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Response of the Duodenum to Morphine.

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The earliest investigators concerned with the response of the intestine to morphine were predominantly of the opinion that this drug produced a relaxation of the muscle of the intestine. More recent investigations have changed this trend of belief by showing that morphine produced an increased pressure within the intestine and increased movements of various segments of the intestine as measured by one or more forms of a balloon method.

It has been pointed out by Krueger[1] and emphasized by Quigley, Highstone and Ivy[2] that erroneous conclusions may be drawn concerning the sum total effect of a drug on the intestinal muscle by using a method which involves inserting a balloon in the lumen of the intestine and recording activity in terms of changes in volume of the balloon. Thus in an attempt to improve the experimental procedure, bolus methods[2] and multiple balloon methods[3] have been devised and used.

The present study is concerned with the muscular response of the duodenum to morphine as measured by a method which gives simultaneous graphic recordings of both the circular and longitudinal muscle activity in a given segment of the duodenum in the intact anesthetized dog.

Methods. The circular contractions of the duodenum were recorded by the method of Krop and Loomis.[4] The balloon inserted in the duodenum was constructed so that its length was not more than 2 cm. Such a balloon would come in contact with about 1 cm length of intestinal mucosa when fully expanded. Observations with this apparatus *in situ* showed that longitudinal movements of the intestine did not record through the manometer. Circular contractions, on the other hand, compressed the balloon and were recorded as changes in the level of the fluid in the manometer. The longitudinal contractions of the duodenum were recorded by the internal organ apparatus described by Jackson.[5] Observations with this apparatus *in situ* showed that the records obtained were predominantly those of longitudinal muscle activity.

Mature mongrel dogs in good health were used throughout the experiments. The dogs were anesthetized with 35 mg per kilo sodium pentobarbital given intravenously. A midline abdominal incision from the xiphoid process of the sternum to about 2 cm above the pubis was made. The intestine was retracted to one side, an incision was made in the pyloric end of the stomach on its anterior surface and the balloon was inserted through the incision into the stomach, directed through the pyloric sphincter and into the duodenum so that it lay about 5 cm distal to the sphincter. Jackson's internal organ apparatus was then sutured to the mucosal surface of the segment of duodenum which contained the rubber balloon within its lumen. The intestine was then replaced in its approximate normal position and the cut edges of the abdominal incision were approximated and sutured.

All injections were given intravenously through one of the superficial branches of the femoral vein. The drugs were dissolved in physiological saline. The volume of each injection was always less than 5 cc and the solutions were maintained at a temperature of 38°C. Each injection of a drug was fol-

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2 Quigley, J. P., Highstone, W. H., and Ivy, A. C., *J. Pharm. and Exp. Therap.*, 1934, **51**, 308.

3 Krueger, H., *J. Pharm. and Exp. Therap.*, 1934, **51**, 440.

4 Krop, S., and Loomis, T. A., *Science*, 1945, **102**, 155.

5 Jackson, D. E., Experimental Pharmacology and Therapeutics, C. V. Mosby Co., 1939, page 89.

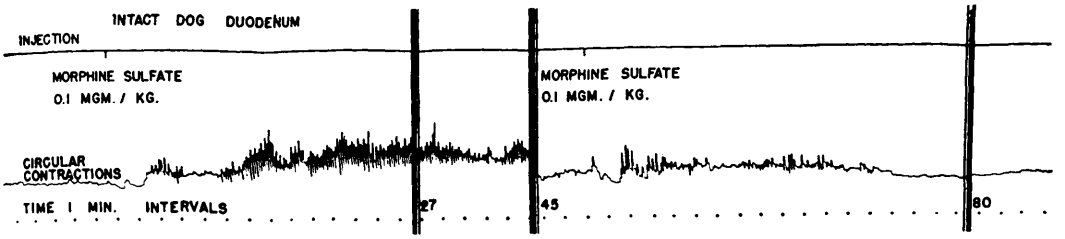

FIG. 1.

The effect of repeated equal doses of morphine sulfate on the circular contractions of the duodenum of the anesthetized dog. The drug was injected intravenously at the points indicated on the injection line.

lowed with about 2 cc of physiological saline. Controls using the saline alone showed that the spontaneous intestinal contractions were not altered by this volume of saline.

Results. Early in the progress of the experiments it was found that repeated equal doses of morphine failed to produce equivalent responses in the intestine. Although the muscular responses would be qualitatively similar the intensity and duration of these responses were much diminished with each additional injection. Fig. 1 demonstrates this tachyphylactic type of phenomenon which occurs in the response of the circular muscle when an intravenous dose of morphine of 0.1 mg per kg is given and then repeated after the activity had returned to normal. After this phenomenon had been repeatedly demonstrated all subsequent experiments were conducted so that the animal received only one injection of morphine.

