Nonopioid Analgesics Shorten the Duration of Postoperative Ileus

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Morphine inhibits propagating and stimulates nonpropagating colon contractions in monkeys and humans. The use of morphine or other opioids that inhibit propulsive contractions prolongs postoperative ileus. In contrast, ketorolac tromethamine, a nonsteroidal analgesic, has no effect on colon contractions in monkeys. In 14 patients having elective abdominal operations, bipolar electrodes were implanted on the right (n = 13) and left (n = 10) colon. Group A (n = 8) received ketorolac, 30 mg IM q6h, for pain relief. Group B (n = 6) needed supplemental morphine, 2–10 mg IV or IM, plus ketorolac to control their pain. Myoelectric activity was recorded from each subject on postop Days 1–5 and analyzed by computer for electrical control activity (ECA), short and long electrical response activity (ERA), and propagation of long ERA. There was a difference between the two groups in return of propagated long ERA bursts that correlated with clinical recovery from postoperative ileus. Postoperative analgesia with ketorolac resulted in faster resolution of ileus compared to morphine plus ketorolac because opioid-induced motor abnormalities in the colon were avoided.

POSTOPERATIVE ILEUS IS AN IMPAIRMENT of gastrointestinal motility that follows an operation and is characterized by abdominal distention, accumulation of gas and fluids in the bowel, and delayed defecation.[1] Ileus leads to a longer hospital stay and an associated need for parenteral fluids and medications. The estimated cost of ileus in postoperative patients is $750,000,000 annually.[2] The causes of postoperative ileus are multifactorial. Sympathetic hyperactivity, peritoneal irritation, metabolic disturbances, and the effects of some drugs (analgesics, anesthetics) have been reported to be associated with postoperative ileus. We have previously shown that use of opioid drugs, such as morphine, for analgesia following an abdominal operation prolongs postoperative ileus.[3–5]

The colon is the last segment of the intestine to recover from postoperative ileus.[6,7] We have demonstrated in humans that IV or IM administration of morphine, in doses appropriate for analgesia, results in increased phasic nonmigrating electrical response activity (ERA) bursts in both the right and left colon.[5,8] ERA is the electrical correlate of phasic smooth muscle contraction and there is a one-to-one relationship between contractions and an ERA burst. In addition, morphine causes a significant decrease in the incidence of propagating long ERA bursts in humans[5,8] as well as in the nonhuman primate.[3,4] Propagating long ERA bursts are the basis for propulsive contractions in the colon. Thus, morphine induces a state of colonic pseudofibrillation in which overall contractile frequency is increased but propagation is inhibited, leading to prolongation of postoperative ileus.

Ketorolac, a nonopioid NSAID analgesic, has been reported to have no effect on colonic motility in nonhuman primates[3] and not to cause postoperative ileus in rats.[9] The use of ketorolac as an analgesic postoperatively has been efficacious.[10–16] Our hypothesis in this study was that patients receiving ketorolac for postoperative pain would recover from postoperative ileus earlier than patients who received opioid analgesics.

Methods

The study was conducted in 14 patients, 8 men and 6 women, ages 28–98, who were having elective abdominal operations (Table 1). The study was reviewed and approved by the Human Research Review Committee of the Medical College of Wisconsin. All patients gave informed consent before participating in the study.

Bipolar electrodes of 0.3 mm Teflon-coated stainless steel wire (PN 316SS1DT, Medwire Corp, Mt Vernon, New York), or electrodes designed for im-

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TABLE 1. *Type of Operation and the Day Postoperative Ileus Clinically Resolved*

Group A (Ketorolac)		Group B (Ketorolac + Morphine)	
Operation	Duration Ileus (Days)	Operation	Duration Ileus (Days)
Esophagectomy	3	Esophagectomy	4
Colostomy	2	Esophagectomy	4
Colectomy	2	Esophagectomy	5
Colectomy	2	Nissen	4
Colectomy	3	Nissen	4
Gastric Bypass	2	Colectomy	4
Gastric Bypass	2		
Roux Y Gastroenterostomy	2		
Mean ± SEM	2.3 ± 0.5		4.2 ± 0.6

* $P < 0.01$ compared to Group A.

plantation into the myocardium (MyoWire M-25B, A & E Medical Corp, Farmingdale, New Jersey), were implanted through the anterior taenia into the circular muscle of the colon, as previously described.[5, 8, 17] Three sets of bipolar electrodes were placed 5 cm apart in the ascending (n = 13) and descending (n = 10) colon, exteriorized through a needle track in the flank and fixed to the skin.

