Opium addiction as a new risk factor of Sphincter of Oddi dysfunction

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Summary

Background:
Sphincter of Oddi dysfunction (SOD) refers to an abnormality of SO contractility. It is a benign, non-calculus obstruction to the flow of bile or pancreatic juice through the pancreaticobiliary junction. Although morphine can cause an excitatory effect on SO motility, there are no comprehensive data about opium as a risk factor in inducing SOD in chronic opium abusers. The aim of the study was to assess potential risk factors, especially opium addiction (OA), in patients with SOD.

Material/Methods:
In a case-control study, opium addiction, cigarette smoking, cholecystectomy, and periampullary diverticulum in patients with SOD were recorded and compared with healthy subjects. SOD was diagnosed by the Geenen-Hogan classification (type I).

Results:
OA (p<0.001) and cholecystectomy (p<0.001) were two independent risk factors in patients with SOD.

Conclusions:
Chronic use of opiates by the oral or inhalational route may induce SOD, but whether chronic use of other morphine derivatives or i.v. drug abuse induce this disorder is not clear and needs further evaluation.

key words: addiction • opium • morphine • SOD • Sphincter of Oddi

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BACKGROUND

The sphincter of Oddi (SO) is the smooth muscle connection between the bile duct and the duodenum. Its physiological function is associated with regular motility characterized by phasic contractions superimposed on the sphincter of Oddi baseline pressure [1]. Sphincter of Oddi dysfunction (SOD) refers to an abnormality of SO contractility. It is a benign, noncalculous obstruction to the flow of bile or pancreatic juice through the pancreaticobiliary junction. SOD may be clinically manifested by pancreaticobiliary pain, pancreatitis, or deranged liver function tests [2].

Although morphine can cause an excitatory effect on SO motility and can increase intrabiliary ductal pressure and delay bile flow to the duodenum [3], there are no comprehensive data about opium as a risk factor in inducing SOD in chronic opium abusers. Opiates or opium, as illicit drugs, contain morphine and their use has increased worldwide in recent years, most abusers using the drugs in three forms: heroin, cocaine, and raw opium. The aim of the study was to assess the potential risk factors, especially opium addiction (OA), in patients with SOD.

MATERIAL AND METHODS

In a study from April 2000–2005, all consecutive patients with SOD who referred for sphincterotomy to our department were evaluated. The diagnosis was according to the Geenen-Hogan classification. The patients had no biliary obstructive lesion based on abdominal computed tomography and ERCP and only patients with type-I Geenen-Hogan [4,5] enrolled in the study. The exclusion criteria were: intake of drugs which affect the sphincter, including either relaxants (anti-cholinergic, nitrates, calcium channel blocker, glucagon) or spastic drugs (cholinergic and narcotics) [2] except for morphine and its derivatives in recent weeks prior to the study; a past history of gastrointestinal surgery except cholecystectomy; abnormal findings in liver sonography; patients with liver cirrhosis, renal failure, diabetes mellitus, or other serious severe concomitant illnesses; positive results of anti-HIV, anti-HCV or HBsAg serum markers; and unreliable patients and patients who did not tolerate the ERCP procedure.

A control group was selected during the same time among dyspeptic subjects who were referred for endoscopy and had no history or clinical evidence of hepatic or GI tract diseases. The patients underwent upper GI endoscopy with the side-view procedure and hepatic ultrasonography. Other tests, including blood indices, liver, renal, and thyroid function tests, and anti-HIV, anti-HCV, and HBsAg were also done. The patients with normal findings were enrolled in the study.

The exclusion criteria were similar in both groups. The groups were matched based on age, sex, and social status. A questionnaire was administered to each participant. The questions regarding opium (and tobacco, alcohol, Nass [a traditional addictive drug]) use were: “Have you ever used opium at least weekly over a six-month period?” If the subject responded with yes, they were asked to indicate the amount and duration; the opium amount was defined in five categories from once a week to more than six times a day. These habits together with demographic data, cholecystectomy history, and periampullary diverticulum were recorded and compared. OA was defined as the use of opium daily for at least one year and tobacco smoking as use of more than one year/pack cigarettes. Diverticula near the papilla or at its edge were recorded. All patients gave written informed consent before entering the study and the protocol was approved by ethics committee of Semnan University of Medical Sciences. The validity and reliability of the self-reported opium-use questionnaire has been assessed in a previous study [6].

Statistical analysis

The independent sample t-test was used to compare the means of the ages. The chi-squared and, if indicated, Fisher’s exact tests were used to compare qualitative variables. Variables that achieved statistical significance in univariate analysis were subjected to multivariate analysis (multi-variable regression). We used stratified analysis (Mantel-Hansel odds ratio) for probable confounding variables. Two-sided p values less than 0.05 were considered to be statistically significant. All of these calculations were carried out using the SPSS version 11.5 program package.

