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Topical methadone and meperidine analgesic synergy in the mouse

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Abstract

Topical analgesics have many potential advantages over systemic administration. Prior work has shown potent analgesic activity of a number of topical opioids in the radiant heat tailflick assay. The current study confirms the analgesic activity of morphine and extends it to two other mu opioids, methadone and meperidine. Combinations of topical morphine and lidocaine are synergistic. Similarly, the combination of methadone and lidocaine is synergistic. While there appeared to be some potentiation with the combination of meperidine and lidocaine, it did not achieve significance. Systemically, prior studies have shown that co-administration of morphine and methadone was synergistic. The combination of morphine and methadone was also synergistic when given topically. In contrast, the combination of morphine and meperidine was not synergistic systemically and it was not synergistic topically. Thus, the pharmacology of topical opioids mimics that seen with systemic administration. Their activity in the topical model supports their potential utility while the local limitation of their actions offers the possibility of a reduced side-effect profile.

Keywords

analgesic; peripheral; opioid; synergy; local anesthetic

1. Introduction

Opioids are potent analgesics acting at many levels of the neuraxis. Although their utility cannot be denied, their use is associated with a number of problematic side-effects, many of which are mediated centrally. The demonstration of peripheral activity of opioids (Joris et al., 1987; Mays et al., 1987; Levine and Taiwo, 1989; Stein, 1993; Kolesnikov et al., 1996a), therefore, raises the possibility of achieving analgesia without many of the side-effects commonly encountered by limiting the site of action of the drug. A variety of opioids are potent analgesics in the radiant heat tail-flick assay when administered topically, including morphine, morphine-6 β -glucuronide, DAMGO, levorphanol and buprenorphine (Kolesnikov et al., 1996a; Kolesnikov et al., 1996b; Kolesnikov and Pasternak, 1999a; Kolesnikov and Pasternak, 1999b; King et al., 2001). In these studies, the analgesic actions seen with topical opioids were limited to the region of the tail exposed to the drug and were not seen in more proximal areas

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not exposed to the drug. Pharmacological studies reveal that the peripheral actions of the opioids display the same pharmacology with regards to antagonist selectivity as seen with systemic or central use. They also show synergy with other classes of drugs, as shown by the marked interactions between peripheral opioids and local anesthetics such as lidocaine (Kolesnikov et al., 2000) and butamben in the radiant heat tail-flick assay (Kolesnikov et al., 2003).

Methadone is a widely used opioid analgesic (Fredheim et al., 2008), with many patients achieving better responses than with other opiates. Yet, methadone has a number of unique difficulties surrounding its use, including its elongation of the QTc interval and its long plasma half-life which can range from 12-36 hours. This prolonged half-life is particularly troublesome with repetitive dosing since dose adjustments may require as much as a week to reach a steady-state. Too frequent dose adjustments can lead to sedation, confusion, bradycardia and even death. Topical approaches might enable the more facile use of the drug and avoid these pitfalls. Indeed, topical methadone is effective in pain relief in open wounds in palliative care patients (Gallagher et al., 2005).

Meperidine is another synthetic opioid that also is more effective in some patients than other opioids, but which also has its own unique issues. While meperidine is an effective analgesic, its N-demethylated metabolite, normeperidine, can be toxic and can induce seizures, particularly in patients with renal insufficiency (Kaiko et al., 1983). Again, topical meperidine would avoid this problem. We now present evidence demonstrating the activity of both meperidine and methadone in a topical analgesia model with pharmacologies similar to that seen with systemic dosing.

2. Materials and Methods

Male CRL:CD-1(ICR)BR mice (25-30 g; Charles River Breeding Laboratory, Bloomington, MA) were maintained on 12-h light/dark cycle with food and water available ad libitum. Mice were housed in groups of five until tested. Morphine was generously provided by the Research Technology Branch of the National Institute on Drug Abuse (Rockville, MD). Lidocaine, methadone and meperidine were purchased from Sigma Chemical Co. (St. Louis, MO). Lidocaine base was used in all experiments unless indicated otherwise. All animal studies have been reviewed and approved by the IACUC. The animal care systems of the MSKCC are fully accredited by AAALAC and are in compliance with the GUIDE FOR THE CARE AND USE OF LABORATORY ANIMALS. We are also in compliance with the Animal Welfare Act and agree to adhere to the Public Health Service "Principles for the Use of Animals" (NIH Manual Chapter 4206).

2.1 Topical Administration

Drugs were applied topically and analgesia assessed as previously described (Kolesnikov and Pasternak, 1999a; Kolesnikov et al., 2000; Kolesnikov et al., 2003). In brief, the distal portion of the tail (2-3 cm) was immersed in a 90% propylene glycol solution containing the indicated drugs for the stated time, usually 2 min. In our initial studies we have demonstrated that propylene glycol alone has no effect when tested in this manner in the radiant heat tail-flick assay. Furthermore, this solvent provides an effective way of solubilizing a wide range of drugs and facilitating their transport into the skin.

