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Opioid-induced esophageal dysfunction — prevalence and manometric findings

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ABSTRACT

Background: prescription opioid use is on the rise. There has been an increasing recognition that chronic opioid consumption can result in esophageal motility disorders, and this association has been named opioid-induced esophageal dysfunction (OIED).

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Aims: to analyze the prevalence of chronic opioid consumption in patients referred for esophageal motility testing in a European center; to describe the clinical characteristics and the association of opioid consumption with esophageal motility disorders.

Methods: a retrospective, descriptive study in patients who had undergone an HRM in a single center. The clinical history in the electronic medical records was reviewed.

Results: the prevalence of opioid prescription in patients referred to our institution was 10.1 %, and 4.8 % of them were chronic active opioid users. There was a 32 % prevalence of OIED. Comparing chronic active opioid users (CAOU) with OIED and CAOU patients without OIED, there was a higher prevalence of males (43.8 % vs 8.8 %; p-value = 0.007). Converting the different opioid medications to morphine milligram equivalent daily dose (MMED), CAOU patients with OIED had a higher MMED than CAOU patients without OIED (125.2 ± 31.3 vs 33.4 ± 5.7 MME; p = 0.041). Dysphagia was the most common indication for performing an HRM in 60.0 % of CAOU patients. Furthermore, dysphagia was more frequent in CAOU patients with OIED (87.5 % vs 47.0 %; p = 0.019).

Conclusions: chronic opioid users with OIED complained mostly of dysphagia. There was an association of male sex and a higher dose of opioids in CAOU patients with esophageal motility disorders.

Keywords: High-resolution manometry. Dysphagia. Opioids. Motility. Esophagus.

INTRODUCTION

Over the last 20 years there has been a dramatic increase in the use of prescription opioids in the western world, especially in North America (1). In Europe, prescription opioids are on the rise but at a much slower rate (2). Opioids have pharmacological effects throughout the gastrointestinal tract, and long-term consumption of opioids due to both cancer and non-cancer pain has been associated with an extensive variety of adverse effects, collectively known as opioid-induced bowel dysfunction (3). Even though opioid-induced constipation is the most common and frequently reported side

effect, many other gastrointestinal side effects such as gastroparesis, acute postoperative ileus, or anal sphincter dysfunction have been described (4).

During the past decade, it has been increasingly recognized that chronic opioid consumption can result in esophageal motility disorders, and this association has been accurately named opioid-induced esophageal dysfunction (OIED) (5). Although an increasingly recognized condition, OIED has been mostly described in American studies, and data on the impact of this new entity in Europe is lacking.

The aim of this study was to analyze the prevalence of chronic opioid consumption in patients referred for esophageal motility testing to a European center, to describe the associated clinical characteristics, and to assess the potential contribution of opioid consumption to the identification of esophageal motility disorders.

METHODS

Patient selection

This was a retrospective, descriptive study in a single center of all consecutive patients, regardless of age, who had undergone high-resolution esophageal manometry (HRM) at the Vall d'Hebron University Hospital between May 2018 and February 2020. The study protocol was approved by the Institutional Review Board at Hospital Vall d´Hebron.

Clinical data extraction

The electronic prescription reports of these patients were reviewed for opioid medication up to one year before the HRM for an initial screening of patients. In a second step, the electronic clinical and prescription reports were reviewed to assess that patients were on active opioid medication during the HRM study. Patients with known esophageal motility disorders, anatomical disorders, prior esophageal surgery, or incomplete clinical or manometric data were excluded from the analysis. Clinical, demographic and manometric data were obtained from the electronic medical records. The clinical history in the electronic medical reports was reviewed to determine: a) the indication for opioid treatment, and b) to ensure that opioid

treatment preceded the symptoms leading to the HRM study. To standardize different opioid dosages, the oral morphine milligram equivalent daily dose (MMED) of opioids was calculated for each medication as a product of the prescribed dose, dose frequency, and a drug-specific standard conversion factor (6).

