Effect of morphine and M-cholinoceptor blocking drugs on human sphincter of Oddi during choledochofiberscopy manometry

Shuo-Dong Wu, Jing Kong, Wei Wang, Qiang Zhang and Jun-Zhe Jin

Shenyang, China

OBJECTIVE: To evaluate the effects of morphine on the human sphincter of Oddi pressure and the antagonism of anticholinergic agents against morphine.

METHODS: The action of these drugs on the sphincter of Oddi (SO) was evaluated by means of choledochofiberscopy manometry in 40 operated patients with T-tube. The patients were divided randomly into 4 groups: anisodamine, atropine, buscopan, and control. The following data were recorded: duodenal pressure (DP), basal pressure of the sphincter of Oddi (BPSO), contractive amplitude of the sphincter of Oddi (CASO), contractive frequency of the sphincter of Oddi (CFSO), contractive duration of the sphincter of Oddi (CDSO), and pressure of the common bile duct (PCBD). Both morphine and anticholinergic agents were given intramuscularly.

RESULTS: After injection of 10 mg morphine, BPSO, CASO, CFSO, and PCBD increased significantly. After injection of 15 mg anisodamine or 0.75 mg atropine, CASO, BPSO declined obviously, and after injection of 20 mg buscopan, CASO, BPSO, CFSO declined obviously, but in anisodamine, atropine and buscopan groups, they differed insignificantly.

CONCLUSIONS: The results illustrate that SO manometry via choledochofiberscopy is a new method for SO dynamic study. Morphine can increase DP, BPSO, CASO, PCBD, but anisodamine atropine and buscopan can antagonize the effect of morphine.

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Key words: biliary manometry via choledochofiberscopy; morphine; anisodamine; atropine; buscopan; contractive amplitude; basal pressure; sphincter of Oddi

Introduction

The sphincter of Oddi (SO) is very important in maintaining the normal bile duct pressure, promoting the gallbladder to excrete and preventing it from reflux. If there is sphincter of Oddi dysfunction (SOD), the infection of the bile duct and cholelithiasis will happen. Sphincter of Oddi manometry (SOM) as the gold standard for evaluating patients with SOD is commonly performed during endoscopic retrograde cholangiopancreatography (ERCP). Acute pancreatitis is a recognized complication from SOM. If the manometry is followed by ERCP, the incidence is increased to 31%.[1] Furthermore, specific technology is required to perform with ERCP. If there is duodenal papillary malformation, the manometry will fail because it cannot be measured for a long time. So its application is limited. To choose an simple approach with few complications, SOM with choledochofiberscopy is performed. The pressure of SO is affected by such factors as neuronal, hormonal and medical mechanisms. As to the medical mechanism, the opioids and anticholinergic agents are often studied, but the results are not identical. In our study,

From the Department of Hepatobiliary, Second Affiliated Hospital, China Medical University, Shenyang 110004, China (Wu SD, Kong J, Wang W, Zhang Q and Jin JZ)

Correspondence: Shuo-Dong Wu, MD (Tel: 86-24-2389 3501 ext 6291)

we evaluated the action of morphine on human sphincter of Oddi pressure and the antagonism of anticholinergic agents against morphine with choledochofiberscopy.

Methods

Patients

Sphincter of Oddi manometry was performed in 40 patients (16 men, 24 women, mean age 53 years, range 21 - 76 years) with PENTAX choledochofiberscopy from November 2001 to January 2002 at the Second Affiliated Hospital, China Medical University, Shenyang, China. All the patients had undergone cholecystectomy and biliary exploration or T-tube drainage at least 1.5 months (mean 2.5 months) ago. They were fasted overnight before manometry.

Manometry

A triple lumen polyethylene manometry catheter of 200 cm long and 1.7 mm in outer diameter was used for manometry. The side holes in the distal end were located 2 mm apart. Each catheter lumen was infused with sterile water at a flow rate of 0.5 ml/min by a minimally compliant hydraulic capillary infusion system. PC polygraph HR (CTD-Synetics Medical Company, Sweden) and relevant program were used to record and analyse the tracings. Manometry was performed after removal of all the stones in the common bile duct. The catheter was introduced via side-pore of choledochofiberscopy into the duodenum directly. When the tracings of the pressure were stable, duodenal pressure-curve were recorded. The catheter was then withdrawn in a stepwise manner, and its position in the sphincter was confirmed by the characteristic pressure changes seen on the screen. It also could be confirmed by direct observation through choledochofiberscopy. The SO and common bile duct motility tracings were recorded respectively. Drugs were administered intramuscularly at 10 min intervals.

Drug administration

Patients randomly received one of four different schemes of drug administration.

Anisodamine group

Morphine was administered after the first measurement. Ten minutes later, the second manometry was performed. Then the procedure was repeated 10 minutes after administration of 15 mg anisodamine.

