agents administered in this manner are restricted to the exposed portions of the tail; proximal regions are not affected (Kolesnikov and Pasternak, 1999a). Antinociception, or analgesia, was defined quantitatively as a tail-flick latency for an individual animal that was twice its baseline latency or greater. Baseline latencies typically ranged from 2.5 to 3.0 s, with a maximum cutoff latency of 10 s to minimize tissue damage in analgesic animals. Group comparisons were performed with the Fisher's exact test. ED_{50} values were determined with the Bliss program (Finney, 1976; Umans and Inturrisi, 1981), as previously reported (Kolesnikov et al., 1999a).

Drug Interactions. Isobolographic analysis was used to determine drug interactions (Talaradia et al., 1997). ED_{50} values were determined for each agent alone. They were then tested together at various doses at a constant ratio based on their respective ED_{50} values. In the figures, all points represent ED_{50} values. Values on the axes represent the ED_{50} values for the indicated drug alone, and the line connecting them corresponds to simple additive interactions. Points lying below the line of additivity indicate synergism. Significance was assumed by the lack of overlap of the confidence limits of the combination value with the confidence limits of the line of additivity.

Results

Topical Lidocaine and Morphine Interactions. First, we assessed the activity of topical lidocaine using the same administration paradigm previously shown active for opioids and NMDA antagonists (Kolesnikov and Pasternak, 1999a). Earlier studies emphasized the importance of exposure time in the activity of morphine. Similarly, the analgesic response to lidocaine was dependent on the exposure time (Fig. 1A). The response from a constant concentration of lidocaine increased from 20% at 30 s to 70% at 2 min. Time action curves revealed a maximal response immediately after removal of the tail from the solution, with a gradual decrease to baseline levels within 20 min (Fig. 1B). This response was slightly shorter in duration than a morphine dose giving the same maximal response. A lower lidocaine dose gave both a decreased maximal response and a shorter duration of action.

Both the free base and salt of lidocaine were examined

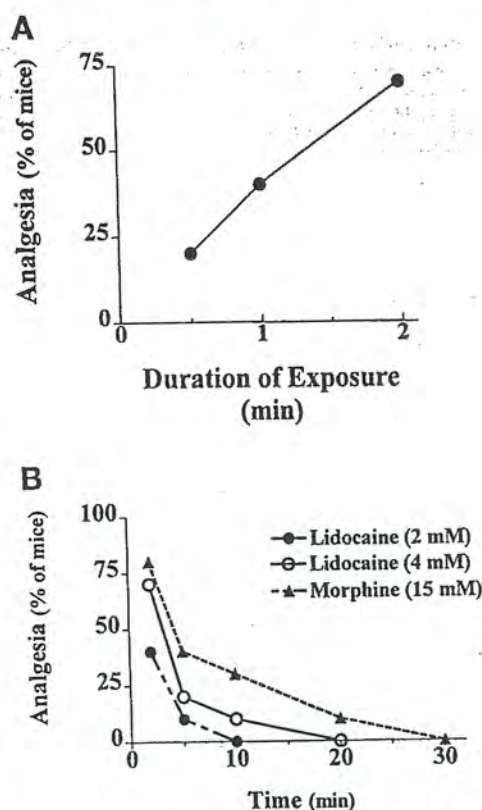


Fig. 1. Time dependence of topical lidocaine analgesia. A, groups of mice ($n \geq 10$) were exposed to a fixed concentration of topical lidocaine (4.3 mM) for 30 s, 1 min, and 2 min and then were tested in the tail-flick assay immediately after termination of drug exposure. B, groups of mice ($n \geq 10$) were treated with lidocaine (4.3 or 2.15 mM) or morphine (15 mM) for 2 min and then tested in tail-flick assay at the indicated time over 30 min.

