

Opioid-induced functional esophagogastric junction obstruction[☆]



Obstrucción funcional de la unión esofagástrica inducida por opiáceos

The side effects of opioids on the gastrointestinal system have been widely recognized in the literature. They exert their action on the enteric nervous system, through the receptors located in the myenteric plexus (Auerbach's plexus) and the submucous plexus (Meissner's plexus), which are distributed throughout the intestinal system. These receptors (named μ , δ and κ) mediate the effects produced in the human gastrointestinal system.^{1,2}

The main adverse effect of opioids studied at the gastrointestinal level has been intestinal dysfunction in the form of constipation, due to the greater understanding of the physiology of opioid receptors in the colon.³ However, the effect on oesophageal motility has been scarcely assessed. There are few clinical studies, and most are retrospective. These studies suggest that the chronic use of opioids leads to a dysfunction in oesophageal motility.

We present the case of a 62-year-old woman with a history of chronic lower back pain, undergoing treatment with transdermal patches of 30 mg (52.5 μ g/h) buprenorphine every 72 h for the past 8 months, who was referred to the Functional Digestive Testing Unit with dysphagia. The patient's dysphagia occurred daily and was predominantly to liquids, thus interfering with her daily life (grade 2, Vantrappen et al.⁴). Other associated symptoms included regurgitation and chest pain, and to a lesser extent the presence of heartburn. A barium swallow study was performed, which was normal, and an upper digestive endoscopy with biopsies was also shown to be normal. The study was continued with a high-resolution manometry (HRM) and a pH-impedancemetry. The manometry was performed after a fasting period of 8 h, in supine position, using a device with perfused catheters (Medical Measurement System [MMS],

Enschede, Netherlands), based on the protocol of our unit.⁵ The manometric diagnosis was established according to the Chicago Classification Criteria of Esophageal Motility Disorders, version 3.0.⁶

The study with high resolution manometry showed a pathological relaxation of the lower oesophageal sphincter (LOS), determined by a 4-second integrated relaxation pressure (4s-IRP) of 12.5 mmHg and increased baseline LOS pressure with a value of 40 mmHg. Based on the Chicago Classification, a functional oesophago-gastric junction (OGJ) obstruction was diagnosed. The pH-impedancemetry study was normal and ruled out reflux disease. Given the findings of the manometry, a computed tomography (CT) scan of the cervicothoracic region was requested to rule out an underlying organic disease. The CT scan was normal.

In light of the patient's symptoms, drug treatment with calcium antagonists was initiated. Nevertheless, the patient's symptoms improved only slightly, and her dysphagia persisted. We then decided to perform a pneumatic dilation session due to the severity of the dysphagia. However, the patient refused. Her medical history was reviewed and, since there were no previous conditions explaining the dysphagia and the initiation of opioid treatment preceded the onset of her symptoms, we decided to discontinue the analgesic treatment with transdermal buprenorphine patches. One month after the withdrawal of the opioids, another clinical and manometric assessment was performed. The HRM showed normal relaxation with a 4s-IRP of 1.4 mmHg and a decrease in baseline LOS pressure from 40 mmHg to 29 mmHg, meeting the Chicago Classification (Table 1 and Fig. 1). From the clinical point of view, the patient presented a significant improvement with occasional symptoms (grade 1, Vantrappen et al.).

The effect of opioids on oesophageal motility has not been widely studied (Table 2). Experimental studies on healthy subjects have demonstrated an increase in baseline LOS pressure with incomplete relaxation on administering opioids.^{7,8} In clinical practice, Kraichely et al. confirmed, in a retrospective study of 15 patients with dysphagia and

Table 1 Recording of high-resolution manometry data during opioid treatment and after opioid withdrawal.

Manometry data	4s-IRP ^a (mmHg)	Baseline LOS pressure (mmHg)	DCI (mmHg sg cm)	Oesophageal aperistalsis	Chicago Diagnosis, v.3.0
With opioids	12.5	40	3348	No	Functional OGJ obstruction
After opioid withdrawal	1.40	29	3200	No	Normal oesophageal function

LOS: lower oesophageal sphincter; DCI: distal contractile integral; 4s-IRP: 4-second integrated relaxation pressure; OGJ: oesophago-gastric junction.