HRM data analysis

Patients were studied in the morning after an overnight fast in the supine position. Following the hospital protocol, medications known to alter esophageal motility testing (calcium channel blockers, buspirone, benzodiazepines) were stopped one day before the study. HRM studies were performed using a catheter (outer diameter: 4.2 mm) with 36 solid-state sensors spaced at 1-cm intervals (Medtronic, Inc., Shoreview, MN, USA). The catheter was calibrated between 0 and 300 mmHg and zeroed to atmospheric pressure before intubation. After calibration, the catheter was passed trans-nasally, and fixed by taping to the nose when the pressure from the pharynx to the stomach was recorded simultaneously. Subjects had a 5 minute adaptation period and the responses to 10 swallows of 5 mL of water administered with a syringe were recorded. HRM tracings were analyzed using commercial analysis software (ManoView, Medtronic, Shoreview, MN, USA). The Manoview software-generated automated analysis was discarded. High-resolution topographical plots of each patient's swallows were analyzed and categorized in a standardized, stepwise manner.

HRM outcome measures

The following HRM parameters were analyzed: a) integrated relaxation pressure (IRP); b) distal latency (DL), and c) distal contractile integral (DCI). The 4-s IRP of 15 mmHg was considered the cutoff threshold for abnormal relaxation of LES (7). Additional pressure metrics of lower esophageal sphincter (LES) resting pressure were also recorded. The Chicago classification of esophageal motility disorders v3.0 (7) was used to classify peristaltic patterns of individual swallows and subsequently categorize the patients into one of the motility disorders, if any abnormalities were found.

Patient's group classification

Patients were classified into two groups according to HRM diagnosis. Patients with opioid-induced esophageal dysfunction (OIED) were defined by the presence of esophagogastric junction outflow obstruction (EGJOO), distal esophageal spasm (DES), achalasia type III, or jackhammer esophagus (JE) on the HRM study (5). Patients with no contractility, ineffective esophageal motility, fragmented peristalsis and normal manometric study were defined as patients without OIED.

Statistical analysis

The statistical analysis was performed using commercial software (SPSS 20.0, SPSS Inc., Chicago, Illinois, USA). Descriptive statistics were used to characterize all patients included. Continuous variables are shown as means and standard deviation, and categorical variables are shown as n (%), unless otherwise stated. The Kolmogorov-Smirnov test was used to check the normality of data distribution. Fisher's exact test was used for two-group comparisons of categorical variables (demographics, HRM study indication, opioid medication). Opioid medication was categorized as a weak agonist (tramadol) or strong agonist (other opioids). For two-group comparisons of quantitative variables (age, LES resting pressure, and MMED), between-group differences were analyzed using the Mann-Whitney U-test. Statistical significance was defined as a p-value < 0.05.

RESULTS

A total of 1,317 patients underwent an HRM during the study period. The prevalence of opioid prescription in patients referred to our institution for a HRM study was 10.1 % (n = 133). Of these, 63 patients (4.8 %) were chronic active opioid users (CAOU) when the HRM study was performed. A previous diagnosis of primary esophageal motor disorder or esophagogastric junction (EGJ) surgery were found in 13 patients, who were excluded from the analysis. A total of 50 patients on CAOU were included in the study. Of these, 16 (32.0 %) patients on CAOU met the criteria for OIED. The HRM diagnosis according to CC v3.0 is described in table 1.

Overall, there was a clear predominance of the female sex 80 % (n = 40), with a mean age of 66.7 (± 12.8) years. Comparing CAOU patients with OIED and CAOU patients

without OIED, there were no differences in comorbidities such as gastroesophageal reflux disease (GERD) (31.2 % vs 20.5 %; p-value = 0.410) or autoimmune diseases known to alter esophageal motility (12.5 % vs 17.6 %; p-value = 0.643) (Table 1). Of note, there was a higher prevalence of male sex in patients with OIED (43.8 % vs 8.8 %; p-value = 0.007) (Table 2).

