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Tolerance to the Effects of Morphine on Intestinal Motility of Unanesthetized Dogs[1]

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ABSTRACT

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A study was designed to determine whether tolerance developed to the intestinal stimulatory effects of morphine and/or whether the fasted pattern of motility showed signs of dependence during chronic administration of morphine. Dogs were implanted with electrodes on the serosal surface of the small intestine. After recovery from operation, the fasted pattern of motility as well as the responses to bolus administrations of morphine sulfate (30, 100 and 300 μg/kg) were determined in each animal. Each animal then was placed on continuous administration of morphine sulfate in dosages of 1.25 to 40 mg/kg/day. Patterns of motility and responsiveness to bolus doses were determined at each dose level. The continuous infusion of morphine then was stopped abruptly and the patterns of motility and responsiveness to bolus administration of morphine again were determined. During control periods, each animal demonstrated a distinctive pattern of motility. Bolus administration of morphine caused a dose-dependent increase in contractile activity. Continuous administration of morphine brought about a temporary disruption of the fasted pattern of motility. This pattern returned toward normal when the same daily dose of morphine was maintained for several days. During continuous administration of morphine, the stimulatory effect of the bolus doses was lost. Abrupt withdrawal of the continuous administration of morphine brought about a disruption of the normal fasted pattern of motility for 1 to 2 weeks. During this time, there was a rapid return of the stimulatory effects of bolus administration of morphine. These results indicate a development of tolerance and physical dependence of the small intestine of the unanesthetized dog to morphine.

Morphine has a profound effect on motility of the gastrointestinal tract of several species, including man and dog. In adequate doses, morphine delays both gastric emptying and intestinal transit, thus causing constipation. The mechanisms for the delays in transit through the gut are not entirely clear. Acute administration of morphine causes an increase in the number of contractions of the intestine. These contractions are thought to be nonpropulsive and organized such that they occlude the lumen and retard transit (Bass *et al.*, 1973; Bass and Wiley, 1965).

The effects of chronic administration of morphine on gastrointestinal motility have not been properly defined. In 1926, Miller and Plant concluded that tolerance to the effects of morphine on the small intestine does not develop. Until recently, this conclusion was unchallenged. In the past few years, however, several reports have appeared which indicate that tolerance to the intestinal effects of morphine can occur. Development of tolerance to the acetylcholine antirelease effect of morphine in guinea-pig isolated ileum (Schaumann, 1957) is well documented (Mattila, 1962; Takagi *et al.*, 1965; Schulz and Goldstein, 1973). Tolerance to the intestinal stimulatory effects of morphine was observed in segments of small bowel removed from morphine-treated dogs (Burks *et al.*, 1974) or can be induced *in vitro* (Burks and Grubb, 1974). In addition to these *in vitro* studies, Weisbrodt *et al.* (1977) reported that tolerance develops to the ability of morphine to retard intestinal transit in unanesthetized rats. Since results of these more recent investigations appeared to conflict with those of Miller and Plant (1926), we decided to reinvestigate with modern techniques the effects of both acute and chronic administration of morphine on the motility of the small intestine of the conscious dog.

Investigations of factors which alter small bowel motility in conscious animals must take into account the normal patterns of bowel motility. Patterns of small bowel motility can be identified by recording the myoelectric activity of the intestinal musculature. The electrical activity of the smooth muscle of the small bowel consists of two basic types of potentials, slow waves and spike potentials. These two activities and their role in controlling contractions of the bowel have been described (Bass, 1968). Basically, slow waves control the distribution and timing of contractions (when they occur at any one site and at

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adjacent sites) while spike potentials signal and initiate the actual contractions. Slow waves and spike potentials are related in that spikes appear only during a specific phase of the slow wave cycle and cannot occur independently of slow waves. The percentage of slow waves accompanied by spike potentials (hence, contractions) and their temporal and spatial distribution depend on the digestive state of the animal. A characteristic pattern called the intestinal migrating myoelectric complex occurs in the fasted dog (Code and Marlett, 1975). This complex consists of four phases. In phase I, none of the slow waves is accompanied by spike potentials. In phase II, spike potentials are superimposed on the slow waves in a seemingly random fashion. During phase III, every slow wave has superimposed spike potentials. Phase III ends rather abruptly (phase IV) and phase I repeats. These phases do not occur only at one particular site but propagate aborally along the bowel. Feeding abolishes this complex and produces a more uniform distribution of slow waves with spike potentials. It is crucial that effects of drugs on intestinal motility be studied against defined backgrounds of myoelectric activity. A recent study of myoelectric activity in unanesthetized rats (Sussman *et al.*, 1978) indicated that bolus injections of morphine abolished the interdigestive migrating myoelectric complex. As specific abolition of the migrating complex could cause apparent decreases in transit, the acute and chronic effects of morphine on this motility pattern were of particular interest.

