

Effects of morphine on colonic myoelectric and motor activity in subhuman primates

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FRANTZIDES, CONSTANTINE T., ROBERT E. CONDON, WILLIAM J. SCHULTE, AND VERNE COWLES. *Effects of morphine on colonic myoelectric and motor activity in subhuman primates*. Am. J. Physiol. 258 (Gastrointest. Liver Physiol. 21): G247–G252, 1990.—We investigated the effects of numerous doses of morphine on colonic myoelectric and motor activity in monkeys. In each of four monkeys (*Macaca arctoides*), combined strain gauge transducers and bipolar electrodes were chronically implanted at four defined sites in the colon and recordings were made for 3 h in fasted, unanesthetized animals before and after intravenous administration of morphine sulfate (10–1,000 $\mu\text{g}/\text{kg}$). The basal fasting pattern of colonic motility was characterized by random contractions, nonmigrating clusters of contractions, and migrating individual contractions. Morphine at very low doses (10–25 $\mu\text{g}/\text{kg}$) had no effect on colonic motility at any site. At doses of 50–200 $\mu\text{g}/\text{kg}$, clusters and migrating contractions were eliminated, but there was an overall increase in the frequency of random contractions without an alteration in contraction amplitude or duration. At morphine doses of 500 and 1,000 $\mu\text{g}/\text{kg}$, contraction clusters and migrating contractions also were not seen, but there was a decrease in the colonic motility index caused entirely by a decreased frequency of random contractions. Both stimulation and inhibition were most marked in the sigmoid colon. Morphine has a dose-dependent biphasic effect on colonic myoelectric and contractile activity and alters colonic motility patterns by inhibiting migrating contractions and clusters of contractions.

motility; colon; monkey; migrating contractions

OPIOID PEPTIDES and opioid receptors are present throughout the gastrointestinal tract (21, 24, 29, 30). Their role in the control of gastrointestinal motility, however, is poorly understood. The effects of morphine on the myoelectric and motor activity of the small intestine have been studied extensively (6, 14, 22, 22, 31, 32). In contrast, investigations of the effect of morphine on colonic motility are few and the results conflicting (15, 18, 23, 25, 33).

A previous study (15) from our laboratory demonstrated little effect of morphine on the motility of either the right or left colon in monkeys. In contrast, morphine appears to have a potent stimulating effect on the colon in dogs (25), and in patients with either ulcerative colitis (18) or diverticulosis (23). Moreover, both in vivo (25) and in vitro (33) studies have suggested that there may be regional differences in the colonic response to morphine. Morphine appears to have a greater stimulating

effect on the left colon in vivo, whereas in vitro it appears to have a more marked effect on the right colon.

These conflicting observations can be attributed to a number of factors: 1) most previous studies of the effects of morphine on colonic motility were based on manometric methods recording from the distal part of the colon, 2) animal species-specific differences also could be partially responsible for the conflicting observations, 3) all previous studies were confined to the assessment of the number of contractions occurring in response to morphine without assessing changes in the overall patterns of colonic myoelectric and contractile activity, and 4) most studies employed only one or two doses of morphine rather than numerous doses with a dose-response approach.

The goals of the present study were to investigate the effects of morphine given in a range of doses on colonic myoelectric and contractile responses and patterns and to determine if regional differences in response to morphine existed within the colon. The ability to perform simultaneous recordings of myoelectric and contractile activity at multiple sites in the colon allows a better understanding of the effect of morphine on slow waves (electrical control activity), spike bursts (electrical response activity), and contractions.

METHODS

Experiments were conducted in four conditioned monkeys (*Macaca arctoides*) of either sex, 8–12 yr old, and weighing 6–8 kg. The protocol for this study was approved by the Animal Welfare Committee of the Medical College of Wisconsin, Milwaukee. *Macaca arctoides* is a particularly suitable species for studying gastrointestinal motility because their bowel, and especially the colon, is similar to that of humans both in anatomic structure and physiological responses. *Macaca arctoides* reproducibly develop postoperative ileus similar to that seen in humans (19); they also mimic humans in expressing a gastrocolic response to ingested food (10). A large body of data regarding motility responses in this species has been accumulated over the past 15 yr in our laboratory.

