Nitroester drug’s effects and their antagonistic effects against morphine on human sphincter of Oddi motility

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Abstract

AIM: To evaluate the effects of nitroester drugs on human sphincter of Oddi (SO) motility and their antagonistic effects against morphine which shows excitatory effect on Oddi’s sphincter motility.

METHODS: The effects of these drugs on SO were evaluated by means of choledochofiberoscopy manometry. A total of 67 patients having T-tubes after cholecystectomy and choledochotomy were involved in the study, they were randomly divided into glyceryl trinitrate (GTN) group, isosorbide dinitrate (ISDN) group, pentaerythritol tetranitrate (PTN) group, morphine group associated with GTN group, morphine associated with ISDN group and morphine associated with PTN 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. Morphine was given intramuscularly while nitroester drugs were applied sublingually.

RESULTS: BPOS and SOCA decreased significantly after administration of ISDN and GTN, BPOS reduced from 10.95±3.49 mmHg to 5.92±4.04 mmHg (P<0.05) evidently after application of PTN. BPOS increased from 7.37±5.58 mmHg to 16.60±13.87 mmHg, SOCA increased from 54.09±38.37 mmHg to 100.70±43.51 mmHg, SOF increased from 7.15±3.20 mmHg to 10.38±2.93 mmHg and CBDP increased 3.75±1.95 mmHg to 10.49±8.21 mmHg (P<0.01) evidently after injection of morphine. After associated application of ISDN and GTN, the four indications above decreased obviously. As for application associated with PTN, SOCA and SOF decreased separately from 100.64±44.99 mmHg to 66.17±35.88 mmHg and from 10.70±2.76 mmHg to 9.04±1.71 mmHg (P<0.05) markedly.

CONCLUSION: The regular dose of GTN, ISDN and PTN showed inhibitory effect on SO motility, morphine showed excitatory effect on SO while GTN, ISDN and PTN could antagonist the effect of morphine. Among the three nitroester drugs, the effect of ISDN on SO was most significant.

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Key words: Sphincter of Oddi; Nitroester drugs; Glyceryl trinitrate; Isosorbide dinitrate; Pentaerythritol tetranitrate; Morphine; Choledochofiberoscopy manometry

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INTRODUCTION

The Oddi’s sphincter is the smooth muscle junction connecting the common bile duct and the duodenum which provides regulation of bile flow and hinders duodenobiliary reflux. During phasic contractions the papilla is closed and bile flow stops. Between phasic contractions the papillary muscle is relaxed and the bile flows from the common bile duct to the duodenum. Oddi’s sphincter manometry (OSM) is considered as the gold standard method for evaluating the function of Oddi’s sphincter. OSM can be directly performed during surgery, or indirectly during ERCP, via a T-tube or percutaneously. A basal pressure and phasic contractions of Oddi’s sphincter can be obtained with OSM.

Nitroester drugs are organic nitrates which have been shown to relax the smooth muscle of blood vessels. This effect has been widely accepted for the treatment of angina pectoris. Nitrates also act on a range of smooth muscles and effectively relax muscles of the gallbladder, the bile duct and the SO (SO) not in superscript[4-6]. 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[7,8], and delay bile flow to the duodenum[9] So morphine should not be used during ERCP manometry or choledochoscopy examination. Few reports have described if nitroester drugs could antagonize the excitatory effect of morphine on Oddi’s sphincter motility.

The first aim of this study is to evaluate the effects of three nitroester drugs on human Oddi’s sphincter motility by choledochoscopy manometry. While the second aim is to assess if nitroester drugs can antagonize morphine’s excitatory effect on SO motor function.
performed, and then the third, 20 min after administration. 20 mg. Ten minutes later, the second manometry was 1 mg while ISDN in doses of 5 mg and PTN in doses of the first measurement. GTN was administered in dose of receive one of the different schemes of drug administration. at 10 min intervals. Patients were selected randomly, to were administered sublingually or injected intramuscularly duct motility tracings were recorded respectively. Drugs through choledochofiberoscopy. The SO and common bile it could also be confirmed by direct observation corrected. The position of catheter in the sphincter was confirmed by the characteristic pressure changes seen on the screen. It could also be confirmed by direct observation through choledochofiberoscopy. The SO and common bile duct motility tracings were recorded respectively. Drugs were administered sublingually or injected intramuscularly at 10 min intervals. Patients were selected randomly, to receive one of the different schemes of drug administration. GTN group, ISDN group and PTN group, one of the three nitroester drugs was administered sublingually after the first measurement. GTN was administered in dose of 1 mg while ISDN in doses of 5 mg and PTN in doses of 20 mg. Ten minutes later, the second manometry was performed, and then the third, 20 min after administration. Morphine associated with GTN group, morphine associated with ISDN group and morphine associated with PTN group. Morphine was administered intramuscularly in doses of 10 mg after the first measurement. Ten minutes later, the second manometry was performed. Then the patient took sublingual administration of 1 mg GTN or 5 mg ISDN or 20 mg PTN. Therefore 10 and 20 min later, the procedure was repeated for the third and the fourth time. Basal pressure of Oddi’s sphincter (BPOS), amplitude of phasic contractions (SOCA), frequency of phasic contractions (SOF), duration of phasic contractions (SOD), DP and common bile duct pressure (CBDP) were recorded and analyzed with a special computer program. Statistical analysis was carried out using the Student’s t-test. Data were expressed as mean±SD. A single-tailed P value<0.05 was considered statistically significant.