Atropine group

The first two procedures of manometry were same as those in the anisodamine group. For the third manometry, the agent was substituted with 0.75 mg atropine.

Buscopan group

The agent was substituted with 20 mg buscopan.

Control group

Morphine was administered after the first measurement. Both 10 minutes and 20 minutes later, manometry was performed for the second and third time.

The basal pressure of the sphincter of Oddi (BPSO), contractive amplitude of the sphincter of Oddi (CASO), contractive frequency of the sphincter of Oddi (CFSO), contractive duration of the sphincter of Oddi (CDSO), and pressure of common bile duct (PCBD) were recorded and analyzed with special program.

Statistical analysis was carried out using the t test. Data were expressed as $\bar{x} \pm s$. A single-tailed P value of <0.05 was considered to be statistically significant.

Results

Forty patients with T-tube underwent SOM. Clear tracings of pressure were obtained. Each group showed pressure data three times and they were compared with the difference of two manometries.

Effect of morphine on the sphincter of Oddi

Administration of 10 mg morphine produced an immediate and marked stimulatory effect on the

Table 1. Comparison of manometric data before and after administration of morphine in 40 patients

Parameters	Before morphine administration (n = 40)	10 min after morphine administration (n = 40)	20 min after morphine administration (n = 10)
Sphincter of Oddi basal pressure (mmHg)	8.90 ± 9.11	22.23 ± 16.04 **	20.51 ± 13.46 **
Sphincter of Oddi contractive amplitude (mmHg)	50.85 ± 36.66	104.97 ± 49.15 **	89.04 ± 62.37 **
Sphincter of Oddi contractive frequency (n/min)	7.22 ± 2.89	9.29 ± 1.93 **	8.85 ± 2.42 **
Sphincter of Oddi contractive duration (s)	4.85 ± 1.65	5.06 ± 1.25	5.04 ± 0.94
Common bile duct pressure (mmHg)	4.97 ± 3.87	8.62 ± 7.43 **	7.32 ± 5.95 **

** $P < 0.01$ compared with themselves.

Table 2. The changed manometric data from the anisodamine group

Parameters	Before morphine administration (n = 10)	10 min after morphine administration (n = 10)	20 min after anisodamine administration (n = 10)
Sphincter of Oddi basal pressure (mmHg)	14.56 ± 12.82	26.93 ± 17.03	11.69 ± 7.88 *
Sphincter of Oddi contractive amplitude (mmHg)	76.77 ± 44.76	132.93 ± 50.44	58.88 ± 28.23 **
Sphincter of Oddi contractive frequency (n/min)	7.61 ± 2.04	10.19 ± 1.34	8.03 ± 2.87
Sphincter of Oddi contractive duration (s)	5.30 ± 1.66	5.76 ± 0.96	6.59 ± 2.00
Common bile duct pressure (mmHg)	5.43 ± 4.13	5.93 ± 3.56	7.18 ± 4.27

* $P < 0.05$, ** $P < 0.01$ compared with the control group.

Table 3. The changed manometric data from the atropine group

Parameters	Before morphine administration (n = 10)	10 min after morphine administration (n = 10)	20 min after atropine administration (n = 10)
Sphincter of Oddi basal pressure (mmHg)	5.82 ± 5.35	24.70 ± 15.86	18.01 ± 16.01 *
Sphincter of Oddi contractive amplitude (mmHg)	52.50 ± 21.55	114.31 ± 30.19	49.87 ± 23.81 **
Sphincter of Oddi contractive frequency (n/min)	4.40 ± 2.56	8.87 ± 1.71	6.59 ± 3.19
Sphincter of Oddi contractive duration (s)	4.67 ± 1.66	5.15 ± 1.24	5.04 ± 1.55
Common bile duct pressure (mmHg)	5.08 ± 4.17	13.28 ± 10.91	7.18 ± 3.30

* $P < 0.05$, ** $P < 0.01$ compared with the control group.

sphincter of Oddi and the bile duct. Ten minutes after the administration, the effect was obvious, and even 20 minutes later the effect persisted (Table 1).

Effect of anticholinergic agents against morphine on the sphincter of Oddi

Administration of 15 mg anisodamine, 0.75 mg atropine, 20 mg buscopan produced an immediate and marked inhibition effect on the sphincter of Oddi and bile duct; 10 minutes later the effect persisted (Tables 2–4).

Table 4. The changed manometric data from the buscopan group

Parameters	Before morphine administration ($n=10$)	10 min after morphine administration ($n=10$)	20 min after buscopan administration ($n=10$)
Sphincter of Oddi basal pressure (mmHg)	7.31 ±6.44	18.44 ±16.11	7.06 ±4.83 *
Sphincter of Oddi contractive amplitude (mmHg)	39.22 ±36.08	85.83 ±38.92	34.74 ±28.49 **
Sphincter of Oddi contractive frequency (n/min)	6.34 ±2.12	9.95 ±1.21	5.91 ±3.95 *
Sphincter of Oddi contractive duration (s)	4.76 ±1.48	4.82 ±0.95	4.98 ±0.77
Common bile duct pressure (mmHg)	3.73 ±2.96	6.37 ±4.28	7.34 ±5.37

* $P<0.05$, ** $P<0.01$ compared with the control group.