2.2 Radiant Heat Tail-Flick Test

Analgesia was defined quantally 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 3.5 s, with a maximum cutoff latency of 10 s to minimize tissue damage in analgesic animals. Since

analgesia was assessed quantally, groups comparisons were performed with the Fisher's exact test. Testing was performed both on the portion of the tail immersed in the treatment solution and a more proximal region of the tail that was not exposed. In no cases did the proximal tail display an analgesic response, confirming a local site of action.

2.3 Drug Interactions

To assess potential drug interactions, ED₅₀ values were determined for each agent alone. We then performed an additional dose-response with a fixed ratio of the two drugs and determined their ED₅₀ and compared it to the drugs alone. Graphical representation was provided by isobolographic analysis in which values on the axes represent the ED₅₀ values for the indicated drug alone and additive interactions lie along the line connecting them. Points lying below the line of additivity indicate synergism while those above it antagonism.

3. Results

3.1 Topical opioid and lidocaine analgesia

As previously reported (Kolesnikov et al., 2000), lidocaine is an effective analgesic in the radiant heat tailflick assay, with potency greater than morphine and a maximal response of nearly 75% (Table 1; Fig. 1). However, its full dose-response curve was biphasic, with doses greater than 5 mM showing progressively lower responses. We then examined topical opioids. As in the initial studies (Kolesnikov et al., 2000), morphine was a potent analgesic topically (Fig 1), with a duration of action of approximately 30 min. Both methadone and meperidine also displayed a dose-dependent analgesic response (Table 1; Fig 1). Methadone had a potency similar to that of morphine while meperidine was significantly more potent. As with morphine, the onset of the response was rapid with detectable analgesia within 2 min after removal of the tail from the opioid solution, the shortest time tested.

To examine the role of opioid receptors in these responses, we examined the effect of systemic naloxone on the topical analgesia of three opioids (Fig. 2). Naloxone administered subcutaneously in the midscapular area blocked the analgesic effects of both topical morphine and methadone almost completely. Meperidine analgesia was also blocked, but not as completely as the other two mu opioids.

3.2 Drug Combinations

Prior work established an analgesic synergy between topical morphine and lidocaine (Kolesnikov et al., 2000) and between morphine and other local anesthetics (Kolesnikov et al., 2003). To determine whether the additional mu opioids displayed the same pharmacological characteristics, we next examined combinations of the drugs.

First, we examined the interactions of the opioids with lidocaine (Fig. 3). Isobolographic analysis showed that the combinations were well below the line of additivity. Looking at the methadone combination, the ED₅₀ values for lidocaine were shifted 4-fold and those of methadone 4.2-fold with no overlap of their 95% confidence limits on the isobologram. Similarly, the combination of lidocaine and meperidine also revealed increased potencies, with shifts of 3-fold and 2.5-fold for lidocaine and meperidine. Although suggestive of synergy, there was overlap of the 95% confidence limits.

When given systemically, the combination of morphine and methadone is synergistic (Bolan et al., 2002). We therefore explored whether or not a similar interaction would exist topically (Fig. 4a). Isobolographic analysis showed synergy between the two drugs, with no overlap of 95% confidence limits, confirming an interaction similar to that seen with systemic administration. The combination shifted the ED₅₀ values for morphine and methadone by 7.6-

fold and 3.2-fold, respectively. The combination of meperidine and morphine was less impressive, even though the ED₅₀ value fell under the line of additivity (Fig. 4b). The shift in ED₅₀ values was far less at only 2.7-fold and 2.4-fold for morphine and meperidine, respectively, and there was overlap of the 95% confidence limits. Simple additivity would be expected to yield shifts of about 2-fold.

4. Discussion

Topical drugs offer a number of advantages over systemic administration, particularly in the minimization of centrally mediated side-effects, as well as limitations. The utility of topical analgesics drugs has been demonstrated both clinically and in animal models (Joris et al., 1987; Mays et al., 1987; Levine and Taiwo, 1989; Stein, 1993; Kolesnikov et al., 1996a). The question of whether the pharmacology of the opioids in the periphery mimicked that of central and systemic drug has not been fully evaluated. Morphine given topically acts through mu receptors and is blocked by antagonists. Prior work demonstrated a similar analgesic activity of the mu opioid peptide DAMGO. However, this has not been explored with additional mu opioids. Methadone is a unique mu opioid. While investigators agree it is a member of the mu opioid family based upon its sensitivity towards selective mu antagonists and its selectivity in receptor binding assays for mu sites, it retains full analgesic potency in CXBK mice, which are insensitive to morphine (Chang et al., 1998). Thus, it is interesting that methadone, like morphine, retains analgesic activity when administered topically. Meperidine also is an effective analgesic topically. Indeed, it over 3-fold more potent than morphine.

Naloxone is a highly selective opioid antagonist. It blocked the analgesia of all three mu analgesics when given systemically, virtually eliminating the actions of both morphine and methadone. Although it was active against meperidine as well, there was an appreciable level of residual analgesia. This raises an interesting question. Intrathecal meperidine produces a sufficient degree of nerve block to perform surgery of the lower limbs and perineum (Acalovschi et al., 1986). This local effect of meperidine may be explained by its ability to block a variety of channels with EC₅₀ values under 200 μ M, including voltage-activated Na⁺ channels, delayed rectifier K⁺ channels, the calcium-activated K⁺ channel, and the voltage-independent flicker K⁺ channel (Brau et al., 2000). Thus, meperidine may have a combination of opioid and local anesthetic activities, raising the additional question of whether these two properties of the drug elicit an interaction like that seen between other opioids and local anesthetics.

