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CASE REPORT | ESOPHAGUS

Effect of Naloxegol on Opioid-Induced Esophageal Motility Disorder

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ABSTRACT

Opioid effects on lower gastrointestinal motility are well documented, and increasing attention is being paid to their effect on esophageal motility. Naloxegol is a μ-opioid receptor antagonist that is used for opioid-induced constipation, but its impact on esophageal motility has not been well documented. We report a case series of 3 patients with coexisting esophageal dysmotility and constipation on chronic opioids that improved both symptoms after starting naloxegol. Based on these observational studies, we propose that formal studies be conducted to assess the effect of naloxegol on opioid-induced esophageal dysmotility.

INTRODUCTION

Gastrointestinal dysmotility due to opioid use is well known and documented in opioid-induced constipation.[1-3] Opioid receptors are also present in the esophagus, and there is increasing interest in opioid-induced esophageal dysfunction (OIED). The effect of chronic opioid use on esophageal dysmotility is reported in opioid-induced spastic disorders, such as achalasia Type III, esophageal gastric junction outlet obstruction, and distal esophageal spasm.[2,4] Most early studies showed decreased lower esophageal sphincter (LES) relaxation with morphine, and some also demonstrate increased high-amplitude contraction.[5] Findings are believed to be primarily due to opioids impairing the inhibitory pathway in the esophagus. More recent studies have demonstrated opioids causing higher rates of spastic contractions with decreased distal latency (DL) and impairment of deglutitive inhibition on multiple rapid swallows (MRS).[5–7] Reversal of these spastic disorders after withdrawing opioids has also been demonstrated.[2,5] Despite the use of μ-receptor antagonists such as naloxegol for opioid-induced constipation and increasing documentation of spastic disorders of the esophagus in the same patients, treatment of opioid-induced esophageal dysmotility with μ-receptor antagonists has minimal associated research.[3] IV naloxone has been shown to reverse acute effects of morphine on LES relaxation on healthy patients.[8,9] A single previous case study described improvement in dysphagia symptoms with naloxegol in a patient diagnosed with opioid-induced achalasia.[10] We present 3 similar patients with OIED who had improvement in symptoms and manometry after naloxegol.

CASE REPORT

Patient 1: A 67-year-old man on oxycodone 30 mg twice daily for chronic back pain was seen in clinic for dysphagia to solids and liquids with regurgitation and chest pain. He had an earlier normal EGD (esophagogastroduodenoscopy) with biopsies negative for eosinophilic esophagitis. Manometry showed jackhammer (hypercontractile) esophagus with a distal contractile integer (DCI) of 10,092 mm Hgcm (Figure 1). He was on a calcium channel blocker and had failed trials of a tricyclic antidepressant and an anticholinergic/antispasmodic. The patient was started on oral naloxegol 25 mg daily for his significant opioid-induced constipation and interestingly reported the resolution of his dysphagia symptoms. Given the significant change in dysphagia symptoms, manometry was repeated before considering myotomy and showed a significant decrease in DCI to 2,559 mm Hgcm ($P < 0.05$). His DL changed from 4.7 to 5.1 and integrated relaxation pressure (IRP) from 17.2 to 7.4 (Figure 1). His multiple rapid swallows (MRS) did have a breakthrough, but this happened on both pre-study and post-study.

