Effect of Analgesic Drugs on the Electromyographic Activity of the Gastrointestinal Tract and Sphincter of Oddi and on Biliary Pressure

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Continuous biliary pressure and electromyographic activity of the sphincter of Oddi and gastrointestinal tract were recorded in conscious opossums following administration of analgesic drugs. Morphine, meperidine, and pentazocin increased significantly the duration of the migrating motor complex (MMC) cycle. Periods of 1–2 minutes of intense burst of spike potentials were seen in the sphincter of Oddi and duodenum following administration of morphine (8 experiments), meperidine (6 experiments), and pentazocin (3 experiments). The biliary pressure in the control studies was similar to that following administration of all analgesics in the animals with gallbladder and following instillation of tramadol, matamizol, and acetylsalicylic acid in animals with no gallbladder. However, the biliary pressure was significantly higher following administration of morphine, meperidine, and pentazocin in the animals with no gallbladder. It is concluded from this study that morphine, meperidine, and pentazocin may cause important disturbances in the motility of the sphincter of Oddi and gastrointestinal tract. These myoelectric disturbances may cause an increase in the biliary pressure in animals that have been subjected to cholecystectomy, but not in animals with intact gallbladder. The gallbladder may accommodate the bile produced by the liver during periods of sphincter of Oddi dysfunction and thus impede an increase in the biliary pressure.

THE EFFECT of analgesics on the motility of the sphincter of Oddi and gastrointestinal tract is still poorly understood. It is well known that narcotics cause disturbance of the motility of the gastrointestinal tract and spasm of the sphincter of Oddi with secondary increase in the biliary pressure.[1-5] However, the effect of narcotics on the sphincter of Oddi has been evaluated only by indirect methods, *i.e.,* manometric, flowmetric, cineradiographic, and radionuclide techniques.[5-11]

Recently, electromyography has been employed to study the dynamics of the sphincter of Oddi.[12-14] This technique provides a more direct evaluation of the sphincter of Oddi and permits quantitation of electromyographic activity changes after various stimuli. It has been demonstrated that, although the motility of the sphincter of Oddi is different from that of the duodenum, there is a correlation between the frequency of bursts of spike potentials in the two places.[13-14] Therefore, it is important to assess the effect of drugs on the motility of the sphincter of Oddi and duodenum simultaneously. The effect of narcotics on the electromyographic activity of the sphincter of Oddi as well as a correlation between the motility of the sphincter and gastrointestinal tract following administration of these drugs has not been evaluated. The present investigation was performed to study the effect of most commonly used analgesic drugs on the electromyographic activity of the gastrointestinal tract and sphincter of Oddi and on biliary pressure.

Methods

Seven opossums of either sex weighing 2.5 to 3.2 kg were anesthetized with intraperitoneal administration of 25 mg of sodium pentobarbital per kg. Upper midline laparotomy was performed.

The opossum was selected for this study because its sphincter of Oddi is mainly extraduodenal and measures 2–3 cm in length, and, therefore, dissection of the pancreas and duodenum is not necessary to implant electrodes. Its main pancreatic duct, as in the human, joins the common bile duct at the proximal portion of the sphincter of Oddi to form a common channel. In addition, this animal lies quietly for many hours without the need of restraints, and

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it exhibits a myoelectric activity of the gastrointestinal tract similar to man.

A PE-50 polyethylene tube was placed in the common bile duct through a small bile duct that connects the right lateral lobule of the liver with the common duct. A total of seven pairs of bipolar extracellular electrodes were implanted, two pairs in the sphincter of Oddi and one pair each in the duodenum, proximal jejunum, midjejunum, terminal jejunum, and terminal ileum. In the sphincter of Oddi, the electrode pairs were placed 1 and 2 cm proximal to the sphincter of Oddi-duodenal junction. The electrodes consisted of silver-plated copper wire insulated with Teflon®.

A Silastic® catheter was placed into the jugular vein for administration of drugs. The catheter and the wires were passed subcutaneously to the interscapular region and stitched to the skin. The wires were previously soldered to a female socket.