Opioid prescription

Data regarding the indication for opioid use were available for 46 patients — chronic back pain in 18 (39.1 %), osteoarthritis in 11 (23.9 %), and fibromyalgia in 8 (17.4 %) were the most common indications for opioids. Interestingly, only two (4.3 %) patients were taking opioids for a cancer-related indication.

The most commonly prescribed narcotic medication was tramadol in 58.0 % (n = 29) of cases; other opioids used by patients are shown in table 1. There were no differences between CAOU patients with OIED and CAOU patients without OIED in the type of opioid prescription (tramadol, 56.2 % vs 58.8 %; p-value = 0.863; other opioids, 43.8 % vs 41.2 %; p-value = 0.863). However, when converting the different opioid medications to MMED, CAOU patients with OIED had a higher MMED than CAOU patients without OIED (125.2 ± 31.3 vs 33.4 ± 5.7 MME; p-value = 0.041) (Table 2).

All 50 CAOU patients started opioid treatment before developing esophageal symptoms. Furthermore, ten CAOU patients with OIED developed esophageal symptoms within 12 months (median, 5 months; range, 1-12 months) after initiating treatment with opioids. Nine patients complained of new-onset dysphagia and one patient had a worsening of previously well-controlled regurgitation. The remaining 40 CAOU patients were on opioids for more than one year before the HRM study was performed, and we could not establish a specific timeline between initiation of opioid treatment and esophageal symptoms.

HRM study

Non-obstructive dysphagia was the most common indication for performing a HRM in 60.0 % (n = 30) of CAOU patients, followed by suspicion of gastroesophageal reflux disease in 32.0 % (n = 16) (Table 1). Other indications for a HRM study were: suspicion

of systemic autoimmune disease in 4.0 % (n = 2), non-cardiac chest pain in 2.0 % (n = 1), and presurgical evaluation of a large hiatus hernia in 2.0 % (n = 1). The study of non-obstructive dysphagia was more frequent in CAOU patients with OIED compared to CAOU patients without OIED (87.5 % vs 47.0 %; p = 0.019) (Table 2). Interestingly, 80 % of CAOU patients without OIED with a hypertensive LES had undergone an HRM for non-obstructive dysphagia.

Evaluating HRM parameters and comparing CAOU patients with OIED and CAOU patients without OIED, CAOU patients with OIED had a significantly higher mean LES resting pressure (41.0 ± 20.9 vs. 27.9 ± 18.3 mmHg, p-value = 0.029) and a higher prevalence of hypertensive LES (62.5 % vs 29.4 %, p-value = 0.034) (Table 2).

DISCUSSION

In our study, we found a prevalence of chronic opioid use in 4.8 % of patients referred for esophageal motility testing, and a prevalence of OIED of 32.0 % in CAOU patients. Clinically, the indications for chronic opioid treatment were mostly non-cancer-related; patients on CAOU with OIED complained mostly of non-obstructive dysphagia and, in our study, there was an association of male sex and higher dose of opioids with the presence of OIED.

Opioids are widely indicated for pain management, anesthesia, and cough treatment. Prescription opioid use has become a global epidemic with substantial increases in opioid prescriptions occurring in Western countries (8). Although the use of opioids in Europe may not be perceived as an “epidemic” like it is in North America, the trends show consistent increases across Western European countries (9). Particularly in Spain, this increase in opioid consumption is mostly due to fentanyl and tramadol (10). In our series, tramadol was the most frequently prescribed opioid, followed by fentanyl, which is in accordance with national trends in Spain.

The prevalence of opioid prescription in patients referred for HRM testing was 10.1 % and almost half of these patients (4.8 %) were CAOU. As expected, the prevalence of opioid use in our study was lower compared to the prevalence in studies performed in North America. In the study by Ratuapli et al. (5), the authors report that up to 19 % of patients referred for HRM testing in their unit were on opioid medication. In our study

we found a lower prevalence of opioid prescription. The study by Babaei et al. (11) reported a 10 % prevalence of CAOU patients referred for esophageal motility testing, which is double the prevalence of CAOU patients we found in our study. Nonetheless, opioid prescription is on the rise in Europe and therefore we can expect an increasing incidence of OIED. Saez-Gonzalez et al. (12) performed a prospective study of patients on chronic opioids complaining of dysphagia in a 15-month period in Spain. They reported 5 patients with OIED (3 with EGJOO and 2 with type-III achalasia) in their study. Interestingly, in their study opioid medication could not be withdrawn in any of the patients. We found 3 times more cases of OIED in a similar period compared to their study, although we evaluated patients retrospectively. We can assume that OIED will become more common in the near future.

