

Effects of narcotic analgesic drugs on human Oddi’s sphincter motility

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INTRODUCTION

Morphine can cause excitatory effect on Oddi’s sphincter motility and therefore induces upper abdominal pain with characteristics of biliary colic in some patients. Morphine could increase intrabiliary duct pressure[1-3], and delay bile flow to the duodenum[4], for this reason, other opioid analgesics rather than morphine are recommended clinically to relieve the pain, especially biliary pain. It is believed that pethidine has less effect on the sphincter than morphine and therefore is usually the drug of choice for pain relief in acute pancreatitis. Pethidine is also commonly used during endoscopic retrograde cholangiopancreatography (ERCP). Because of potential interference, all narcotic analgesic drugs, including pethidine, are proscribed during Oddi’s sphincter manometry (OSM). However, the performance of OSM with only diazepam sedation was difficult as pethidine markedly improves ERCP tolerance.

The aim of this study was to evaluate the effects of four analgesic drugs on human Oddi’s sphincter motility by choledochoscope manometry, and to understand the different clinical responses to analgesics.

MATERIALS AND METHODS

Patients

OSM was performed for 70 patients (25 men, 45 women, and mean age 55.5 years, range 35-77 years) with PENTAX choledochoscope at the Second Affiliated Hospital of China Medical University between November 2001 and December 2003. All patients underwent cholecystectomy and choledochotomy, at least 1.5 mo (mean 2.5 mo) after T tube drainage. The patients were fasted overnight before manometry.

Methods

A triple lumen polyethylene manometry catheter 200 cm in length with an outer diameter of 1.7 mm was used for manometry. The three side holes in the distal end were located 2 mm apart. Sterile water was infused through the catheter at a flow rate of 0.5 mL/min by a hydraulic capillary infusion system. PC polygraph HR (Swedish CTD-Synetics medical company) and relevant program were used to record and analyze the tracings. Manometry was performed after all the stones were removed from the common bile duct. The catheter was introduced via the side-pore of choledochoscope into duodenum directly, when the pressure was stable, duodenal pressure-curve was recorded. It was then withdrawn in a stepwise fashion, the position of catheter in the sphincter could be confirmed by direct observation through choledochoscope or by the characteristic pressure changes on the screen. The Oddi’s sphincter and common bile duct motility tracings were recorded respectively. Drugs were administered intramuscularly at 10 min intervals.

Patients were randomly administered one of the four different drugs. Morphine was administered in a dose of 0.1 mg/kg after the first measurement, the second and third manometries were performed respectively 10 min and 20 min later. Each of the other three analgesics was administered in a dose of 1 mg/kg. The procedures were same as in morphine group.

Basal pressure of Oddi’s sphincter (BPOS), amplitude of phasic contractions (SOCA), frequency of phasic contractions (SOF), duration of phasic contractions (SOD), duodenal pressure (DP) and common bile duct pressure (CBDP) were scored and analyzed. All narcotic analgesic drugs were administered intramuscularly.

RESULTS:

Levels of BPOS, SOCA and SOF were increased after injection of morphine and Ap-237 (P<0.05), level of CBDP was increased from 4.97±3.87 mmHg to 8.62±7.43 mmHg (10 min later) and 7.32±5.95 mmHg (20 min later) after injection of morphine (P<0.01). No apparent change occurred after intramuscular injection of pethidine. Level of BPOS was increased from 7.01±5.50 mmHg to 2.87±2.78 mmHg 10 min after injection of tramadol and SOCA was decreased from 63.34±35.29 mmHg to 45.90±27.86 mmHg (10 min later, P<0.05) and 35.97±24.30 (20 min later, P<0.01) after administration of tramadol.

CONCLUSION:

All these findings indicate that Oddi’s sphincter manometry via choledochoscope is a practical and new way to study the dynamics of Oddi’s sphincter. The regular dose of morphine and Ap-237 could increase BPOS, SOF and SOCA. Morphine could increase the level of CBDP, demonstrating an excitatory effect on the sphincter of Oddi. Pethidine had no effect on Oddi’s sphincter motility. Tramadol shows an inhibitory effect on the motility of the sphincter of Oddi and decreases levels of BPOS and SOCA.

