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Opioid-induced esophageal dysfunction, prevalence and manometric findings

Luis Gerardo Alcalá-González (ORCID 0000-0003-3247-1539)[1,2], Alba Jimenez-Masip (ORCID 0000-0003-0502-0185)[1], Lucia Relea-Pérez (ORCID 0000-0002-3673-5346) [3], Claudia Barber-Caselles (ORCID 0000-0003-4711-2731) [1,2], Elizabeth Barba-Orozco (ORCID 0000-0002-5986-6592) [4].

[1]Gastroenterology Department. Vall d'Hebron Hospital Universitari. Vall d'Hebron. Barcelona. Spain.

[2]Facultad de Medicina. Universitat Autònoma de Barcelona. Bellaterra. Spain.

[3]Gastroenterology Department. Hospital Universitario Puerta de Hierro. Madrid. Spain.

[4]Gastroenterology Department. Neurogastroenterology and Motility Unit. Hospital Clinic of Barcelona. University of Barcelona. Barcelona. Spain

Corresponding authors: Elizabeth Barba Orozco.

Department of Gastroenterology, Neurogastroenterology and Motility Unit, Hospital Clínic, Barcelona, Spain. C. de Villarroel, 170, 08036 Barcelona, Spain

E-mail : BARBA@clinic.cat

ABSTRACT

Background

Prescription opioids usage 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).

Aims

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

Methods

Retrospective descriptive study in patients who had HRM performed in a single center. The clinical history in the electronic medical reports was reviewed.

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Results

The prevalence of opioid prescription in patients referred to our institution was 10.1 % and 4.8 % patients were on active chronic opioid use. We found a 32 % prevalence of OIED. Comparing chronic active opioid user (CAOU) patients with OIED and CAOU patients without OIED, there was a higher prevalence of male sex (43.8 % vs 8.8 % p value=0.007). Converting the different opioids medication 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 % in CAOU patients. Furthermore, dysphagia was more frequent in CAOU patients with OIED (87.5 % vs 47.0 % p= 0.019).

Conclusions

Patients on chronic opioids with OIED complained mostly dysphagia. We found an association of male sex and a higher dose of opioids in CAOU patients with esophageal motility disorders

Abbreviations used in this paper

CAOU chronic active opioid user **DCI** distal contractile integral DES distal esophageal spasm **DL** distal latency EGJ esophagogastric junction **EGJOO** esophagogastric junction outflow obstruction **GERD** gastroesophageal reflux disease **HRM** high resolution esophageal manometry **IRP** integrated relaxation pressure **JE** jackhammer esophagus **LES** lower esophageal sphincter **MME** morphine milligram equivalent MMED morphine milligram equivalent daily dose **OIED** opioid-induced esophageal dysfunction

Keywords

High resolution manometry, dysphagia, opioids, motility, esophagus

INTRODUCTION

Over the last 20 years, the use of prescription opioids has seen a dramatic increase 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, 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 there has been an increasing recognition 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 in a European center and to describe the clinical characteristics and the potential contribution of opioids consumption in the detection of esophageal motility disorders.

METHODS

Patient selection

Retrospective descriptive study in a single center of all consecutive patients regardless of age who had high resolution esophageal manometry (HRM) performed at Vall d'Hebron University Hospital between May 2018 and February 2020. The study protocol had been approved by the Institutional Review Board of the University 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 and those with incomplete clinical or manometric data were excluded from 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, we calculated the oral morphine milligram equivalent daily dose (MMED) of opioids 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 supine position, following hospital protocol, medication known to alter esophageal motility testing (calcium channel blockers, buspirone, benzodiazepines) was stopped one day prior to 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 it to the nose when the pressure from pharynx to the stomach was recorded simultaneously. Subjects had a 5 minute adaptation period and the responses to 10 swallows of 5 mL 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 15mmHg was considered the cutoff threshold for abnormal relaxation of LES (7). Additional pressure metrics of lower esophageal sphincter (LES) resting pressure was 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 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 the presence of absent contractility, ineffective esophageal motility, fragmented peristalsis and normal manometric study were defined as patients without OIED.

Statistical Analysis

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. For two group comparison of categorical variables (demographics, HRM study indication, opioid medication), Fisher's exact test was used, Opioid medication was categorized as weak agonist (tramadol) or strong agonist (other opioids). For two group comparison of quantitative variables (age, LES resting pressure and MMED), between-group differences were analyzed using Mann-Whitney U test. Statistical significance was defined as p Value < 0.05.