The goals of the present experiment were to: 1) confirm the normal fasted pattern of motility of a group of unanesthetized dogs; 2) determine the effects of acute bolus administration of morphine on the fasted pattern of motility; 3) determine the effects of continuous infusion of morphine sulfate on the fasted pattern of motility; 4) determine whether continuous infusion of morphine alters responses to bolus administration of morphine; and 5) determine the effects of abrupt discontinuation of continuous morphine administration on the responsiveness of the bowel to acute administration of morphine.

Materials and Methods

Four adult, mongrel dogs were anesthetized with thiopental sodium, 20 mg/kg i.v., and inhalation of methoxyflurane. Laporatomy was performed under aseptic conditions and 14 electrodes were sewn on the serosal surface of the small intestine. The monopolar silver-wire electrodes were spaced at equal distances (about 25 cm apart) along the entire small intestine from the gastroduodenal junction to the ileocecal junction. A coil of silver wire was placed s.c. in the right flank to serve as a reference electrode. Details of constructing and implanting similar electrodes have been reported (McCoy and Bass, 1968). During the same operation, a sterile polyvinyl catheter (inside diameter, 0.7 mm) was placed into the superior vena cava through a cutdown in the external jugular vein. The wires from the electrodes and the catheter from the superior vena cava were tunneled s.c. to exit through the skin in the midscapular region. Immediately after surgery, each animal was placed in a harness which allowed for almost complete freedom of movement as well as continuous infusion of i.v. fluids. The only movement the animal could not make within the harness was to roll over on its back. The dogs were taken from their cages for daily exercise and to allow for periodic recording of myoelectric activity.

Electrical potential changes at 7 of the electrodes (selected from the 14 on the basis of location and clarity of recording) were recorded separately with the coil of wire in the right flank serving as a reference for each electrode. Output from the electrodes was recorded with a Beckman type R-411 Dynograph through the resistor-condenser input of 9806 A couplers at a time constant of 0.3 sec. The upper or high-frequency cut-off control was set at 100 Hz. Recording sessions were 2 to 4 hr in length.

The animals were allowed to recover for 10 to 14 days after surgery. Then control recordings of myoelectric activity were obtained over a period of 3 to 4 weeks during which time the normal interdigestive pattern (14–16 hr after the last meal) was established in each animal. During the recovery period and during the control recordings, all animals were infused i.v. with normal saline, 500 ml/day by means of the implanted i.v. catheter. It was also during the time of the control recordings that the responses to acute administration of morphine sulfate in doses of 30, 100 and 300 μg/kg were determined. Morphine was always given at a time when phase III of a myoelectric complex was present in the middle portion of the intestine. The three dose levels of morphine were administered at least 3 days apart as i.v. boluses in random order in each animal. After completion of the control experiments, each animal was placed on a program of continuous administration of morphine sulfate. In each case, the daily dose of morphine was dissolved in 500 ml of saline and given over a 24-hr period. Three of the animals were first given a dose of 1.25 mg/kg/day. The daily dose was then increased in stepwise increments to a maximum of 10 mg/kg/day (one animal) or 40 mg/kg/day. The doses as well as the number of days that each animal was maintained at each daily dose are presented in table 1. After stabilization of myoelectric patterns at each dose level of morphine infusion, effects of bolus i.v. doses of morphine were determined.

Once the responsiveness of the intestine was established during continuous infusion of the largest daily dose of morphine, the drug infusion was terminated abruptly. In its place, 500 ml of normal saline was infused per day. During the first week of this withdrawal period, the responsiveness of the intestine to bolus administration of morphine was determined daily. Recordings were continued after 1 week of withdrawal in order to determine whether or not normal fasted patterns of motility returned.

Data were analyzed in two ways. In order to evaluate 1) the fasted pattern of motility, 2) the effect of continuous morphine administration on the pattern and 3) the pattern during withdrawal, the number of slow waves with superimposed spike potentials was counted at three intestinal sites (upper, middle and lower) during each 2 min of the experiment. This total was then divided by the total number of slow waves that occurred during the same 2-min period and was expressed as described previously (Weisbrodt *et al.*, 1975). In order to evaluate the effects of bolus administration of morphine on the myoelectric activity, the number of slow waves with spike potentials which occurred on all seven channels 4 min immediately preceding the injection of morphine and 4 min immediately after injection of morphine were counted. These data are expressed as number of slow waves with spike potentials per electrode per minute.

The morphine sulfate employed in the experiments was obtained from Merck Chemical Co., Rahway, NJ. Doses were calculated as the salt form. Data were analyzed statistically by means of the Student's *t* test (Goldstein, 1964).