(Fig. 2). Both were active, but the salt was less effective and plateaued at a 50% to 60% response. As expected, the free base form of lidocaine was more active, achieving a 75% response. However, it displayed a biphasic dose-response curve, with increases in concentration beyond 20 mM revealing a progressive lowering of analgesic activity. Morphine also was active, as previously reported (Kolesnikov and Pasternak, 1999a), with a potency intermediate between the two

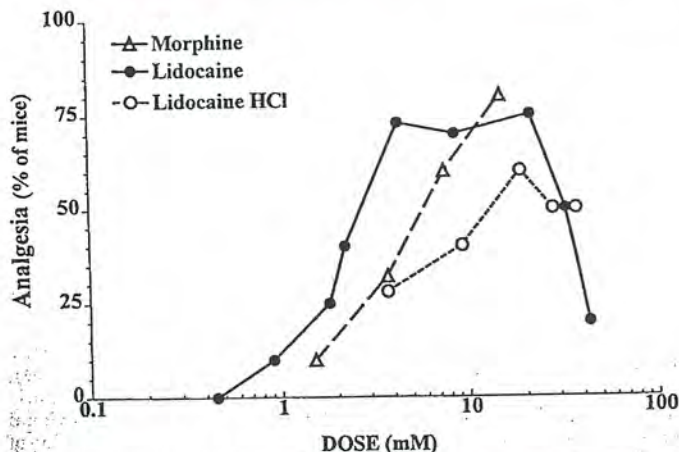


Fig. 2. Effects of topical lidocaine and morphine. Groups of mice ($n \geq 10$) were exposed to the indicated concentration of the free base of lidocaine, lidocaine HCl, or morphine for 2 min and tested immediately afterward.

TABLE 1

Analgesic potency of lidocaine and opioids alone and in combination

ED₅₀ values were determined from dose-response curves and presented with 95% confidence limits. For lidocaine, the ED₅₀ value was determined only from the initial portion of the curve. Combinations were also examined using increasing doses of a fixed ratio of the indicated drugs. ED₅₀ values were determined and presented with the 95% confidence limits. The relative potency of the various drugs in combination were compared with the same drug alone as a ratio. The fixed ratios were as follows: lidocaine/morphine, 0.5; lidocaine/buprenorphine, 2.4; lidocaine/levorphanol, 0.5.

Treatment	Lidocaine		Opioid	
	ED ₅₀ Value	Ratio	ED ₅₀ Value	Ratio
	mM		mM	
Lidocaine alone	2.5 (2.0, 3.4)		6.1 (4.3, 8.4)	
Morphine alone			1.1 (0.7, 1.5)	
Buprenorphine alone			5.0 (3.8, 7.8)	
Levorphanol alone			1.7 (1.2, 2.2)	3.6
Lidocaine/morphine	0.85 (0.6, 1.1)	2.9	0.94 (0.6, 1.6)	5.3
Lidocaine/levorphanol	0.47 (0.3, 0.8)	5.3	0.18 (0.12, 0.240)	6.1
Lidocaine/buprenorphine	0.44 (0.3, 0.6)	5.7		

forms of lidocaine (Table 1). The antagonist naloxone given alone was without effect.

Initially we assessed potential interactions between lidocaine and morphine using a fixed, low dose of each (Fig. 3A). Alone, lidocaine and morphine produced peak responses of only 20%. Together, their peak response was 80%, far greater than anticipated from simple additive interactions ($P < .004$). Comparing the areas under the curve gave even more dramatic differences. As anticipated, naloxone (1 mg/kg, s.c.),

given 20 min before agonist treatment, completely reversed the effects of the combination (data not shown).

To further assess the possibility of synergy, we next employed isobolographic analysis (Tallarida et al., 1997). A dose-response curve was generated using increasing doses of a fixed ratio of lidocaine/morphine. The ED₅₀ value fell well below the line of additivity, indicating synergism (Fig. 3B). The lack of overlap of the confidence limits of the combination value with those of the line of additivity confirmed its significance.

