

Effect of Morphine on Small Bowel Propulsion after Intestinal Ischemia

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OPIOIDS are known to reduce the motility of both the colon and the small intestine.¹ However, some investigators have reported, both in animal models and in humans, that morphine increases duodenal motility.^{2,3} *In vivo* studies of the effect of morphine on small bowel motility are complicated because most have been performed in the postoperative period,^{4,5} where the additional trauma of laparotomy and bowel manipulation had already affected bowel motility.

Previous studies have reported that intestinal ischemia also causes prolonged inhibition of bowel motility.^{6,7} The effect of morphine on intestinal motility has not been well assessed in situations in which ischemic injury to the bowel occurs without concurrent surgical injury. Recently, Zhang *et al.*⁸ reported that in a rat model of intestinal ischemia and reperfusion, pretreatment with morphine before ischemia and reperfusion markedly attenuated intestinal injury. The aim of the current study was to evaluate the effect of morphine on small bowel propulsion activity in a rat model in which controlled bowel ischemia was caused without concurrent abdominal surgery.

Materials and Methods

Animal Preparation

The use of rats for this study was approved by the Hebrew University Institutional Animal Care and Use Committee (Jerusalem, Israel). The rat model used for this study has been described previously.⁹⁻¹¹ Briefly, two preparatory procedures were performed in male Sabra rats that weighed 180-220 mg: insertion of an epidural catheter and placement of a nylon thread around the superior mesenteric artery (SMA).

Epidural Catheter. Under pentobarbital anesthesia (30 mg/kg, intraperitoneal injection), the epidural space was exposed at the level of the fifth intervertebral lumbar space. A 0.61-mm (OD) polyethylene catheter (Intra-

medic Polyethylene Tubing; Clay Adams, Parsippany, NJ) was threaded cephalad to approximately the level of the T9 vertebra. The proximal end of the catheter was tunneled under the skin to the posterior cervical area and sealed with modeling clay. All epidural injections were made *via* this catheter after exposure of its end and without further surgical interventions. Proper location of the epidural catheter was assessed by injecting 0.1 ml lidocaine, 2%, into the epidural catheter and observing the freely moving rat dragging its hind limbs.

Ischemia. Three days after the insertion of the epidural catheter, a midline laparotomy incision was performed under ether anesthesia, and the SMA was identified. A monofilament 3-0 nylon thread was passed around the SMA to create a loop, and both ends were then threaded through a double-lumen tube, which, after tunneling, was located in the posterior cervical region. Pulling on both ends of the nylon thread compressed the SMA, resulting in total ischemia of the small bowel. Adequacy of this method was assessed immediately before abdominal closure by observing whether pulsations were eliminated in the feeding mesenteric branch arteries and whether, on release of the ligature, there was return of pulsations. All experiments were performed 1 week after the insertion of the nylon thread around the SMA.

Propulsion. Under a brief period of ether anesthesia, propulsion studies were performed. *Via* a polyethylene nasogastric tube, 1 ml of a semisolid mixture of Arabic gum (Sigma Chemical, St. Louis, MO), activated charcoal, and saline was administered into the stomach. Ninety minutes later, the animal was killed with ether, the abdomen was opened, and ligatures were placed around the pylorus and ileocecal valve. The gastrointestinal tract, from the stomach to the cecum, was dissected and freed from its mesentery. The intestine was then measured by laying it longitudinally. The total length of the small intestine and the length of small bowel filled with the black meal were recorded. Net results of motility are expressed by the fraction of the total length of the small bowel filled with the black material (transit index). These procedures have been described previously.^{10,11}

Experimental Protocol

The experimental protocol is depicted in figure 1. Rats were randomly assigned to the different study groups: three control groups (the SMA was exposed but not occluded) and three ischemia groups (n = 7-10/group):