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The aim of this study was to evaluate the effects of four analgesic drugs on human Oddi’s sphincter motility by choledochoscope manometry, and to understand the different clinical responses to analgesics.
Data were expressed as mean±SD. A single-tailed P value <0.05 was considered statistically significant.

RESULTS
Seventy patients with T-tubes had no evidence of ampullary abnormality underwent OSM. Clear tracings of pressure and phasic contractions were acquired. Data were compared.

Effect of morphine on Oddi’s sphincter motility
Morphine at the dose of 0.1 mg/kg produced an immediate and marked stimulatory effect on the sphincter of Oddi and bile duct, which was obvious 10 min after injection. Levels of BPOS, SOCA, SOF and CBDP were all significantly increased (P<0.01) and the effect persisted for 20 min (Table 1). Ten patients (25%) had an increased BPOS between 30-40 mmHg, four patients had an increased BPOS over 40 mmHg after drug administration.

Effect of pethidine on Oddi’s sphincter motility
No statistical difference before and after administration of pethidine (1 mg/kg). Pethidine showed no apparent effect on Oddi’s sphincter motility (Table 2).

Effect of Ap-237 on Oddi’s sphincter motility
Marked increased levels of BPOS, SOCA and SOF were observed 10 min after injection of Ap-237, and high levels of BPOS and SOF persisted for 20 min, which showed an excitatory effect on Oddi’s sphincter motility (Table 3).

Effect of tramadol on Oddi’s sphincter motility
Levels of BPOS and SOCA were obviously reduced 10 min after administration of tramadol, which maintained at low levels for 20 min and showed an inhibitory effect of tramadol on Oddi’s sphincter motility. (Table 4)

DISCUSSION
The most important development in our understanding of Oddi’s sphincter motility came with the advent of Oddi’s sphincter manometry (OSM) in the mid-1970s. Then, it was considered as the gold standard method for evaluating the function of Oddi’s sphincter. OSM could be directly performed during surgery, or

| Table 1 | Manometric data before and after administration of morphine in 40 patients (mean±SD) |
|---------|----------------------------------------------------------------------------------|
|         | Before morphine administration (n=40) | 10 min after morphine administration (n=40) | 20 min after morphine administration (n=10) |
| Oddi’s sphincter basal pressure (mmHg) | 8.90±9.11 | 22.23±16.04* | 20.51±13.46 b |
| Amplitude of phasic contractions (mmHg) | 50.85±36.66 | 104.97±49.15 d | 89.04±62.37* |
| Frequency of phasic contractions (n/min) | 7.22±2.89 | 9.29±1.93* | 8.85±2.42* |
| Common bile duct pressure (mmHg) | 4.97±3.87 | 8.62±7.43 | 7.32±5.95 |

*P<0.05 vs themselves, n represents the number of patients involved in the research.

| Table 2 | Manometric data before and after administration of pethidine in 10 patients (mean±SD) |
|---------|----------------------------------------------------------------------------------|
|         | Before pethidine administration (n=10) | 10 min after pethidine administration (n=10) | 19 min after pethidine administration 20 (n=10) |
| Oddi’s sphincter basal pressure (mmHg) | 7.06±5.07 | 11.24±6.11 | 6.68±4.32 |
| Amplitude of phasic contractions (mmHg) | 78.52±40.23 | 95.65±45.49 | 70.35±31.67 |
| Frequency of phasic contractions (n/min) | 7.31±1.95 | 6.49±2.81 | 7.92±2.07 |
| Common bile duct pressure (mmHg) | 4.23±2.83 | 4.70±3.87 | 3.91±3.36 |

n represents the number of patients involved in the research.