The animals were housed at a fully equipped animal facility at the Zablocki Veterans Administration Medical Center. They had not been used in previous experiments of any kind. After procurement, animals were quarantined for 45 days, admitted to our closed colony, and

trained to sit in a restraining chair. A fixed routine was followed daily to maintain conditioning and to reduce the effects of environmental factors on the motility responses recorded. For example, animals were placed in restraint chairs at the same time each day for a fixed period of time whether or not recordings were to be made.

At laparotomy, four extraluminal combination strain gauge transducer-bipolar electrode units were sutured to the seromuscular layer of the colon, at the cecum (RC) opposite the ileocecal valve, at the hepatic flexure (HF), at the splenic flexure (SF), and at the midsigmoid colon (SC). All operations were conducted after an overnight fast and by using aseptic surgical technique, and under general anesthesia induced with pentobarbital sodium (25 mg/kg). For placement of the recording devices on the colon, a midline laparotomy incision was made and the desired bowel segments were identified. The electrode-strain gauge units were sewn to the bowel with 4-0 monofilament suture, pushing the electrode tips into the muscle and orienting the unit so the strain gauge responded maximally to contractions of the circular muscle. The location and the distance between the units were precisely recorded.

The electrode-strain gauge units were fabricated from a miniature strain gauge (EA-06-031DE-120, Measurements Group, Raleigh, NC) bonded to a copper-beryllium shim, together with two flexible stainless steel Teflon-coated wires, all potted together in silicon rubber to form a unit $0.75 \times 2 \times 0.3$ cm in size (13). The tips of the electrodes protruded 3 mm and were 3 mm apart. The combination electrode-strain gauge unit recorded electrical and contractile events from the same bowel segment.

Lead wires from the strain gauge-electrode units were tunneled subcutaneously to the subscapular area and soldered to a plug connector. The fascia was closed with 2-0 monofilament suture and the hide was closed with subcuticular suture. A silicone rubber catheter, inserted into the external jugular vein, served for the subsequent administration of morphine. Recovery from anesthesia and early postoperative care was provided in a designated area under close supervision of a specially trained animal handler. After recovery from operation, the animals were placed in a restraining chair and the wires and plug were protected by a jacket.

Experiments began 15 days postoperatively. The monkeys were fasted for 14–16 h before each experiment. On each study day, recordings were made for 3 h, the last hour serving as the base line or control for the test period. Morphine sulfate was then administered through the jugular catheter in bolus doses of 10, 25, 50, 100, 200, 500, or 1,000 $\mu\text{g}/\text{kg}$. Each dose was studied in triplicate in separate experiments ~ 1 wk apart, and the order of doses was randomized for each replicate. Sufficient time was allowed to elapse between individual studies (1 dose/day) for the effects of the previous dose to completely clear. After morphine administration, recordings were continued for a further 3 h; the responses in the first hour after administration of morphine constituted the test period.

Myoelectrical and contractile activity were recorded

on an eight-channel Beckman polygraph (R611) and simultaneously on magnetic tape (Hewlett-Packard 3968A) for later computer analysis (5). For myoelectrical recordings, the lower and upper cutoff frequencies were set at 0.16 and 30 Hz, respectively. For the analysis of morphine effect on colonic motility, the contraction frequency, amplitude, and duration during the hour immediately preceding morphine administration (control) were compared with the respective values during the hour immediately after the injection. Colonic slow-wave frequency during the same time periods was determined by using a fast-Fourier transform method (5) on a Nova 4X computer (Data General). The presence, direction, and propagation velocity of migrating contractions also was determined. Migration was defined as the appearance of a single contraction or cluster of contractions at a minimum of three successive recording sites and at a constant velocity.

The study was designed to utilize each monkey as its own control. The base-line period was compared with the experimental period for each dose level at each location. Values are expressed as means \pm SE for each of the subgroups. The data representing change from the control period to the postmorphine injection period were analyzed by two-way analysis of variance (ANOVA) to determine whether the change was different from location to location (RC, HF, SF, and SC). ANOVA of the data at each individual dose administered "early" vs. "late" in the experimental design was also carried out. To determine the effect of each dose level, the before and after measurements were analyzed by using the paired *t* test with three degrees of freedom. A two-tail probability of 0.05 or smaller was accepted as indicating a significant change.

