Effect of Transdermal Fentanyl Patches on the Motility of the Sphincter of Oddi

Hyun Cheol Koo, Jong Ho Moon, Hyun Jong Choi, Kyoung Hwa Hwang, Hyo Jin Maeng, Hyung Ki Kim, Jong Kyu Park, Su Jin Hong, Young Koog Cheon, Young Deok Cho, Joon Seong Lee, and Moon Sung Lee

Digestive Disease Center, Department of Internal Medicine, Soon Chun Hyang University School of Medicine, Bucheon and Seoul, Korea

Background/Aims: Pain is one of the most troublesome symptoms of pancreatitis. Transdermal fentanyl patches (TFPs) are long-acting analgesics with a reduced risk of dependency. This prospective study evaluated the effect of TFPs on sphincter of Oddi (SO) motility for the management of pain in pancreatitis. **Methods:** SO manometry (SOM) was performed using triple-lumen catheters anterogradely inserted through the percutaneous transhepatic route during cholangioscopy in 16 patients. The basal pressure, amplitude, and frequency of the SO were assessed before and after applying a TFP at 24 hour at doses of 25 and 12.5 μ g/hr, respectively. **Results:** Two of 16 patients receiving a 25 μ g/hr. TFP were excluded because of adverse side effects (headache and/or nausea). The mean basal pressure, amplitude, and frequency of SOM did not change significantly in the 25 μ g/hr TFP group (n=4 patients). Parameters of SO function also did not significantly change in the 12.5 μ g/hr TFP group (n=11 patients). **Conclusions:** TFPs below a dose of 25 μ g/hr may not affect the motility of the SO. Administration of TFPs at lower dosages seems to be a safe analgesic treatment for the pain control of patients with pancreatitis without affecting the function of the SO. (*Gut Liver* 2010;4: 368-372)

Key Words: Sphincter of Oddi manometry; Transdermal fentanyl patch; Pancreatitis

INTRODUCTION

Abdominal pain is a major problem for patients with acute or chronic pancreatitis, and for physicians who manage pancreatitis. Frequently, large doses of narcotic analgesics are required to control the pain. At present, morphine use should be avoided due to its association with spasms of the sphincter of Oddi (SO), which might worsen pancreatitis.^{1,2} Meperidine is recommended for the management of pain due to pancreatitis because it does not elevate SO pressure.¹⁻³ However, meperidine does have some disadvantages. Meperidine has a short action time coupled with a long half-life of toxic metabolites. Most importantly, meperidine produces euphoria, which can rapidly lead to drug dependency.³

Currently, transdermal fentanyl patches (TFPs) have been used widely for cancer pain. The advantages of TFPs include a long-action time, reduced occurrence of withdrawal symptoms, and increased patient comfort. Importantly, these advantages are not associated with opioid-induced euphoria, and resultant drug dependency is rare.⁴ Although TFPs have more advantages compared to meperidine in pain control of pancreatitis, no previous studies have examined the effect of TFPs on SO motility.

The aim of the present study is to evaluate the effect of TFPs on SO motility.

Correspondence to: Jong Ho Moon

Digestive Disease Center, Soon Chun Hyang University Bucheon Hospital, Soon Chun Hyang University School of Medicine, 1174 Jung-dong, Wonmi-gu, Bucheon 420-767, Korea

Tel: +82-32-621-5094, Fax: +82-32-621-5080, E-mail: jhmoon@schbc.ac.kr

Received on January 14, 2010. Accepted on March 31, 2010.

DOI: 10.5009/gnl.2010.4.3.368

MATERIALS AND METHODS

1. Patients

We prospectively studied 16 patients who underwent percutaneous transhepatic biliary drainage (PTBD), with or without a history of cholecystectomy between October 2006 and December 2008. The indications for PTBD were intrahepatic duct (IHD) stones in fifteen patients and difficult common bile duct (CBD) stones failed by conventional lithotripsy procedures in one patient. Patients with a history of previous endoscopic sphincterotomy, pancreatobiliary operation, gastric bypass, acute recurrent pancreatitis, pancreatobiliary malignancy, or suspected sphincter of Oddi dysfunction (SOD) were excluded.

The mean age of the patients was 65.5 years and ranged from 59 to 82 years. Two of 16 patients receiving a 25 μ g/hr TFP (25 μ g TFP) were excluded due to adverse side effects such as headache or nausea. Fourteen patients were enrolled and underwent cholangioscopy for 25 μ g TFP. On next cholangioscopy, 3 of 14 patients were excluded because of completely removed stones, so eleven patients were reevaluated for 12.5 μ g/hr TFP (12.5 μ g TFP) after 1 week later (Fig. 1). The baseline clinical data of patients are shown on Table 1. The study was approved by our institutional review boards. All patients were provided with written informed consent.