Synergy offers a number of potential advantages in the management of pain. Nonsteroidal anti-inflammatory drugs, for example, can synergize with opioids, possibly helping to explain the utility of the combinations with oxycodone and hydrocodone (Zelcer et al., 2005). Earlier work from our group observed a marked analgesic synergy between morphine and methadone when the drugs were administered systemically (Bolan et al., 2002). Yet, there was no synergy between their inhibition on gastrointestinal transit, resulting in an increased therapeutic index when used in combination. In the current studies, a similar analgesic synergy was seen when the drugs were given topically. With systemic administration there is the potential of activating interacting circuits. However, this seems unlikely with topical drugs acting only on the nerve terminals. While the use of the combination may prove valuable, how these two mu drugs interact is not clear.

The interaction between morphine and meperidine was not particularly impressive and did not achieve statistical significance. In our earlier work with systemic drugs, we did not observe any synergy between morphine and meperidine (Bolan et al., 2002). Thus, these topical studies appear to recapitulate the systemic ones.

Our prior demonstration of topical synergy between morphine and a series of local anesthetics (Kolesnikov et al., 2000; Kolesnikov et al., 2003) was similar to interactions seen at the level of the spinal cord (Saito et al., 1998). In the current study, we show that methadone also synergizes with topical lidocaine. The data with meperidine is less clear. While there is a suggestion of an interaction, it did not achieve statistical significance.

In conclusion, we now show that a series of mu opioids are capable of eliciting a topical analgesic action. Furthermore, they appear to show the same pharmacological interactions as seen previously.

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Fig 1. Topical lidocaine and opioid analgesia

Groups of mice (n=20) received topical lidocaine (0.9-7.2 mM), morphine (1.5-20 mM), methadone (2.6-20 mM) or meperidine (0.4- 15 mM) and were examined for analgesia using the radiant heat tailflick assay, as described in Methods.

Fig. 2. Sensitivity of topical mu opioid analgesia to naloxone

Groups ($n=10$) of animals received systemic naloxone (1 mg/kg, s.c.) given in the midscapular region 20 min or saline before topical drug administration of the indicated opiate (10 mM). Analgesia was assessed using the tail-flick assay, as described under Methods.

Fig. 3. Topical opioid/lidocaine interactions

Opioid/lidocaine interactions were assessed using dose-response curves of the drugs alone and using a fixed a fixed ratio of a) lidocaine/methadone (1:2) or b) lidocaine/meperidine (1:1). The ED_{50} value of the combination with the 95% confidence limits was determined from the dose-response curve and is given in Table 1. The data is presented as an Isobologram in which only ED_{50} values are shown. The values on the axis represent the ED_{50} values of the drugs alone. The line connecting these two points represents the line of additivity. The combination of lidocaine and methadone revealed no overlap of the 95% confidence limits, implying a statistically significant interaction. The combination of lidocaine and meperidine did show overlap and thus did not reach statistical significance.

Fig. 4. Topical opioid interactions

Opioid/opioid interactions were assessed using dose-response curves of the drugs alone and using a fixed a fixed ratio of a) morphine/methadone (2:1) or b) morphine/meperidine (3.5:1). The ED_{50} value of the combination with the 95% confidence limits was determined from the dose-response curve and is presented in Table 1. The data is presented as an Isobologram in which only ED_{50} values are shown. The values on the axis represent the ED_{50} values of the drugs alone. The line connecting these two points represents the line of additivity. The combination of morphine and methadone revealed no overlap of the 95% confidence limits, implying a statistically significant interaction. The combination of morphine and meperidine did show overlap and thus did not reach statistical significance.

TABLE 1

Topical analgesia with opioid and opioid combinations

	Drug ED ₅₀ , mM (95% conf limits)			
	Ratio			
	Lidocaine	Morphine	Meperidine	Methadone
Alone	2.3 (2, 3.4)	6.3 (3.7, 8.3)	1.8 (1.1, 2.4)	5.0 (3.7, 6.8)
Combinations				
Lidocaine +	0.8 (0.6, 1.1)		0.7 (0.6, 0.9)	
Meperidine	3		2.5	
Lidocaine +	0.6(0.4, 0.7)			1.2 (0.9, 1.7)
Methadone	4			4.2
Morphine +		2.2 (1.2, 2.6)	0.72 (0.6, 0.8)	
Meperidine		2.7	2.4	
Morphine +		0.8 (0.6, 1.1)		1.6 (1.2, 2.1)
Methadone		7.6		3.2

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 ratios of drug dose in combination to that of the drug alone are presented in bold. The relative potency of the various drugs in combination was compared with the same drug alone as a ratio. The fixed ratios were as follows: lidocaine/meperidine, 1; methadone/lidocaine, 2; morphine/meperidine, 3.5; methadone/morphine, 2