Morphine Effects on Human Colonic Myoelectric Activity in the Postoperative Period

Constantine T. Frantzides, MD, PhD, Verne Cowles, PhD, Basil Salaymeh, MD, Ercument Tekin, MD, Robert E. Condon, MD, MS, Milwaukee, Wisconsin

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Colonic myoelectrical activity was studied in 25 patients, 18 of whom received morphine sulfate, using bipolar electrodes placed in the ascending and descending colon during laparotomy. Baseline myoelectrical activity was recorded daily, then morphine (3 to 15 mg) was administered intravenously, intramuscularly, or epidurally, and recordings continued. Seven activity patterns were observed during recovery from postoperative ileus. During the first 2 postoperative days, morphine at any dose did not affect colon myoelectrical activity. From the third postoperative day on, morphine given intravenously or intramuscularly initiated clusters of short, nonmigrating, phasic spike bursts occurring on each successive slow wave in 14 of 18 patients, which lasted for 30 to 45 minutes. When morphine was administered epidurally, there was no colonic response in any patient. These findings suggest that: (1) morphine intravenously or intramuscularly induces predominantly nonmigrating colonic spike bursts; (2) morphine-induced activity alters the normal pattern of colonic motility during recovery from postoperative ileus; and (3) these phenomena are not due to direct action of morphine on the spinal cord since epidural morphine had no effect.

The current understanding of human colonic motility is based in large part upon older radiologic observations of ingested barium in the colon [1,2] and manometric studies using balloons or open-tipped catheters [3,4]. Although intraluminal pressure recording devices have been used successfully in the esophagus [5-8], they do not provide accurate measurement of discrete motor events in the wall of the colon [9]. The probable reason is that the colon normally has an open-chambered lumen in contrast to the esophagus, which is collapsed.

The electrical activity of gastric and small intestinal smooth muscle is well documented [10,11], and such activity has been extensively studied in animals [12-16]. Human colonic smooth muscle activity is less well defined; most recordings have been obtained from the most accessible parts of the large bowel [17-20]. Only a few studies have been published using chronically implanted serosal electrodes in vivo [21-24].

We initiated this series of observations to define myoelectric activity of the human colon in the postoperative period using chronically implanted serosal electrodes. In addition, we investigated the effects of morphine, administered intravenously, intramuscularly, or epidurally, on colonic myoelectric activity.

**PATIENTS AND METHODS**

Studies were conducted in 25 patients undergoing elective abdominal operations. The experiments were reviewed and approved by the Human Research Review Committee of the Medical College of Wisconsin. Informed consent was obtained from all patients prior to participation in the study.

Teflon-coated stainless steel bipolar electrode pairs were implanted in the ascending and descending colon during laparotomy, using the techniques previously described by us [24]. Electrical signals were recorded on a polygraph (Model 7, Grass Instrument, Quincy, MA), with lower and upper cutoff frequencies set at 0.04 and 35 Hz, and simultaneously on a magnetic FM tape recorder (Model 3968A, Hewlett-Packard, San Diego, CA), beginning on the first postoperative day (3 to 8 h/d) and continuing for 4 to 15 days in all 25 patients. Respiration was monitored by a pneumograph in 11 patients. Analysis of the frequency and duration of electrical control activity (ECA) (slow waves) and of electrical response activity (ERA) (spike bursts) was made both visually and by computer for each electrode pair.

The effect of morphine was studied in 18 patients. On each study day, recordings were made for 2 hours, the last hour serving as the control period. Morphine sulfate (3 to 15 mg) was then administered intravenously, intramuscularly, or epidurally, and recordings were continued for...
a further 2 hours; the responses in the first hour after administration of morphine constituted the test period.

The paper recordings were inspected visually to identify and eliminate obvious artifacts. The electrode signal was low-pass filtered below 0.3 Hz to select ECA and re-recorded on paper. Blocks of data were then selected for analysis, and the presence and direction of phase-locking were determined. The ECA tape record was low-pass filtered at 1 Hz and sampled at 2 Hz from 60 to 120 data blocks of 64 seconds each. Each data block was digitized and processed by fast-Fourier transformation, with resolution of 0.47 cpm, using a computer (PC Limited 286-8, Austin, TX) to display the power spectrum from which the dominant slow-wave frequency was determined.

The electrode record was also band-pass filtered between 0.7 and 10 Hz, using the same data blocks as for ECA analysis, to select spike bursts, and was re-recorded on paper for visual analysis. These records were examined for single bursts, short (less than 5 seconds) and long (greater than 5 seconds) spike bursts, and clusters (three or more bursts in succession).

The presence, direction, and propagation velocity of migrating spike bursts were determined, migration being defined as the appearance of a single spike burst or cluster of spike bursts, at a constant velocity between three successive electrode sites.

The study design compared the baseline with the experimental period at each location so that each patient was his or her own control. Data were analyzed by comparison of means and grand means using analysis of variance and Student's *t*-test.