Experiments were started 7–10 days after the operation and were performed on conscious, nonmedicated animals. The opossums were fasted for 12 hours before each study. Electromyographic activity and biliary pressure were recorded on an eight-channel Gould Brush instrument (Gould Inc., Recording Systems Division, Cleveland, OH) using a paper speed of 1 mm/sec, low frequency cut-off filter of 0.5–1.0 Hz, high frequency cut-off filter of 10–30 Hz, and an overall sensitivity of 25 to 50 mV. For each recording session, a male socket connected to the recording instrument was plugged into the opossum's socket.

The biliary catheter was attached to the recording instrument through a Gould pressure transducer. The catheter was perfused with 0.9 sodium chloride solution at a constant rate of 0.05 ml/min, employing a glass capillary infusion system (C.F.S. Intraflo II, Sorenson Research Co. Inc., Salt Lake City, UT).

To eliminate the pressure secondary to the resistance of water flow into the tube, another catheter equal to that placed into the opossum's biliary duct was perfused with sodium chloride solution at a flow rate of 0.05 ml/min. The tip of the external catheter was placed at the same height as the tip of the biliary catheter while the opossum was lying on its abdomen. The pressure recorded from the external catheter was considered to be zero level.

The sensitivity of the pressure recording system was tested by elevating the tip of the external catheter 10 cm. This caused an increase in pressure of 7.5 mmHg. The time constant at flow rate of 0.05 ml/min was 1.61 seconds. The time constant was defined as the time in seconds for the pressure to rise to two-thirds of 10 mmHg.

After one to two spontaneously occurring migrating motor complexes (MMCs) had been recorded as control, a bolus intravenous administration of an analgesic drug was performed 15 minutes after the beginning of phase I of the MMC in the duodenum. The following substances and doses were studied: morphine hydrochloride, 0.2 mg/kg (E. Merck, Darmstadt, FRG); meperidine, 1.0 mg/kg (Hoechst AG, Frankfurt at Main, FRG); pentazocin, 0.5 mg/kg (Winthrop GmbH, Neu-Isenburg, FRG); tramadol hydrochloride, 2.0 mg/kg (Grünenthal GmbH, Stolberg, FRG); sodium metamizol, 20 mg/kg (Hoechst AG, Frankfurt am Main, FRG) and acetylsalicylic acid, 10 mg/kg (Bayer AG, Leverkusen, FRG). A total of 14 observations was obtained for each drug. Each substance was administered two times in each animal with an interval of at least 3 days between the infusions. Morphine at 0.2 mg/kg was also administered 10 minutes after the beginning of phase II of the MMC in the duodenum in seven additional experiments. Following administration of each substance, at least two additional MMCs were recorded.

Later, five of the seven opossums were subjected to cholecystectomy to evaluate the effect of analgesics on the biliary pressure of animals with no gallbladder. The recordings and the administration of the drugs were performed as previously described.

The MMC is a characteristic pattern of motility of the gut observed during the fasting state in man, opossum, dog, and other animals, which migrates the gastrointestinal tract cyclically from the stomach to the terminal ileum. For analysis of the myoelectric recordings, the MMC was divided into four sequential phases, as suggested by Code and Marlett.[15] Phase I is the quiescent phase in which occasional or no spike potentials are observed. Phase II consists of irregular spike potentials that increase in frequency and intensity throughout the phase. Phase III is characterized by regular spike potentials of high amplitude that accompany 100% of the slow waves. During phase IV, the frequency and amplitude of action potentials rapidly decrease to start a new migrating motor complex. While slow waves are always present and are not associated with muscle contraction, spike potentials are not usually continuous, are followed by muscle contraction, and are superimposed on slow waves.

Honda et al. and Coelho et al. have shown that there is a temporal correlation between the MMC phases in the duodenum and sphincter of Oddi.[13,14] All phases in the sphincter of Oddi start almost simultaneously with the MMC phases in the proximal duodenum. Therefore, the myoelectric activity of the sphincter of Oddi was also divided into four phases. The myoelectrical tracings were divided into 2-minute intervals, and the average frequency of slow waves with superimposed spike potentials during the entire duration of each phase of the MMC in the sphincter of Oddi and duodenum was determined. The duration of each MMC phase in the duodenum was also calculated. The duration of the entire MMC was determined by measuring the time interval between two consecutive phases III in the duodenum. The effect of the

