The 'mystery' of opioid-induced diarrhea

Silviu Bril MD¹, Yoav Shoham MD MHA¹, Jeremy Marcus MD²

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Bowel dysfunction, mainly constipation, is a well-known and anticipated side effect of opioids. The physician prescribing an opioid frequently confronts the challenge of preventing and treating bowel dysfunction. Different strategies have emerged for managing opioid-induced constipation. These strategies include physical activity, maintaining adequate fluid intake, adhering to regular daily bowel habits, using laxatives and other anticonstipation medications and, recently, using a peripheral opioid antagonist, either as a separate drug or in the form of an opioid agonist-antagonist combination pill. What options exist for the physician when a patient receiving opioids complains of diarrhea, cramps and bloating, rather than the expected constipation? The present article describes a possible cause of opioid-induced diarrhea and strategies for management.

Key Words: *Lactose intolerance; Opioid; Pain*

There is an old saying among pain specialists that 'God gave them two hands so that while one hand prescribes an opioid, the other will prescribe a laxative'. Indeed, bowel dysfunction, mainly constipation, is a well-known and anticipated side effect of opioids (1,2). The physician prescribing an opioid frequently confronts the challenge of preventing and treating bowel dysfunction. Moreover, numerous studies have concluded that constipation contributes to poor compliance and treatment failure among patients receiving opioids, particularly in elderly and cancer pain patients (3,4). Different strategies have emerged for managing opioid-induced constipation (5-7). These strategies include being physically active, maintaining adequate fluid intake, adhering to regular daily bowel habits, using laxatives and other anticonstipation medications and, recently, using a peripheral opioid antagonist, either as a separate drug or in the form of an opioid agonist-antagonist combination pill (8-12).

What options exist for a physician when a patient receiving opioids complains of diarrhea, cramps and bloating, rather than the expected constipation?

THE 'SECRET INGREDIENT'

Excipients are the components of a drug other than the active substance. They have several purposes, including the improvement of appearance, bioavailability, stability and palatability of the drug. They often comprise the majority of the mass or volume of administered drug, and are considered to be inactive ingredients. Lactose is one of the most widely used excipients in the pharmaceutical industry. It is considered to be inert, inexpensive, nontoxic and chemically stable, and it tends not to react with the active ingredient of the drug (13). Lactose is also very palatable and, thus, makes drugs that contain it taste better. Although not always mentioned in the drug's leaflet, it has been estimated that lactose is a component of approximately 20% of prescription medications and 6% of over-the-counter medications (14). Studies designed to determine the amount of lactose in drugs that might cause bowel symptoms in patients experiencing hypolactasemia are scarce.

Le « mystère » de la diarrhée induite par les opioïdes

Le dysfonctionnement intestinal, principalement la constipation, est un effet secondaire anticipé et bien connu des opioïdes. Le médecin qui prescrit un opioïde affronte souvent le problème de la prévention et du traitement du dysfonctionnement intestinal. Diverses stratégies ont émergé pour prendre en charge la constipation induite par les opioïdes. Ces stratégies incluent l'activité physique, le maintien d'un apport suffisant de liquides, l'adhésion à des habitudes intestinales quotidiennes régulières, l'utilisation de laxatifs et d'autres médicaments contre la constipation et, récemment, l'utilisation d'un antagoniste périphérique des opioïdes, soit sous forme de médicament distinct, soit sous forme d'un comprimé opioïde agoniste-antagoniste mixte. Quelles possibilités s'offrent au médecin dont le patient qui prend des opioïdes se plaint de diarrhée, de crampes et de ballonnements, plutôt que de la constipation prévue? Le présent article décrit une cause possible de diarrhée induite par les opioïdes et des stratégies de prise en charge.

THE 'HIDDEN' LACTOSE

Lactose is a disaccharide that consists of galactose and glucose molecules. It comprises approximately 2% to 8% of the solids in milk. One millilitre of milk contains 47.2 mg of lactose (15,16). Lactose digestion is the rate-limiting step in the overall process of its absorption. Lactose is hydrolyzed by intestinal lactase to glucose and galactose on the microvillus membrane of intestinal absorptive cells. In individuals with lactase deficiency, up to 75% of lactose passes unabsorbed through the small intestine toward the colon (17).

The prevalence of hypolactasia varies widely among ethnic backgrounds. Estimates range from 2% in persons from northern Europe to nearly 100% in adult Asians and American Indians. The black and Ashkenazi Jewish populations have hypolactasia prevalences of 60% to 80%, and the Latino population has a prevalence of 50% to 80% (18). Clinical symptoms of lactose intolerance include diarrhea, abdominal pain and flatulence after ingestion of lactose-containing products (17). These symptoms have been attributed to low intestinal lactase levels, which may be due to mucosal injury or, much more commonly, reduced genetic expression of the enzyme lactase (19-20). Lactose intolerance varies from person to person and may change with age (21). The majority of the world's ethnic groups develop low intestinal lactase levels during the period from childhood to adolescence and are considered to have primary lactose intolerance (19). The secondary form of lactose intolerance occurs as a result of gastrointestinal pathology, eg, celiac disease or infections that involve the small intestine (19,21). Lactose intolerance should not be confused with a milk allergy: intolerance is caused by lactase enzyme deficiency, while a milk allergy is an immune reaction to milk proteins. Milk allergies affect 20% of patients with symptoms suggestive of lactose intolerance (22).