RESULTS

The basal fasting pattern of colonic motility was characterized by random contractions with interposed clusters of contractions. The clusters each consisted of groups of 5–10 contractions and were observed at all sites. These clusters occurred randomly at each recording side and did not appear to migrate either orally or aborally. Individual contractions, however, originating in the right colon at a frequency of 3–4/h were observed to migrate to the sigmoid colon at a velocity of $\sim 1 \pm 0.3$ cm/s (Fig. 1). Basal contraction frequency in the sigmoid colon ($46.3 \pm 3.2/\text{h}$) was significantly greater than that in the right colon ($15.4 \pm 1.6/\text{h}$). Contraction frequencies in the hepatic and splenic flexures were similar ($30.2 \pm 2.8/\text{h}$ and $32.2 \pm 3.8/\text{h}$) and intermediate between those of the right and left colon. Contractions were found to correlate with spike bursts on a 1:1 basis (Fig. 1).

Morphine at low doses (10 and 25 $\mu\text{g}/\text{kg}$) had no effect on colonic motility at any site, but with higher doses (50–1,000 $\mu\text{g}/\text{kg}$) excitatory and inhibitory effects were observed within 5 min after administration. Doses of 50, 100, and 200 $\mu\text{g}/\text{kg}$ morphine increased colonic motility (Fig. 2). This change resulted entirely from an increase in contraction frequency (Fig. 3); there was no alteration in contraction amplitude or duration (Table 1). At doses of 500 and 1,000 $\mu\text{g}/\text{kg}$, morphine administration was