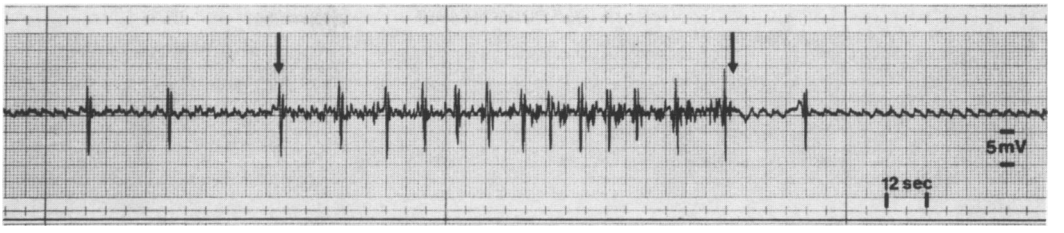


FIG. 1. Electromyographic recording of the sphincter of Oddi of an opossum 20 minutes after administration of morphine at 0.2 mg/kg, showing a 2-minute intense spike activity (between arrows).

drugs was analyzed statistically by means of the Student's two-tailed, paired t-test, and the difference among the drugs was determined by analysis of variance. In the text, the values are expressed as mean ± standard deviation.

Results

Myoelectric Activity

Administration of all analgesics did not disrupt the MMC cycle. All four phases of the MMC could be easily identified in the sphincter of Oddi and gastrointestinal tract, and phase III migrated from the duodenum to the terminal ileum. However, periods of 1–2 minutes of intense spike activity were observed simultaneously in the sphincter of Oddi (9.7 ± 1.7 bursts of spikes/min) and duodenum (13.4 ± 2.3 bursts of spikes/min) during phase II of the MMC following administration of morphine in eight experiments (57.1%), meperidine in six (42.9%), and pentazocin in three (21.4%) (Fig. 1). These periods of intense spike activity did not migrate distally to the jejunum. Tramadol, metamizol and acetylsalicylic acid did not cause these periods of intense spike activity.

The frequency of bursts of spike potentials of each MMC phase in the duodenum and sphincter of Oddi and the duration of the MMC cycle in the duodenum, both before and after administration of the analgesics, are shown in Tables 1 and 2. Morphine, meperidine, and pentazocin caused a significant increase in the frequency of bursts of spikes in the duodenum during phase II of the MMC ($p < 0.01$). Morphine caused a higher increase than meperidine and pentazocin ($p < 0.05$), but the increase in the frequency of bursts of spikes was similar for meperidine and pentazocin. Tramadol, metamizol, and acetylsalicylic acid did not change the frequency of bursts of spikes in the duodenum and the duration of the MMC cycle. Although there was a temporary increase in the spike activity in the sphincter of Oddi during the 1–2 minute periods of intense spike activity, there was no change in the frequency of bursts of spike potentials in the sphincter of Oddi during the entire duration of each MMC phase following administration of all analgesics.

Morphine, meperidine, and pentazocin caused an increase in the duration of the MMC cycle ($p < 0.01$) (Table 1). The prolongation of the MMC cycle was due to an

TABLE 1. *Myoelectric Activity of the Duodenum before and after Administration of Analgesics*

Analgesic	Frequency of Bursts of Spikes (bursts of spikes/min)				Cycle Duration† (min)
	Phase I‡	Phase II	Phase III	Phase IV	
Morphine					
Before	0	3.9 ± 1.4	17.1 ± 0.7	4.5 ± 1.0	86.3 ± 16.6
After	0	6.1 ± 1.0*	17.1 ± 0.8	4.0 ± 1.5	167.1 ± 18.1*
Meperidine					
Before	0	3.3 ± 0.7	17.2 ± 0.6	4.7 ± 1.3	88.3 ± 8.5
After	0	4.5 ± 0.9*	17.3 ± 0.7	4.2 ± 1.5	143.4 ± 18.5*
Pentazocin					
Before	0	3.3 ± 0.5	17.0 ± 0.8	3.9 ± 1.2	81.7 ± 13.6
After	0	4.3 ± 0.6*	16.6 ± 0.7	4.6 ± 1.2	129.1 ± 18.9*
Tramadol					
Before	0	3.3 ± 0.7	17.4 ± 0.6	4.1 ± 1.4	87.0 ± 13.9
After	0	3.8 ± 1.0	17.6 ± 0.6	4.8 ± 1.1	85.9 ± 14.3
Metamizol					
Before	0	3.5 ± 1.1	17.1 ± 0.9	4.3 ± 1.2	86.4 ± 9.7
After	0	3.6 ± 0.9	17.1 ± 0.7	4.4 ± 1.2	85.3 ± 18.1
Acetylsalicylic acid					
Before	0	3.2 ± 0.6	17.2 ± 0.8	4.2 ± 1.3	84.6 ± 7.8
After	0	3.6 ± 0.5	16.8 ± 0.9	4.7 ± 1.2	87.1 ± 9.5

