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RAPID COMMUNICATION

Choledochoscope manometry about different drugs on the Sphincter of Oddi

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Abstract

AIM: To assess the effects of H_2-receptor blocking pharmacon, protease inhibitor, and gastro kinetic agents on the human Sphincter of Oddi (SO) motility by choledochoscope manometry.

METHODS: One hundred and seventy-five patients with T tube installed after cholecystectomy and choledochotomy were assessed by choledochoscope manometry. They were randomly assigned into groups of H_2-receptor blocking pharmacon, protease inhibitor, and gastro kinetic agents. The Sphincter of Oddi basal pressure (SOBP), amplitude (SOCA), frequency of contractions (SOF), duodenal pressure (DP), and common bile duct pressure (CBDP) were scored and analyzed.

RESULTS: SOBP and SOCA were significantly decreased after Cimetidine administration, and no statistical difference was seen in the Famotidine group. In the Gabexate mesilate group, SOBP had decreased significantly. In the Ulinastatin group, SOCA decreased when Ulinastatin was given at the rate of 2500 U/min; when Ulinastatin administration was raised to 5000 U/min, SOBP, SOF and SOCA all experienced a fall. SOBP and SOCA for Domperidone and SOCA for Mosapride groups all decreased distinctly after administration.

CONCLUSION: The regular dosage of Cimetidine showed an inhibitory effect on the motility of SO, while Famotidine had no obvious effects otherwise. Gabnexata mesilate, Ulinastatin and gastro kinetic agents also showed inhibitory effects on the SO motility.

Key words: Sphincter of Oddi; Medicamentum; Choledochoscope manometry

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INTRODUCTION

The Sphincter of Oddi (SO) plays a vital role in maintaining the normal bile duct pressure, promoting gallbladder excretion and preventing from reflux. When Sphincter of Oddi dysfunction (SOD) occurs, the incidence rate for bile duct infection and cholelithiasis will greatly increase. The Sphincter of Oddi Manometry (SOM) is the gold standard for examining the SOD- in which the SO pressure is well accommodated by the abundance of nerves and hormone receptors on the SO. This study assessed the effects of H_2-receptor blocking pharmacon, protease inhibitor and gastro kinetic agents on the human SO pressure measured by choledochoscope manometry, and reveals the effects of different drugs on the SO pressure, which in turn provides the theoretical basis for clinical medication.

MATERIALS AND METHODS

Patients

Between the years 2002 and 2006, 175 individuals (59 men and 116 women, with a mean age of 56

years old, ranging from 21 to 80 years old) were subject to choledochofiberscope examination from the Department of the First Minimally-Invasive and Biliary Surgery of Shengjing hospital affiliated to the China Medical University were chosen. According to the random number table, adult subjects were further randomized into groups of H_2-receptor blocking pharmacon, protease inhibitor, and gastro kinetic agents. Every patient in each group has had cholecystectomy, biliary exploration, and T tube drainage troubled by biliary calculi. Choledochoscope examination was conducted two months after the procedures prior to manometry measurement. All the patients can close their T tube at 15 days post-operation continuously. The common bile duct diameter varied from 0.8 cm to 1.2 cm. Before the manometry was performed, all the patients were informed in detail of the procedure aims and probable dangers, with informed consent form signed.

Manometry system

The apparatus used were PC polygram HR (CTD-Synectics Medical Company, Sweden), triple lumen polyethylene manometry catheter (Wilson-Cook Medical Company, America), low compliance water perfusion system, nitrogen pump and PENTEX LX-750 Fiber Choledochoscope (PENTEX Company, Japan). A triple lumen polyethylene manometry catheter was 200 cm in length with an outer diameter of 1.7 mm. The three sided holes in the distal end were 2 mm apart facing different directions.