RESULTS
Sixty-seven patients with T-tube who had no evidence of ampullary abnormality underwent SOM. Clear tracings of pressure and phasic contractions were acquired. Every group had data of three or four times which were compared and contrasted.

Effect of solo nitroester drugs on the SO motility
Ten minutes after sublingual administration of 5 mg ISDN or 1 mg GTN, BPOS and SOCA decreased markedly (P<0.05). Even 20 min later, the effects still persisted (P<0.05) (Tables 1 and 2). As for the PTN group, BPOS reduced significantly 20 min after administration (P<0.05). SOCA and CBD decreased slightly 10 and 20 min after application, but it is not statistically significant (Table 3).

Effects of nitroester drugs antagonize morphine on the SO motility
Morphine at a dose of 10 mg produced an immediate and markedly stimulatory effect on the SO and the common bile duct. Levels of BPOS, SOCA, SOF and CBDP significantly increased 10 min after injection (P<0.01) (Table 4). Then 10 min after sublingual application of TPN, the four

| Table 1 | Manometric data before and after administration of GTN in 10 patients (mean±SD) |
|------------------------|---------------------------------|------------------------|------------------------|
|                        | Before GTN administration (control) | 10 min after GTN administration | 20 min after GTN administration |
| Sphincter of Oddi basal pressure (mmHg) | 9.70±4.54 | 5.71±4.95<sup>c</sup> | 5.80±4.2<sup>c</sup> |
| Amplitude of phasic contractions (mmHg) | 88.8±68.77 | 52.0±23.59<sup>c</sup> | 49.7±32.6<sup>c</sup> |
| Frequency of phasic contractions (n/min) | 6.71±2.21 | 7.32±2.69 | 5.57±2.05 |
| Common bile duct pressure (mmHg) | 5.4±4.40 | 4.19±4.19 | 5.4±4.39 |

<sup>a</sup>P<0.05, <sup>b</sup>P<0.05 vs themselves, n = 10 (n represents the number of patients involved in the research).

| Table 2 | Manometric data before and after administration of ISDN in 16 patients (mean±SD) |
|------------------------|---------------------------------|------------------------|------------------------|
|                        | Before ISDN administration (control) | 10 min after ISDN administration | 20 min after ISDN administration |
| Sphincter of Oddi basal pressure (mmHg) | 10.78±10.79 | 5.56±4.38<sup>d</sup> | 5.40±4.78 |
| Amplitude of phasic contractions (mmHg) | 92.06±33.36 | 60.8±33.64<sup>d</sup> | 38.1±18.38<sup>d</sup> |
| Frequency of phasic contractions (n/min) | 7.88±2.58 | 6.83±4.63 | 7.13±4.47 |
| Common bile duct pressure (mmHg) | 4.49±5.33 | 3.42±1.56 | 3.13±2.17 |

<sup>a</sup>P<0.05, <sup>b</sup>P<0.05<sup>c</sup>P<0.01 vs themselves, n = 16 (n represents the number of patients involved in the research).
Prior to that time, the SO motility was evaluated by indirect and transphincteric flow studies via a T-tube either during surgery, or indirectly during ERCP, via a T-tube or percutaneously. In this study we studied nitroester drugs’ effects and their antagonistic effects against morphine on human SO motility via choledochofiberoscopy manometry.