* Indicates that this value is significantly greater than the corresponding value above at the 1% level, $p < 0.01$.

† Duration of the MMC.

‡ Phases of the migrating motor complex (MMC).

TABLE 2. *Myoelectric Activity of the Sphincter of Oddi before and after Administration of Analgesics*

Analgesic	Frequency of Bursts of Spike Potentials (bursts of spikes/min)			
	Phase I*	Phase II	Phase III	Phase IV
Morphine				
Before	1.2 ± 0.6	3.2 ± 0.7	4.9 ± 0.5	2.9 ± 0.5
After	1.6 ± 0.5	3.3 ± 0.7	4.6 ± 0.4	3.3 ± 0.5
Meperidine				
Before	1.6 ± 0.7	3.2 ± 0.7	5.0 ± 0.6	3.2 ± 0.4
After	1.2 ± 0.5	3.5 ± 0.8	5.3 ± 0.5	3.3 ± 0.4
Pentazocin				
Before	1.1 ± 0.7	3.7 ± 0.8	4.6 ± 0.6	3.3 ± 0.5
After	1.4 ± 0.5	3.2 ± 0.3	4.2 ± 0.3	3.0 ± 0.3
Tramadol				
Before	1.4 ± 0.9	3.8 ± 0.6	4.6 ± 0.4	3.0 ± 0.4
After	1.3 ± 0.6	3.2 ± 0.9	4.6 ± 0.4	2.8 ± 0.3
Metamizol				
Before	1.1 ± 0.5	3.1 ± 0.6	4.5 ± 0.6	2.8 ± 0.4
After	1.4 ± 0.8	3.4 ± 0.5	4.1 ± 0.6	3.2 ± 0.6
Acetylsalicylic acid				
Before	1.0 ± 0.5	3.3 ± 0.4	4.4 ± 0.4	2.9 ± 0.4
After	1.4 ± 0.8	3.6 ± 0.4	4.7 ± 0.4	3.2 ± 0.4

* Phases of the migrating motor complex (MMC).

increase in duration of both phases I and II. The increase in the duration of the MMC cycle was longer for morphine than for meperidine and pentazocin ($p < 0.01$), and it was similar for meperidine and pentazocin. Administration of morphine during phase II of the MMC also prolonged the duration of the MMC cycle to 152.4 ± 14.7 minutes (control 88.7 ± 11.9 minutes; $p < 0.01$).

Biliary Pressure

In most experiments, pressure oscillations of 1–3 mmHg were observed simultaneously with respiratory movements and with each burst of spike potentials in the sphincter of Oddi (Fig. 2). Although the basal pressure remained constant during the four phases of the MMC, there was a variation of the number of pressure oscillations related with the frequency of bursts of spike potentials in the sphincter of Oddi among the four phases of the MMC. There were no changes in the mean biliary pressure during the periods of intense spike activity in the sphincter of Oddi and duodenum.

The mean biliary pressure before and following administration of analgesic drugs in the animals with and without gallbladder is shown in Table 3. There was no significant change in the biliary pressure following administration of all analgesics in the animals with gallbladder. However, the biliary pressure was significantly higher following administration of morphine, meperidine, and pentazocin in the animals that were subjected to cholecystectomy ($p < 0.01$) (Fig. 3). There was no difference in pressure elevation between morphine, meperidine, and pentazocin. The biliary pressure remained constant following administration of tramadol, metamizol, and acetylsalicylic acid in the animals with no gallbladder.