The effect of opioids on esophageal motility consists mainly of LES alterations. In healthy volunteers, acute opioid administration results in increased LES basal pressure and incomplete LES relaxation (13,14). Saez-Gonzalez also described a clinical case with OIED associated to EGJOO, and the resolution of the esophageal motility disorder after suspending the treatment with opioids (15). Interestingly, the administration of opioid-antagonist naloxone and methylnaltrexone did not significantly alter esophageal contractile response to deglutition or distention (16), and thus the mechanism responsible for these effects is still not fully understood. When analyzing HRM metrics of CAOU patients with OIED, we found a significantly higher mean LES resting pressure value as compared to patients without OIED, and this finding is consistent with those reported by American studies (5,12). Of note, CAOU patients with OIED had a significantly higher prevalence of hypertensive LES. Even though this finding has been described in previous studies, we found an association with hypertensive LES and non-obstructive dysphagia as the indication to perform the HRM study.

In CAOU patients, non-obstructive dysphagia was the most common reason to perform a HRM, and it was significantly more common in CAOU patients with OIED than in CAOU patients without OIED. Furthermore, non-obstructive dysphagia was also more common in CAOU patients with a hypertensive LES, even in the absence of major esophageal motility disorder on HRM. Schindler et al. (17) performed a study to

evaluate the effects of the association of opioid treatment and alcohol intake on EGJ disorders. They found that non-obstructive dysphagia is more common in patients taking opioids, even in the absence of quantifiable EGJOO disorders, thus suggesting either a subclinical outlet dysfunction or an influence on the sensory component. In the study by Babaei et al. (11), the authors also report a higher prevalence of dysphagia in chronic opioid users compared to naive patients referred for HRM testing. Interestingly, in the study by Snyder et al. (18) dysphagia was the most common indication for performing a HRM, and non-obstructive dysphagia was more frequent in patients with OIED. However, the suspicion of reflux disease was the most common indication for performing HRM testing in patients without OIED, which is similar to our findings. Cifuentes et al. (19) evaluated patients with no cardiac chest pain taking opioids who underwent HRM and ambulatory pH monitoring testing. Of note, they found that opioid consumption was associated with a significantly lower esophageal total acid exposure. They attribute this finding to a higher LES resting pressure, which reduces reflux episodes, and a greater DCI, which may enhance esophageal acid clearance. These findings suggest that CAOU patients complain mostly of non-obstructive dysphagia, and that a hypertensive LES is suggestive of opioid activity, even in the absence of a major motility disorder during a HRM study.

In our study we found an association between male sex and CAOU patients with OIED. Our findings are in contrast to those of previous American studies, as there were no differences between genders in CAOU patients with OIED in them. There are some gender differences in prescription opioid misuse that could justify this association. According to one study, men are more likely to increase opioid dose without authorization, and are more likely to abuse alcohol and other illicit drugs (20). As stated previously, alcohol consumption has been associated with EGJOO disorders (17), and OIED is more frequent with higher doses of opioids. Nonetheless, prospective data are needed to clarify the meaning of this association.

Our study has some limitations. First, we cannot ascertain a causal relationship between OIED and chronic opioid usage due to the retrospective nature of the study. Therefore, our findings can only suggest that there is an association. However, opioid medication was started a few months before they developed esophageal symptoms in

10 out of 16 patients. Whether opioids are the primary cause or they exacerbate an underlying esophageal disorder remains to be determined. Another limitation of our study is the small sample size and the absence of a control group without exposure to opioids. Although the study was performed with patients from a wide geographical area, this was a single-center study, which limits generalizability. To our knowledge, this study is the first to describe the prevalence of chronic opioid consumption and the prevalence of OIED in patients referred for esophageal motility studies in a European center. Future prospective studies are needed to confirm whether there is a causal relationship between opioid treatment and esophageal motility disorders.