Fig. 1. Outline of patient selection and reasons for exclusion. PTBD, percutaneous transhepatic biliary drainage; TFP, transdermal fentanyl patch.

Table 1. Baseline Clinical Characteristics of the Patients

	12.5 μ g TFP	25 μ g TFP
Patients, n	11	14
Age, yr	66.1	64.4
Gender, M/F	4/7	5/9
No. of cholecystectomies	3	4
IHD stones	11	13
CBD stones	0	1

TFP, transdermal fentanyl patch; IHD, intrahepatic duct; CBD, common bile duct.

2. Sphincter of Oddi manometry (SOM)

Medications that could affect the SO were withheld for 48 hours before the procedure. Patients underwent SOM after a 12-hour fast without any sedative agents. A cholangioscope (CHF-P20Q; Olympus Co., Tokyo, Japan) was inserted through the PTBD site with low-flow saline fluid and a triple-lumen 5 Fr catheter into the ampulla in an antegrade fashion through the working channel of the cholangioscope (Fig. 2). The triple-lumen catheter was pulled back from the duodenum to the ampulla for the best position, and then SOM tracing was performed using a water-perfused catheter system (Andorfer Medical Specialists, Glendale, WI, USA). Parameters such as the mean basal pressure, amplitude, and frequency were evaluated by SOM tracing in the same manner as the baseline parameters of all patients before applying the TFP. Follow-up cholangioscopy was performed 3 or 4 days later. Twenty-four hours before a follow-up cholangioscopy was performed, a 25 μ g TFP was applied on the anterior chest to maintain a steady-state plasma fentanyl concentration. During follow-up cholangioscopy, the parameters of SOM were evaluated in the same manner as the baseline parameters. If the patients had remnant biliary stones, a third cholangioscopy was performed 1 week later with a 12.5 μ g TFP, and the parameters were recorded again.

The basal sphincter pressure was recorded as the baseline pressure between phasic waves by normalizing to the duodenal luminal pressure. Recordings were sustained for a minimum of 30 minutes. The mean of all basal sphincter recordings was used as the actual basal sphincter

Fig. 2. Cholangioscopic view showing the antegradely inserted triple-lumen catheter.

Table 2. Changes in Sphincter of Oddi Manometry in the 12.5 and 25 μ g/hr TFP Groups

TFP	Parameters	Before	After	p-value
12.5 μ g	Basal pressure, mm Hg	10.8 $\pm$ 2.3	12.6 $\pm$ 4.1	0.06
	Amplitude, mm Hg	128.1 $\pm$ 31.3	158.6 $\pm$ 27.2	0.06
	Frequency, /min	3.6 $\pm$ 0.7	3.7 $\pm$ 1.2	0.86
25 μ g	Basal pressure, mm Hg	11.3 $\pm$ 3.9	14.2 $\pm$ 5.8	0.28
	Amplitude, mm Hg	116.2 $\pm$ 25.1	151.6 $\pm$ 46.6	0.06
	Frequency, /min	4.1 $\pm$ 1.2	4.5 $\pm$ 0.9	0.42

TFP, transdermal fentanyl patch.

pressure for data analysis. The amplitude of SO contractions (mm Hg) was measured from the peak to the base of the waves, with SO maximal basal pressure as a zero reference. The frequency of SO contractions was measured as the number of waves per minute.

A basal sphincter pressure ≥ 40 mm Hg and tachyoddia were considered abnormal. Tachyoddia was considered to be present when the phasic contraction frequency was greater than 7 per minute by Rome III criteria.^{5,6}

3. Statistical analysis

Values are reported as the mean ($\pm$ SEM). Statistical comparisons between groups were performed using the paired samples t-test. $p < 0.05$ was considered statistically significant.

RESULTS

Three of 11 patients in the 12.5 μ g group and four of 14 patients in the 25 μ g group had cholecystectomy previously. Eleven patients applied a 12.5 μ g TFP without any adverse effects. The SOM of all patients were evaluated successfully. None of the patients had an abnormal basal sphincter pressure prior to administration of the TFP. The effects of the TFP on the SO motility in the 12.5 μ g ($n=11$) and 25 μ g TFP groups ($n=14$) are shown on Table 2.

The basal sphincter pressure of the 25 μ g TFP group was not significantly altered by TFP administration (before, 11.3 $\pm$ 3.9 vs after, 14.2 $\pm$ 5.8; $p=0.28$). These findings were similar in the 12.5 μ g TFP group (before, 10.8 $\pm$ 2.3 vs after, 12.6 $\pm$ 4.1; $p=0.06$).