Discussion

The focus of the biliary dynamic study has been on the sphincter of Oddi. The most important development in our understanding of pressure dynamics of the sphincter of Oddi came with the advent of SOM. SOM via choledochofiberscopy uses the principle, system and program similar to those used in manometry via endoscopic retrograde cholangiopancreatography (ERCP). First, the choledochofiberscopic approach allows easy and accurate recording of sphincter of Oddi pressure without technical problems of ERCP such as complications of acute pancreatitis, sedation of some drugs before manometry, and long time manometry. The position of manometric catheter in the sphincter is confirmed by the characteristic pressure changes on the screen. It also could be confirmed by direct observation through choledochofiberscopy. Second, there are many patients with T-tube in clinics. They need to be checked by choledochofiberscopy before removal of T-tube. So it is easy to get enough patients for manometry with choledochofiberscopic approach; however, it is difficult to get relatively normal values of the sphincter of Oddi via choledochofiberscopic manometry because the patient with T-tube often suffer from biliary diseases. Moreover, whether much irrigation of natural saline during choledochofiberscopic procedure will affect the motility of the sphincter of Oddi is unknown.

In our study, the patients were all subjected to post-cholecystectomy, compared with the use of choledochofiberscopy.[2] The manometry values such as common bile duct pressure and sphincter of Oddi basal pressure, sphincter of Oddi contractive amplitude were lower.

We found that the administration of 10 mg morphine produced an immediate and marked stimulatory effect on the sphincter of Oddi and bile duct. The effect was marked within 10 minutes after the administration and it persisted even 20 minutes later. The contractive amplitude and basal pressure of the splincter of Oddi, frequency duration and common bile duct pressure increased markedly. Morphine provided a resistance to flow through the sphincter of Oddi. These results are similar to those reported by Helm et al,[3] who studied the effect of morphine on the sphincter of Oddi by using ERCP manometry. In their study, following intravenous injection of 2.5 or 5 μg/kg morphine, the contractive frequency increased. But it did not affect the contractive amplitude and basal pressure of the sphincter of Oddi after intravenous injection of 5 or 10 μg/kg morphine; both contractive amplitude and basal pressure of the sphincter of Oddi increased. Thompson[4] also found that morphine can induce spasm in the sphincter of Oddi and should not be used in the treatment of acute pancreatitis. Nardi test can be used in screening the patients suspected with SOD. In our study, some patients with gallstones, showed marked increase of CASO, BPSO, PCBD after administration of morphine. This will help to judge whether SOD will happen in these patients.

Anticholinergic agents mediate the pressure of

the sphincter of Oddi by inhibiting the cholinergic receptors on the smooth muscle. The results of the effect of anticholinergic agents on the sphincter of Oddi are not identical. Carrigues et al[5] observed intravenous injection of 0.5 mg atropine only resulted in change of the contractive frequency other than basal pressure and contractive amplitude of the sphincter of Oddi. Furthermore, the effect persisted only a short time. Many reports, however, suggested that after administration of atropine, the contractive amplitude and basal pressure of the sphincter of Oddi decreased obviously. Huang et al[6] found after intravenous injection of 20 mg buscopan the contractive amplitude, basal pressure and contractive frequency of the sphincter of Oddi are decreased markedly, which is similar to the effect of EST.[7] Anticholinergic agents are limited in use because of the complications of cardiovascular diseases, but we did not find such cardiovascular complications, except that some patients experienced droughty in mouth occasionally. We can continue to study these drugs in more patients, if they are confirmed to be safe. If they are effective in some extent, they will be used in SOD non-surgically. They also can be used in the treatment of biliary pancreatitis. When appearence of abdominalgia of unknown origin, anticholinergic agents can be used safely.

Clinically, analgesics and anti-spasmolytics are often used to relieve the biliary-type colic, but the mechanism is unknown. We found intramuscular administration of 15 mg anisodamine, 0.75 mg atropine or 20 mg buscopan could block the effect of morphine on the sphincter of Oddi, which is not in consistent with that of Thune et al[8] that morphine may increase the sphincter contraction frequency, possibly mediated via stimulation of μ-receptor. In their study, following the intravenous administration of morphine, the frequency of sphincter of Oddi contraction increased, but no changes appeared in amplitude, basal pressure or wave propagation direction. Thune et al also found that this effect was reduced by naloxone (0.04 mg bolus) not by atropine and that pretreatment with atropine did not inhibit the effect of morphine. Our study suggested that the effect of morphine can be antagonized by M-cholinoceptor blocking drugs, so the sphincter of Oddi may be affected by many factors acting on different position, and these factors may affect each other.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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