Results

Recordings obtained from fasted animals during the continuous infusion of saline exhibited both slow waves and spike

TABLE 1
Duration (days) of treatment

Dog No.	Saline	Morphine (mg/kg/day)						Withdrawal
		1.25	2.5	5	10	20	40	
1	24	5	2	14	13			27
2	27	6	4	4	8	8	4	29
3	21	5	6	6	8	2	9	14
4	29						38	10

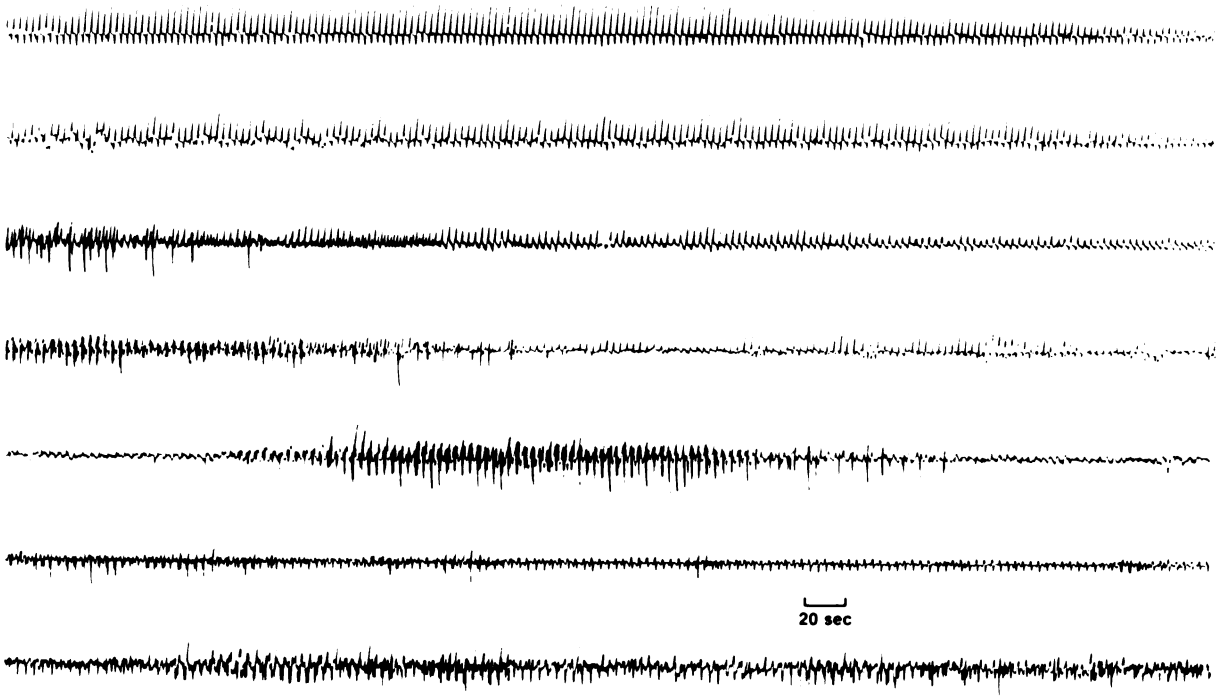

Fig. 1. Electrical activity of small intestine of the dog. Traces show electromyograms from seven electrodes which were placed equidistant along the intestine. Top tracing is from electrode placed 10 cm from gastroduodenal junction. Dog had been fasted for 16 hr. The top two traces show phase I activity. Phase IV activity is seen on tracings 3 and 4. Tracing 5 shows phases II, III, IV and I. The bottom two tracings show phase II activity.

potentials at all electrode sites in each of the dogs (fig. 1). Slow waves were always present and their frequency ranged from 17 to 19 cycles per minute in the duodenum to 11 to 14 cycles per minute in the ileum. Spike potentials were present as cyclical recurring myoelectric complexes (fig. 2). The time from the end of phase IV of one complex to the end of phase IV of the next complex at any one electrode site was approximately the same in all animals, averaging 80 min. Acute i.v. administration of morphine sulfate to the animals which were receiving saline caused a simultaneous appearance of spike potentials at all levels of the bowel. The stimulation was dose-dependent, lasted less than 10 min and was followed by the return of the normal fasted pattern of motility (figs. 3 and 4).

Initiation of continuous morphine infusion always caused a disruption of the normal fasted pattern of spike potential activity. The disruption was most pronounced during the first day that the daily dose was increased. Figure 5 illustrates the results of increasing the daily dose from 5 to 10 mg/kg/day. The day before this recording was taken, myoelectric activity showed the normal fasted pattern. The dosage was increased at the beginning of the recording session. During the session, there was a loss of the normal pattern of migrating spike potential activity. Disruption of the normal pattern lasted for several days (1-6), depending on dosage. If the same daily dose level was maintained, however, there was a return toward the normal pattern of interdigestive activity. In one animal, normal myoelectric complexes returned and the overall level of spike potential activity was near control levels by the 6th day of receiving 10 mg/kg/day of morphine. The other animals did not uniformly demonstrate such a complete return toward normal; however, myoelectric complexes were always evident by the 3rd or 4th day of administration of a given daily dose.