Method

Every patient was fasted overnight and kept drug-free to avoid biliary passage pressure changes before the examination. The computer manometry parameter was set at nitrogen pressure 40 kPa and the water velocity at 0.5 mL/min. After the manometry tubes were connected and the T tube removed, choledochoscope was inserted through the T tube sinus tract to observe the papilla vermicular movements at the end of the common bile duct to see whether if there was stenosis, fibrosis or calculus present. All the tested patients had never had EST, balloon dilation of the papilla or papilla plastic repair. During the operation we often used mollis urinary canal of F8 as an alternative to the metallic probe to pass the papilla avoiding the damage of papilla. The papilla moved properly, no parenchyma diseases were found and the regular lockage movements were found. For those patients who had stones in the common bile duct, the stones were removed first. Thirty minutes after the removal, the manometry catheter was introduced *via* the side-pore of choledochoscope, through the papilla into the duodenum under the euthyphoria, and 30 s later the manometry was performed. The catheter is then dragged to the SO; its position in the SO could be confirmed by direct observation through choledochoscope and by the phase waves displayed on the monitor. The SO contractions were recorded in one continuous act by the manometry. Following the SO, the catheter then moved into the common bile duct where the pressure was measured. Lastly, the drugs were then administered. The entire procedure described runs in repetition for every 10 min. The manometry was repeated and the curves were recorded. The administration program is shown in Table 1. The Medication dosage abides by clinic. Ulinastatin was given in different dosage due to clinical application.

Parameter observation

The Sphincter of Oddi basal pressure (SOBP), amplitude (SOCA), frequency of contractions (SOF), duodenal pressure (DP), and common bile duct pressure (CBDP) were scored and analyzed. The pressure of duodenum was used as null point.

Statistical analysis

SPSS 11.5 statistical package was adopted for analysis. The statistical data of our research were all measurement data in a normal distribution. DP was used as null point, and the relative magnitude of the remaining indexes were computed. The results were expressed by mean ± SD. The means of the sample before and after the administration were compared, and we also conducted the matched-pairs interclass *t*-test.

RESULTS

Effects of H_2-receptor blocking pharmacon on SO pressure (Table 2)

SOBP and SOCA were decreased after Famotidine administration, but there was no statistical difference. SOBP and SOCA decreased noticeably after Cimetidine administration, which indicated that Cimetidine had negative inotropic effects on the SO.

Effects of protease inhibitor on SO pressure (Table 3)

In the Gabexate mesilate group, SOBP decreased apparently with the rate of 2500 U/min, which had a statistical significance. SOCA and SOF experienced a tendency to drop but it was insignificant statistically. In the Ulinastatin group, SOCA decreased evidently with Ulinastatin when given at 2500 U/min. SOBP, SOF and SOCA all decreased obviously with Ulinastatin at 5000 U/min, and 20 min later such decrease became more apparent.

Effects of gastro kinetic agents on SO pressure (Table 4)

SOBP and SOCA decreased markedly 20 min after oral administration of Domperidone, which had a statistical significance. SOCA decreased markedly 10 min after administration of Mosapride. There was no obvious change in the indexes after oral administration of Tegaserod.

DISCUSSION

The focus of biliary tract kinetic research is the SO, and

Table 1 Single administration program

Group	Cases	Medication name	Medication dosage	Medication channel
H_2-receptor blocking pharmacon	20	Famotidine	40 mg	intravenous injection
	20	Cimetidine	200 mg	intravenous injection
Protease inhibitor	25	Gabexate mesilate	2.5 mg/min	intravenous injection with micro pump continuing
	25	Ulinastatin	2500 U/min	intravenous injection with micro pump continuing
	25	Ulinastatin	5000 U/min	intravenous injection with micro pump continuing
Gastro kinetic agents	20	Domperidone	10 mg	Take orally
	20	Mosapride	5 mg	Take orally
	20	Tegaserod	12 mg	Take orally

Table 2 Effects of H_2-receptor blocking pharmacon on SO pressure (mean ± SD)

	Famotidine (n = 20)			Cimetidine (n = 20)		
	Before administration	10 min after administration	20 min after administration	Before administration	10 min after administration	20 min after administration
SOBP (mmHg)	9.63 ± 8.48	5.92 ± 4.41	4.97 ± 6.53	9.63 ± 8.16[a]	4.96 ± 4.43[a]	3.10 ± 3.16[b]
SOCA (mmHg)	96.21 ± 53.12	85.31 ± 59.48	78.18 ± 64.01	106.55 ± 73.58	79.24 ± 59.93	52.09 ± 37.11[c]
SOF (times/min)	9.82 ± 3.18	10.57 ± 3.88	8.35 ± 2.01	8.30 ± 2.84	10.57 ± 2.82	11.44 ± 4.39
CDBP (mmHg)	5.09 ± 7.74	5.63 ± 5.33	2.42 ± 5.28	6.54 ± 4.16	9.03 ± 9.53	5.87 ± 5.07