Signals from the electrodes were recorded with a multi-channel telemetry system (Koningsburg Instruments Pasadena, Calif.) manufactured to our specifications and having lower and upper cutoff frequencies of 0.01 and 100 Hz, respectively. The output of the telemetry system was recorded on paper and by a magnetic FM tape recorder (Model 3968A, Hewlett-Packard Corp., San Diego, Calif.) for later computer analysis. Analysis of electrical control (ECA) and electrical response (ERA) activity was accomplished as previously reported.[17, 18] The dominant ECA frequency was defined as that frequency in each minute of data with the greatest power spectrum magnitude and was classified as being in the low (0–9 cpm), mid (9–15 cpm), or high (15–45 cpm) range. Relative tenancy is the proportion of time occupied by ECA in each frequency range and was determined in each minute of data. The duration of each ERA burst was measured and the frequency (number/hour) and mean duration of short and long ERA bursts determined. The duration of short ERA bursts was less, and of long ERA bursts was greater, than 6.7 seconds.[17, 18] The number/hour of propagated long ERA bursts also was determined. Propagation was considered to occur when ERA bursts appeared sequentially at three electrode sites in the same segment of colon at a constant propagation velocity.[17]

The patients were divided into two groups. Group A (n = 8) consisted of patients who received only ketorolac for postoperative analgesia. Group B (n = 6) comprised patients who received ketorolac but who also needed supplemental morphine to control their postoperative pain. The effect of ketorolac tromethamine, 30 mg IM every 6 hours, on colonic myoelectric activity was studied from the first through the fifth postoperative days. On each day, recordings were made for at least 1 hour before injection of ketorolac and were continued for another 2 hours following the injection. Morphine, 2–10 mg IV or IM, was given in addition as needed in group B patients.

Clinically, postoperative ileus was considered to have resolved when spontaneous passage of flatus and stool was noted. The data of group A were compared to that of group B by the Wilcoxon rank sum test and by an unpaired *t*-test to determine if there was a difference between the groups. A *P*-value of ≤ 0.05 was considered to represent a significant difference between data sets.

Results

Clinical recovery from postoperative ileus occurred between the second and the fifth postoperative day in the two groups of patients. Group A patients (ketorolac only) recovered from postoperative ileus by 2.3 ± 0.5 days (mean ± SD), whereas those in group B (ketorolac + morphine) required 4.2 ± 0.6 days ($P < 0.05$). The relationship between the various operative procedures and clinical recovery from postoperative ileus is recorded in Table 1.

ECA was present in both groups from the first postoperative day. The dominant ECA frequency was mainly in the low and mid range in both patient groups. As expected, there was no difference between the groups in the relative tenancy of the dominant ECA frequency throughout the recovery period (Table 2). The expected downshift in ECA frequency[8, 17] from the mid to the low range was observed. There also was no difference between the two groups in the frequency of short or long duration ERA bursts (Table 3 and 4).

There was a difference between the groups in propagating long duration ERA bursts. Propagating bursts were present in the right colon on the first postopera-

TABLE 2. *Relative Tenancy (%) of ECA in the Low (1–9 cpm), Mid (9–15 cpm), and High (15–45 cpm) Frequency Ranges During Recovery From Postoperative Ileus (Mean ± SEM)*

Postop Day	Group A (ketorolac)			Group B (+morphine)		
	low	mid	high	low	mid	high
Right Colon						
1	48 ± 10	50 ± 9	2 ± 1	56 ± 11	43 ± 10	2 ± 1
2	56 ± 11	43 ± 10	1 ± 1	62 ± 7	36 ± 9	2 ± 1
3	84 ± 6	15 ± 6	1 ± 1	75 ± 12	23 ± 9	2 ± 1
4	85 ± 14	15 ± 9	0 ± 0	73 ± 13	26 ± 8	1 ± 1
5	74 ± 12	25 ± 7	1 ± 1	75 ± 12	22 ± 6	3 ± 1
Left Colon						
1	27 ± 5	72 ± 9	1 ± 1	35 ± 11	64 ± 9	1 ± 1
2	51 ± 9	48 ± 7	1 ± 1	62 ± 13	36 ± 9	2 ± 1
3	73 ± 10	25 ± 6	2 ± 1	68 ± 11	31 ± 6	1 ± 1
4	83 ± 13	14 ± 6	3 ± 1	84 ± 10	14 ± 8	2 ± 1
5	65 ± 12	34 ± 8	1 ± 1	70 ± 9	28 ± 6	2 ± 1

tive day in group A (ketorolac), but did not appear in group B (ketorolac + morphine) patients until the third postoperative day (Table 5). In the left colon, propagation of long duration ERA bursts began on the second postoperative day in group A, whereas in group B propagation did not appear until postoperative Day 3. The frequency of propagated long ERA bursts, even on the third day postoperatively, was still significantly depressed in group B compared to group A. There was no difference in propagation velocity between the two groups (Table 5).