There was a loss of the stimulatory response to acute administration of morphine during the time in which the animals were receiving continuous administration of the drug. Daily doses of 1.25, 2.5 and 5 mg/kg altered the responses to all three acute doses (fig. 3). The response was variable since in two of the animals, all three doses still produced a slight stimulation but in one animal, inhibition of activity occurred. Daily doses

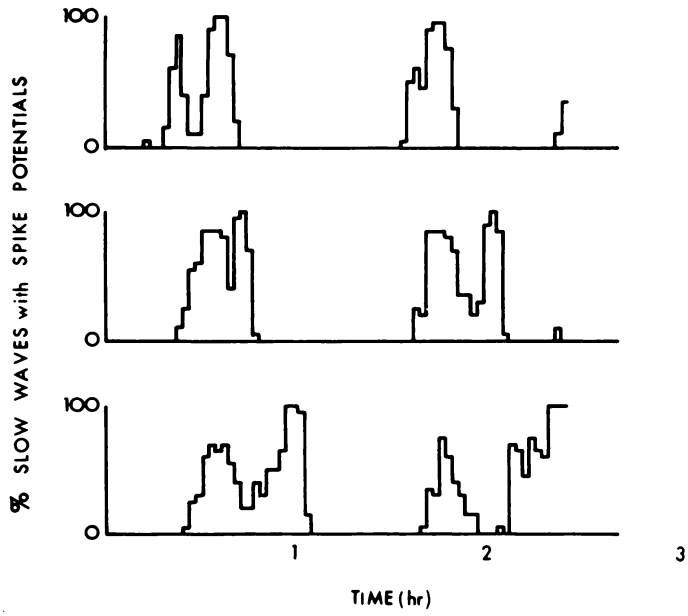

Fig. 2. Temporal distribution of slow waves with spike potentials during fasting. Tracings from three electrodes (one in proximal, one in middle and one in distal small bowel) in one dog were analyzed. The distribution of spike potentials is characteristic of the migrating myoelectric complex. Similar results were obtained during fasting in each dog.

of 10, 20 and 40 mg/kg abolished the stimulatory response to all three bolus doses in all four dogs (figs. 3 and 6). In fact, a significant inhibition of spike potential activity was seen with bolus doses of 300 μg/kg.

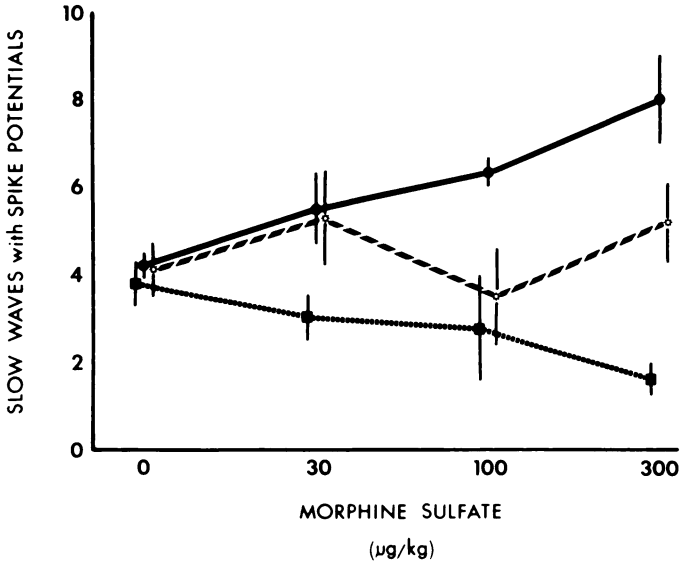

Fig. 3. Responses of the small intestine to i.v. bolus injections of morphine sulfate, 0, 30, 100 and 300 μg/kg. Slow waves with spike potentials were counted for each tracing for 4 min after injection, averaged and expressed as number of spikes per minute per electrode site. Continuous line (●——●) indicates response to bolus injections during daily infusion of saline; broken line (☆— — —☆) indicates responses to bolus injections during daily infusions of morphine sulfate, 1.25, 2.5 or 5 mg/kg; dashed line (■- - -■) indicates responses to bolus injections during daily infusion of morphine sulfate, 10, 20 or 40 mg/kg.

Abrupt discontinuance of the daily infusion of morphine was followed by several events. First, the animals showed mild signs of withdrawal. Loss of appetite, mild diarrhea, agitation and muscular weakness were obvious for 2 to 4 days. Second, the normal pattern of interdigestive myoelectric activity was disrupted. Figure 7 illustrates the activity on the 3rd day of withdrawal from a dose of 40 mg/kg/day. No myoelectric complexes were evident during the first 80 to 90 min of recording (before the bolus injection of morphine). Such abnormalities persisted in each animal for approximately 2 weeks during which there was a gradual return to normal interdigestive myoelectric activity. Third, there was a return of responsiveness to acute administration of morphine after 2 to 3 days (table 2). As seen in figure 8, 300 μg/kg of morphine sulfate again caused a stimulation of spike potential activity. Figure 7 also illustrates a phenomenon which was observed in two of the dogs. Bolus administration of morphine not only caused an immediate increase in spike potential activity at all three sites, but it also caused a later temporary appearance of normal interdigestive activity (as evidenced by the appearance of a period of propagated phase III activity). In the other animals, morphine caused a stimulation as well as a temporary change in the pattern;

TABLE 2

Response to acute administration of morphine during withdrawal

Day of Withdrawal	Before Morphine	Morphine (300 μg/kg)
1	3.2 ± 0.5[a, b]	4.2 ± 0.9
2	4.1 ± 0.5	8.3 ± 1.2*
3	3.3 ± 0.1	8.5 ± 0.6*
≥4	3.3 ± 0.4	6.8 ± 0.8*

[a] Slow waves with spike potentials per electrode per minute.
[b] Mean ± S.E.M.
* Indicates a significant difference from before morphine $P < .05$.

