Mini Review

Opioid Induced Bowel Dysfunction

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ABSTRACT

Orally manufactured opioids are routinely administered analgesics to relieve severe pain, and as a result, many patients encounter undesirable effects such as OIBD/OIC. This disorder has a significant detrimental influence on health-related QoL and inhibits patients' regular job and social activities. Thus, OIBD/OIC presents a challenge to patients and their healthcare providers, and clinicians are encouraged to explore the physical and mental difficulties of OIBD/OIC in order to discover unique solutions such as commencing focused treatment.

Keywords: Opioid; Bowel dysfunction; Musculoskeletal

Introduction

Despite the fact that opioids were initially intended to be used primarily for acute severe pain, such as post-operative pain and terminal palliative care, orally administered opioids are now widely used to treat chronic non-malignant pain in Western countries. As a result, more than 240 million opioid prescriptions are written each year in the United States, the majority of which are for back pain and other musculoskeletal conditions [1,2], and opioid prescriptions have quadrupled in the last three decades [1-5]. Different theories have been proposed, and clinicians' prescribing behaviour differs not only between countries, health-care institutions, and people. Surprisingly, the number of people suffering from side effects is on the rise. Respiratory depression, sedation, and opioid addiction are among serious side effects of opioids. The number of major side effects reported by patients in response to long-term opioid usage, such as drowsiness, nausea, cognitive impairment, and bowel dysfunction, is less risky, but nevertheless harmful and burdensome.

Opioid Induced Bowel Dysfunction

The opioid medicines, such as morphine, work by binding to receptors on neuronal cell membranes in the spine and brain to provide pharmacological effects such as analgesia. Tolerance develops fast to most opioid-induced adverse effects that originate in the brain, such as nausea and cognitive impairment, according to empirical evidence. Opioids bind to peripherally acting mu-opioid receptors, such as those in the myenteric and submucosal plexuses of the whole wall of the Gastrointestinal (GI) tract, just as they do in the CNS. Treatment may result in clinically significant side effects known as Opioid Induced Bowel Dysfunction (OIBD) if tolerance is not present [5-7]. This can cause debilitating symptoms by interfering with GI motility, secretion, and sphincther function [6]. OIBD and OIC are under-diagnosed but common and debilitating opioid-related side effects. OIC occurs in 11% of individuals in placebo studies, whereas chronic constipation occurs in 33% to 94% of non-cancer and cancer opioid-treated patients [5]. In an attempt

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to prevent the consequences of such bowel dysfunction, individuals may reduce their opiate consumption, perhaps worsening their pain. In the Patient Reports of Opioidrelated Bothersome Effects (PROBE) trial, 322 patients with chronic pain from the United States and the European Union were enrolled, and one-third of them said they had missed doses, reduced the dose, or stopped taking opioid medication to relieve bowel-related side effects. Following this, 92 percent of patients reported increasing pain, with 86 percent reporting a decrease in their Quality of Life (QoL) and daily activities [8]. An American survey found that more than half of patients took less opioid than prescribed because of negative side effects [9]. Despite the fact that health care providers appear to underestimate the impact of OIBD, it is clear that OIC results in lower QoL, more hospitalizations, and more time off work, all of which limit appropriate clinical management and increase socio-economic expenses.

The GI tract is made up of two layers of smooth muscle: a longitudinal layer and a circular layer, both of which are innervated by the Enteric Nervous System (ENS). The ENS is divided into two plexuses: the myenteric plexus, which is situated between the two muscular layers, and the submucosal plexus, which is situated within the submucosa. The ENS expresses three types of opioid receptors, and opioid receptors, which are all G-protein-coupled receptors. The opioid receptor is the most broadly distributed of these and is thought to be the primary mediator of opioid effects on the GI tract in humans [9]. The main impact of opioid receptor activation is a reduction in the synthesis of cyclic Adenosine Monophosphate (cyclic AMP), which suppresses the release of excitatory and inhibitory neurotransmitters and, as a result, cell activity. Endogenous opioids, such as enkephalins and endorphins, coordinate sensory, motor, and secretory activity in the gut under normal conditions and decrease intestinal motility when necessary. Exogenous opioids, on the other hand, affect enteric neurons and alter the natural equilibrium of transmitters. As a result, as shown in [8], opioid administration can cause GI motility dysfunction, reduced GI secretion and increased absorption, and GI sphincter dysfunction. These synergistic effects may interact and impact one another in a complicated interaction, all of which contribute to OIBD's multifarious symptomatology.

