

EFFECT OF METOCLOPRAMIDE ON MOTOR  
FUNCTION OF THE ESOPHAGUS  
AND THE CARDIAC SPHINCTER

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The contractile activity of the cardiac sphincter and esophagus was recorded by means of a balloon, stretching from the stomach into the esophagus and fixed to a catheter, in acute experiments on cats and chronic experiments on dogs. Intravenous injection of metoclopramide into cats in a dose of 0.5-0.6 mg/kg and subcutaneous injection of the compound into dogs in a dose of 0.1-0.15 mg/kg significantly increased the pressure in the cardiac sphincter, stimulated movement of the distal part of the esophagus, and potentiated the esophago-gastric inhibitory reflex. The action of metoclopramide, which persisted in vagotomized dogs, was phasic in character and lasted for 2.5-3 h. It is concluded that metoclopramide is a promising drug for use in diseases of the distal part of the esophagus including the cardiac sphincter.

KEY WORDS: motor activity of the esophagus; cardiac sphincter; metoclopramide.

Metoclopramide has been suggested as a substance normalizing the evacuatory function of the digestive tract [12]. The effect of metoclopramide on motor activity of the gastro-intestinal tract has been the subject of many publications [5, 7, 8], but data on the location of its action are extremely contradictory. This is particularly true of the ability of metoclopramide to stimulate esophageal motor activity and the cardiac sphincter [5, 7, 9-11, 13].

The investigation described below was carried out to study the effect of metoclopramide on esophageal motor activity and on the cardiac sphincter in dogs and cats.

EXPERIMENTAL METHOD

Chronic experiments were carried out on 4 mongrel dogs weighing 10-12 kg, and a supradiaphragmatic vagotomy was performed on 2 of the animals beforehand. The motor activity of the esophagus and cardiac sphincter was recorded graphically by means of a rubber balloon, filled with 1-2 ml air, fixed to a vinyl chloride catheter, which the dog swallowed before the experiment.

Acute experiments were carried out on 20 cats weighing 3.5-4 kg, anesthetized with a mixture of chloralose, urethane, and pentobarbital. Fistulas into the fundal portion of the stomach were formed in all the cats. Of the esophagus and cardiac sphincter a rubber balloon filled with 0.5-1 ml air, passed through the mouth into the stomach before the beginning of the investigation, was used.

Both in the dogs and in the cats the balloon was gradually drawn from the stomach into the esophagus to record the intrasphincteric pressure, after which the motor activity of different parts of the esophagus was recorded. In the anesthetized cats the motor activity of the stomach was recorded by means of a balloon holding 8 ml air, which was introduced through the fistula into the fundal part.

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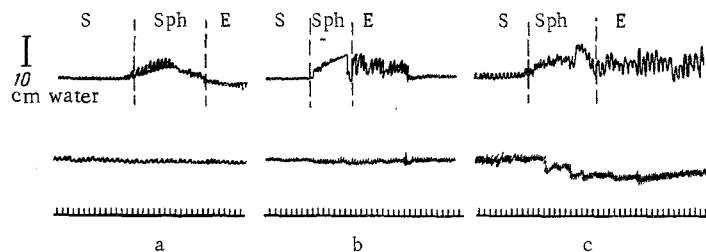


Fig. 1. Motor activity of fundal part of stomach (S), distal third of esophagus (E), and contractions of cardiac sphincter (Sph) in cats before (a) and 10 (b) and 65 min (c) after intravenous injection of 0.5 mg/kg metoclopramide. The character of responses of the distal part of the esophagus and cardiac sphincter to metoclopramide in the intact and vagotomized dogs was indistinguishable from that in cats, although the initial effect of metoclopramide was observed only 10-15 min after the injection. The duration of action of metoclopramide in dogs was 2.5-3 h. The dose of metoclopramide injected subcutaneously into the dogs had to be limited to 0.1-0.15 mg/kg, for injection of larger doses was accompanied by general excitation of the animals of such severity that the experiment could not be continued. Meanwhile in the anesthetized cats, which received doses of metoclopramide 5-6 times greater by intravenous injection, no excitation was present.

Metoclopramide was injected subcutaneously into the dogs in a dose of 0.1-0.15 mg/kg and intravenously into the cats in a dose of 0.5-0.6 mg/kg.

#### EXPERIMENTAL RESULTS AND DISCUSSION

The experiments showed that metoclopramide affects the motor activity of the distal parts of the esophagus only, including the inferior esophageal sphincter. In anesthetized cats the initial effect of metoclopramide was observed 3-5 min after its administration and was expressed as an increase in amplitude of the contractions of the distal part of the esophagus caused by stretching of that area, together with an increase in pressure in the cardiac sphincter. In 45% of experiments a very small increase in tone also was observed in the fundal part of the stomach. The effect of metoclopramide was maximal 30-35 min after injection. At this time the amplitude of contractions of the distal part of the esophagus was almost doubled compared with the spontaneous level. The contractions of this part of the esophagus became continuous in character (Fig. 1) and the pressure in the cardiac sphincter rose from 10 to 13-14 cm water, 30-40% above the spontaneous level. Meanwhile peristaltic contractions appeared in the fundal part of the stomach. The duration of the stimulant action of metoclopramide on motor activity of the distal portion of the esophagus and cardiac sphincter in cats was 40-50 min, after which some weakening of contractile activity of the esophagus and lowering of pressure in the cardiac sphincter to the spontaneous values were observed for a period of 15-20 min. Meanwhile the motor response of the fundal part of the stomach remained intact. Between 60 and 100 min after the injection the contractions of the distal part of the esophagus again began to increase in intensity and the pressure in the cardiac sphincter rose to values recorded in the sphincter in response to the initial stimulant action of metoclopramide. This second stimulant action of metoclopramide was observed for 1.5-2 h. The fact will be noted that the esophago-gastric inhibitory reflex [1] was considerably strengthened during the action of metoclopramide.

These experiments thus confirmed observations of other workers [5, 11, 13] to the effect that metoclopramide stimulates contractions of the distal portion of the esophagus only, including the cardiac sphincter, i.e., structures whose extramural and intramural innervation is similar to that of the stomach [3, 6]. The results obtained on vagotomized dogs confirmed the view that the effects of metoclopramide are independent of integrity of the vagus nerves [13] and can be transmitted to nervous structures contained in the smooth muscles of these parts of the digestive tract, the sensitivity of which to acetylcholine is considerably increased during the action of metoclopramide [8].

Unlike Guelrud [10], who found that the duration of action of metoclopramide does not exceed 40-60 min, we found that it has a prolonged stimulant effect on motor activity. This is very important if the sub-

stance is to be used clinically. The presence of an intermediate period of weakening of the stimulant effect of metoclopramide could explain the mistaken judgements of the character and duration of action of metoclopramide.

The ability of metoclopramide to increase the pressure in the cardiac sphincter and, at the same time, to stimulate motor activity of the distal third of the esophagus, while, at the same time, the esophago-gastric reflex is strengthened and the cardiac sphincter still remains capable of relaxation during swallowing, suggests that this substance is a promising agent for use in the treatment of reflux esophagitis and disturbances of the transport function of the lower third of the esophagus. Compared with peripheral cholinolytics, which can be used for these purposes [2, 4], metoclopramide evidently has much weaker side effects.

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