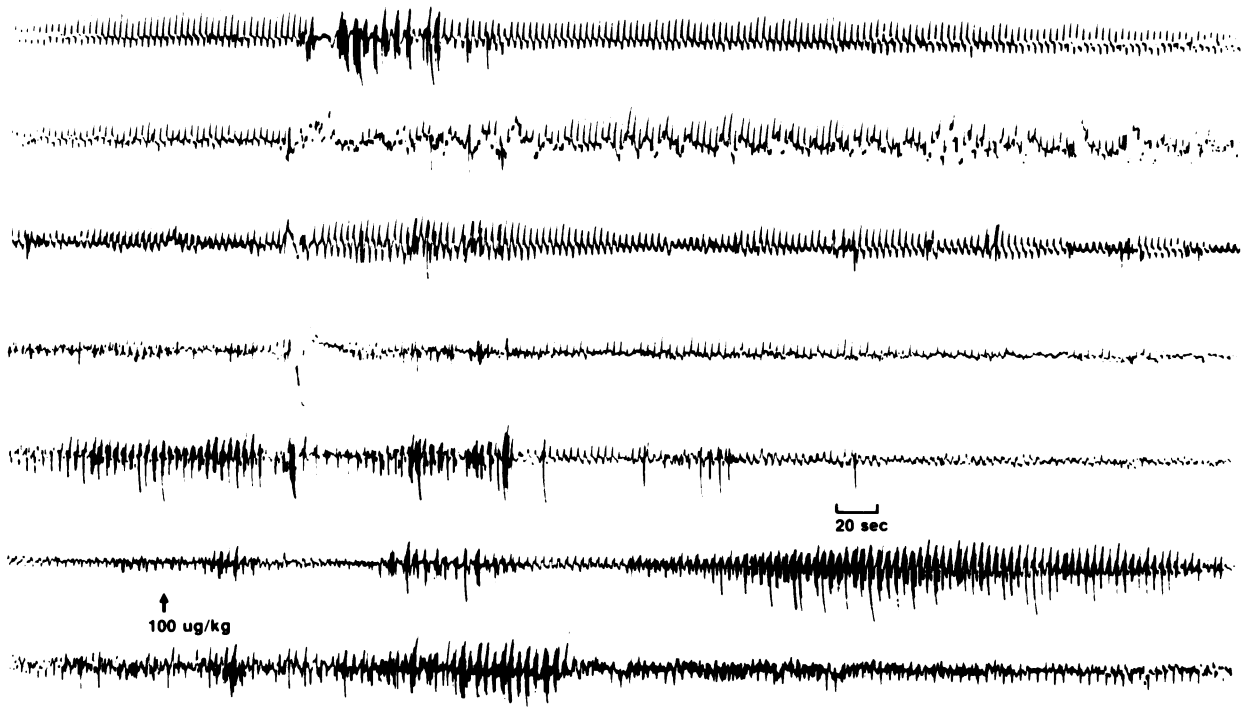

Fig. 4. Myoelectric responses of the small intestine to bolus i.v. injection of morphine sulfate, 100 μg/kg. Electrode placement is as described for figure 1. Animal was receiving daily infusion of saline. Phase III of a migrating complex was present in midintestine (tracing 5) at the time of morphine administration. After brief stimulation (spike potentials) at all levels of the intestine, the migrating myoelectric complex resumes in tracing 6.

however, the change toward a normal pattern was not as complete.

Discussion

Recent studies indicate that the number and pattern of contractions (slow waves with spike potentials) in many species differ between the fasted and fed conditions. The dogs used in the present study all demonstrated normal interdigestive myoelectrical activity. The presence of a well defined interdigestive pattern provides a drug-independent measure of the functional integrity of the extrinsic and intrinsic control mechanisms of the bowel. For this reason, bolus doses of morphine were given during a specific phase of the pattern; that is, when phase III of the complex was midway down the bowel. The presence of the