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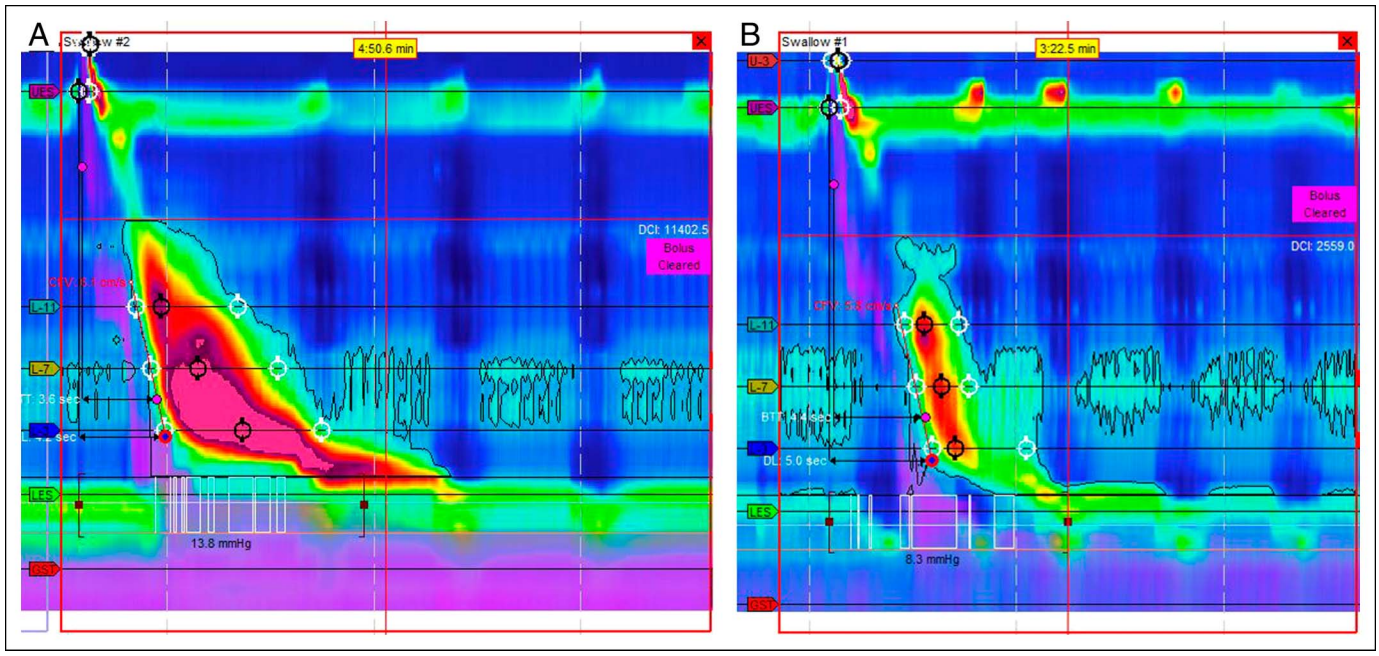

Figure 1. (A) Initial and (B) final manometry for patient 1.

Patient 2: A 73-year-old woman presented with systemic lupus erythematous on oxycodone 10 mg every 6 h with progressively worsened dysphagia and regurgitation for more than 4 years. She was malnourished and required gastrostomy tube placement for added nutrition. EGD demonstrated a tight LES and dilated esophagus. Her manometry showed achalasia Type III with DCI of 5,900 mm Hg cm (Figure 2). She was a poor candidate for surgery and was unable to decrease her oxycodone because of pain. She was started on naloxegol 25 mg for constipation, which was decreased to 12.5 mg the next day for cramping. She noted decreased regurgitation and moderate improvement in dysphagia and was able to tolerate liquids or soft foods in small amounts after just 48 h. Repeat manometry completed 4 days after starting naloxegol demonstrated a DCI decrease from 5,900 to 2,887 mm Hgcm ($P < 0.05$) (Figure 2). Other values include a change in DL from 1.8 to 4.5 and IRP from 24.4 to 27.3.