| Table 3 | Manometric data before and after administration of Ap-237 in 10 patients (mean±SD) |
|---------|----------------------------------------------------------------------------------|
|         | Before Ap-237 administration (n=10) | 10 min after Ap-237 administration (n=10) | 20 min after Ap-237 administration (n=10) |
| Sphincter of Oddi basal pressure (mmHg) | 6.42±5.10 | 11.33±9.39* | 11.34±8.40* |
| Amplitude of phasic contractions (mmHg) | 52.56±30.99 | 87.03±51.72* | 50.06±29.11 |
| Frequency of phasic contractions (n/min) | 5.62±1.34 | 7.72±2.16* | 9.28±3.98* |
| Common bile duct pressure (mmHg) | 4.20±3.97 | 4.82±2.30 | 3.25±2.30 |

*aP<0.05, bP<0.01 vs themselves, n represents the number of patients involved in the research.

| Table 4 | Manometric data before and after administration of tramadol in 10 patients (mean±SD) |
|---------|----------------------------------------------------------------------------------|
|         | Before tramadol administration (n=10) | 10 min after tramadol administration (n=10) | 20 min after tramadol administration (n=10) |
| Sphincter of Oddi basal pressure (mmHg) | 7.01±5.50 | 2.87±2.78* | 6.39±5.37 |
| Amplitude of phasic contractions (mmHg) | 63.34±35.29 | 45.90±27.86* | 35.97±24.30* |
| Frequency of phasic contractions (n/min) | 7.24±2.52 | 8.14±2.54 | 7.07±3.70 |
| Common bile duct pressure (mmHg) | 4.41±2.65 | 3.97±4.69 | 4.96±2.82 |

*aP<0.05, bP<0.01 vs themselves, n represents the number of patients involved in the research.
indirectly during ERCP, via a T-tube or percutaneously. A basal pressure and phasic contractions of Oddi’s sphincter could be obtained with OSM.

OSM during ERCP is a useful tool in the evaluation of patients with unexplained pancreaticobiliary pain or recurrent idiopathic pancreatitis\(^{[12-17]}\). However, it might provoke serious pancreatitis\(^{[18-19]}\). It is a technical procedure, because it requires selective deep bile duct and/or pancreatic duct cannulation during active duodenal peristalsis and in suboptimally anesthetized patients. These features account for the relatively high failure rate (up to 20%) even in expert hands\(^{[20]}\).

OSM via choledochofiberoscopy allows easy and accurate recording of Oddi’s sphincter pressure and makes a long time maneuver of manometry possible. The position of manometric catheter in the sphincter can be monitored on the screen with the characteristic phasic contractions. It also could be confirmed by direct observation through choledochofiberoscopy. And it is easy to get enough patients for manometry. However, it is difficult to get a relative normal value of the sphincter of Oddi via choledochofiberoscopy manometry, for patients with a T-tube tract often suffer from hepatobiliary or pancreatic diseases. Furthermore, whether irrigation of natural cold saline and the semi-closed state of bile duct during choledochofibersopic procedure affect the motility of the sphincter of Oddi is unknown.

Morphine and pethidine are the two most commonly used analgesic drugs. Their effects on the sphincter of Oddi have well been researched. Helm et al.\(^{[21]}\) studied the effect of morphine on SO using OSM during ERCP. In a small cumulative dose of 2.5-5 \(\mu\)g/kg, morphine increased the frequency of phasic contractions to a maximum of 10-12/min, but it did not affect the mean amplitude of phasic contractions and the mean SO basal pressure. As the cumulative dose was increased from 10 to 20 \(\mu\)g/kg, no further increase in the frequency of phasic pressure waves was seen. Instead, the phasic wave amplitude and the mean SO basal pressure increased. Blaut et al.\(^{[22]}\) found that morphine increased the intraductal biliary pressure (IDP) with OSM via a T-tube, but the high intraductal biliary pressure caused by morphine could be counteracted by transcutaneous electrical nerve stimulation (TENS). Elta et al.\(^{[23]}\) performed ERCP manometry to evaluate the effect of pethidine at therapeutic doses on SO manometry, and found that after administration of pethidine the frequency of phasic contractions increased, but the mean SO basal pressure did not change. Using the same method, Sherman et al.\(^{[24]}\), found that biliary sphincter basal pressure and phasic wave amplitude were not significantly altered by pethidine, but phasic frequency increased and phasic duration decreased slightly after administration of pethidine, sphincter basal pressure of the pancreatic and the common channel’s sphincters was not significantly altered, but their phasic wave amplitude decreased, phasic frequency increased, and phasic duration decreased.