9.63 ± 8.16 *vs* 4.96 ± 4.43, [a]$P < 0.05$; 9.63 ± 8.16 *vs* 3.10 ± 3.16, [b]$P < 0.01$; 106.55 ± 73.58 *vs* 52.09 ± 37.11, [c]$P < 0.01$.

Table 3 Effects of protease inhibitor on SO pressure (mean ± SD)

		Ulinastatin 2500 U (n = 25)	Ulinastatin 5000 U (n = 25)	Gabexate mesilate (n = 25)
SOBP (mmHg)	Before administration	11.53 ± 4.22	11.81 ± 5.21	14.33 ± 3.74
	10 min	11.96 ± 7.91	9.16 ± 5.97	12.31 ± 4.15
	20 min	9.25 ± 4.43	8.70 ± 4.50[a]	11.61 ± 4.50[b]
SOCA (mmHg)	Before administration	78.63 ± 35.96	65.21 ± 23.46	94.84 ± 39.64
	10 min	64.79 ± 22.25	63.73 ± 33.52	90.60 ± 38.69
	20 min	53.35 ± 25.52[c]	47.13 ± 21.53[d]	80.55 ± 27.58
SOF (t/min)	Before administration	6.67 ± 2.15	7.38 ± 2.58	7.01 ± 1.57
	10 min	6.03 ± 2.10	5.29 ± 2.39[e]	6.45 ± 1.24
	20 min	5.57 ± 1.92	4.65 ± 2.47[f]	6.14 ± 1.73
CDBP (mmHg)	Before administration	7.34 ± 3.06	9.06 ± 4.50	9.68 ± 3.25
	10 min	8.03 ± 3.97	8.51 ± 5.41	10.87 ± 4.55
	20 min	7.47 ± 4.21	8.80 ± 3.50	11.07 ± 4.05

11.81 ± 5.21 *vs* 8.70 ± 4.50, [a]$P < 0.05$; 14.33 ± 3.74 *vs* 11.61 ± 4.50, [b]$P < 0.05$; 78.63 ± 35.96 *vs* 53.35 ± 25.52, [c]$P < 0.01$; 65.21 ± 23.46 *vs* 47.13 ± 21.53, [d]$P < 0.01$; 7.38 ± 2.58 *vs* 5.29 ± 2.39, [e]$P < 0.01$; 7.38 ± 2.58 *vs* 4.65 ± 2.47, [f]$P < 0.01$.

Table 4 Effects of gastro kinetic agents on SO pressure

		Domperidone (n = 20)	Mosapride (n = 20)	Tegaserod (n = 20)
SOBP (mmHg)	Before administration	10.30 ± 4.99	12.56 ± 13.02	7.11 ± 4.08
	10 min	12.79 ± 13.47	5.36 ± 6.70	9.44 ± 5.25
	20 min	6.40 ± 3.66[a]	6.00 ± 5.74	12.93 ± 31.97
SOCA (mmHg)	Before administration	110.52 ± 37.80	83.44 ± 46.16	74.62 ± 26.06
	10 min	97.20 ± 59.96	45.06 ± 31.32[c]	71.74 ± 37.63
	20 min	68.67 ± 41.02[b]	52.48 ± 44.19	58.54 ± 37.19
SOF (t/min)	Before administration	6.84 ± 2.43	7.13 ± 3.21	6.55 ± 2.49
	10 min	8.03 ± 6.52	6.33 ± 3.07	6.07 ± 3.31
	20 min	8.86 ± 7.56	5.74 ± 2.41	5.88 ± 1.47
CDBP (mmHg)	Before administration	5.78 ± 6.59	3.92 ± 3.58	2.9 ± 3.71
	10 min	5.38 ± 2.23	1.74 ± 1.77	3.36 ± 2.98
	20 min	4.34 ± 4.75	1.95 ± 3.43	4.07 ± 5.27

10.30 ± 4.99 *vs* 6.40 ± 3.66, [a]$P < 0.05$; 110.52 ± 37.80 *vs* 68.67 ± 41.02, [b]$P < 0.01$; 83.44 ± 46.16 *vs* 45.06 ± 31.32, [c]$P < 0.01$.

the SO pressure is recognized as the index reflecting the SO motor function. SO manometry plays an important role in illustrating the disease etiology, pathogenesis, and turnover.