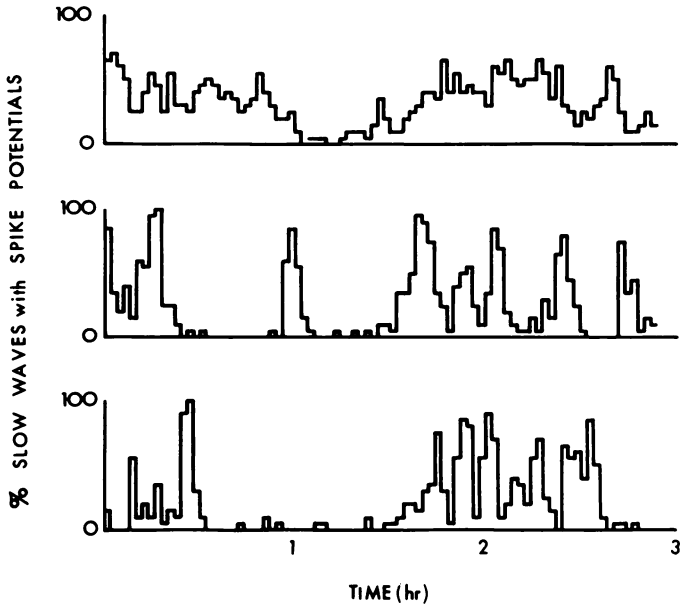

Fig. 5. Temporal distribution of slow waves with spike potentials during the 3-hr interval after increasing the daily infusion of morphine sulfate from 5 to 10 mg/kg. Analysis is as described for figure 2. Note disruption of myoelectric complexes (compare to fig. 2). Similar disruptions occurred in each animal every time the daily infusion dose of morphine sulfate was increased.

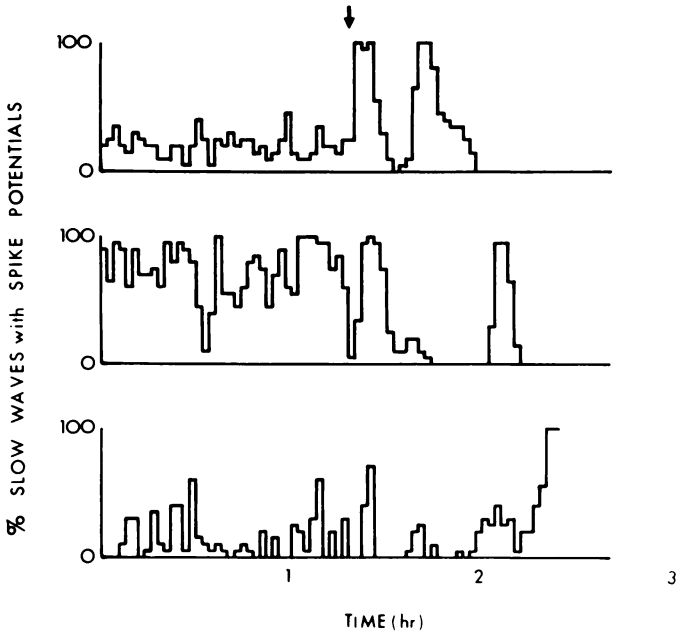

Fig. 7. Temporal distribution of slow waves with spike potentials during the 3rd day after abrupt discontinuation of daily morphine infusion. Analysis is as described for figure 2. Note absence of myoelectric complexes during the first 80 to 90 minutes of recording. At arrow, morphine sulfate, 300 μg/kg, was injected. A relatively normal myoelectric complex returned after administration of morphine.