Discussion

Multiple-balloon kymographic recording studies have shown that morphine and related drugs cause an increase of the nonpropulsive type of rhythmic segmental contractions and a decrease of propulsive contractions of the gut.[16] Our electromyographic study confirms these findings. We observed an increase in the myoelectric activity of phase II, which is associated with nonpropulsive segmental contractions of the gut. Both the frequency of bursts of spike potentials and the duration of phase II were increased. In addition, periods of intense spike activity were occasionally recorded during this phase. The frequency of phase III, which is associated with peristaltic contractions, was decreased. These changes were more

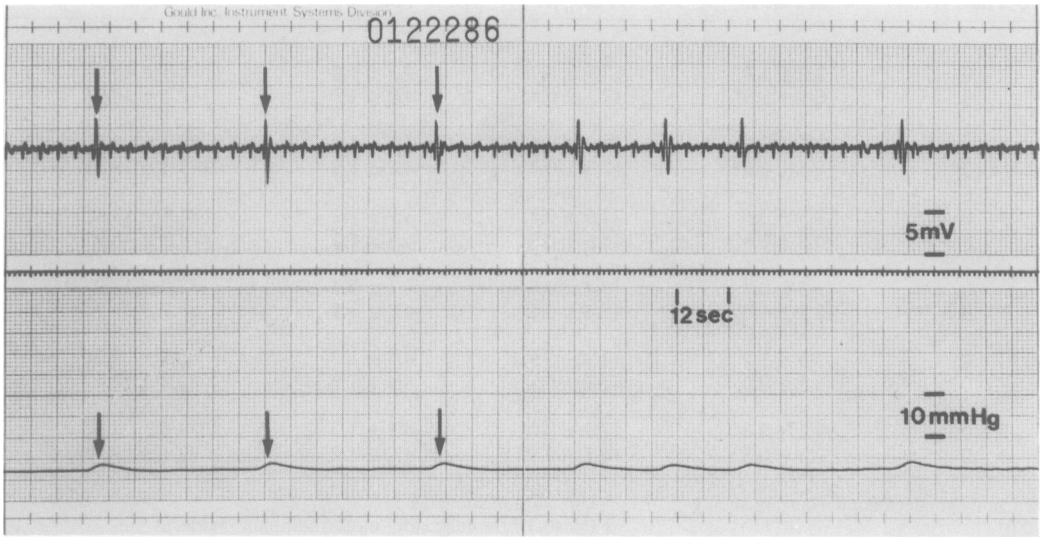


FIG. 2. Simultaneous recording of the electromyographic activity of the sphincter of Oddi and biliary pressure of an opossum. Temporary elevation of the biliary pressure with each sphincter of Oddi spike potential is illustrated (arrows).

intense with morphine than with meperidine and pentazocin. The reduction of phase III frequency observed following administration of morphine, meperidine, and pentazocin may be a contributory factor in the ethiopathogenesis of intestinal constipation caused by these drugs. In fact, decrease of propulsive contractions of the stomach and small intestine is thought to be responsible for most of the constipating effect of morphine.[17] Stewart et al. reported that morphine decreased the transit of radioactive material in the small intestine of rats.[18]

Sarna et al. have observed appearance of phase III-like activity in the gastrointestinal tract following administration of morphine during phase II of the MMC, but not during phase I in dogs.[19] We have observed no appearance of phase III-like activity following administration of morphine either during phase I or II of the MMC. However, we have recorded periods of intense spike activity that were of shorter duration than phase III. This difference may be related to the different species employed.[19]