RESULTS

Twenty-six patients with SOD were referred to our GI clinic for sphincterotomy. Two cases were omitted because of underlying diseases and incomplete data. The remaining patients were enrolled in the study. Sphincterotomy was successful in 21 and was not in 3 cases (one addicted). All data and findings are presented in Table 1. The mean duration of symptoms was 24.3 days (range: 7–60 days). None of the patients were i.v. drug abusers. The routes of opium administration were smoking in 6 (67%) and oral in 3 (33%) patients and the type of opium used was raw opiate in 7 (78%) and shi neh (a refined opium product) in two patients (22%). Duration of the addiction was 3.5 years in one patient and more than 10 years in others (in 3 cases more than 20 years), with a mean of 14.4±5.2 years. Eight of the 11 males (72.7%) and 1 of the 13 females (7.6%) were addicted. It was shown that in this area, self-reported use of illicit drugs can be reliable and valid and is similar to reports from other populations [7].

In univariate analysis only two risk factors were found to be significantly discriminatory, i.e. OA (p<0.001) and cholecystectomy (p<0.001), as positive risk factors. In contrast, cigarette smoking and periampullary diverticulum were not discriminatory. In a multi-variable regression analysis, OA (p<0.001) and cholecystectomy (p<0.001) remained independently discriminatory. Moreover, by Mantel-Hansel analysis the SOD odds ratio was 25 time greater in patients addicted to opium (OR=25.5, P=0.006).

DISCUSSION

The duration of opium administration was at least 3.5 years in patients with OA; this means that chronic use of an opiate by the oral or smoking route was a risk factor for this disorder.

SOD may occur in pediatric or adult patients at any age; however, patients with SOD are typically middle-aged fe-
males. This disease affects females more frequently than males and has indicated a high association with work absenteeism, disability, and healthcare use. Cholecystectomy is a known risk factor for this disorder [4,5]. Manometry is the diagnostic test of choice for SOD, but it was not necessary to perform it in patients with type-I Geenen-Hogan classification. Although SOD most commonly occurs after cholecystectomy [2,8], it may be present with the gallbladder in situ. Cholecystectomy, at least in the short-term, suppresses the normal inhibitory effect of pharmacological doses of CCK on the SO. The mechanism of this effect is unknown [8]. Morphine and its derivatives can increase sphincteric tonicity and result in SOD. Manometry studies showed that morphine can increase the basal pressure of the sphincter, the common bile duct pressure, and the frequency and amplitude of phasic contractions [9,10]. The effects of morphine on the sphincter are mediated by more than one opioid receptor [10,11]. Thus its effects are more complex than once believed [10–12]. Therefore, morphine can be used as a stimulatory test in diagnosing of SOD [2].

Although morphine may be a cause of SOD, the effect of chronic opiate abuse in inducing SOD is unknown. Opiates are analgesic drugs and can induce euphoria, so they are often abused as illicit drugs. In recent years, OA has been a major problem in Iran. Iran’s neighbor Afghanistan is the largest opium producer and along the road of poppy transit to Europe. Based on a WHO report, more than 2.8% of the adult population of Iran is addicted [13]; in one study the prevalence of addiction among rural men in the north of this country was even 21% [6]. In Iran, opium is typically either eaten or smoked in one of three forms: raw opium; sookhteh, or opium dross, the pyrolized opium residue that is scraped from opium pipes; and shireh, a refined opium product made by boiling either raw opium or sookhteh and collecting the residue; other drugs such as heroin or cocaine are rare [6]. In this study, no patients were i.v. drug abusers.

The first report about the effects of OA in inducing SOD was by Sharma, who reported eight patients in chronic OA patients in 2001[14]. Our study is the first report evaluating opium as a risk factor of SOD. It is interesting that in males the likely cause for SOD is OA, so if we ignore the addicted patients, the results are similar to a previous report in which the disease was seen more in females, particularly patients with cholecystectomy [4]. We think that in OA, chronic use of an opiate increases the tonicity of the sphincter, which terminates to SOD.

Even though the size of the common bile duct (CBD) increases with age and in healthy females [15–17], we showed that the diameter of the CBD in OA was more than in the control group and its size had a direct relation to addiction duration [18]. We did not find any causes for this, but we think that the use of opium for a long time resulted in CBD dilatation by inducing sphincter spasm, although dilatation of the common bile duct alone is insufficient evidence for establishing the diagnosis of SOD [15,16]. One of our study’s limitations was that patients in the control group may have had SOD type III, which is diagnosed only by manometry, but due to its risks and ethical issues we could not perform it.

**CONCLUSIONS**

Although SOD is a heterogonous disorder in which many factors play roles in its induction, this study showed that chronic use of opium by the oral or inhalational route may be one of the several risk factors which induce it. A well-defined GI complication of OA is constipation because opiates decrease colon motility [19]; now we have added SOD to its complication list. The possibility that chronic use of other morphine derivatives or i.v. drug abuse induce SOD needs further evaluation.

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**REFERENCES:**


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