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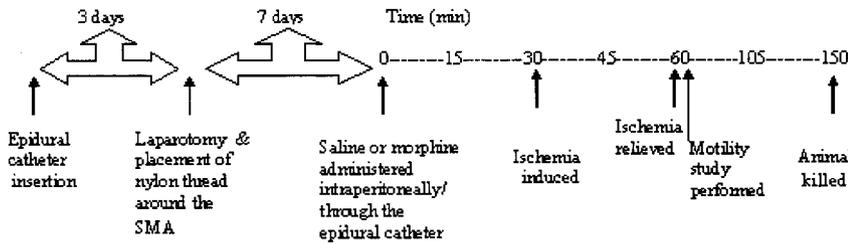


Fig. 1. Experimental protocol. SMA = superior mesenteric artery.

- Group I. Control, EP- IP-: 0.1 ml and 1 ml saline were administered through the epidural catheter and intraperitoneally, respectively.
- Group II. Control, EP+ IP-: 0.1 ml (0.02 mg) morphine hydrochloride was administered through the epidural catheter, and 1 ml saline was injected intraperitoneally.
- Group III. Control, EP- IP+: 0.1 ml saline was administered through the epidural catheter, and 1 ml (0.2 mg) morphine hydrochloride was injected intraperitoneally. No bowel ischemia was induced in the control groups.

Sixty minutes after administration of saline and/or morphine, a motility study was performed. Groups IV (ischemia, EP- IP-), V (ischemia, EP+ IP-), and VI (ischemia, EP- IP+) received the same agents as groups I, II, and III, respectively. However, 30 min after administration of saline and/or morphine, intestinal ischemia was induced for 30 min. Immediately after release of ischemia, motility studies were performed. In all experiments, as previously described, 90 min after administration of the marker meal into the animals' stomachs, the animals were killed and laparotomy was performed.

Statistical Analysis

Unpaired *t* tests were performed for intergroup comparison. To test for intragroup differences, comparisons were made using one-way analysis of variance with Newman-Keuls multiple comparison test as the *post hoc* test. A *P* value less than 0.05 was considered significant. Data are expressed as mean ± SD.

Results

The data are summarized in table 1. The bowel length was not significantly different among the groups and averaged 73 ± 5, 69 ± 4, 72 ± 4, 72 ± 5, 68 ± 6, and 71 ± 4 cm for groups I-VI, respectively.

In control groups, the marker meal passed 96.8 ± 2.6, 97.4 ± 5.1, and 85.7 ± 15.2% of the total length of the small bowel, respectively. Compared with the other two control groups, the transit index was significantly lower (*P* = 0.03) with intraperitoneal morphine (group III).

Total ischemia to the small bowel resulted in pronounced postischemic adynamic ileus in all three ischemic groups. Compared with the matching control

group, the transit index was significantly (*P* < 0.001) lower with ischemia.

Morphine administered either into the epidural space or intraperitoneally before induction of ischemia (groups V and VI) significantly attenuated the inhibitory effect of ischemia on intestinal propulsion; higher transit indexes were achieved with morphine pretreatment when compared with saline pretreatment. There were no significant differences in intestinal propulsion indexes between the rats pretreated with epidural morphine and those pretreated with intraperitoneal morphine.

Discussion

The current study shows that the effect of ischemic injury to the small bowel can be partially attenuated by morphine pretreatment. These data extend recent findings by Zhang *et al.*,⁸ who demonstrated that the intestinal injury elicited by ischemia and reperfusion was markedly attenuated by pretreatment with morphine. In contrast to our study, which relied on a functional endpoint, in the study of Zhang *et al.*, the methods of quantifying injury relied primarily on assessment of terminal ileum histology and the ratio of tissue wet weight to dry weight. Also, unlike that study in which injury was assessed during laparotomy, the unique animal model used in this study, in which the SMA can be totally occluded for a predetermined period without laparotomy, excludes the potential confounding factor of laparotomy-induced changes in intestinal motility. Finally, the current study shows that a similar beneficial effect could be achieved when morphine was administered either intraperitoneally or into the epidural space. These data might have significant implications for clinical use of morphine in patients with intestinal ischemia.