Thus far, the direct manometry is the gold standard to evaluate the SO motor function. At present, the most

common and recognized method is the endoscopic retrograde cholangiopancreatography (ERCP) simultaneous manometry. Although the endoscope manometry is widely used, its shortcomings do exist, such as the profuse endoscopic technique experience needed, the short manometry time and the pancreatitic risk[1]. Choledochoscope manometry adopts the same manometry theorem, manometry system and software with ERCP but uses different ways of catheterization manometry. Before the T tube is removed after a bile duct operation, the regular choledochoscopy is needed to avoid residual stones. When manometry is performed through choledochoscope, the measuring tube can reach the biliary tract directly and transit the SO. It is easy to operate, and no medication is required for the operation. Long term manometry research can be conducted with rare complications. In addition, the position of the measuring tube can be defined under the orthophoria in choledochoscope manometry, which makes the result more precise. The effects of the drugs on SO can be observed in choledochoscope manometry. However the shortcomings of choledochoscope manometry do exist, the subjects are all the patients with bile duct stone and post-operation, it is difficult to obtain the relative normal values. In this experiment, all the patients had clear pressure graphs, and no complications occurred. The effects of H_2-receptor blocking pharmacon, protease inhibitor, and gastro kinetic agents had on the SO composed to a pleasant result.

The confirmed SO activity rhythm increasing drugs at present are opium, Anticholinesterase drug, α-adrena receptor blocking pharmacon and H_1-receptor blocking pharmacon. While the SO activity rhythm decreasing drugs are M cholinergic receptor blocker, nitroester drugs, Ca-ion channel blocker, gastro kinetic agents and ®- receptor blocking pharmacon. We studied many different drugs according to the clinical practical medication.

Nitroester drugs can relax vascular smooth muscle, gastrointestinal tract smooth muscle and the SO. M cholinergic receptor has blocking function by inhibiting the cholinergic receptor on the smooth muscle. Our previous research had shown that Nitroester drugs and M cholinergic receptor have inhibitory effect on the SO[2,3]. It is commonly believed that morphine functions through the μ acceptor. It was found in the former research that morphine had excitatory effects on the SO motility[4-6]. Our experiment had shown that morphine had excitatory effect and tramadol had inhibitory effect on the SO, while pethidine had no apparent effect[7]. The effects of somatostatin and its analogue octreotide on the SO are distinct in different genera, and the mechanism of somatostatin accommodation on the SO motility has not been known yet[8]. Our previous research showed that administration density of somatostatin and its analogues should be paid special attention in clinical application, because small dose can excite the SO, which may increase the basic pressure, restrain biliary and pancreatic fluid, exacerbate the obstruction factors and finally affect the curative effect[9].

Histamine, H_2-receptor blocking pharmacon, Famotidine and Cimetidine are often clinically used for the treatment of gastric acid related diseases such as peptic ulcer, gastrinoma and gastroesophageal reflux. Recently their effects on gastrointestinal motility have been given more and more attention, but the inhibitory mechanism hasn't been known. In the experiment regarding the effects of histamine on the SO of opossum, Toouli *et al*[10] found that histamine' inhibitory effect on the SO was aroused by stimulating the H_1 receptor mediated inhibitory nerve, and the inhibitory nerve was non-adrenergic and non-cholinergic nerve having nothing to do with H_2 receptor. Sand *et al*[11] also found that histamine' inhibitory effect on the SO was mediated by H_1 receptor. While the research of Maples *et al*[12] showed that H_2 receptor agonist betazole could increase CDBP and was correlated to duodenum myoelectricity activity. After the antagonistic effect of Cimetidine, the duodenum myoelectricity activity and CDBP decreased to the baseline level, which showed that H_2-receptor blocking pharmacon had inhibitory effect on the biliary tract. The effect of Cimetidine on gastrointestinal motility might vary in different species and sites of action, but the mechanism was controversial. Some people believed that Cimetidine had the anti-effect on acetylcholine, so the effect on gastrointestinal motility was related to M receptor. Others believed that the inhibitory effect of Cimetidine occurred *via* the endogenous prostaglandin receptor. In our research, we found that SOBP and SOCA had the decreasing tendency after the administration of Famotidine, but there was no statistical difference. SOD, SOF and CDBP showed no difference, which indicated that they had no obvious effect on the SO. The experiment also showed that common dose of Cimetidine had inhibitory effect on the SO. Famotidine and Cimetidine were both H_2-receptor blocking pharmacon and mainly inhibited gastric acid secretion, however Famotidine was more effective. However, there was no identical display in the effect on the SO motility, so it might be concluded that their effect on the SO had nothing to do with the effect of H_2 receptor.