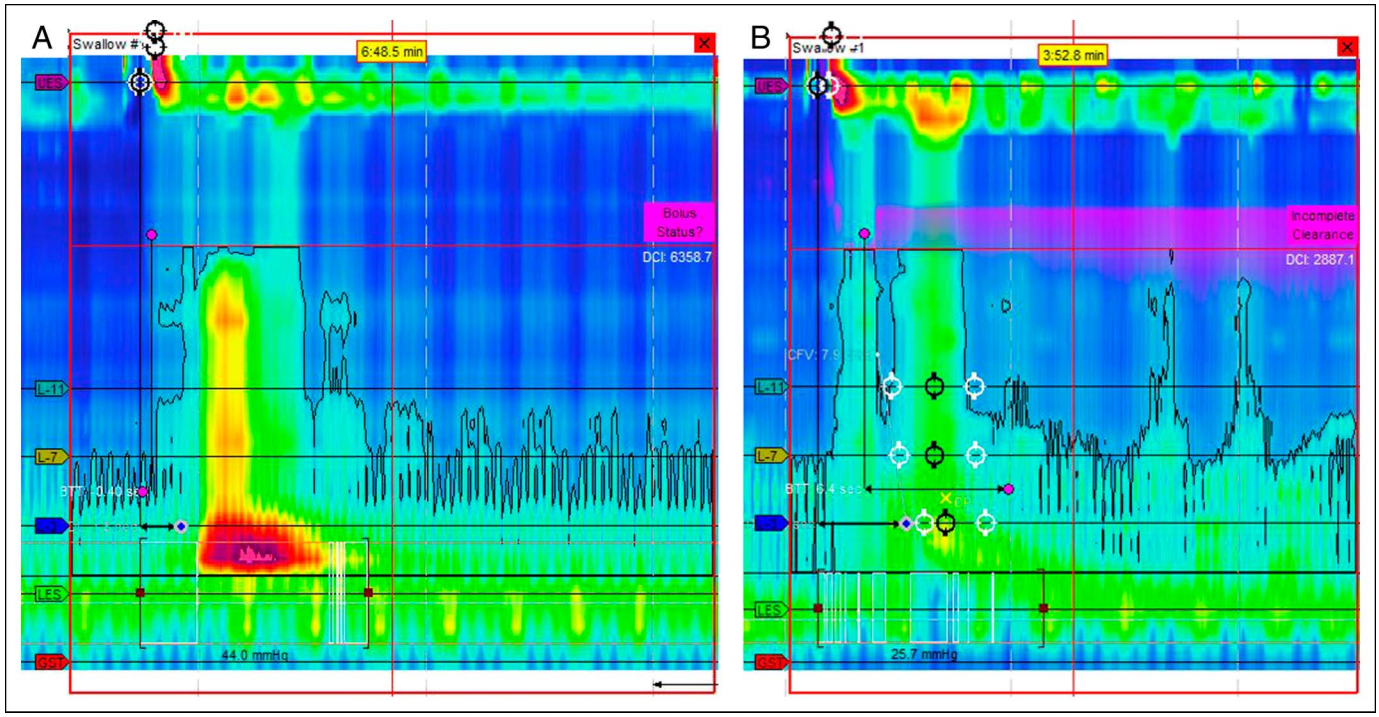

Figure 2. (A) Initial and (B) final manometry for patient 2.