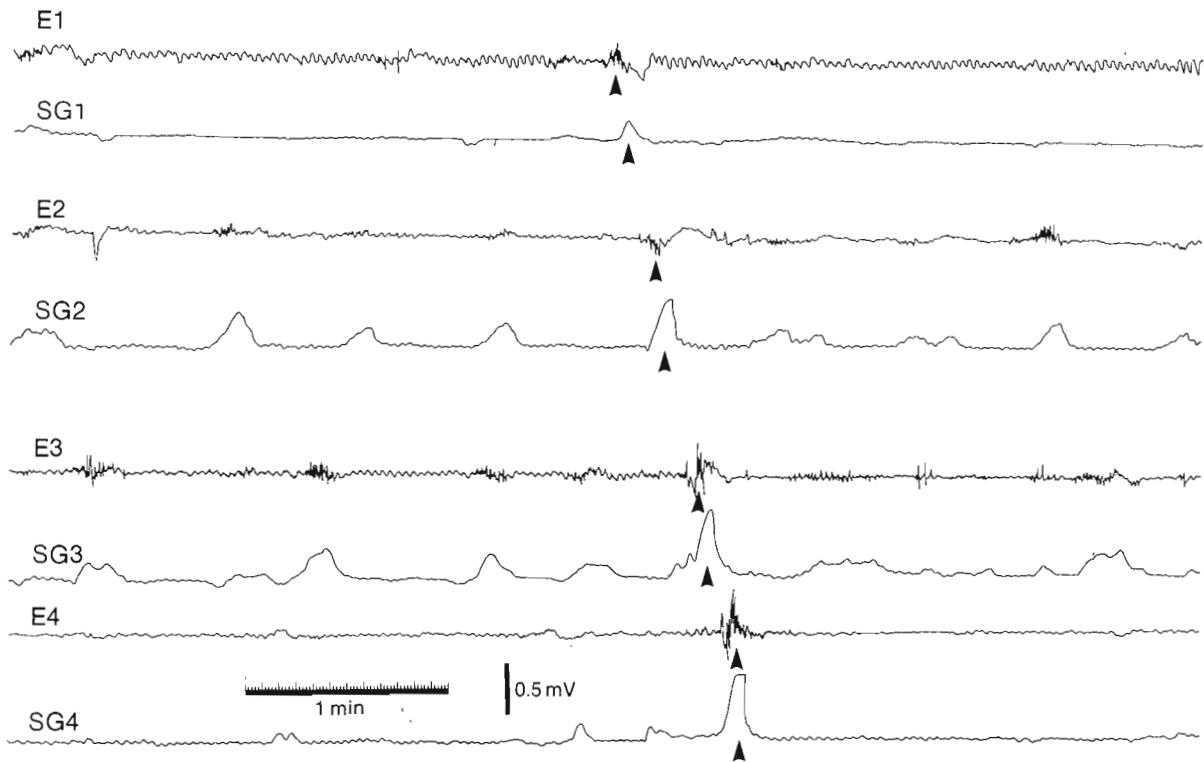


FIG. 1. Migrating contractions and associated spike bursts are indicated by arrows. These contractions start in the right colon and migrate relatively rapidly (~ 1 cm/s) to the sigmoid colon. Bipolar electrodes (E) and strain gauge transducers (SG) sutured to colon at 4 defined sites.

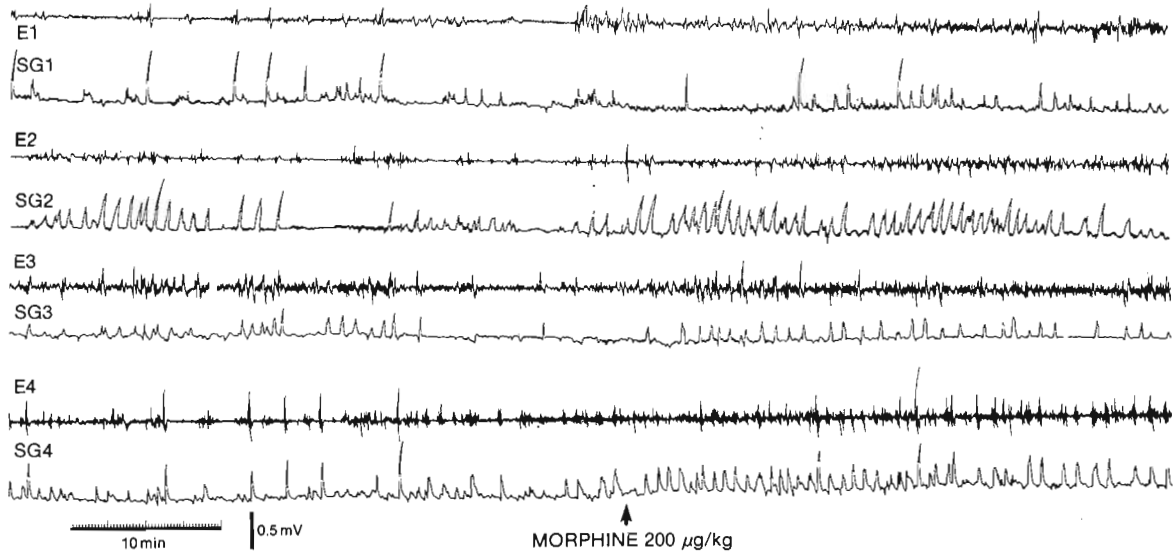


FIG. 2. Morphine ($200 \mu\text{g}/\text{kg}$ iv) stimulates colon myoelectric and motor activity at all recording sides.

associated with a significant decrease in colonic motility (Fig. 4). The inhibitory effect of high doses of morphine was the result of a decrease in contraction frequency (Fig. 5). The excitatory and inhibitory effects of morphine were seen at all sites but were most marked in the sigmoid colon (Fig. 6). Morphine at and above doses of $50 \mu\text{g}/\text{kg}$ eliminated migrating individual contractions in the colon. Additionally, contractions no longer appeared in clusters but occurred only randomly. Analysis of variance of the data at each individual dose showed no

difference between doses administered early or late in the experimental design (Table 2).

The dominant slow-wave frequency was 3-4 cycles/min. There were no significant differences in the slow-wave frequency between individual segments. Morphine did not cause any significant alteration in slow-wave frequency at any site (Table 1). None of the doses of morphine induced vomiting or produced any visible alteration in animal behavior.