Nitroester drugs can relax vascular smooth muscles, including that of gastrointestinal tract. They also can effectively relax the muscle of Oddi’s sphincter. Among these drugs the effect of glyceryl trinitrate (GTN) on the SO has been well researched. There are relatively few reports about isosorbide dinitrate (ISDN) and no report about pentaerythritol tetranitrate (PTN) on the SO motility. Staritz et al[9] first reported that sublingual administration of 1.2 mg of GTN markedly lowered the SO basal tone and phasic contraction amplitude. Later on, Brandstatter et al[10] also found a remarkable decrease of the BPOS and the phasic SO contraction amplitude. Further, Staritz et al[11] and Uchida et al[12] found that sublingual GTN enables the endoscopic extraction of small (6-12 mm) increased indications decreased markedly to normal levels ($P<0.01$), but the effects were transient. As for 20 min after administration, all the indications had no difference to that of 10 min after morphine injection (Table 5) BPOS, CBDP and SOCA lowered significantly 10 and 20 min after application of ISDN, SOF decreased obviously 20 min after administration ($P<0.05$) (Table 6). BPOS decreased evidently 10 and 20 min after the usage of PTN, SOF slowed down slightly 10 min after administration ($P<0.05$) (Table 7).

### DISCUSSION

The advent of OSM in the mid-1970s was the most important development in understanding of the motility of the SO. Prior to that time, the SO motility was evaluated by indirect methods such as cineradiography, contrast media drainage time, and transphincteric flow studies via a T-tube either during or after biliary tract surgery. From then on, OSM has obtained widespread application in the evaluation of patients for SO dysfunction (SOD). OSM could be directly performed during surgery, or indirectly during ERCP, via a T-tube or percutaneously. In this study we studied nitroester drugs’ effects and their antagonistic effects against morphine on human SO motility via choledochofiberoscopy manometry.

| Table 3 | Manometric data before and after administration of PTN in 11 patients (mean±SD) |
|----------|--------------------------------------------------------------------------------|
| Before PTN administration (control) | 10 min after PTN administration | 20 min after PTN administration |
| Sphincter of Oddi basal pressure (mmHg) | 10.95±7.49 | 8.59±1.90 | 5.92±4.04 |
| Amplitude of phasic contractions (mmHg) | 86.19±42.04 | 68.08±38.23 | 59.51±27.35 |
| Frequency of phasic contractions (n/min) | 7.04±1.50 | 5.95±2.79 | 7.31±2.80 |
| Common bile duct pressure (mmHg) | 7.26±4.25 | 4.83±4.13 | 5.57±3.49 |

$^aP<0.05$ vs themselves, $n=11$ ($n$ represents the number of patients involved in the research).

| Table 4 | Manometric data before and after administration of morphine in 30 patients (mean±SD) |
|----------|--------------------------------------------------------------------------------|
| Before morphine administration (control) | 10 min after morphine administration |
| Sphincter of Oddi basal pressure (mmHg) | 7.37±5.58 | 16.60±13.87$^b$ |
| Amplitude of phasic contractions (mmHg) | 54.09±38.37 | 100.70±43.51$^c$ |
| Frequency of phasic contractions (n/min) | 7.15±3.20 | 10.38±2.93$^a$ |
| Common bile duct pressure (mmHg) | 3.75±1.95 | 10.49±8.21 |

$^aP<0.01$, $^bP<0.01$, $^cP<0.01$ vs themselves, $n=30$ ($n$ represents the number of patients involved in the research).

| Table 5 | Antagonism of GTN against morphine on the SO motility in 10 patients (mean±SD) |
|----------|--------------------------------------------------------------------------------|
| 10 min after morphine administration (control) | 10 min after GTN associated administration | 20 min after GTN associated administration |
| Sphincter of Oddi basal pressure (mmHg) | 12.49±5.40 | 6.46±6.88$^a$ | 13.47±7.69 |
| Amplitude of phasic contractions (mmHg) | 96.56±48.49 | 56.54±27.19$^a$ | 63.89±34.56 |
| Frequency of phasic contractions (n/min) | 8.98±1.34 | 6.96±1.83$^a$ | 7.66±2.50 |
| Common bile duct pressure (mmHg) | 10.99±4.75 | 4.94±3.27$^a$ | 7.87±4.72 |

$^aP<0.01$, $^bP<0.01$, $^cP<0.01$ vs themselves, $n=10$ ($n$ represents the number of patients involved in the research).

| Table 6 | Antagonism of ISDN against morphine on the SO motility in 10 patients (mean±SD) |
|----------|--------------------------------------------------------------------------------|
| 10 min after morphine administration (control) | 10 min after ISDN associated administration | 20 min after ISDN associated administration |
| Sphincter of Oddi basal pressure (mmHg) | 24.63±19.55 | 5.43±4.82$^a$ | 9.8±6.22$^a$ |
| Amplitude of phasic contractions (mmHg) | 112.89±35.04 | 39.65±21.08$^a$ | 43.45±28.65$^a$ |
| Frequency of phasic contractions (n/min) | 11.46±3.83 | 8.82±2.67 | 8.52±2.21$^a$ |
| Common bile duct pressure (mmHg) | 11.79±8.21 | 6.05±4.76$^a$ | 5.75±3.87$^a$ |

