Endoscopic Manometry of the Sphincter of Oddi in Dogs
Pharmacological Effects of Anticholinergic and Selective
Antimuscarinic Agents

Toshihiro MIURA, Shigeru HARASAWA, Kazuhiro KIKUCHI and Takeshi MIWA

Department of Internal Medicine, School of Medicine,
Tokai University
(Received March 31, 1987)

A dog model was used for direct measurement of the sphincter of Oddi using endoscopy. The effects of anticholinergic agents and a selective antimuscarinic agent on the canine sphincter of Oddi motility were studied. Manometric tracing at the canine sphincter showed rhythmical phasic contractions which were not affected by respiration. The mean values of the basal motility were as follows: the peak pressure was 61.5 ± 2.2 (m ± SE) cmH₂O, trough pressure was 21.8 ± 1.2 cmH₂O, and the frequency was 17.4 ± 0.2 waves/min. Intravenous administration of atropine sulfate, butylscopolamine bromide and also pirenzepine significantly reduced the amplitude and frequency of canine sphincter contractions. From these results, it appeared that the cholinergic autonomic nervous system might be the one of the regulators of the canine sphincter of Oddi activity.

(Key Words: Endoscopic manometry, Sphincter of Oddi, Anticholinergic agent, Selective antimuscarinic agent)

INTRODUCTION

Since Oddi's demonstration of a muscular sphincter at the distal end of the common bile duct, it has been thought that a malfunctioning sphincter mechanism is one of the factors involved in the etiology of cholangitis, cholelithiasis, biliary colicky pain, jaundice and pancreatitis. Many studies (1–15) using both human and animal models have been reported which elucidate the physiology and pharmacological regulation of the sphincter of Oddi, as well as the role of the sphincter of Oddi in the pathogenesis of pancreatic and biliary diseases.

Previously the sphincter of Oddi was accessible only indirectly for manometric studies using surgical procedures (2, 10, 15). However, recently in humans, the direct approach to studying the sphincter of Oddi has become possible with the availability of side-viewing duodenoscopes allowing direct sphincter cannulation (1, 3, 5, 8, 12, 14).

In phase 1 of the present study, a dog model was used for direct measurement of the sphincter of Oddi by endoscopy.

Anticholinergic agents are used for the treatment of many gastrointestinal diseases, and the spasmolytic effects of these drugs on the gastrointestinal tract are well known. Pirenzepine is a selective antimuscarinic agent, and the therapeutic dose of pirenzepine is known to reduce gastric secretion without suppression of gastrointestinal motility. However, the effects of these drugs on biliary tract motility, especially the sphincter of Oddi, have not been thoroughly investigated.

In phase 2, the pharmacological effects of anticholinergic agents, such as atropine sulfate, butropium bromide and butylscopolamine bromide and the antimuscarinic agent, pirenzepine, on the canine sphincter of Oddi were studied.
MATERIALS AND METHODS

Mongrel dogs weighing between 8.0 and 14.0 kg, fasted for 24 hours and anesthetized with pentobarbital sodium (25 mg/kg) were used. The dogs were placed in the left lateral position.

The pressure was measured endoscopically by the open-tip infusion method using a pediatric duodenofiberscope (PJF, Olympus) 8.8 mm in outer diameter/(Fig. 1). The manometric catheter was 1.5mm in outer diameter, made of Teflon, and has side hole (0.5 mm in size) 3 mm from the distal tip/(Fig. 2). During the study, the manometric catheter was continuously perfused with distilled water from a hydraulic capillary infusion system (Arn-}

![Diagram of the manometric catheter.](image)

Fig. 1 Instrumental design of the endoscopic open-tip infusion manometric method.

Fig. 2 Diagram of the manometric catheter.
Endoscopic Manometry of the Sphincter of Oddi in Dogs—111

RESULTS

1. Basal pressures of the canine sphincter of Oddi.

The intraluminal duodenal pressure was 8.7 ± 0.5 (mean ± SE) cmH$_2$O.

After the catheter was inserted from the duodenum into the papilla, the pressure increased immediately, and the endoscopic manometric tracing at the canine sphincter of Oddi showed rhythmical phasic contractions which were not affected by respiration and duodenal peristalsis. (Fig. 4).

The mean values of the basal motor activities were as follows: the peak pressure was 61.8 ± 2.2 cmH$_2$O, and the trough pressure was 21.8 ± 1.2 cmH$_2$O. The frequency of the phasic contractions was 17.4 ± 0.2 waves/min.

2. Effects of anticholinergic agents.

a) Atropine sulfate

Intravenous administration of 0.1 mg/kg of atropine sulfate had a significant suppressive effect on the canine sphincter of Oddi. The phasic contractions disappeared within 15 to 40 seconds after injection, and the pressure level was 15.2 ± 1.9 cmH$_2$O (Fig. 5). This disappearance was prolonged for at least 1 min, and reductions in the amplitude and frequency continued for about 6 min.

After administration of 0.01 mg/kg of atropine, the peak pressure and frequency of the phasic contractions were also decreased. The amplitude of the peak pressure was reduced from 66.3 ± 4.5 to 48.7 ± 4.7 cmH$_2$O (Fig. 6).

b) Butropium bromide

Intravenous administration of 0.1 mg/kg of butropium bromide significantly reduced the amplitude and frequency, as in the case of atropine sulfate (Fig. 7).