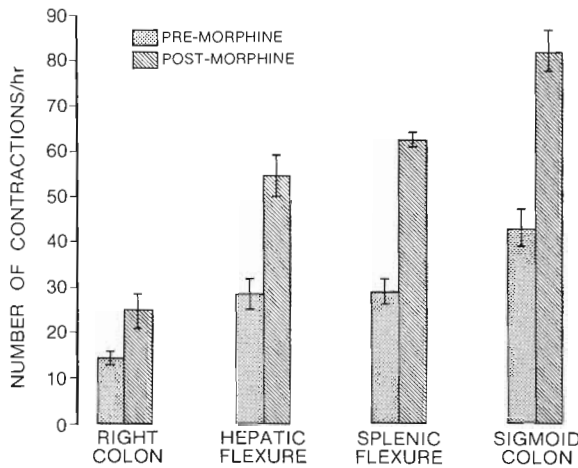


FIG. 3. Mean number of contractions per hour at 4 colon recording sites before and after morphine (100 $\mu\text{g}/\text{kg}$ iv). At each site differences are significant ($P < 0.02$, paired t test).

DISCUSSION

Fasting colonic motor activity in the monkey is characterized by three patterns: randomly occurring contractions, nonmigrating clusters of contractions, and migrating individual contractions. The frequency of spike bursts and associated contractions was always higher in the sigmoid than in the right colon.

Morphine at doses of 50, 100, and 200 $\mu\text{g}/\text{kg}$ increased random colon contraction frequency, but doses of 500 and 1,000 $\mu\text{g}/\text{kg}$ decreased contraction frequency. These observations suggest that morphine exerts a dose-dependent biphasic effect on colonic motility and are in agreement with a recent study (28) demonstrating that low doses of morphine induce migrating myoelectric complexes in the small intestine of dogs, whereas high doses inhibit migrating myoelectric complex cycling. The mechanism of the biphasic effect of morphine on bowel motility is obscured. One may speculate that at lower doses morphine stimulates only excitatory receptors and at higher doses inhibitory, or both excitatory and inhibitory receptors with an overall inhibitory effect. Our experimental protocols do not allow any inferences to be made on such mechanisms, since no specific blockers to μ -, κ -, or δ -receptors were used.

Both stimulation and inhibition responses were least marked in the right colon; frequency responses to administration of morphine progressively increased in magnitude from proximal to distal colon recording sites. The most pronounced effects were seen in the left colon. These results agree with the findings of Rinaldo et al. (25), who noted that morphine induced increased activity

of the colonic circular muscle in dogs. The effect was more pronounced in the distal than in the proximal colon. Wienbeck et al. (33), however, showed in isolated cat colon that morphine (3 μM) increased spike activity predominantly in the proximal colon. They also noted a decrease in spike activity at morphine concentrations of 100 μM . These differences in responses might be because of species variation or differences in methodological approach (in vivo vs. in vitro).

The administration of morphine to humans causes an immediate increase in colonic basal intraluminal pressure (4). Adler et al. (1), studying patients with a colostomy, showed that morphine (5–6 mg) increased the tone of the descending colon and caused a marked decrease in propulsive movements. These investigators described the same phenomena in dog colon (2); propulsive activity was abolished while nonpropulsive activity was increased for several hours after administration of morphine.

The results of the present studies are in some disagreement with those previously reported by our group. Our previous report (15) showed an insignificant increase in contractions in the right colon in response to morphine and no discernible response in the sigmoid colon; the other narcotics studied (meperidine and codeine) did cause inhibition of colon contractions. In the present experiments, both increases and decreases in colon contractions were observed, depending on the morphine dose studied. This difference in results is probably a reflection of the methods employed in the two studies. Specifically, in the 1980 paper (15) "contractions associated with spike bursts were counted manually" and we presume some data was lost because of background noise. In the present report, data was generated from four different colon sites (in contrast to two sites only in the previous study) and more powerful computer-based analyses of the data were employed. Moreover, in contrast to the multiple doses of morphine employed in the present study, only two doses were administered in the previous experiments (15).