^a Pathological 4s-IRP > 6.5 mmHg.⁵

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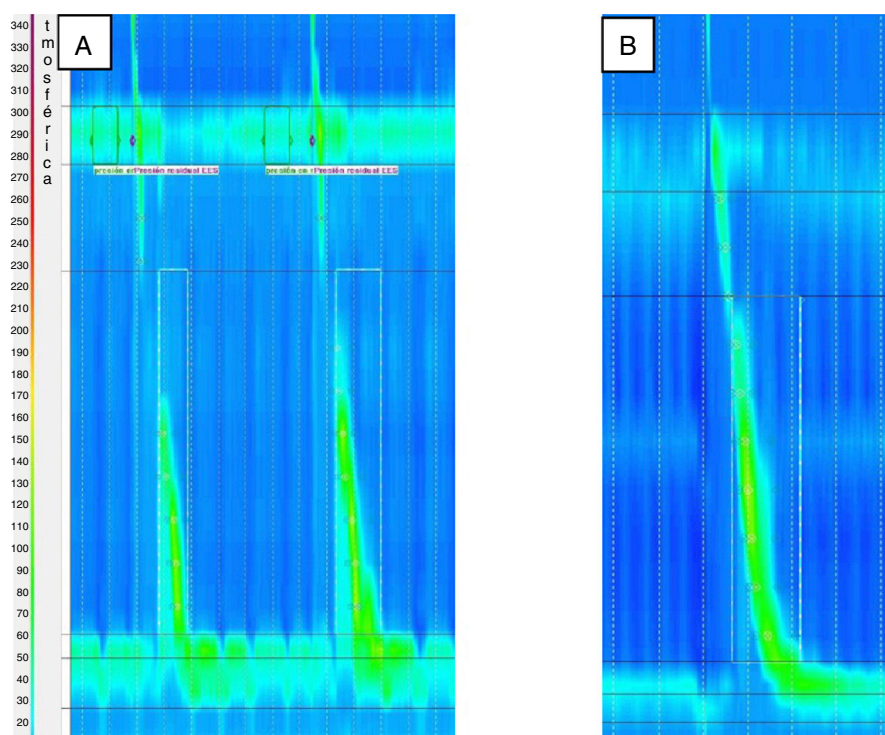


Figure 1 High-resolution manometry during opioid treatment and post-suspension. (A) Functional OGJ obstruction during opioid treatment. Pathological LOS relaxation is seen with normal peristasis. (B) Normal oesophageal motility after suspending the opioid treatment. Normal LOS relaxation.

Table 2 Different studies addressing the effect of opioids on oesophageal motility.

Study	Year	Subjects	Type of study	Intervention	Results
Dowlatsahi et al. ⁷	1985	15 healthy	Experimental	IV Morphine 0.2 mg/kg in 10 subjects	Increased LOS pressure + incomplete LOS relaxation
Penagini et al. ⁸	1996	8 healthy	Experimental	IV Morphine 80 µg/kg	Reduced LOS relaxation
Kraichely et al. ⁹	2010	15 patients undergoing opioid treatment	Retrospective	Chronic opioid treatment	Elevated baseline LOS pressure Incomplete LOS relaxation
González et al. ¹¹	2015	5 patients undergoing opioid treatment	Prospective. Case series	Chronic opioid treatment	Pathological LOS relaxation + increased baseline LOS pressure. Type III achalasia and functional OGJ obstruction as per the Chicago criteria
Ratuaply et al. ¹⁰	2015	121 patients undergoing opioid treatment	Retrospective	Chronic opioid treatment	Pathological LOS relaxation + increased baseline LOS pressure. Type III achalasia + functional OGJ obstruction are more common in patients undergoing treatment with opioids

LOS, lower oesophageal sphincter; iv, intravenous; OGJ, oesophago-gastric junction.

opioid consumption, an oesophageal motility disorder in the form of incomplete LOS relaxation and elevated baseline LOS pressure determined by HRM.⁹ Recently, a retrospective study of 121 patients on chronic opioid treatment suggested that oesophageal motility disorders with pathological LOS relaxation—such as functional OGJ obstruction and type III achalasia—are more common in patients undergoing chronic opioid treatment. This oesophageal motility disorder has been termed: opioid-induced esophageal dysfunction (OIED).¹⁰ On the other hand, it is suggested that suspending treatment with opioids reverses the oesophageal motility disorder.