The mean contraction frequency in the 25 μ g TFP group changed from 4.1 $\pm$ 1.2 per minute to 4.5 $\pm$ 0.9 per minute ($p > 0.05$). The mean contraction frequency in the 12.5 μ g TFP group changed from 3.6 $\pm$ 0.7 per minute to 3.7 $\pm$ 1.2 per minute ($p > 0.05$). No evidence of tachyoddia was observed. Also, the mean SO contraction amplitudes were not statistically different between the 12.5 μ g and 25 μ g TFP groups.

DISCUSSION

Many patients with acute or chronic pancreatitis suffer from abdominal pain, and pain management is one of the cornerstones in the treatment of pancreatitis.⁷⁻⁹ Although experts recommend starting with non-narcotic analgesics followed by weak narcotics, using strong opioids is often necessary. Several papers report that opioids are among the best analgesics in the treatment of the pain of pancreatitis.^{1,7} However, opioid treatment may be complicated or clouded by opiate addiction and dependence.

Several opioid analgesics are used to control the pain of pancreatitis. Of these opioids, meperidine, but not morphine, has been recommended because morphine induces bile flow stasis, SO spasms, and results in increasing the pressure of the CBD and pancreatic duct.^{3,5,10,11} Drawbacks of meperidine compared to other opioids include renal dysfunction, tremors, and convulsions due to the accumulation of the metabolite normeperidine.¹² One important disadvantage of meperidine is the development of dependency due to euphoria.

TFPs contain a synthetic opioid agonist that is equally effective as oral morphine.⁴ TFPs have a lower incidence and impact of side effects. Patients prefer TFPs because they are easy to use.^{13,14} The advantages of TFPs are long-acting times, minimal occurrence of withdrawal symptoms, and enhanced patient comfort. Importantly, the opioid-induced euphoria and resultant drug dependency are rare because of slow release and maintenance concentration of TFPs.⁴

Occasionally, TFPs are used for the severe pain associated with chronic pancreatitis.¹⁵ However, the effect of TFPs on the SO has been uncertain.

SOM has been used widely in the assessment of patients for SO dysfunction. This procedure can be performed during surgery, percutaneously (transhepatic or via T-tube tract), but is most commonly utilized during ERCP. When performed during ERCP, this procedure is technically demanding, associated with procedure-related pancreatitis, and has a failure rate of up to 20%, even in

expert hands.^{5,16} In the present study, SOM performed through the PTBD site was evaluated for a higher success rate, fewer complications, and greater reproducibility. All patients felt comfortable during SOM, and no sedation was needed.

Our results show that TFPs up to 25 $\mu\text{g/hr}$ dosage do not statistically alter basal sphincter pressure, amplitude, or frequency. Only two patients refused TFP treatment due to nausea or headache. Except for two cases, no procedure-related adverse effects were observed in any patient who underwent SOM with 12.5 and 25 μg TFPs. Abnormal parameters such as a basal sphincter pressure greater than 40 mm Hg or tachyoddia were not observed.

Several limitations of this study should be noted. Our study included one case of CBD stones showing normal manometric findings. Yuasa *et al.*¹⁷ reported that there was no significant difference in the SO basal pressure and amplitude among the location of stones and cholecystectomy. However, there may have been an effect of the presence of CBD stones on baseline manometric findings. Some patients with CBD stones can be related with SO motility disorder. Therefore, our study excluded patients with suspected SOD before applying the TFP.

This study involved a small number of cases and did not evaluate for the higher doses of TFPs ($>25 \mu\text{g/hr}$). Therefore, the result of this pilot study could be changed if the number of enrolled cases increases and the higher dose of TFPs are used, especially in the patients with pancreatitis who have moderate to severe pain. Therefore, multicenter studies using TFPs with higher doses are needed to confirm our results.

Although our method of evaluating SOM through the PTBD site was a safer and easier procedure compared to conventional ERCP, it did not exactly reflect the pressure of the pancreatic duct. The best method to relate TFPs with the pancreatic duct is to measure the pancreatic duct pressure directly, but the present study did not include the evaluation of the pancreatic duct. However, since the CBD and pancreatic duct pressures are much lower than those in the SO, our study is still valid using indirect methods. Future studies directly measuring pancreatic duct pressure will be necessary to determine the exact effect of TFPs on the pancreatic duct. And also, enrolled patients did not have pancreatitis and may have different sphincter motility compared to those with pancreatitis. However, it is actually difficult to investigate the patient with pancreatitis.

In conclusion, the results of the present study suggest that administration of TFPs seems to be a safe medical treatment for pain control in patients with pancreatitis regarding its effects on the SO. Further studies should be

performed to advance our findings.

ACKNOWLEDGEMENTS

We thank nursing staffs at our Digestive Disease Center for their assistance in this study.

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