We also explored the relationship of lidocaine and morphine combinations by defining the ED₅₀ values of each agent alone and in combination with a fixed dose of the other rather than a ratio (Table 2). Low doses of morphine with little activity alone markedly enhanced the potency of lidocaine. The effect seemed to plateau, with little advantage seen by increasing the morphine concentration from 3 to 4.5 mM. Similar results were seen with the morphine dose-response curves. Again, a low dose of lidocaine facilitated morphine analgesia, with little additional effect seen after doubling the lidocaine concentration from 0.9 to 1.8 mM. Thus, the enhanced activity of the combination of the drugs was most evident at low concentrations of each.

Topical Lidocaine and Other Opioids. We next explored whether the synergy seen with morphine/lidocaine combinations extended to other opioids with other receptor mechanisms of action, including levorphanol and buprenorphine. Topically, levorphanol and buprenorphine both yielded full analgesic responses, with ED₅₀ values of 5.0 and 1.1 mM, respectively (Fig. 4; Table 1).

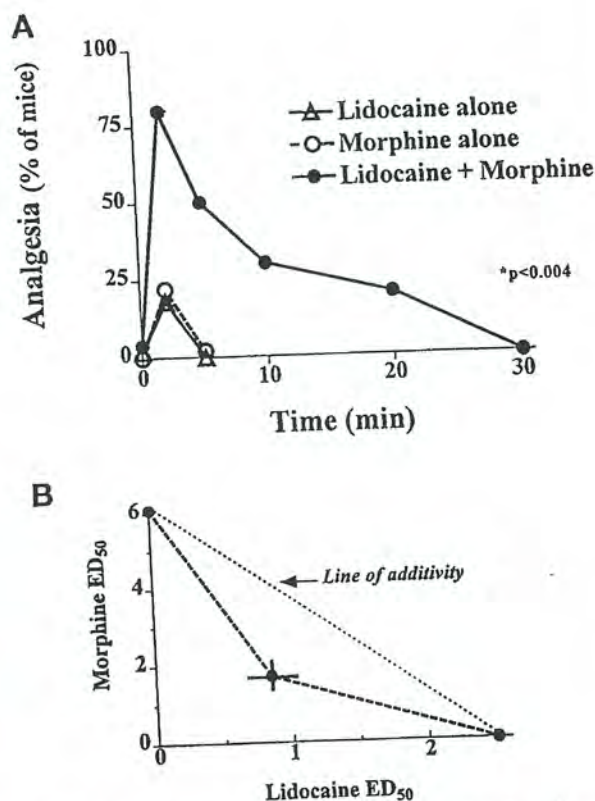


Fig. 3. Topical lidocaine and morphine interactions. A, groups of mice received either topical morphine (1.5 mM; $n = 10$) or lidocaine (0.9 mM; $n = 10$) alone or both together ($n = 20$). The combination was significantly ($P < .004$) more active at peak effect than the sum of two individual agents. B, using a fixed lidocaine/morphine ratio of 0.5, the ED₅₀ value of combination was determined with the 95% confidence limits. The presence of the ED₅₀ value below the line of additivity indicates the presence of synergy, confirmed by the lack of overlap between the 95% confidence limits for the drugs.

TABLE 2

Effects of fixed doses of morphine or lidocaine on the others analgesic potency

ED₅₀ values with 95% confidence limits were determined from at least three doses of topical lidocaine alone or with the indicated morphine concentration, or with topical morphine alone or with the indicated concentration of lidocaine.