Butropium bromide at a dose of 0.01 mg/kg also reduced the amplitude and frequency, but the phasic contractions did not disappear.

c) Butylscopolamine bromide

Butylscopolamine bromide at a dose of 0.1 mg/kg had similar effects as the same dose of another anticholinergic drugs. Phasic contractions of the canine sphincter of Oddi disappeared.

Fig. 3 Chemical structures of four drugs used in this study.
Fig. 4  Representative manometric recording of the canine sphincter of Oddi with phasic activity and duodenal pressures. The upper tracing is a recording of respiration. PS means duodenal peristalsis.

Fig. 5  Effect of 0.1 mg/kg of atropine sulfate on the canine sphincter contractions. The phasic contractions disappeared immediately.

Fig. 6  Effect of 0.01 mg/kg of atropine sulfate. The amplitude and frequency were reduced.
Butylscopolamine bromide at a dose of 0.01 mg/kg, reduced the amplitude from 54.5 ± 4.5 to 30.0 ± 0.5 cmH2O.

3. Effect of pirenzepine
Intravenous administration of pirenzepine at doses of 1 and 10 mg/kg also significantly reduced the amplitude and frequency. The phasic contractions disappeared after a dose of 10 mg/kg (Fig. 8).

After administration of 1 mg/kg, the peak pressure was reduced from 62.3 ± 9.9 to 38.5 ± 2/2 cmH2O (Fig. 9).

DISCUSSION
We described a method for measuring sphincter of Oddi motility in the dog using an endoscopic procedure, and the effects of anticholinergic agents and a selective antimuscarinic agent.

Previous studies designed to evaluate the sphincter of Oddi in experimental animals were performed using surgical procedures such as laparotomy and the percutaneous method (6, 7, 9–11, 13). Manometric studies have yielded indirect recordings of the pressure gradient across the sphincter of Oddi segment rather than direct pressure recordings (9). In human, previous studies also required surgical procedures (2, 15). However, in 1975, direct measurement of human papillary region activity was made possible by direct cannulation to the papilla endoscopically by Nebel (8). This endoscopic method had the following characteristics: 1) a direct approach to the papilla was possible; 2) surgical procedures were unnecessary; and 3) frequent manometric measurements were possible in the same subject.

We applied this endoscopic manometric method to an animal experimental study of the sphincter of Oddi. The dog was chosen as the experimental animal because it was a suitable size for the endoscopy, and the canine sphincter of Oddi has been confirmed histologically. In 1965, Hauge and Mark (6) reported the first direct measurement of common bile duct motility and the sphincter mechanism using a multiple lumen catheter which was inserted through the cystic duct into the common duct and sphincter of Oddi of a laparotomized dog. They found that 1) the high pressure zone of the canine sphincter mechanism was about 2 cm in length. 2) There was an intrinsic contractile rhythm of the sphincter of Oddi, which had a functional triple sphincter mechanism. 3) No common duct peristalsis could be demonstrated. In 1980 Miranda et al. (7) also reported the manometric characteristics of the sphincter of Oddi in dogs using a surgical procedure, and found no differences in pressure values during general anesthesia an in the conscious state.

We first used a duodenofiberscope (JF-B4, Olympus), 11 mm in outer diameter, in the manometric study, but the measurement failed because the canine duodenal lumen was only about 25 mm in inner diameter, and the canine choledochus orifice was about 4 mm in size. Therefore, it was difficult to search, and obtain a front view of the papilla and hence, cannulation was impossible. We next used a thinner duodenoscope, a pediatric duodenofiberscope (PJF, Olympus), 8.8 mm in outer diameter. Using the pediatric duodenoscope, the cannulation was improved, and manometry of the canine sphincter of Oddi was successful.

The endoscopic manometric tracing in the sphincter zone showed rhythmical phasic con-
Pirenzepine, a selective antimuscarinic agent, also significantly reduced the phasic contractions, and the effect of 10 mg/kg of pirenzepine was almost the same as the effect of 0.1 mg/kg of atropine sulfate on the canine sphincter activity. Atropine sulfate was considered to have blocking effects on cholinergic receptors of the sphincter of Oddi 10 to 100-fold greater than those of pirenzepine. Garrigues et al. (4) reported the effects of atropine and pirenzepine on the sphincter of Oddi activity in humans. Their results indicated that 10 mg of pirenzepine and 0.5 mg of atropine intravenously both significantly decreased the phasic contractions, and pirenzepine had stronger effects than atropine.

In any case, pirenzepine significantly reduced the sphincter of Oddi contractions in both dogs and humans, and these results suggested the active influence of muscarinic receptors on the motility of the sphincter of Oddi.

In conclusion, this endoscopic manometric procedure was possible and useful in evaluating the canine sphincter of Oddi motility. Us-

![Figure 8](image-url)

**Fig. 8** Ten mg/kg of pirenzepine also significantly reduced canine sphincter activity.

![Figure 9](image-url)

**Fig. 9** Effect of 1 mg/kg of pirenzepine.
ing this method, the pharmacological effects of anticholinergic and antimuscarinic agents on the canine sphincter of Oddi were evaluated. The effects of various other drugs on the sphincter activity will be clarified later.

ACKNOWLEDGMENT

The authors wish to thank Mr. Kazutoshi Sekizawa, Miss Harumi Tsutaya, Miss Michiyo Miyagawa, and Miss Hiromi Hida for their kind cooperation.

This work was supported, in part, by a grant of the Japanese Foundation for Research and Promotion of Endoscopy.

REFERENCES