Table 1. Small Bowel Motility*

Group†	EP- IP-, %‡	EP+ IP-, %‡	EP- IP+, %‡
Control	96.8 ± 2.6‡	97.4 ± 5.1‡	85.7 ± 15.2‡§
Ischemia	18.1 ± 8.9	42.7 ± 18.2	35.9 ± 15.6

Values are mean ± SD. n = 7-10 animals/group.

* Expressed as the percentage of the total length of the small bowel filled with the marker meal (transit index). † See text for explanation. ‡ *P* < 0.05 compared with the corresponding ischemic group. § *P* < 0.05 compared with the other two control groups. || *P* < 0.05 compared with the group in which ischemia was induced without pretreatment with morphine.

EP = epidural; IP = intraperitoneal.

The mechanism by which pretreatment with morphine improved intestinal function after intestinal ischemia was not addressed in the current study. Opioid receptors have been implicated in protecting several organ systems from hypoxic or ischemic events.^{12,13} In rat small intestine, systemic administration of morphine mimicked the protective activity of ischemic preconditioning on intestinal ischemic injury.⁸ A direct effect of morphine on motilin or nitric oxide release or through modulation of the immune function can also partially explain the observed effect.¹⁴⁻¹⁶ Another possible mechanism may be through the analgesic properties of morphine. Many noxious stimuli, such as pain and ischemia, could evoke sympathetic activation, which produces intestinal motility inhibitory effects.¹⁷ Therefore, morphine might indirectly attenuate the depressive effect of ischemia on bowel motility by reducing the sympathetic response elicited by pain, with resultant unopposed parasympathetic activity. Morphine has been shown to increase gastrointestinal motility by central actions on the central nervous system and by peripheral actions on the intestines.³

Despite the observed protective effect of epidural morphine on bowel motility, because blood concentrations of morphine were not measured, we cannot conclude from this report that morphine acts primarily on the central nervous system and not through direct action on the intestine.

In the current study, in animals in which no intestinal ischemia was caused, the transit index was significantly lower with systemic morphine compared with epidural morphine. The reason for this difference is not clear, but it may be that in these animals, intestinal propulsion was primarily influenced by the direct action of morphine on intestinal opioid receptors and not through its activity within the central nervous system.¹⁸ It may also be that higher doses of epidural morphine would have produced a similar inhibitory effect.

The unique animal model used in this study, as in others before,^{10,11} in which the SMA can be totally obstructed for a predetermined period without laparotomy, ascertains that the effect of bowel ischemia on gastrointestinal motility was unbiased by any effect of open abdominal surgery. The technique for measurement of intestinal transit used in this study is a well-established method and has been extensively used to examine the effects of various surgical manipulations and therapeutic and toxic agents on intestinal motor function.^{10,11,19,20} This study, however, has several limitations. Most importantly, propulsion studies were conducted under ether anesthesia, which has been previously reported to inhibit intestinal motility²¹ and therefore could have influenced the results. Also, only one dose of morphine was evaluated. Because the effects of morphine may change with the dose administered,^{2,3}

other regimens may not result in the observed effect. Finally, morphine has differential effects on gastric and small intestine motility, and therefore, the observed effects may be partially explained by its effect on gastric emptying.

Our findings suggest a potential modality for attenuation of posts ischemic adverse bowel effects. If this is the case, morphine may not only serve to alleviate pain in the clinical situation of ischemic injury to the bowel, but it may also enhance restoration of bowel activity in the immediate posts ischemic period. The reason for the observed different responses of the intestine to morphine administration during control and after the induction of ischemia has yet to be elucidated.