	ED ₅₀	95% Confidence Limits	Shift
	mM		
Lidocaine alone	2.5	(2.0, 3.4)	
+Morphine 1.5 mM	1.0	(0.4, 1.8)	2.5
+Morphine 3.0 mM	0.8	(0.6, 1.1)	3.1
+Morphine 4.5 mM	0.7	(0.5, 0.9)	3.6
Morphine alone	6.1	(4.3, 8.4)	
+Lidocaine 0.45 mM	3.6	(2.6, 4.5)	1.7
+Lidocaine 0.9 mM	1.5	(0.9, 2.6)	4.1
+Lidocaine 1.8 mM	1.3	(0.6, 1.3)	4.7

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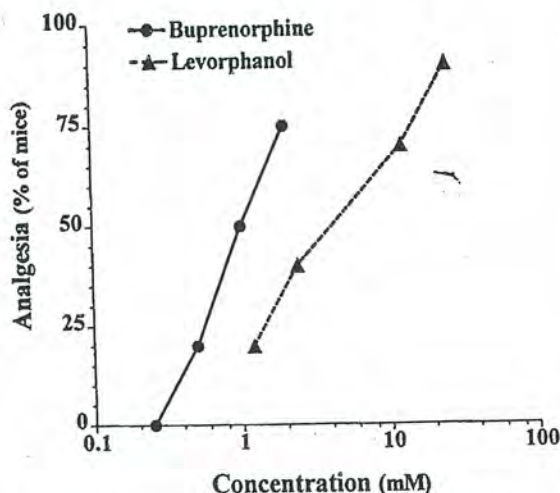


Fig. 4. Effects of topical buprenorphine and levorphanol. Groups of mice ($n \geq 10$) were exposed to the indicated concentration of the drug for 2 min and were tested immediately afterward.

Combinations of low doses of lidocaine and these opioids gave greater than additive analgesic actions (Fig. 5). The results with levorphanol closely resembled those of morphine, with the combination of low lidocaine and levorphanol doses giving a maximal response far beyond that expected by simple additive interactions ($P < .03$) as well as a prolonged duration far exceeding that of either alone (Fig. 5A). Although each drug alone had no effect beyond 5 min, together their response lasted for greater than 20 min. The effects of the combination of doses were readily antagonized by naloxone. The response to lidocaine alone (2.5 mM) was insensitive to naloxone (1 mg/kg, s.c.). (Data not shown.)

Buprenorphine and lidocaine gave similar results. The maximal responses of the two together were far beyond those anticipated by simple additive interactions (Fig. 5B). The duration of the response of the combination also markedly differed from that of either agent alone. Alone, each drug lasted less than 10 min. In contrast, the duration of the response of the combination was quite prolonged. The peak effect of the combination was 80% and persisted for 10 min. Analgesia could still be demonstrated after 45 min. Indeed, the duration of the response from the lidocaine/buprenorphine combination exceeded that seen with any of the other opioids tested. Naloxone significantly lowered the response of the combination.

Isobolographic Analysis of Lidocaine/Opioid Interactions. We next examined the combinations of the additional opioids isobolographically using dose-response curves with fixed ratios of the two drugs in combination (Fig. 6; Table 1). Combining levorphanol with lidocaine enhanced their relative potencies over 5-fold, which was more than the enhancement of morphine by lidocaine. Isobolographic analysis was consistent with synergy (Fig. 6A). Buprenorphine and lidocaine together shifted their individual ED_{50} values approximately 6-fold. Again, isobolographic analysis indicated synergy (Fig. 6B).

Discussion

Lidocaine is a widely used local anesthetic (Woosley and Funck-Brentano, 1988). It acts through the blockade of sodium channels, a mechanism distinct from the opioids. In the