RESULTS

Colon electrical activity: Slow waves (ECA) were present on the first postoperative day in all patients. Their amplitude waxed and waned, but they were never absent. Power spectrum analysis of ECA showed dominant frequencies in a lower (2 to 9 cpm) and a higher (9 to 14 cpm) range. In the right colon, a shift from the higher to the lower slow wave frequency range was observed as recovery progressed. The left colon demonstrated less change in slow wave frequency, the dominant frequency remaining in the higher range throughout the period of postoperative observation.

Simultaneous recordings from different electrodes often showed completely different patterns of ERA. No spikes at all might be observed in one bowel segment, while another showed great activity, and a third showed only a few spikes of low amplitude. The characteristic ERA of the colon throughout our postoperative observations was phase-unlocked independent spike bursts occurring randomly at different colon sites. Clusters of phase-locked spike bursts, migrating in either an oral or aboral direction, also were occasionally seen.

Colonic electrical activity became progressively more complex through the third postoperative day with the appearance of more bursts and clusters. The appearance of long spike bursts, some of which propagated exclusively in the aboral direction, was noted on the fourth or fifth postoperative day and was accompanied by passage of flatus and defecation. Together with the ability of the patient to consume solid food, these features indicated return of "normal" colon motility.

Based on our studies, we characterize these colonic ERA (spike burst) patterns as follows: Type 1. Independent solitary spike bursts in both the right and left colon, initially present on the first or second postoperative day. Type 2. Spike bursts in clusters lasting 8.5 ± 3.4 minutes, each ERA burst occurring on each successive slow wave (ECA), covering less than 50% of the slow wave (spike burst duration: 2.3 ± 0.3 seconds), at a mean frequency of 11.4 ± 0.8 per minute. These spikes are observed in both the right and left colon after the second postoperative day. Type 3. Spike bursts in clusters superimposed on and covering greater than 50% of each successive slow wave (spike burst duration: 4.1 ± 0.6 seconds). The mean duration of clusters was 10.2 ± 4.3 minutes; the frequency of spike bursts within clusters was 10.9 ± 0.6 per minute. This activity was present in both the right and left colon after the third postoperative day (Figure 1). Type 3M. Type 3 activity slowly migrating oral or aboral with a mean velocity of 2.1 ± 0.4 cm/min. The spike bursts had a mean duration of 4.4 ± 0.6 seconds, and the clusters lasted for 5.9 ± 2.0 minutes. The mean frequency of spike bursts within the clusters was 10.7 ± 0.6 per minute. Type 3M activity appeared after the third postoperative day. Type 4. Clusters of three or more nonmigrating long spike bursts (mean duration: 13.8 ± 2.7 seconds) observed in the right and left colon after the second postoperative day. The mean cluster duration was 3.7 ± 1.4 minutes; the mean frequency of spike bursts within the cluster was 2.9 ± 0.6 per minute (Figure 2). Type 4M. More rapidly migrating oral or aboral (mean velocity: 1.2 ± 0.1 cm/second) type 4 activity was observed in the right and left colon after the third postoperative day; it was frequently associated with complaints of "gas pains" and, sometimes with defecation. Type 5M. Individual long spike bursts (mean duration: 12.9 ± 2.8 seconds) always migrating aboral (mean velocity: 1.95 ± 0.52 cm/second) in the right and left colon. Type 5M activity usually appeared on the fourth postoperative day and was often associated with the passage of flatus or defecation (Figure 3).

Morphine effects. Morphine did not cause alteration of ECA frequency at any colon site (Table 1). During the first two postoperative days, administration of morphine did not have any discernible effect on colonic ERA. But, from the third postoperative day onward, intravenous or intramuscular morphine stimulated colonic electrical response activity in 14 of 18 patients (Figure 4). In contrast to intravenous and intramuscular administration, when morphine was administered epidurally, there was no colon ERA response in any patient (Figure 5). The characteristic excitatory effect of intravenous or intramuscular morphine was seen at all sites but was more marked in the sigmoid colon and consisted of clusters of short, phasic, stationary (nonmigrating) spike bursts occurring on each successive slow wave lasting for 30 to 45 minutes after which the colon returned to its former activity state.

The most important effect of morphine-induced ERA
was interruption of normal migrating myoelectrical colonic complexes. Rarely, morphine induced clusters of spike bursts, predominantly in the left colon, which preferentially exhibited cephalad migration (mean velocity: 1.6 to 2 cm/min); this phenomenon was observed only four times and in different patients. In four patients, morphine had no effect on colonic electrical activity. Three of these unresponsive patients had long-standing insulin-dependent diabetes, and the fourth had fecal incontinence.

**COMMENTS**

The observations in this study expand our previous reports [23,24]. The electrical activity of the human colon in the postoperative period demonstrates progressive changes in both ECA (slow waves) and ERA (spike bursts) as recovery progresses. More organized patterns of phasic activity and of migrating spike bursts appear after the second or third postoperative day. Long duration migrating spike bursts appear after the fourth postoperative day and are associated with passage of flatus and defecation, indicating return of normal bowel function [23,24].