THE CLINICAL PROBLEM

Rarely, patients taking opioids will complain of diarrhea and bloating rather than the anticipated constipation. Physicians should be familiar with the possibility of this potential side effect, its cause and potential treatments. Table 1 shows the lactose content of popular opioid drugs.

¹Center for Pain Medicine, Sourasky Medical Center, Tel Aviv, Israel; ²Washington Nephrology Associates, Washington, DC, USA

Correspondence: Dr Yoav Shoham, Center for Pain Medicine, Sourasky Medical Center, 6 Weizman Street, Tel Aviv 64239, Israel.

Telephone 972-3-5236231, fax 972-2-9085301, e-mail dr.yoavshoham@gmail.com

TABLE 1
Lactose content of opioid medications

Drug	Lactose content, mg
OxyContin (Purdue Pharma, Canada)	
10 mg	69.25
20 mg	59.25
40 mg	32.25
80 mg	78.50
Morphine (controlled release)	
10 mg	90
30 mg	70
100 mg	0
200 mg	0

Data provided were retrieved from the manufacturers

For example, a 10 mg tablet of OxyContin (Purdue Pharma, Canada) contains approximately 70 mg of lactose – hardly enough to cause symptoms of lactose intolerance, even if taken several times a day. Montalto et al (23) investigated the clinical significance of lactose doses typically found in pharmacological agents by performing a randomized, crossover, double-blinded study evaluating breath hydrogen production and symptoms in 77 lactose-intolerant subjects following the ingestion of 400 mg of lactose or placebo. Neither breath hydrogen levels nor symptoms were significantly different between the lactose and placebo groups.

We should keep in mind that many patients use other drugs for treatment of chronic illnesses, and lactose is present in some amount in most diets. Therefore, adding a drug that contains even a small amount of lactose may be sufficient to exceed the clinical threshold of lactose intolerance in a given patient. The resulting gastrointestinal symptoms may lead to patients electing to stop taking the ‘offending’ drug.

DIAGNOSIS OF LACTOSE INTOLERANCE

Lactose intolerance can be diagnosed by measuring lactose absorption, measuring products of lactose nonabsorption, performing mucosal biopsies of the small intestine and, rarely, by genetic testing (17). Practically, lactose intolerance may be suggested by patient history, and the diagnosis supported by tests involving dietary manipulation. Two formal tests are commonly used in patients suspected of having lactose intolerance. In the lactose tolerance test, blood glucose levels are obtained at 0 min, 60 min and 120 min after ingestion of a 50 g test dose (in adults). An increase in blood glucose of less than 1.1 mmol/L (20 mg/dL) plus the development of symptoms is diagnostic. False-positive and false-negative test results occur in up to 20% of normal subjects (24). The lactose tolerance test has a sensitivity of 75% and a specificity of 96%. However, it is burdensome and time consuming, and has largely been replaced by the lactose breath hydrogen test. The breath hydrogen test measures lactose nonabsorption. The test is based on the principle that lactose passing undigested to the colon undergoes bacterial fermentation, and the hydrogen produced can be measured by breath analysis. A hydrogen concentration that is more than 20 ppm over baseline after lactose ingestion is usually considered to be diagnostic of lactose malabsorption. The hydrogen breath test is simple to perform, has a sensitivity and specificity that are superior to the absorption test, and has become the most commonly used test to diagnose lactose intolerance (25).

TREATMENT OF LACTOSE INTOLERANCE

Several principles guide the treatment of lactose intolerance in the absence of a correctable underlying disease. These include reducing lactose intake, concomitantly using enzyme substitutes, and maintaining adequate intake of calcium and vitamin D (19,24). Although

often used by patients, the benefit of probiotics for the treatment of lactose intolerance remains unproven (26).

CONCLUSIONS AND RECOMMENDATIONS

Although some manufacturers list lactose as an excipient in drug leaflets, they are not required to quantify the amount present. One study (14) identified that the ingestion of certain medications, either alone or in combination, may result in the consumption of more than 10 g of lactose per day (in addition to the amount consumed in the diet). Therefore, when prescribing a lactose-containing opioid, especially for older patients who are taking several other drugs, physicians should be aware of the possibility that the patient will experience diarrhea rather than the expected constipation, due to lactose intolerance. When a drug containing lactose causes diarrhea, it should not be considered a ‘true’ side effect of the drug because the offending ingredient is not the active opioid substance, but its carrier. Based on our experience, diarrhea is an infrequent complaint of patients receiving opioid medications. Nevertheless, physicians who specialize in pain management should be familiar with infrequent side effects of opioid treatment and of lactose intolerance as a possible cause of such symptoms. In our clinic, we encountered an elderly patient with such symptoms. Although we did not conduct lactose tolerance tests to prove lactose intolerance, switching to nonlactose-containing opioid drugs did resolve her gastrointestinal symptoms. The different strategies for managing lactose intolerance, as mentioned above, can help alleviate the gastrointestinal symptoms caused by lactose in opioid drugs, and allow the patients to adhere to the opioid treatment and benefit from its analgesic effect, rather than declaring treatment failure. The physician prescribing opioids for the treatment of pain should be familiar with the lactose content of different drugs, some of which contain no lactose at all; therefore, they will be able to ‘tailor’ the most suitable drug to the patient.

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