In human and guinea pig gastrointestinal tracts, opioid peptides and opioid receptors have been identified; the highest concentrations are in the antrum and duodenum (7, 20, 29). In rats, however, maximal opioid peptide immunoreactivity has been demonstrated in the myenteric nerve fibers of the colon (16). The effects of morphine observed in different species correspond well with those areas in which enkephalinergic innervation has been demonstrated and where, presumably, opioid receptors are present (12). The distribution of opioid receptors in monkey gastrointestinal tract has not yet been de-

TABLE 1. Effect of morphine sulfate administration on contraction amplitude and duration and on slow-wave frequency

	Contraction Amplitude, cm		Contraction Duration, s		Slow-Wave Frequency, cycles/min	
	Premorphine	Postmorphine	Premorphine	Postmorphine	Premorphine	Postmorphine
Right colon	0.92 \pm 0.15	1.11 \pm 0.30	12.40 \pm 1.74	13.03 \pm 2.57	3.63 \pm 0.25	3.63 \pm 0.18
Hepatic flexure	1.31 \pm 0.20	1.33 \pm 0.16	13.34 \pm 2.09	13.06 \pm 2.47	3.24 \pm 0.32	2.98 \pm 0.3
Splenic flexure	0.84 \pm 0.11	0.87 \pm 0.14	10.95 \pm 1.17	12.01 \pm 1.80	4.19 \pm 0.32	4.13 \pm 0.2
Sigmoid colon	2.21 \pm 0.12	2.20 \pm 0.43	15.12 \pm 1.62	15.46 \pm 1.25	3.22 \pm 0.25	3.01 \pm 0.1

Values are means \pm SE for 12 individual experiments. Dose of morphine sulfate given was 200 $\mu\text{g}/\text{kg}$ body wt.

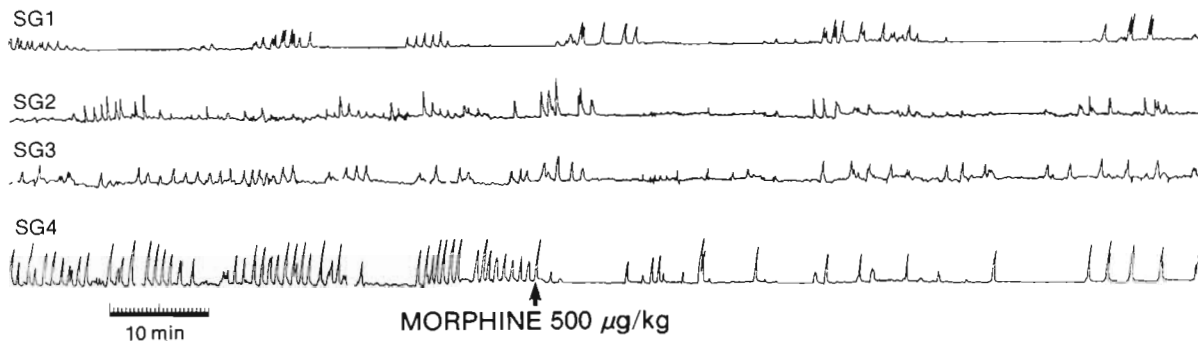


FIG. 4. Morphine (500 µg/kg iv) inhibits colon contractions at all sites.

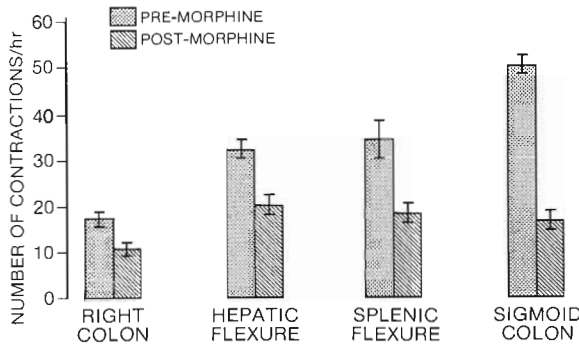


FIG. 5. Mean number of contractions per hour at 4 colon recording sites before and after administration of morphine (500 µg/kg iv). At each site differences are significant ($P < 0.02$, paired t test).

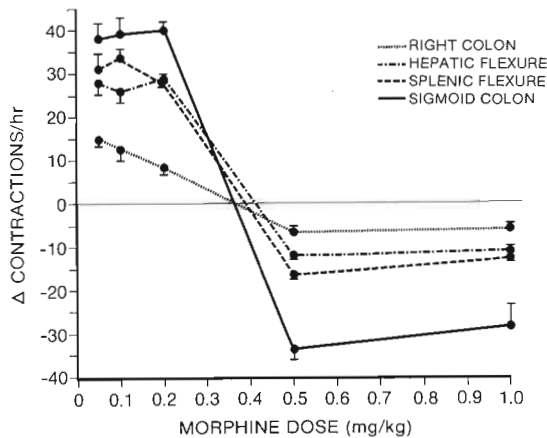


FIG. 6. Changes in mean response (contraction/h) at each of 4 colon recording sites induced by administration of morphine. Lower doses (50, 100, and 200 µg/kg) show an excitatory effect, whereas high doses (500 and 1,000 µg/kg) show an inhibitory effect. In all cases mean changes are different from zero and level of significance ranges from 0.002 to 0.02.

finer. Such studies might explain the hypersensitivity of the sigmoid colon to morphine compared with that of the right colon.