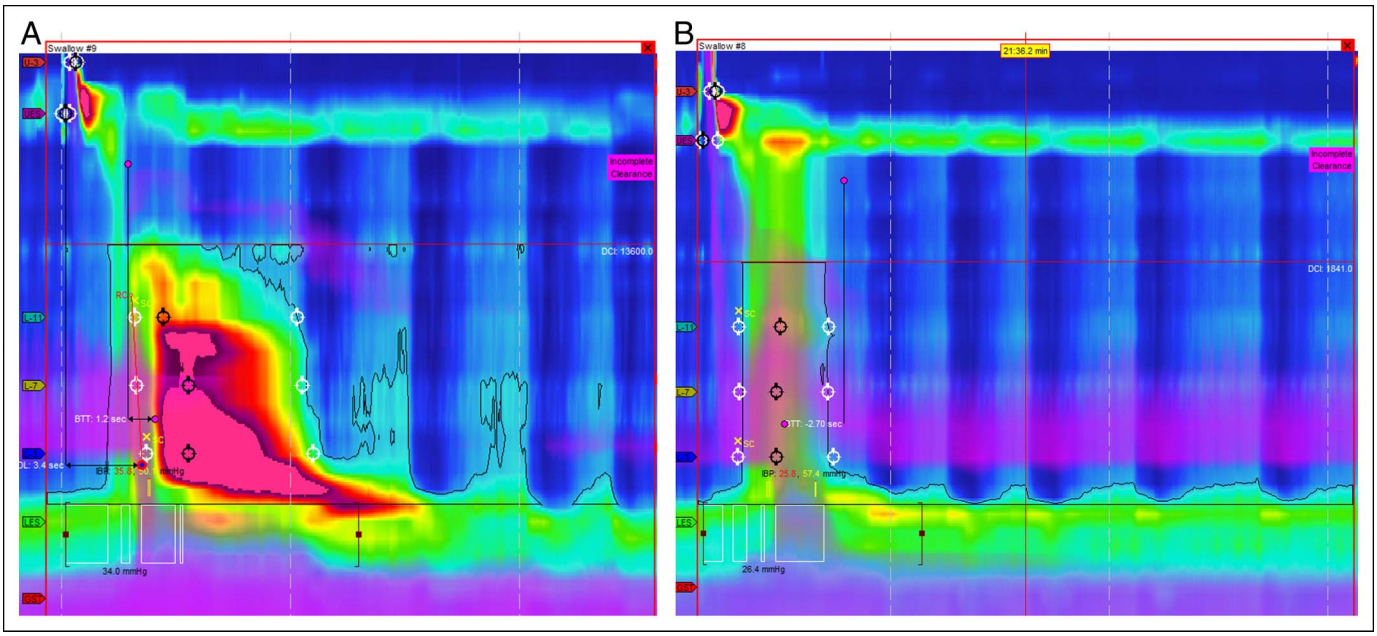

Figure 3. (A) Initial and (B) final manometry for patient 3.

Patient 3: A 58-year-old woman presented with chronic pain and prior back surgeries on morphine SR 15 mg twice daily, intrathecal pump, and oxycodone 15 mg every 4 h. She had been seen in the clinic for worsening dysphagia and regurgitation of liquids and solids and with weight loss. Her manometry demonstrated achalasia Type III with DCI of 6,696 mm Hgcm on presentation (Figure 3). She had an EGD with empiric dilation with minimal benefit and normal esophageal biopsies. The patient had opioid-induced constipation for which she was taking stool softeners and lubiprostone with a suboptimal response. She was started on naloxegol 25 mg daily for constipation, which improved her constipation. Intriguingly, she also reported a significant improvement in her dysphagia and regurgitation. She noted near resolution of symptoms within 1 day and only rare dysphagia if eating too quickly. Repeat manometry 1 month after starting naloxegol demonstrated Type II achalasia with a decrease in DCI from 5,456 to 2,043 mm Hgcm ($P < 0.05$) (Figure 3). The other values of DL changed from 1.6 to 1.7 and IRP from 30.7 to 27. She later decreased her dosage of naloxegol to 12.5 mg daily because of abdominal pain, and symptom response was sustained.

DISCUSSION

Patients with a longstanding opioid use often experience constipation that is usually treated with μ-receptor antagonists, such as naloxegol. A subset of these patients can also develop esophageal dysmotility that can result in dysphagia and regurgitation. Recent literature has reported OIED which manifests as spastic disorders, such as Type III achalasia, esophageal gastric junction outlet obstruction, and distal esophageal spasm.[1,2] No definitive therapeutic interventions are available to these patients apart from discontinuing opioid medications, which may not be realistic for many patients. After intervention with naloxegol, the 3 featured patients demonstrated improvement in symptoms and manometric parameters, including DCI values compared with a 2-tailed paired *t* test.

Two of our patients had achalasia Type III which converted to Type II achalasia after naloxegol use with decreased spasticity and improved clinical symptoms. Type III achalasia is one of the more common presentations in opioid-induced esophageal dysmotility.[1,2,4,11] In one study, 25% of the achalasia patients were found to be on opiates.[11] Another study demonstrated a higher prevalence of achalasia in chronic opioid users (13%) than in opioid-naive patients (1%) with dysphagia.[4] Our third patient also had a significant decrease in spasticity with the change of manometric signature from jackhammer esophagus to a normal motility pattern. Type III achalasia and jackhammer esophagus are often treated with myotomy or calcium channel blockers with their antecedent side effects and may not always be the best option. Naloxegol/μ-receptor antagonist is a safer and less invasive option.

Our limited, retrospective study is based on observation in 3 patients, and further formal investigation with a randomized control study is needed to elucidate the effect of μ-receptor antagonists on OIED. In future studies, MRS evaluation on all patients and EndoFLIP, if available, should be considered.[5,6] If a further investigation confirms our observation, it could result in significant improvement of dysphagia and quality of life for many patients and possibly avoid more invasive interventions.

DISCLOSURES

Author contributions: C. Ulteig, K. Ciezki, and T. Sharma wrote the article and reviewed the literature. M. Jacobson and M. Singh wrote the article. T. Sharma is the article guarantor.

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