Discussion

Ketorolac was chosen for this study because of properties thought to be beneficial in postoperative management of pain, and because in animal studies it did not adversely affect colonic motility as do opioid analgesics.[3,5,19] In a subset of patients in whom adequate analgesia was achieved with ketorolac, earlier return of propagating ERA bursts and of passage of flatus and stool were documented, thus supporting our hypothesis in these patients.

Ketorolac is thought to provide analgesia by inhibiting cyclo-oxygenase and, therefore, prostaglandin, prostacyclin, and thromboxane synthesis. Prostaglandins, depending on the type, dose, species, and intestinal muscle layer studied, have been reported to increase, decrease, or have no effect on contractile activity of gastrointestinal smooth muscle.[20–26] An increase in intestinal motility after administration of prostaglandin inhibitors has been reported.[26–29] We did not find any enhancement of colonic motility with ketorolac in this study in patients, nor in a previous study of nonhuman primates.[3] Our data suggest that endogenous prostaglandins either do not have a role in normal human colonic motility, or that the dose of ketorolac we used does not inhibit prostaglandin synthesis. In the latter case, pain relief would also have to have been mediated through some other mechanism, which is unlikely.

At the doses used in this study, ketorolac provided adequate pain control for 8 of the 14 patients. The other 6 patients required supplemental morphine to achieve adequate postoperative pain relief. This unpredictable analgesic response also has been noted clinically with other NSAIDs. In a given patient, one or another of the drugs in the class may be very effective, whereas other NSAID agents are less effective or are ineffective. Predicting response is not possible, and a trial of therapy is always needed. In addition, in the context of postoperative analgesia in which parenteral agents are required, the number of available drugs is limited. What is needed is a larger number of parenteral formulations of NSAIDs coupled

TABLE 3. *Short ERA Burst Frequency (Number/Hour) During Recovery From Postoperative Ileus (Mean ± SEM)*

Postop Day	Right Colon		Left Colon	
	Group A	Group B	Group A	Group B
1	33 ± 15	28 ± 17	37 ± 12	47 ± 14
2	30 ± 7	42 ± 12	66 ± 15	51 ± 7
3	67 ± 15	52 ± 12	52 ± 10	71 ± 14
4	69 ± 18	54 ± 11	49 ± 8	77 ± 14
5	70 ± 93	92 ± 13	63 ± 9	47 ± 9

TABLE 4. *Long ERA Burst Frequency (Number/Hour) During Recovery From Postoperative Ileus (Mean ± SEM)*

Postop Day	Right Colon		Left Colon	
	Group A	Group B	Group A	Group B
1	10.2 ± 1.4	7.1 ± 0.7	3.1 ± 0.8	5.4 ± 1.2
2	11.3 ± 2.1	7.3 ± 1.1	7.9 ± 2.2	6.7 ± 1.4
3	13.6 ± 1.8	12.4 ± 3.2	15.3 ± 3.6	8.8 ± 2.6
4	19.4 ± 3.2	20.3 ± 4.1	13.9 ± 2.2	17.4 ± 3.6
5	24.2 ± 5.2	11.4 ± 2.9	26.1 ± 5.3	20.0 ± 3.1

TABLE 5. *Frequency and Velocity of Propagation of Long Duration ERA Bursts (Mean ± SEM)*

Postop Day	Group A (Ketorolac)		Group B (+Morphine)	
	Number/Hour	Velocity (cm/s)	Number/Hour	Velocity (cm/s)
Right Colon				
1	1.2 ± 0.5	0.58 ± 0.34	0*	
2	1.5 ± 0.3	0.65 ± 0.21	0*	
3	3.0 ± 0.4	0.85 ± 0.20	0.9 ± 0.3	0.74 ± 0.19
4	1.5 ± 0.3	0.63 ± 0.15	1.4 ± 0.2	0.86 ± 0.23
5	1.7 ± 0.2	0.83 ± 0.2	1.6 ± 0.2	0.77 ± 0.22
Left Colon				
1	0		0	
2	1.2 ± 0.3	0.65 ± 0.21	0*	
3	2.0 ± 0.4	0.85 ± 0.20	0.3 ± 0.1*	0.74 ± 0.19
4	1.5 ± 0.3	0.63 ± 0.15	1.4 ± 0.2	0.86 ± 0.23
5	1.7 ± 0.2	0.83 ± 0.21	1.6 ± 0.2	0.77 ± 0.22

* $P < 0.05$ compared to Group A.

with some test method to determine their efficacy in a specific patient. NSAIDs could become primary agents for postoperative analgesia, with benefits to patients and to health care costs, if these problems were solved.

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