The mechanism of these effects is not clear. The involvement of the nitric oxide pathway has been suggested as an underlying cause of the effects of opioids on oesophageal motility.⁹

Taking into account both our case and the literature review, it can be concluded that chronic opioid use could lead to oesophageal motility disorders, primarily motility disorders that occur with pathological relaxation and hypertonia of the lower oesophageal sphincter, similar to achalasia or functional OGJ obstruction. As such, these drugs should be taken into account in the differential diagnosis of oesophageal motility disorders and caution should also be exercised in the interpretation of an oesophageal manometry performed on patients receiving opioids.

Conflicts of interest

The authors declare that they have no conflicts of interest.

References

1. Wood JD, Galligan JJ. Function of opioids in the enteric nervous system. *Neurogastroenterol Motil.* 2004;16 Suppl. 2:S17–28.
2. Sternini C, Patierno S, Selmer IS, Kirchgeßner A. The opioid system in the gastrointestinal tract. *Neurogastroenterol Motil.* 2004;16 Suppl. 2:S3–16.
3. Camilleri M. Opioid-induced constipation: challenges and therapeutic opportunities. *Am J Gastroenterol.* 2011;106:835–42.
4. Vantrappen G, Hellemans J, Deloof W, Valembois P, Vandenbroucke J. Treatment of achalasia with pneumatic dilatations. *Gut.* 1971;12:268–75.
5. Ortiz V, Poppele G, Alonso N, Castellano C, Garrigues V. Evaluation of esophagogastric junction relaxation by 4-second Integrated Relaxation Pressure in achalasia using High Resolution Manometry with water-perfused catheters. *Neurogastroenterol Motil.* 2014;26:1551–6.
6. Kahrlas PJ, Bredenoord AJ, Fox M, Gyawali CP, Roman S, Smout AJ, et al. The Chicago classification of esophageal motility disorders, v.3.0. *Neurogastroenterol Motil.* 2015;27:160–74.
7. Dowlathshahi K, Evander A, Walther B, Skinner DB. Influence of morphine on the distal oesophagus and the lower oesophageal sphincter – a manometric study. *Gut.* 1985;26:802–6.
8. Penagini R, Picone A, Bianchi PA. Effect of morphine and naloxone on motor response of the human esophagus to swallowing and distension. *Am J Physiol.* 1996;271:G675–80.
9. Kraichely R, Arora AS, Murray JA. Opiate-induced oesophageal dysmotility. *Aliment Pharmacol Ther.* 2010;31:601–6.
10. Ratnaparkhy SK, Crowell MD, DiBaise JK, Vela MF, Ramirez FC, Burdick GE, et al. Opioid-induced esophageal dysfunction (OIED) in patients on chronic opioids. *Am J Gastroenterol.* 2015;110:979–84.
11. González ES, Bellver VO, Jaime FC, Cortés JA, Gil VG. Opioid-induced lower esophageal sphincter dysfunction. *J Neurogastroenterol Motil.* 2015;2:618–20.

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Tibolone-induced acute hepatitis: Well-known drug, little-known complication



Hepatitis Aguda por Tibolona: Medicamento Común, Alerta Incomún

With an increase of prescription medication and herbal supplemental use, drug induced liver injury (DILI) has become progressively a more important entity when considering acute hepatitis aetiology. The unpredictable fashion and low frequency of idiosyncratic DILI, along with the highly variable clinical scenarios it can assume, turns DILI into an under-recognised event. Therefore, clinical suspicion, thorough medical history and many a time confirmatory histology remain the most relevant clues for diagnosis and imputability.

Tibolone is a synthetic oestrogen commonly used to minimize menopause symptoms. It is usually well tolerated and liver toxicity has been previously reported only in three occasions.^{1–3} The authors report a case of tibolone acute hepatitis with cytolytic pattern.

A 45-year-old female was referred to the Hepatology Clinic because of abnormal liver function tests. She was asymptomatic and denied fever, rash, anorexia or malaise. The physical examination was unremarkable: no jaundice, no scratch lesions, liver and spleen were not palpable. She had no history of alcohol intake and denied over the counter use of drugs or herbal products. She also denied extramarital sexual contacts and recent travels abroad.

In her medical history, she pointed out that due to menopausal symptoms, she had been prescribed, 6 months earlier, with tibolone 2.5 mg, which she has been taking regularly. Just before starting, she had a complete blood count and liver function tests with normal profile. She presented