The effects of morphine on colonic myoelectric activity are important to understand since morphine is a commonly used analgesic. Previous studies in primates [25] have shown that there is a dose-related effect of morphine on the colon. Doses of 50 to 200 μg/kg morphine, corre-
TABLE 1
Mean Electrical Control Activity Frequency

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Mean 5.86 6.24  9.63 9.46

Figure 4. Mean number of spike bursts per hour at two colon recording sites before and after intravenous administration of morphine. Differences are significant at both sites.

Figure 5. Epidural morphine has no significant effect on colon myoelectric activity.

Sponding to doses used clinically, cause an increase in the frequency of random, nonpropagating spike bursts and contractions. At higher doses, there is inhibition of colonic electrical and contractile activity. In addition, all doses of morphine inhibited the migrating spike bursts that are associated with propulsion and defecation. These findings in animals are in agreement with our current observations in humans.

Morphine in humans induces phasic, stationary (nonmigrating) spike bursts in the entire colon, most prominently in the left colon. In addition, morphine interrupts type 3, 4, and 5 ERA when these are present postoperatively. Thus, intramuscular or intravenous administration of morphine in the later postoperative stages disrupts normal recovery of colon motility.

While morphine has a potent excitatory action that generates spike bursts, it appears to have no effect on the other major component of electrical activity, the ECA. These findings are similar to those described by Wienbeck et al [26] from in vitro studies of the cat colon. Our in vivo studies in primates also have shown that morphine has no effect on colonic ECA frequency [25].

Epidural administration of morphine had no effect on colonic electrical activity. The precise mechanisms of morphine action are not established at present. There are studies that suggest a central [27] or a peripheral [28,29] mechanism of morphine action on the gut. Studies in rat colon indicate that the morphine excitatory effect may be due either to direct action on colonic smooth muscle or to presynaptic inhibition of nonadrenergic inhibitory nerves [29]. There also is some evidence that serotonin-mediated central effects of morphine may influence colonic motility [27]. Our observations suggest that the lower spinal cord is not involved in morphine-induced excitation of the colon, since morphine administered epidurally had no effect.

Four of our patients had no colonic response to mor-
phine administration, although the drug was an effective anodyne in them. Three of these patients were insulin-dependent diabetics; the fourth was 80 years of age and had fecal incontinence. We speculate that these nonresponsible patients may have lost functional opioid receptors in the colon as a result of their underlying disease.

In summary, our studies indicate that morphine administered intramuscularly or intravenously has an excitatory effect on the colonic electrical response activity in most patients. This effect is most pronounced in the left colon. The increased electrical activity does not lead to enhanced phase-locking or other coordinated myoelectric responses. Rather, morphine disrupts such activity when it is present. The morphine responses are not due to a direct action of morphine on the spinal cord.

REFERENCES

DISCUSSION

Keith A. Kelly (Rochester, MN): Dr. Frantzides, I believe that if we give patients morphine after an operation, it may prolong postoperative ileus. Does the use of morphine prolong postoperative ileus? Does it speed the recovery from ileus, or doesn’t it make a difference? Was there a difference in the recovery from ileus between the patients who received morphine epidurally and those who received it systemically?

Arthur H. Aufses, Jr. (New York, NY): Could I enlarge on that question? Do you have any data relating to patient-controlled analgesia with morphine? That has become a very common way of handling analgesia, and the patients like it. But many of us have the impression that it substantially slows down recovery of gastrointestinal function.

Alan G. Thorsen (Omaha, NE): Did you look at the difference in return of function between those with epidural versus intravenous morphine?

Robert E. Condon (Milwaukee, WI): I have a comment that may clarify the epidural situation. The epidural catheters are managed by the anesthesia service, and they are only in place for 48 hours. Patients subsequently receive parenterally administered morphine. Therefore, we don’t really have clean data that can answer the questions that are being posed. But we all feel, because morphine clearly disrupts normal patterns of recovery, that it can adversely affect the time period during which recovery from postoperative ileus occurs. We see disruption of
normal motility as late as 1 week postoperatively in patients who get an occasional dose at that time.

Gordon L. Telford (Milwaukee, WI): In the dog, intrathecal morphine has no effect on gastrointestinal motility. The opioid receptors in the spinal cord do not control intestinal motility. The effect on gastrointestinal motility depends on how much escapes from the spinal cord into the systemic system. If there is an improvement in patient recovery from ileus during the postoperative period, it's most likely because the intrathecal doses are lower than the systemic doses. If the same dose is given intramuscularly as is given intrathecally, there is no gastrointestinal motility response. Therefore, the smaller doses that are given intrathecally result in a more rapid recovery clinically.

Constantine T. Frantzides (closing): Dr. Kelly, we did not assess a group of patients that had not received morphine and had the same magnitude of operation and duration of anesthesia as in patients who have received morphine, so I cannot answer your question directly. But indirectly, I assure you that morphine distorts the motility patterns we normally see during recovery, and I believe that morphine affects the recovery from postoperative ileus.

Dr. Aufses, as I mentioned, all 25 patients that we studied received morphine postoperatively. So it's very difficult to say whether the administration of morphine would affect recovery. We would have to have, of course, a control number of patients who wouldn't receive any analgesia, or at least any of the opiate analgesics, to enable us to make comparisons with the experimental group.

Dr. Thorson, the answer to your question is no.