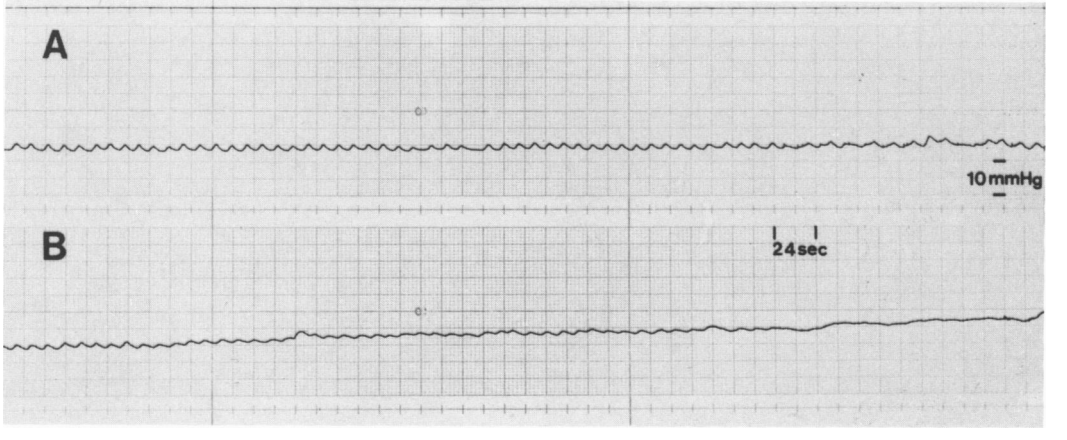
Several studies have been conducted to evaluate the effect of analgesics on biliary pressure.[5-11] These studies have suggested that therapeutic doses of morphine, meperidine, and pantazocin may cause a marked increase in pressure in the biliary tract. Most of these studies were performed after cholecystectomy or following catheterization and obstruction of the cystic duct.[7-10] In addition, infusion of large volumes of fluids into the small bile ducts employed in some of these studies may have caused artificial elevation of the biliary pressure. Only closure of the sphincter of Oddi, without concomitant increase in bile production or infusion of extraneous fluids, does not increase the pressure in the biliary tree. It is well established that morphine does not increase bile secretion.[17] Therefore, we decided to evaluate the effect of analgesics on the biliary pressure of animals with and without gallbladder, employing a very sensitive method of pressure recording that requires infusion of only minimal amounts of fluid.

TABLE 3. *Biliary Pressure before and after Administration of Analgesics in Animals with and without Gallbladder*

	Biliary Pressure (mmHg)	
Analgesic	With Gallbladder	Without Gallbladder
Morphine		
Before	13.3 ± 2.1	13.2 ± 2.3
After	13.8 ± 2.2	17.2 ± 1.5*
Meperidine		
Before	12.4 ± 2.2	12.9 ± 2.3
After	13.6 ± 2.2	16.2 ± 1.9*
Pentazocin		
Before	13.1 ± 2.8	13.1 ± 2.9
After	12.3 ± 2.3	17.0 ± 2.1*
Tramadol		
Before	13.3 ± 2.4	12.4 ± 2.6
After	12.6 ± 2.4	13.3 ± 2.5
Metamizol		
Before	12.0 ± 2.3	13.3 ± 2.3
After	12.9 ± 2.6	11.9 ± 2.3
Acetylsalicylic acid		
Before	13.2 ± 2.3	12.7 ± 2.3
After	13.1 ± 2.0	13.1 ± 2.5

* Indicates that this value is significantly greater than the corresponding value above at the 1% level, $p < 0.01$.

We have observed no significant biliary pressure change following administration of analgesics when saline solution was infused at 0.05 ml/min in animals with intact gallbladder. The gallbladder is probably able to accommodate the bile produced by the liver during periods in which the sphincter of Oddi is closed and thus impede pressure increase in the biliary tract. However, the biliary pressure was significantly higher following administration of morphine, meperidine, and pentazocin in opossums that had been subjected to cholecystectomy. These findings suggest that administration of morphine, meperidine, and pentazocin to subjects with no gallbladder or no functioning gallbladder, such as in instances of acute or chronic cholecystitis and acute pancreatitis, may cause an increase in biliary pressure.



FIGS. 3A and B. Biliary pressure recordings of an opossum 10 minutes after administration of morphine at 0.2 mg/kg in two different experiments, before (recording *A*) and after (recording *B*) cholecystectomy. The mean biliary pressure remained constant in the experiment in which the gallbladder was intact, but the pressure increased gradually in the experiment following cholecystectomy.

It is concluded from this study that morphine, meperidine, and pentazocin may cause important disturbances of the motility of the sphincter of Oddi and gastrointestinal tract. Following administration of morphine, meperidine, and pentazocin, the biliary pressure increases in animals that have been subjected to cholecystectomy, but not in animals with intact gallbladder. It is possible that a functioning gallbladder may impede an increase in biliary pressure during periods of dysfunction of the sphincter of Oddi by accommodating the bile produced by the liver.

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