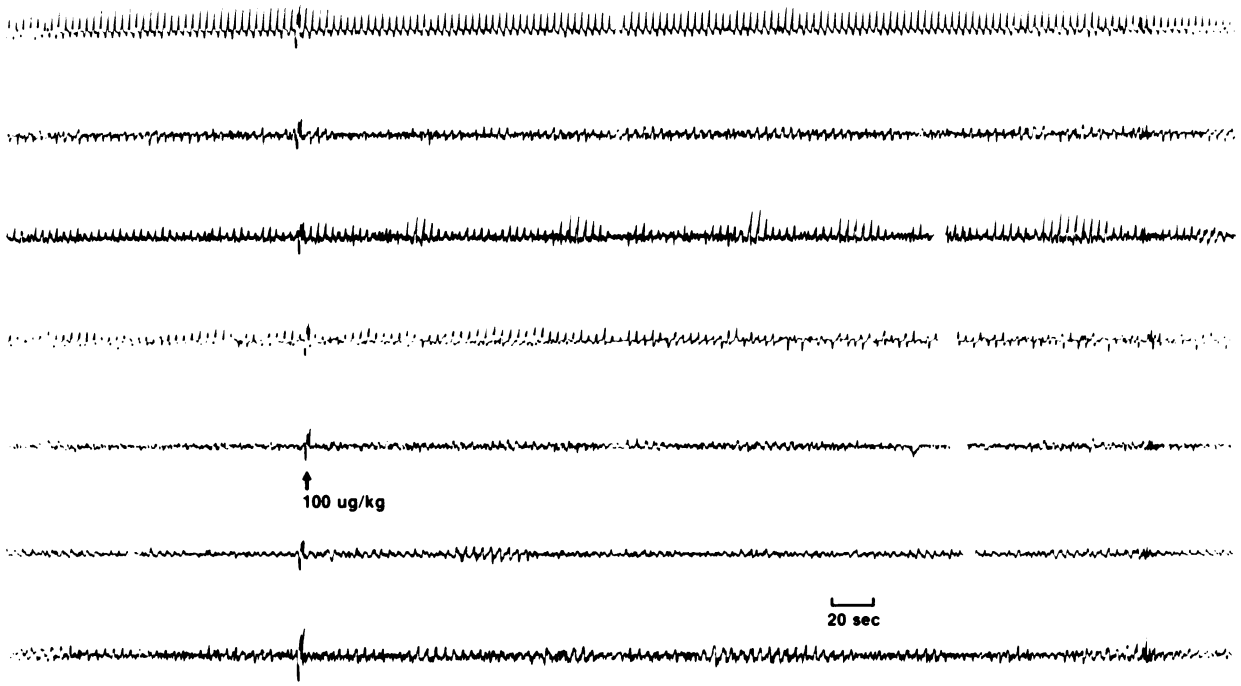

Fig. 6. Tolerance of the small intestine to bolus injection of morphine sulfate, 100 μg/kg. Electrode placement is as described for figure 1. Animal was receiving daily infusion of morphine sulfate, 10 mg/kg. See figure 3 for quantitative analysis of data.

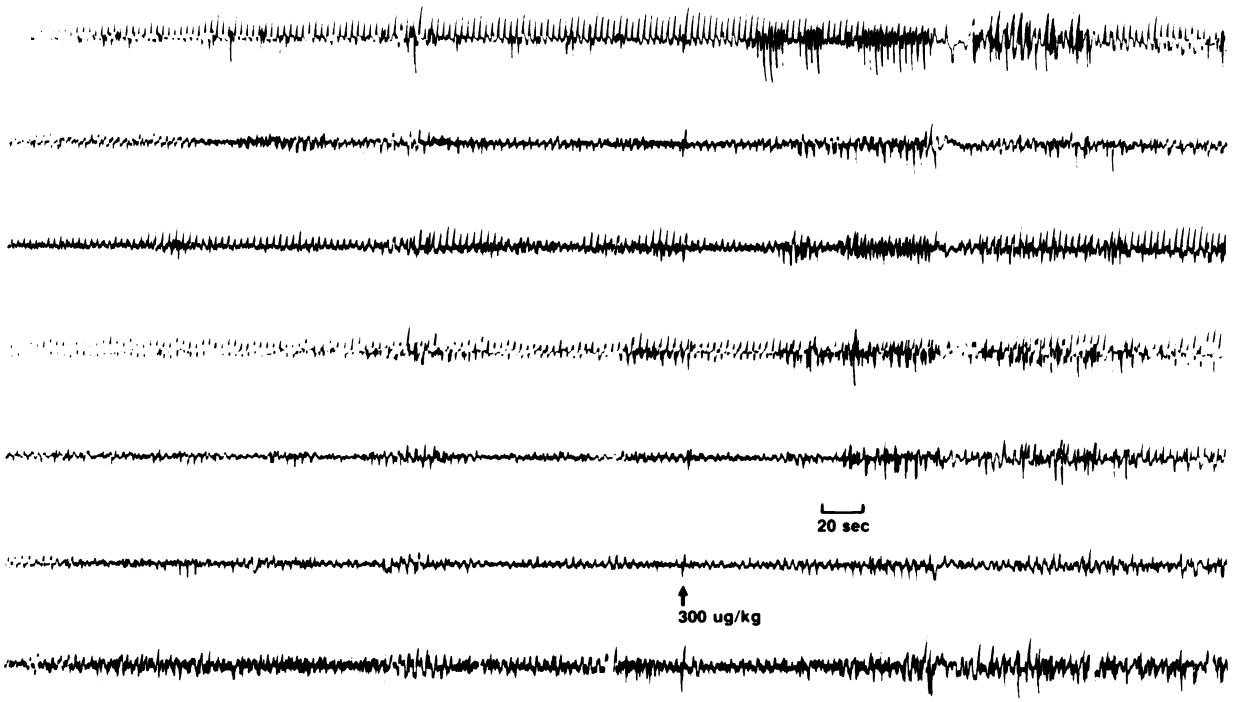

Fig. 8. Myoelectric response of the small intestine to a bolus i.v. injection of morphine sulfate, 300 μg/kg, during the second day of withdrawal from morphine infusion. Electrode placement is as described in figure 1. Note stimulatory response (increase in occurrence of spike potentials) to morphine.

pattern was also utilized to determine the amount of disruption caused by the continuous infusion of morphine, to determine the development of tolerance and to determine the response to withdrawal of the daily infusion.

In this study, bolus administrations of morphine sulfate in naive animals caused a dose-dependent increase in the number of slow waves with spike potentials. These data agree with results obtained in several other studies which demonstrated a stimulation of contractions of the small intestine by morphine (Bass and Wiley, 1965; Miller and Plant, 1926). Small doses of morphine for bolus i.v. injection were deliberately chosen to limit the duration of the response and to avoid inadvertant development of tolerance.