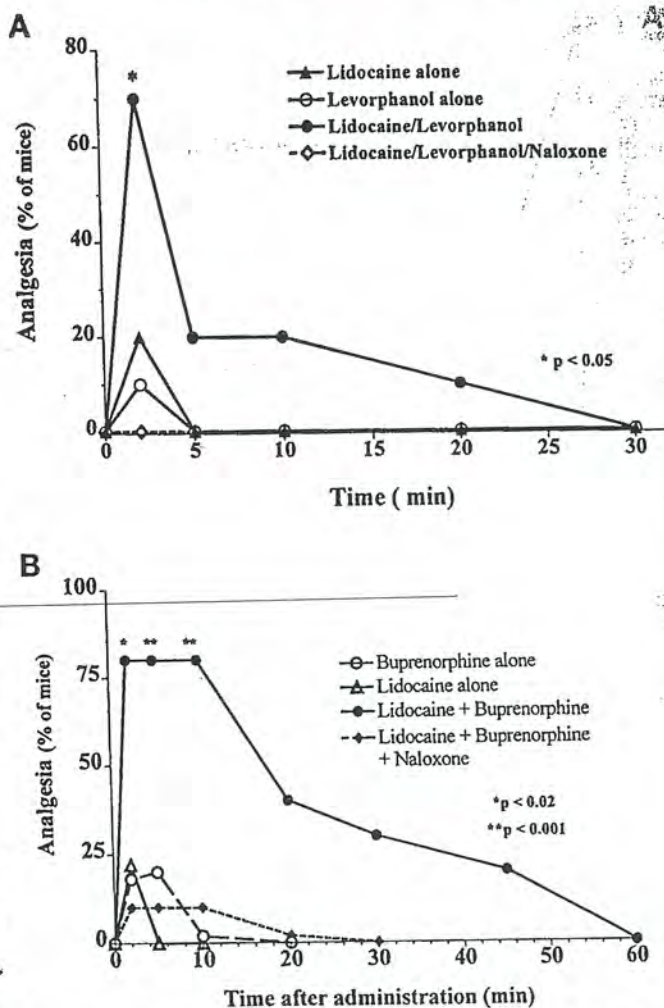


Fig. 5. Effects of combinations of low doses of opioids with lidocaine. A, groups of mice ($n = 20$) received either topical lidocaine (0.9 mM) or levorphanol (1.8 mM) or the combination of the two for 2 min and were tested in the tail-flick assay over 30 min. Another group of mice ($n = 10$) received naloxone (1 mg/kg, s.c.) 20 min before the topical drug application and was tested in tail-flick assay. Naloxone significantly reduced the response. B, groups of mice ($n = 20$) received either topical lidocaine (0.9 mM) or buprenorphine (0.5 mM) or the combination of the two for 2 min and then were tested in the tail-flick assay over 60 min. Another group of animals received naloxone (1 mg/kg, s.c.) 20 min before the topical drug application. Naloxone significantly reduced the response.

current study, lidocaine was effective topically in the radiant heat tail-flick assay, working only on the portion of the tail exposed to the drug and with a potency greater than morphine. As anticipated, the free base was more effective than the salt, presumably due to its greater lipophilicity. However, its dose-response curve was biphasic, with concentrations greater than 20 mM giving a progressive decrease in response. The reasons for this are not clear, but it is interesting that lidocaine concentrations above 15 mM can be toxic to neurons in primary culture (Gold et al., 1998).

All of the opioids tested were effective topical analgesics. The activity of levorphanol and buprenorphine extends the activity to drugs working on opioid systems other than simply μ receptors. Levorphanol elicits analgesia through both μ and κ_3 receptors (Moulin et al., 1988; Tive et al., 1992). Buprenorphine has a complex mechanism of action that is not entirely clear (Leander, 1987; Kamei et al.,