RESULTS

A total of 1317 patients underwent an HRM during the study period. The prevalence of opioid prescription in patients referred to our institution for HRM study was 10.1 % (n=133). From these, 63 patients (4.8 %) were on chronic active opioid use (CAOU) when the HRM study was performed. Patients with previous diagnosis of primary esophageal motor disorder or esophagogastric junction (EGJ) surgery were found in 13 patients and were excluded from analysis. A total of 50 patients on CAOU were included in our study. From 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 female sex 80 % (n=40), with a mean age 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).

Noteworthy, 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 11 (23.9 %) and fibromyalgia 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 58.0 % (n=29), other opioids used by patients are shown in table 1. There were no differences between CAOU patients with OIED and CAOU 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). But, when converting the different opioid medication 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 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 the initiation of opioid treatment and the esophageal symptoms.

HRM study

Non-obstructive dysphagia was the most common indication for performing an HRM in 60.0 % (n=30) of CAOU patients, followed by suspicion of gastroesophageal reflux disease 32.0 % (n=16) (table 1). Other indications for HRM study were; suspicion of systemic autoimmune disease 4.0 % (n=2), non-cardiac chest pain 2.0 % (n=1) and presurgical evaluation of a large hiatus hernia 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 an HRM performed for non-obstructive dysphagia.

Evaluating HRM parameters, 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 of 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, we found an association of male sex and a 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 to 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), they 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. In the study by Babaei et al (11), they reported a 10 % prevalence of CAOU patients referred to esophageal motility testing, which is double of 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 months period in Spain. They reported 5 patients with OIED (3 EGJOO and 2 Type III Achalasia) in their study. Interestingly, in their study, opioid medication was not able to be withdrawn in any of the patients. Compared to their study, we found 3 times more cases of OIED in a similar study period, although we evaluated patients retrospectively. We can assume that OIED will become more common in the near future.

The effect of opioids in esophageal motility consists mainly in LES alterations, in healthy volunteers, acute opioids administration results in an increased LES basal pressure and incomplete LES relaxation (13, 14). Saez-Gonzalez also describe a clinical case with OIED associated to EGJOO and the resolution of the oesophageal 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 compared to patients without OIED, and this finding is in accordance to those

reported by American studies (5, 12). Noteworthy, CAOU patients with OIED had a significantly higher prevalence of a 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 an HRM, and it was significantly more common in CAOU patients with OIED than 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 disorders on HRM. Schindler et al (17) performed a study to evaluate 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, suggesting either subclinical outlet dysfunction or an influence in the sensory component. In the study by Babaei et al (11) they 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), even though dysphagia was the most common indication for performing an HRM and non-obstructive dysphagia was more frequent in patients with OIED, 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 non cardiac chest pain taking opioids that underwent HRM and ambulatory pH monitor testing, noteworthy; they found that opioid consumption is 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 that may enhance esophageal acid clearance mechanism. 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 an HRM study.

In our study, we found an association between male sex and CAOU patients with OIED. Our findings contrast with those in previous American studies, as there were no differences between genders in CAOU patients with OIED in their studies. 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 before, alcohol consumption has been associated with EGJOO disorders (17) and OIED is more frequent with higher doses of opioids. Nonetheless, prospective data is necessary to clarify the meaning of this association.

Our study has some limitations. First, because of the retrospective nature of the study, we cannot ascertain a causal relationship between OIED and chronic opioid usage; therefore, our findings can only suggest that there is an association. Still, in 10 out of 16 patients, opioid medication was started a few months before they developed esophageal symptoms. Whether opioids are the primary cause or they exacerbate an underlying esophageal disorder remains to be determined. Another limitations of our study are the small sample size and the absence of a control group without exposure to opioids. Although the study was conducted with patients from a wide geographical area, it was a single center study which limits the 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 Centre. Future prospective studies are needed to confirm whether there is a casual relationship between opioid treatment and esophageal motility disorders.

CONFLICT OF INTEREST

Luis Alcalá, Lucia Relea, Alba Jiménez, Claudia Barber and Elizabeth Barba, declare no conflicts of interest.

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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 (>40mmHg), n (%)	20 (40)

EGJ: esophagogastric junction, **GERD**: Gastroesophageal reflux disease, **HRM**: High resolution manometry, **LES**: lower esophageal sphincter, **SD**: standard deviation

*5 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 (>40mmHg), 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.

Mann-Whitney U test was used to compare continuous variables.