Gabexate mesilate and Ulinastatin are the common clinical protease inhibitor; proteinase inhibitor, and the common drugs for pancreatitis treatment. They have been reported to be effective on the prevention of post-ERCP pancreatitis[13,14]. However, at present, there are few studies on the effect of Gabexate mesilate on the SO. Research by Kobayashi *et al*[15] on Gabexate mesilate's inhibitory effect on the SO in dogs was realized by non-adrenergic and non-cholinergic passageway. Di Francesco *et al*[16] adopted the endoscope manometry to study Gabexate mesilate's effect on the SO. SOCA and SOF decreased after the administration, while SOBP showed no apparent

change. The pertinent literatures and reports on Ulinastatin's effect on the SO have not been seen yet. We found that SOBP decreased with the intravenous injection of Ulinastatin 2.5 mg/min, and SOCA and SOF showed no apparent change. SOBP, SOCA, and SOF decreased obviously 20 min after the administration of Ulinastatin at 2500 U/min. SOBP and SOF decreased obviously 10 min after the administration of Ulinastatin at 5000 U/min, and 20 min later the decrease became more apparent and SOCA also decreased apparently. Therefore, it could be supposed that Ulinastatin's effect on the SO was related to the medication time and drug concentration. Our results of manometry indicate that Gabexate mesilate and Ulinastatin had some influence on the SO. The administration of these agents could reduce the incidence of post-ERCP pancreatitis.

Domperidone is the peripheral dopamine receptor blocker, and has strong affinity with D2 receptor especially the gastrointestinal dopamine receptor. It has no cholinergic activity and it is free of atropine inhibition[17]. The results of the studies on Domperidone's effect on the SO are different. Tankurt *et al*[18] found in the experiment that in the Domperidone group Gallbladder contraction increased apparently after administration. He believed that Domperidone's effect on the Gallbladder was nonspecific, and might not depend on dopamine receptor. However, its effect on the SO has not been reported. We found in the experiment that SOBP and SOCA decreased after the administration of Domperidone, and it might have non-adrenergic and non-cholinergic mechanisms. Mosapride stimulates the release of acetylcholine by exciting the 5-HT_4 of the myenteric nerve plexus, and strengthens the movement of the gaster and duodenum[19]. No reports on Mosapride's effect on the SO have been known yet. However, for the homoplastic cisapride there are studies and reports on its inhibitory effect on the SO, and it can be inferred that the effect is regulated by non-adrenergic and non-cholinergic nerves[20]. Our study results showed that Mosapride had an inhibitory effect on the SO, and its' mechanism of action might be similar to or the same as cisapride. Tegaserod is 5-HT_4 receptor partial agonist[21]. In the Tegaserod group, we didn't find the similar inhibitory effect on the SO, which might be related to Tegaserod's high selectivity towards the receptor. In addition, the result might also be influenced by the short administration time we spent on manometry.

Above all, we adopted simple but effective choledochoscope manometry to study the SO motility, and explored the effect of many kinds of drugs on the SO rhythm, which profited our clinical practice. However, their mechanisms of action are not the same, and they may function in different aspects such as nerves, hormone etc. Their influence on different species may be also different. Their mechanisms of action warrant further study.

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