Tolerance to the effects of morphine was demonstrated in two ways. First, the normal patterns of interdigestive myoelectric activity returned toward normal when a particular dose of morphine administered by continuous infusion was maintained for several days. For three of the four animals, however, the return to normal was not complete at higher dosages of morphine. The second way in which the development of tolerance was demonstrated was by loss of the effect of acute bolus administration of morphine. Instead of observing a dose-dependent increase in spike potential activity in tolerant animals, a decrease in activity was actually seen. Conversion with tolerance from stimulatory to inhibitory responses to bolus injections of morphine suggests the presence of more than one type of opioid receptor activated by morphine, as has been proposed (Martin *et al.*, 1976; Kosterlitz and Leslie, 1978). Selective tolerance at the receptor which mediates stimulatory responses could thereby uncover an opioid receptor which mediates intestinal inhibition. Development of tolerance to bolus administration of morphine was more prominent during infusion of the daily higher doses. With the daily lower doses, variability among animals was seen.

The observations made during the week after abrupt withdrawal of the daily dose of morphine can be explained by development of physical dependence. The symptoms of anorexia, diarrhea and weakness are seen during the withdrawal of most animals from chronic administration of the narcotics. In the dog, these signs and symptoms, although present, were not as marked as we had expected. The disruption in the pattern of myoelectric activity during withdrawal also points to a degree of physical dependence of the small intestine. In fact, motility of the small intestine appears to be very sensitive since normal motility returned only a week or more after behavioral withdrawal symptoms had abated. The possibility that the motility patterns became physically dependent on the narcotic was further suggested by the fact that acute administration of morphine during the withdrawal period could bring about a temporary return of a normal motility pattern. In most cases, the return was only partial, so that some degree of caution must be exercised in this interpretation.

Responsiveness to acute administration of morphine reappeared early during withdrawal from chronic administration. This early return could be explained in several ways. First, we examined the return of responsiveness to only the largest bolus dose of morphine. Perhaps if we had examined the return of responsiveness to lower dosages, a longer period of withdrawal would have been required. Second, perhaps the tolerance to the intestinal stimulatory effects of morphine is not as prolonged as for the other effects of the narcotics. Finally, the tolerance seen to the acute stimulatory effects of morphine could be "acute tolerance" (Kosterlitz and Waterfield, 1975). Acute tolerance differs from long-term tolerance in that it develops rapidly, requires relatively large doses of the narcotic and is easily reversed upon washing out of the drug. Although possible, development of acute tolerance does not seem likely in our experiments. The daily doses of morphine to produce tolerance

were not excessive when compared to those used by Miller and Plant (1926). Secondly, return of responsiveness did take 2 to 3 days during which time little morphine should have been present in the blood. Moreover, Burks *et al.* (1974) have demonstrated that intestinal segments taken from dogs which had been previously treated with daily doses of morphine showed signs of tolerance. In these isolated, vascularly perfused segments, no morphine was present in the perfusing solution.

Tolerance to the effects of morphine on the parameters which we monitored was rather complete. This does not mean, however, that complete tolerance develops to all of the actions of morphine on gastrointestinal motility. In fact, clinical studies indicate that patients who receive morphine chronically are bothered by constipation (Jaffe, 1975). This apparent discrepancy with our data can be explained at least two ways. First, propulsion of intraluminal contents could still have been impeded even though the patterns of myoelectric activity had returned to normal. Although data are not available in the dog, Weisbrodt *et al.* (1977) found that tolerance did develop to the antipropulsive actions of morphine in the rat. Thus, if the dog intestine responds similarly, this possibility is not likely. Second, morphine could have been acting at other sites to produce constipation. For example, it is known that morphine also delays gastric emptying and retards movement of material through the colon. It may be that tolerance did not develop to these actions of morphine. Lack of development of tolerance to the actions of morphine on organs other than the small intestine also may explain why three of our dogs failed to demonstrate a complete return to normal interdigestive patterns of small intestinal myoelectric activity during continuous morphine administration. If gastric emptying continued to be delayed by morphine, then food might have been present 14 to 16 hr after the last meal. This in turn could have presented the recording of normal interdigestive patterns, thus impairing the demonstration of a complete development of tolerance.

In conclusion, these experiments demonstrated that: 1) spike potential activity (hence, contractions) of the small intestine of the dog is increased in a dose-dependent manner by morphine; 2) tolerance develops to this stimulatory effect in that chronic administration of morphine blocks the acute response to morphine; 3) the normal motility patterns of the fasted dog are temporarily disrupted by chronic administration of morphine but that tolerance also develops to this disruptive effect; and 4) abrupt withdrawal of the chronic administration of morphine is followed by a disruption of the normal patterns of motility for a week or more and a concurrent return of responsiveness to acute administration of morphine. Therefore, these studies demonstrate a development of tolerance and physical dependence of the small intestine of the unanesthetized dog to morphine.

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