Opioid Effects on Motility

A careful balance between the release of acetylcholine, nitric oxide, and vasoactive intestinal peptide from enteric neurons onto the longitudinal and circular layers controls normal gut motility coordination. Furthermore, the fundamental role of the "pacemaker" cell-network in the gut wall, known as Cajal's interstitial cells, is to generate spontaneous electrical activity. Peristaltic motions are created in the two muscular layers, which are then regulated by hormonal and neurotransmitter influences, resulting in proper motility. Because opioids diminish neuronal excitability and neurotransmitter release in the ENS, their administration has a major impact on gastrointestinal motility. As a result, the circular muscle layer experiences stronger and more frequent phasic, non-migrating muscle contractions (known as "spike bursts"), as well as an increase in resting contractile tone (less relaxation). This condition is also characterised by a decrease in propulsive contractions of the longitudinal muscle layer. When these effects combine, they result in greater segmental contraction and decreased propulsive forward peristalsis. The precise mechanism causing these altered motility patterns has yet to be completely investigated; nevertheless, prolonged GI transit time may represent underlying dysmotility. Several *in vivo* human studies have established that opioids delay stomach emptying, oro-cecal transit, and colonic transit time. A recent study also shown that opioids lower the number of colonic mass movements. Constipation is the most obvious side effect of opioid-induced GI dysmotility and subsequent delayed transit.

Abdominal pain is a commonly reported symptom of OIC, and it is often described as spasmodic, convulsive, and severe. During bouts of constipation, patients frequently experience what they call "false alarms," in which they feel the pressure of a spontaneous bowel movement. However, these were frequently ineffective and ineffective, and as a result, when patients stated that they needed to be near toilet facilities, they acted appropriately and went to the toilet. Furthermore, patients frequently report that the only relief from OIC symptoms was making a bowel movement. As a result, the defecation

method finally tested some of the constipated patient's strength, who described themselves as weary at the end. Finally, the psychological anxiety of constipation can lead to anorexia because patients avoid re-filling their bowels in order to avoid further OIC. Furthermore, these patients frequently experience stress and exhaustion, which explains why they avoid social events and express the hardship of their constant need to be near bathroom facilities [10]. As a result, it has been demonstrated in other patients that during periods of constipation, quality of life suffers as a result of damaged optimism, depleted energy, overall well-being, and negative emotions leading to worry or even a sense of desperation. Unsurprisingly, QoL in reaction to constipation linked adversely with age, with constipated women experiencing lower QoL than constipated men. In a brief interview study of constipated older women in Sweden, patients eventually reported themselves as being alone, tortured or freed, depending on the status of the intestine. As a result, they felt mostly ignored by the healthcare system, which exacerbated their stress and worry. Patients suffering from chronic pain who develop OIC may have similar experiences. Constipation is a transient and highly private matter for the vast majority of sufferers.

Treatment

When it comes to treating OIBD, the standard guideline is to begin OIBD prophylaxis in all patients taking opioid medication. There is limited evidence that fibres and lifestyle changes relieve constipation in general, and many patients are unable to exercise or increase their fluid intake because to comorbidity. Laxatives are thus advised as first-line treatment in all patients who are administered opioids. Osmotic agents (magnesium, lactulose, polyethylene glycol), stimulants (bisacodyl, senna), bulking agents (methylcellulose, psyllium), and stool softeners are some of the subgroups of laxatives (anionic surfactants). Although the efficiency of laxatives in classical is still debated, their efficacy in OIBD is generally insufficient. As a result, laxatives have little effect on sphincter tone, motor and secretory alterations in the upper gut. Treatment with laxatives may create side effects such as unpleasant taste, bloating, gas, and reflux, which, together with the lack of efficacy, may explain why approximately one-third of patients omit, reduce, or even cease opiate medication to relieve unwanted symptoms. Although data is limited, opioid rotation may be beneficial in lowering OIBD. Some opioids with noradrenergic system actions, such as tapentadol, may also sustain analgesic efficacy while having fewer deleterious effects on the gut. A more rational approach to treatment is to utilise opioid antagonists with limited effects in the gut, which have been shown to be efficacious in a number of studies, including a meta-analysis. It is possible to obtain a combined prolonged release formulation of oxycodone and naloxone in a 2:1 ratio. The gradual release of naloxone guarantees that the majority is processed in the liver and that less than 2% is released into the systemic circulation, preserving analgesia. As a result, the antagonist is mostly active in the "gut compartment". Because naloxone is largely metabolised in the liver, patients with hepatic impairment may have higher bioavailability, and the fixed combination with oxycodone can make treatment problematic in circumstances when opioid rotation is required.

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