Two principal types of response to the drugs used were obtained. One of the types of response was an increased level of tonus with either an increase or no change in the frequency and amplitude of the normal spontaneous contractions. This type of response is referred to in this paper as "increased activity." The second type of muscular response was a decreased level of tonus and either a decrease or no change in the frequency and amplitude of the normal spontaneous contractions. This type of response is referred to as "decreased activity."

Table I summarizes the gross qualitative responses obtained on a series of experiments conducted on 28 dogs. In all experiments acetylcholine was used as a control drug. The table shows that 0.05 mg per kg of this compound, given intravenously, produced an increased activity of the circular muscle in all but one of 25 experiments. In simultaneous records this type of response occurred in the longitudinal muscle in 18 of the 25 experiments. In one of the experiments both the circular and longitudinal muscle records showed decreased activity. In 5 of the experiments the longitudinal muscle showed decreased activity while the circular muscle responded by an increased activity.

A dosage range of morphine of from 0.01 mg per kg to 1.0 mg per kg was used. The smallest dose of morphine which was consistently effective in producing an alteration in the intestinal muscular activity was 0.05 mg per kg. Fig. 2 shows the type of record obtained. A similarly equivalent qualitative response was obtained in five such experiments. Table I summarizes the response obtained with 0.1 and 0.5 mg per kg of morphine in the series of seventeen experiments on seventeen different dogs. The table shows that the circular muscle responded with an increased activity in 16 of the 17 experiments. In 13 of the experiments the longitudinal muscle showed either no significant response or a decreased activity. With a dose of morphine of 0.5 mg per kg the response of the circular muscle was that of increased activity in all of the 17 experiments. In contrast to this, the longitudinal musculature showed increased activity in only two of the 17 experiments, whereas in 10 of the experiments the result was that of decreased activity and in 5 experiments there was no observable alteration in muscle activity.

One mg per kg of morphine produced an increased activity in the circular muscle in 6 experiments, and in 5 of the 6 experiments a decreased activity was the response recorded

TABLE I.

Summary of Frequency and Type of Response of Duodenal Muscle to Acetylcholine, Morphine, Barium, and Atropine. Maximum and minimum duration of response is presented rather than mean and standard error, since accurate determination of duration of time before the record returned to normal was indefinite within limits of approximately 10 minutes.

	0.05 mg/kg Acetylcholine Longitudinal muscle	0.05 mg/kg Acetylcholine Circular muscle	0.1 mg/kg Morphine SO_4 Long. m.	0.1 mg/kg Morphine SO_4 Circ. m.	0.5 mg/kg Morphine SO_4 Long. m.	0.5 mg/kg Morphine SO_4 Circ. m.	1.0 mg/kg Morphine SO_4 Long. m.	1.0 mg/kg Morphine SO_4 Circ. m.	1.0 mg/kg Barium Chloride Long. m.	1.0 mg/kg Barium Chloride Circ. m.	2.0 mg/kg Atropine SO_4 Long. m.	2.0 mg/kg Atropine SO_4 Circ. m.
1. No. of experiments	25	25	17	17	17	17	6	6	5	5	3	3
Response: (number of exper. showing:)												
2. Increased activity	18	24	4	16	2	17	0	6	5	5	0	0
3. Decreased activity	5	1	6	1	10	0	5	0	0	0	3	3
4. No significant response	2	0	7	0	5	0	1	0	0	0	0	0
5. Range of duration of response (min)	2-16	2-9	40-110	40-100	30-160	40-160	60-200	60-280	—	—	—	—

FIG. 2.

The "increased activity" of the circular muscle and simultaneous "decreased activity" of the longitudinal muscle produced by 0.05 mg per kg of morphine sulfate following a control acetylcholine injection. Time is recorded as dots at one minute intervals.

by the longitudinal muscle apparatus. Fig. 3 is a typical record of this result.

These results show that the type of response was essentially independent of the dose of morphine used over the range which was studied. The duration of the response was similar in both the circular and longitudinal groups (Table I) for a given dose of morphine. The duration of response generally was greater with higher doses than with the lower doses over the range studied.

Barium chloride in a dose of 1.0 mg per kg consistently produced an increased activity in both the circular and longitudinal muscle records. When morphine is given at the time when a maximum response to barium is present generally little or no alteration in the activity of the duodenal muscle occurs.