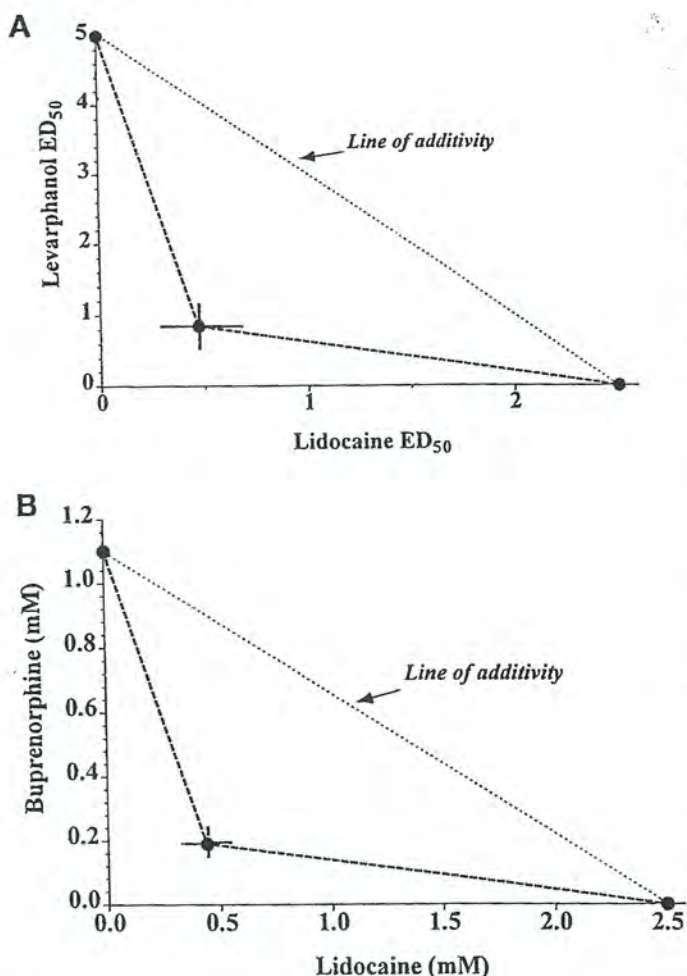


Fig. 6. Isobolographic analysis of lidocaine interactions with levorphanol and buprenorphine. **A**, using a fixed lidocaine/levorphanol ratio of 0.5, the ED₅₀ value of the combination with the 95% confidence limits was determined from the dose-response curve. The point falls below the theoretical line of additivity between the ED₅₀ values for each drug alone, indicating synergy. The lack of overlap between the 95% confidence limits for the drugs alone and the combination implies the synergy is significant. **B**, using a fixed lidocaine/buprenorphine ratio of 2.4, the ED₅₀ value of the combination with the 95% confidence limits was determined from the dose-response curve. The point falls below the theoretical line of additivity between the ED₅₀ values for each drug alone, indicating synergy. The lack of overlap between the 95% confidence limits for the drugs alone and the combination implies the synergy is significant.

1995a,b, 1997; Walker et al., 1995). Although it has high affinity for virtually all classes of opioid receptors in binding studies, it also has widely varying efficacies for the various classes of receptors. Topically, buprenorphine was particularly effective, with a potency 5-fold greater than that of morphine. The limited ability of naloxone to reverse the combination of buprenorphine and lidocaine implies that at least a portion of the response from buprenorphine was evoked from non- μ -opioid receptors.

Opioid analgesic synergy has been well established. Initially, it was observed among regions simultaneously exposed to opioid (Yeung and Rudy, 1980; Rossi et al., 1993, 1994; Kolesnikov et al., 1996b), followed by the demonstration of synergy between different classes of opioids (Adams et al., 1993). Morphine also has been reported to demonstrate synergy with lidocaine centrally (Saito et al., 1998a,b). We now

find synergy peripherally between topical opioids and a local anesthetic.

The combination of a low dose of morphine and lidocaine clearly revealed activity far beyond simple additive interactions, as did similar studies with the other opioids. These strongly suggested synergy among the opioids with lidocaine. This was not unexpected. Synergistic interactions might be more likely when drugs act on different mechanisms, as shown here with the opioids and lidocaine. Isobolographic analysis confirmed synergy between lidocaine and the opioids. The most impressive interaction was between buprenorphine and lidocaine, which had the greatest potentiation and the longest duration of action. However, it is not clear whether this resulted from its receptor selectivity or other factors such as its greater lipophilicity, which would enhance its ability to become diffused through the skin.

The demonstration of synergy between lidocaine and more than one opioid receptor ligand deserves more study. It will be of interest to define the opioid receptor mechanisms involved more clearly. However, even without a full understanding of how these agents interact, the demonstration of topical synergy between a local anesthetic and opioids opens many clinical possibilities in pain management.

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