The only study directly comparing morphine to pethidine with OSM was done in 1990 by Thurow et al.\(^{[25]}\). They compared the effect of morphine and pethidine on patients intraoperatively after surgical placement of a catheter across the SO. Morphine was associated with an increase in phasic wave frequency, but no change was found in basal sphincter pressure, amplitude, or wave propagation direction. Pethidine showed a dose-dependent decrease in phasic wave frequency but without significant changes in the basal sphincter pressure, contraction amplitude or wave propagation direction.

We found that morphine could increase the basal pressure of Oddi’s sphincter, common bile duct pressure, frequency and amplitude of phasic contractions. Morphine showed an excitatory effect on the sphincter of Oddi, and might be a cause of Oddi’s sphincter dysfunction (SOD). SO may function as a peristaltic pump to actively expel fluid from the sphincter segment into the duodenum. The SO segment fills with fluid from the common bile duct (CBD) only during the diastolic interval between phasic contractions. Outflow of fluid from the CBD is reduced or arrested when (1) the frequency of phasic contractions increases sufficiently to compromise diastolic filling of the sphincter segment, (2) phasic contractions propagate retrograde or occur simultaneously along the sphincter segment, or (3) passive filling of the sphincter segment is prevented by a BPOS that exceeds the CBDP. Morphine could cause functional obstruction of the SO by all three of these mechanisms\(^{[11]}\). OSM shows a diagnostic value for Oddi’s sphincter dysfunction. Elevated basal pressure (>40 mmHg) was the most important manometric finding in Oddi’s sphincter dysfunction and its borderline was about 30-40 mmHg. Our study found that 10 patients (25%) had an increased BPOS between 30-40 mmHg, four patients had an increased BPOS over 40 mmHg. So morphine can cause spasm of SO and should not be used during ERCP manometry or choledochofiberscopy examination. After administration of pethidine, no patients had an elevated BPOS up to 30 mmHg. Pethidine could be used for an additional analgesia during OSM. This may improve both patient’s tolerance and the success rate of the procedure. But we should be cautious in patients with renal failure, hepatic failure or central nervous system diseases. For the pethidine metabolite, normeperidine, might invoke seizures at high doses or in patients with renal failure. Hubert et al.\(^{[16]}\) reports that pethidine invoked seizures in a patient with Oddi’s sphincter dysfunction.

Tramadol has the same analgesic effect as morphine. But it has little effect on the respiratory system and circulation system, and can be used in old patients with respiratory system diseases. There were only a few researches about its effect on the sphincter of Oddi. Staritz et al.\(^{[17]}\) and Brandstatter et al.\(^{[18]}\) performed ERCP manometry to evaluate the effect of tramadol on SO manometry, and found that it had no apparent effect on Oddi’s sphincter motility. Our study indicated that tramadol could decrease BPOS and the amplitude of phasic contractions, showing an inhibitory effect on the sphincter of Oddi, and tramadol could be used during ERCP manometry and choledochofiberscopy examination.

As a fast acting analgesic, Ap-237 has little effect on visceral pain. A MEDLINE search found no report about its effect on the sphincter of Oddi. We found that Ap-237 could increase BPOS, amplitude and frequency of phasic contractions, showing an excitatory effect on the sphincter of Oddi, and Ap-237 should not be used in patients with hepatobiliary and pancreatic diseases.

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