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Table 1. Demographic characteristics of chronic active opioid users

	Chronic active opioid users (N = 50)
Mean age, years ± SD	66.7 ± 13.1
Age range	35-89
Gender, female (%)	40 (80)
Associated diseases	
GERD, n (%)	12 (24 %)
Autoimmune disease, n (%)	8 (16 %)
Neck and head radiotherapy, n (%)	1 (2 %)
Opiate medication	N = 50
Tramadol, n (%)	29 (58 %)
Fentanyl*, n(%)	8 (16 %)
Oxycodone*, n (%)	5 (10 %)
Buprenorphine, n (%)	4 (8 %)
Metadone, n (%)	2 (4 %)
Tapentadol*, n (%)	2 (4 %)
Indication for opioid treatment, n (%)	N = 46 (92 %)
Chronic back pain, n (%)	18 (39.1 %)
Osteoarthritis, n (%)	11 (23.9 %)
Fibromyalgia, n (%)	8 (17.4 %)
Other, n (%)	5 (10.9 %)
Indication for HRM study	N = 50
Non obstructive dysphagia, n (%)	30 (60)
GERD suspicion, n (%)	16 (32)
Other, n (%)	4 (8)
HRM diagnosis CC v3.0	N = 50
Normal HRM, n (%)	22 (44)
Ineffective esophageal motility, n (%)	12 (24)
Jackhammer esophagus, n (%)	8 (16)

EGJ outflow obstruction, n (%)	4 (8)
Distal esophageal spasm, n (%)	3 (6)
Achalasia type III, n (%)	1 (2)
HRM LES metrics	
Mean LES resting pressure, mmHg (SD)	42.1 ± 20.1
Hypertensive LES (> 40 mmHg), n (%)	20 (40)

EGJ: esophagogastric junction; GERD: gastroesophageal reflux disease; HRM: high-resolution manometry; LES: lower esophageal sphincter; SD: standard deviation. *Five patients with concomitant use of tramadol, 2 patients with fentanyl, 2 patients with tapentadol, and one patient with oxycodone.

Table 2. Comparison between CAOU patients with OIED and CAOU patients without OIED

	CAOU patients with OIED (n = 16)	**CAOU patients without OIED (n = 34)**	*p*-value
Mean age years (range)	71 (35-83)	65 (26-89)	0.758
Gender, Male, n (%)	7 (43.8)	3 (8.8)	0.007
Associated diseases			
GERD, n (%)	5 (31.2)	7 (20.5)	0.410
Autoimmune disease, n (%)	2 (12.5)	6 (17.6)	0.643
Neck and head radiotherapy, n (%)	0	1 (6.2)	
Indication for HRM study			
Non-obstructive dysphagia, n (%)	14 (87.5)	16 (47.0)	0.019
GERD suspicion, n (%)	1 (6.3)	15 (44.1)	0.007
Other, n (%)	1 (6.2)	3 (8.9)	0.754
Opioid medication			
Tramadol	9 (56.2)	20 (58.8)	0.863
Other opioid	7 (43.8)	14 (41.2)	0.863
Morphine equivalent dosing, mg (SD)	125.2 ± 31.3	33.4 ± 5.7	0.041
HRM LES metrics			
LES resting pressure, mmHg (SD)	41.0 ± 20.9	27.9 ± 18.3	0.029
Hypertensive LES (> 40 mmHg), n (%)	10 (62.5)	10 (29.4)	0.034

EGJ: esophagogastric junction; GERD: gastroesophageal reflux disease; HRM: high-resolution manometry; LES: lower esophageal sphincter; SD: standard deviation; OIED: opioid-induced esophageal dysfunction. Fisher´s exact test was used to compare categorical variables. The Mann-Whitney U-test was used to compare continuous variables.