References

1. Kaufman PN, Kversky B, Malmiud LS, Maurer AH, Somers MB, Siegel JA, Fisher RS: Role of opiate receptors in the regulation of colon transit. *Gastroenterology* 1988; 94:1351-6
2. Lewis TD: Morphine and gastroduodenal motility. *Dig Dis Sci* 1999; 44: 2178-86
3. Telford GL, Hoshmonai M, Moses AJ, Szurszewski JH: Morphine initiates migrating myoelectric complexes by acting on peripheral opioids receptors. *Am J Physiol* 1985; 249:G557-62
4. Ingram DM, Catchpole BW: Effect of opiates on gastroduodenal motility following surgical operation. *Dig Dis Sci* 1981; 26:989-92
5. Wilder-Smith CH, Hill L, Wilkins J, Denny L: Effect of morphine and tramadol on somatic and visceral sensory function and gastrointestinal motility after abdominal surgery. *ANESTHESIOLOGY* 1999; 91:639-47
6. Walus KM, Eugene DJ: Relation between small intestine motility and circulation. *Am J Physiol* 1981; 241:G1-15
7. Chou CC, Gallavan RH: Blood flow and intestinal motility. *Fed Proc* 1982; 41:2090-5
8. Zhang Y, Wu YX, Hao YB, Dun Y, Yang SP: Role of endogenous opioids peptides in protection of ischemic preconditioning in rat small bowel. *Life Sci* 2001; 68:1013-9
9. Eimerl D, Papir-Kricheli D: Epidural capsacin produces prolonged segmental analgesia in the rat. *Exp Neurol* 1987; 97:169-78
10. Udassin R, Eimerl D, Schiffman J, Haskel Y: Epidural anesthesia accelerates the recovery of posts ischemic bowel motility in the rat. *ANESTHESIOLOGY* 1994; 80:832-6
11. Udassin R, Eimerl D, Schiffman J, Haskel Y: Posts ischemic intestinal motility in rat is inversely correlated to length of ischemia: An in vivo animal model. *Dig Dis Sci* 1995; 40:1035-8
12. Chien S, Oeltgen PR, Diana JN, Salley RK: Extension of tissue survival time in multiorgan block preparation with a delta opioid DADLE. *J Thorac Cardiovasc Surg* 1994; 107:964-7
13. Mayfield KP, D'Alecy LG: Delta-1 opioid agonist acutely increases hypoxic tolerance. *J Pharmacol Exp Ther* 1994; 268:74-7
14. Poitras P, Boivin M, Lahaie RG, Trudel L: Regulation of plasma motilin by opioids in the dog. *Am J Physiol* 1989; 257:G41-5
15. Fox-Threlkeld JET, Daniel EE, Christrinda F, Itruly VJ, Cipris S, Woskowska Z: Identification of mechanisms and sites of actions of mu and delta opioids receptor activation in the canine intestine. *J Pharmacol Exp Ther* 1994; 268:689-700
16. Narayan P, Singh VK, Agarwal SS, Tandon R, Haq W, Raghurib R, Dhar MM: Immunomodulation by opioid peptidomimetic compound. *Neuroimmunomodulation* 2001; 9:134-40
17. Burnstock G, Wong H: Systemic pharmacology of adrenergic agonists and antagonists: Effect on the digestive system. *Handbook of Experimental Pharmacology*. Vol 54. Edited by Szekeres L. New York, Springer-Verlag, 1981, pp 129-59
18. Manara L, Bianchi G, Ferretti P, Tavani A: Inhibition of gastrointestinal transit by morphine in rats results primarily from direct drug action on gut opioids sites. *J Pharmacol Exp Ther* 1986; 237:945-9
19. Reilly JA, Quigley EMM, Forst CF, Rikkens LF: Small intestinal transit in the portal hypertensive rat. *Gastroenterology* 1991; 100:670-4
20. Reynell PC, Spray GH: The simultaneous measurement of absorption and transit in the gastrointestinal tract of the rat. *J Physiol (Lond)* 1956; 131:452-62
21. Huge A, Kreis ME, Jehle EC, Ehrlein HJ, Starlinger M, Becker HD, Zittel TT: A model to investigate postoperative ileus with strain gauge transducers in awake rats. *J Surg Res* 1998; 74:112-8