Certain doses of morphine (0.5–1.0 mg/kg) used in this study would have exerted a toxic effect if administered to humans, potentially causing respiratory arrest and death. Even lower doses are known to cause nausea and/or vomiting in dogs and humans. It appears that monkeys tolerate high doses of morphine without any signs of respiratory depression, nausea, drowsiness, euphoria, sleep, or vomiting. This effect was not due to develop-

TABLE 2. Effects of morphine on colonic contraction frequency, administered at different times in the experimental design

Morphine	Right Colon	Hepatic Flexure	Splenic Flexure	Sigmoid Colon
50 µg/kg				
Early	33.5±1.89	63.75±1.98	54.5±4.42	78.25±3.97
Middle	32.75±3.01	54.5±2.28	48.25±2.33	78.25±2.90
Late	31.5±1.35	54.0±2.15	58.75±4.31	82.5±1.25
100 µg/kg				
Early	29.75±2.07	53.25±3.93	63.0±1.62	82.75±2.75
Middle	27.0±2.47	59.5±2.70	62.25±1.43	79.5±2.02
Late	20.25±1.98	51.5±4.82	62.0±1.27	84.25±2.13
200 µg/kg				
Early	29.25±1.82	60.75±1.98	57.25±3.03	82.24±0.89
Middle	31.75±1.56	61.0±0.35	57.75±1.67	83.5±3.09
Late	26.75±1.67	58.25±2.67	55.75±3.21	83.25±1.67
500 µg/kg				
Early	10.0±0.61	18.75±1.19	17.0±0.94	18.75±2.43
Middle	9.5±0.83	19.75±1.34	19.75±1.67	16.75±1.19
Late	10.5±1.60	22.0±1.27	16.75±1.52	14.25±1.29
1 mg/kg				
Early	12.75±1.67	20.25±0.41	20.0±0.71	16.25±1.95
Middle	11.0±1.27	22.0±1.06	19.75±1.14	17.5±1.75
Late	10.0±1.27	22.0±2.03	16.75±1.52	19.0±1.12

Values are means ± SE.

ment of tolerance to morphine, since doses were administered at random and the effect on colon motor activity of a given dose was not different when it was administered early vs. late in the experimental design. Moreover, the doses employed in the present study were far below those used in studies by Burks et al. (8, 9) in dogs to induce morphine tolerance with respect to effects on intestinal motility.

Based on the half-life of morphine, it is estimated that even the highest dose (1 mg/kg) employed in our study would have been cleared within the 24-h interval allowed between study points. Therefore, the time points of the study were such that additive effects would be unlikely.

Migrating individual contractions with a propagation velocity of 1.0 cm/s were described by Alvarez (3) in the rabbit six decades ago. This type of colonic activity is considered to be propulsive and is characterized by strong contractions that progress caudad over a long length of bowel (26, 27). We have recently described aborad-migrating long spike bursts occurring in the human colon during recovery from postoperative ileus (11, 17). This electrical activity of the colon was associated with pas-

sage of flatus or defecation, and its appearance signaled recovery from functional postoperative ileus.

The inhibitory effect of morphine on migrating contractions observed in the present study may be one of the factors involved in morphine-induced constipation. The colonic hypermotility induced by the lower doses of morphine represents uncoordinated nonpropulsive circular muscle contractions; this type of activity did not appear to migrate from one recording site to another. The same type of stationary nonmigrating contractions in response to morphine have been described in the cat colon by Wienbeck et al. (34).

Studies, however, combining simultaneous monitoring of myoelectric and contractile colonic activities with transit time determinations of the movement of intraluminal colonic contents are indicated to fully explore the effects of morphine on colonic motility and propulsion.

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