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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 tail-flick 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.

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-6β-glucoronide, 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 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 to 36 h. 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

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(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, group 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, ED_{50} 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 ED_{50} and compared it to the drugs alone. Graphical representation was provided by isobolographic analysis in which values on the axes represent the ED_{50} 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 tail-flick 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.

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+ Meperidine	0.8 (0.6, 1.1) 3-fold		0.7 (0.6, 0.9) 2.5-fold	
Lidocaine+ Methadone	0.6 (0.4, 0.7) 4-fold			1.2 (0.9, 1.7) 4.2-fold
Morphine+ Meperidine		2.2 (1.2, 2.6) 2.7-fold	0.72 (0.6, 0.8) 2.4-fold	
Morphine+ Methadone		0.8 (0.6, 1.1) 7.6-fold		1.6 (1.2, 2.1) 3.2-fold

ED_{50} values were determined from dose–response curves and presented with 95% confidence limits. For lidocaine, the ED_{50} 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. ED_{50} 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.

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 ED_{50} 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

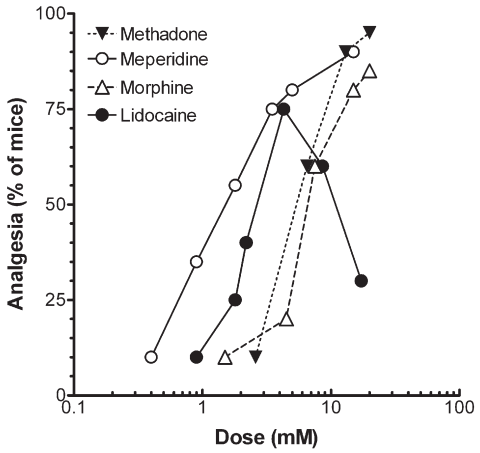

Fig. 1. Topical lidocaine and opioid analagesia. Groups of mice ($n = 20$) received topical lidocaine (0.9–7.2 mM), morphine (1.5–20 mM), methadone (2.6–20 mM) or meperidine (0.4–15 mM) and were examined for analgesia using the radiant heat tail-flick assay, as described in Materials and methods.