Atropine repeatedly produced a decreased activity in both the circular and longitudinal muscle of the duodenum. A dose of morphine of 0.1 mg per kg produced an increased activity in the circular muscle in the atropinized animal at a time when a control acetylcholine injection produced no response. The response of the longitudinal musculature in an atropinized animal was indefinite since atropine frequently produced such a profound decreased tonus and often completely abolished all activity of the muscle. However, when slight activity remained in the longitudinal muscle after administration of atropine, it was abol-

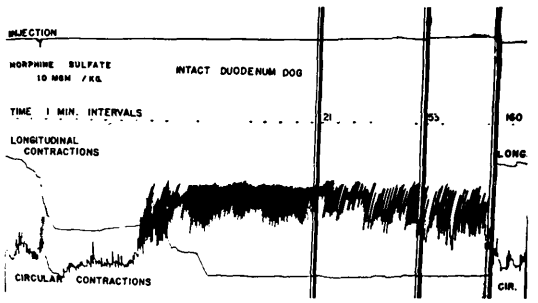

FIG. 3.
The "increased activity" of the circular muscle and the simultaneous "decreased activity" of the longitudinal muscle of the intact segment of the dog duodenum as it is produced by a dose of 1.0 mg/kg of morphine sulfate.

ished by the subsequent administration of morphine.

Atropine only partially decreased the increased activity in the circular muscle produced by morphine. Atropine also abolished any activity present in the longitudinal muscle group when given following the injection of morphine.

In 3 experiments in the physostigminized animal, morphine produced a response of a type similar to that most frequently produced in the normal animal. This was a decreased activity of the longitudinal muscle and an increased activity of the circular muscle (Fig. 7). However, the mean duration of the response to morphine (0.1 mg per kg) in the eserinized animal was 222 minutes (3 experiments) whereas the maximum duration of response obtained in the normal dog to 0.1 mg per kg of morphine was 110 minutes (17 experiments).

Discussion. The evidence in the literature at the present time indicates that morphine does not produce a consistently specific type of effect on smooth muscle throughout various parts of the gastrointestinal tract.[1-3,6-9,11-13] Furthermore, reports concerned with the effect of morphine on the atropinized or eserinized intestine are not consistent in the same or different animals.[7,10,14]

Acetylcholine and barium chloride consistently produced increased activity in both the circular and longitudinal muscle layers with the experimental arrangement described in this paper. Atropine sulfate consistently produced decreased activity of both of these muscle layers. The most consistent response produced by morphine injected intravenously was that of an immediate increased activity of the circular muscle layer and a decreased activity of the longitudinal muscle layer. This type of response was marked and prolonged and records always showed a return to normal when allowed sufficient time. Occasionally there occurred an immediate very brief (5 minutes or less) interval of little change or an increased activity of the longitudinal muscle or a decreased activity of the circular muscle following the injection of morphine.

Summary and conclusions. 1. The phenomenon of tachyphylaxis of the intestinal musculature to morphine was demonstrated.

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2. The most consistent response of the circular muscle of the duodenum to morphine was an increase in the many phases of muscular activity. This includes elevation of the tonus level with increased frequency and amplitude of the normal spontaneous tonic contractions.

3. The most frequent though not completely consistent response of the longitudinal muscle was found to be either a decrease or an abolition of the many phases of the muscle activity. This includes a depression of the tonus level with a decreased frequency and amplitude of the normal spontaneous tonic contractions.

4. The type of response of the duodenum to morphine was independent of the original state of tonus and independent of the dose over the range of 0.01 mg to 1.0 mg per kg.

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Protective Action of Dibenamine After Hemorrhage and After Muscle Trauma.*

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Wiggers and associates[1,2] have demonstrated that dogs given the sympatholytic substance Dibenamine showed a higher survival rate than controls from shock produced by hemorrhage. The inference made is that abolition of a severe vasoconstriction normally following hemorrhage protects the life of the animal.

In a series of dogs under morphine-nembutal anesthesia, 6 arterial hemorrhages of 5 cc/kg b.w. each, were performed at 10 minute intervals. Aortic pressure pulse contours were recorded during the hemorrhage period, and for an additional hour. All wounds were then closed, and the animals returned to their cages. Cardiac outputs were calculated from the pressure pulse contours,[3] and in a selected series by the dye injection method,[4] and vasomotor resistance (Rv) calculated as the mean aortic pressure less 20 mm Hg divided by the flow per second.[5] Specific gravity values of plasma and whole blood were determined at 10 minute intervals by the falling drop technic.

This experiment was done during the summer months, so that an expectedly sub-lethal hemorrhage proved fatal in 13 of 14 dogs, with an average survival of the 13 dogs of 4 hours. Ten more dogs were given 10-20 mg/kg Dibenamine,† in 50 cc saline, *i.v.*, one hour before the hemorrhage was begun. The completeness of the sympathetic block was demonstrated by the injection of epinephrine 5 minutes before the first bleeding. Nine of these animals survived. To rule out the possible effect of the salt solution itself, the last 5 of the control series received 50 cc saline one hour before the hemorrhage. All of these dogs died.

Systolic and diastolic pressure values for

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† We are indebted to Dr. W. Gump of Givaudan-Delawanna, Inc., for the Dibenamine Hydrochloride used in this study.