$^aP<0.05$, $^bP<0.05$, $^cP<0.05$, $^dP<0.01$, $^eP<0.01$ vs themselves, $n=10$ ($n$ represents the number of patients involved in the research).
common bile duct (CBD) stones. Because of its potential side effect, such as severe headache, Luman et al.[12] recently demonstrated that topical infusion 5 or 10 mg of GTN significantly decreased the basal SO tone and phasic motor function. They stated that local administration of GTN was not accompanied by adverse effects. Wehrmann et al.[13] found that topical application of GTN or ISDN evoked a profound inhibition of SO motor function, and the effect of ISDN was longer than that of GTN. However, locally administered GTN did not facilitate selective bile-duct access during routine ERCP. Yasuyoshi et al.[14] described the removal of small common bile duct stones through the combined use of intravenous injection of ISDN and baskets and/or balloons without the use of endoscopic sphincterotomy. Stones were completely removed in 15 of the 18 patients.

We found that both GTN and ISDN could decrease BPOS and SOCA, PTN could reduce SOCA, showed inhibitory effects on SO. Among the three drugs, the effect of ISDN on SO was most significant. Nitroester drugs are nitric oxide (NO) donors, application of NO donors could significantly inhibit SO motor function.[15,16] The effect of cholecystokinin, a major hormone with relaxing properties, on the SO was mediated through stimulation of non-adrenergic non-cholinergic (NANC) nerves. Sari et al.[17] found that nitroglycerin increased the cyclic GMP concentration. Neither tetrodotoxin (TTX) nor vasoactive intestinal polypeptide (VIPa) modified this response. It could also increase the cyclic AMP concentration, which was blocked by both TTX and VIPa. This indicated that relaxation of the SO by NO donors involves a glibenclamide-sensitive mechanism which was closely related to increased formation of cyclic AMP but not of cyclic GMP. So we thought the mechanism which was closely related to increased formation of cyclic AMP but not of cyclic GMP. This indicated that relaxation of the SO by NO donors involves a glibenclamide-sensitive mechanism which was closely related to increased formation of cyclic AMP but not of cyclic GMP. Nitroglycerin has been used to reverse the spasm induced by narcotic usage.[21,22] But there was no research in manometry evaluated if nitroester drugs can antagonize the excitatory effect of morphine on Oddi’s sphincter motility. We found that all the three nitroester drugs could antagonize the excitatory induction induced by morphine. But the mechanism was not well known, and needs to be researched further.

The risk of pancreatitis induced by ERCP cannot be eliminated presently. The etiology of ERCP-induced pancreatitis is multifactorial. Attempts to prevent this complication by using administration of glucagon[23,24], nifedipine[25,26], hydrocortisone[27] and octreotide[28] have been disappointing. Somatostatin[29,30] is effective in reducing the incidence of pancreatitis after therapeutic ERCP, but the cost is relatively expensive. Sudhindran et al.[31] found prophylactic treatment with GTN reduced the incidence of pancreatitis following ERCP but did not reduce the extent of hyperamylasemia or the severity of pancreatitis.

In summary, our results indicate that all the three nitroester drugs have inhibitory effects on human SO, they also can antagonize the excitation effect of morphine on SO. Among them the effect of ISDN is most obvious. This action is mediated through stimulation of the NANC nerves. These drugs could be used for several purposes: (1) to remove small- and medium-sized common bile duct stones through intact papillae; (2) to facilitate cannulation of the ampulla in diagnostic ERCP; (3) to relieve the pain caused by biliary colic in patients with SO dysfunction; (4) to reverse the spasm of Oddi’s sphincter induced by narcotic usage; and (5) to reduce the incidence of pancreatitis following ERCP.

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Table 7  Antagonism of PTN against morphine on the SO motility in 10 patients (mean±SD)

|                          | 10 min after morphine administration (control) | 10 min after PTN associated administration | 20 min after PTN associated administration |
|--------------------------|-----------------------------------------------|---------------------------------------------|---------------------------------------------|
| Sphincter of Oddi basal pressure (mmHg) | 13.25±9.63                                    | 10.61±11.00                                 | 13.12±12.09                                 |
| Amplitude of phasic contractions (mmHg) | 100.6±4.44                                    | 75.8±3.21                                   | 66.17±3.55                                  |
| Frequency of phasic contractions (n/min) | 10.70±2.76                                    | 9.95±1.08                                   | 9.04±1.71                                   |
| Common bile duct pressure (mmHg)     | 6.99±6.30                                     | 6.49±3.66                                   | 4.48±1.15                                   |

*P<0.05, *P<0.05 vs themselves, n = 10 (n represents the number of patients involved in the research).
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