

Are we able to Manage Effectively Opioid-Induced Bowel Dysfunction?

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Opioid-Induced Bowel Dysfunction

Opioid-Induced Bowel Dysfunction (OIBD) is commonly associated with the chronic use of opioid analgesics and affects 80-90% of treated patients [1]. OIBD comprises constipation, anorexia, nausea and vomiting, gastro-oesophageal reflux, delayed digestion, abdominal pain, flatulence, bloating, hard stool, straining during bowel movement and incomplete evacuation. In some cases, it may lead to more serious complications such as bowel faecal impaction with overflow diarrhoea and faecal incontinence, pseudo-obstruction (that may cause anorexia, nausea and vomiting), disturbance of drug absorption, urine retention and urine incontinence. OIBD may decrease patients' compliance and in consequence inappropriate opioid dosing and insufficient analgesia. OIBD also significantly deteriorates patients' quality of life. One third of patients treated with opioid analgesics does not adhere to the prescribed opioid regimen or simply quit the treatment due to OIBD symptoms [2].

Outline of Patomechanism of Opioid-Induced Bowel Dysfunction

The patomechanism of OIBD comprises both peripheral and central mechanisms. The peripheral opioid effect on μ -opioid receptors in the gut wall plays the main role here [3]. High density of μ -opioid receptors was found in neurons of myenteric and submucosal plexus and immune cells in the lamina propria [4]. Opioid receptors (predominantly μ , also κ and δ) are located in the gut wall in the myenteric plexus and in the submucosal plexus. The former are responsible for GI motility and the latter for secretion. The μ -opioid receptors are activated in the wall of the stomach, small and large intestine by endogenous (enkephalins, endorphins and dynorphins) and exogenous (codeine, dihydrocodeine, hydrocodone, tramadol, morphine, oxycodone, hydromorphone, fentanyl, buprenorphine, methadone) opioids and modify GI function. Activation of μ -opioid receptors inhibits excitatory and inhibitory neural pathways within the enteric nervous system that coordinates motility. Inhibition of excitatory neural pathways depresses peristaltic contractions. The blockade of inhibitory neural pathways increases GI muscle activity, elevates resting muscle tone, spasm and non-propulsive motility patterns. These mechanisms are responsible for delayed gastric emptying and slowing the intestinal transit [5]. The central mechanism of opioid effects on GI tract was demonstrated as intracerebroventricular administration of morphine in rats inhibited gastrointestinal propulsion. This effect was reversed by intracerebroventricular administration of naloxone and vagotomy. Intrathecal administration of morphine reduced gastroduodenal motility and intramuscular morphine gave additional effects. Thus both central and peripheral opioid effects play a role in opioid GI effects [6].

Treatment of Opioid-Induced Bowel Dysfunction

General measures comprise the meticulous assessment and applying prophylactic measures matched to patients' general condition. Change of diet (increased food and fluid intake), more physical activity, sitting position during bowel movement and privacy during defecation process are recommended. Patients treated with opioids should be considered for prokinetic administration (metoclopramide,

domperidone, itopryd) [7]. Reversible causes such as hypercalcemia should also be treated. Discontinuing or decreasing doses of drugs that may contribute to constipation development (such as tricyclics, neuroleptics, anticholinergics) should also be considered. Patients and families should be educated about the ways of prevention and treatment of OIBD. In majority of patients with OIBD laxatives need to be administered. The general recommendation is to combine oral administration of osmotic agents (usually lactulose or macrogol) which have an osmotic effect in the colon with stimulants activating neurons in the myenteric and submucosal plexus in colon and reducing absorption of water and electrolytes from the intraluminal contents: anthracenes (senna), polyphenolics (bisacodyl) or sodium picosulphate [8].

However, these drugs display limited efficacy in patients suffering from OIBD; moreover, they may cause several adverse effects and must be administered on a regular basis. Other groups of laxatives are faecal lubricants (liquid paraffin), stool softeners (surfactants: sodium docusate); however they are usually ineffective when administered alone. The use of bulk-forming agents such as fibre, bran, methylcellulose and psyllium seeds has limited role in patients with OIBD and advanced disease as enough fluids (at least 2 l per day) should be co-administered and may lead to viscous mass formation and pseudo obstruction development [9]. Castor oil is not recommended due to its sudden stimulating effect on bowel motility and the risk of developing strong abdominal cramps. If the oral laxatives are found to be ineffective, rectal treatment is considered. The possibility of opioid switch in the treatment of OIBD should be considered usually rotating codeine to tramadol and morphine to transdermal fentanyl. However, in contrast to clinical studies [10,11], observational surveys do not provide evidence for advantages of transdermal fentanyl over other opioid analgesics with respect to bowel function [12,13].

New approach comprises opioid antagonists with peripherally restricted mode of action as is the case with methylnaltrexone [14] or both central and peripheral effects such as naloxone. However, naloxone is nearly completely inactivated in the liver and has negligible systemic bioavailability when administered orally in controlled-release tablets with oxycodone in a dose ratio 1:2. Oxycodone provides analgesia and naloxone acts only in gastrointestinal tract blocking μ -opioid receptors and preventing constipating effect of oxycodone [15]. Both methylnaltrexone and naloxone do not evoke opioid withdrawal symptoms and may be used in OIBD, especially when oral laxatives are ineffective [16]. Such an approach allows avoiding rectal measures that may affect patients' quality of life [17]. However, long-term safety

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Received May 11, 2012; Accepted May 14, 2012; Published May 16, 2012

Citation: Leppert W (2012) Are we able to Manage Effectively Opioid-Induced Bowel Dysfunction?. *J Autacoids* 1:e113. doi:10.4172/2161-0479.1000e113

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of opioid receptor antagonists are not well established [18,19] and high costs of such therapies may be an important issue, although recent pharmacoeconomic analyses of oxycodone/naloxone provided encouraging results [20].

Summary

Returning to the question in the title are we really effective in the treatment of OIBD? It seems that we have made a huge progress introducing recently opioid receptor antagonists to clinical practice either acting as peripheral only antagonist effects (methylnaltrexone) that is effective in 50-60% of treated patients or a central and peripherally acting antagonists (naloxone) in combination with an opioid analgesic oxycodone which significantly reduces the constipating effect of oxycodone. However, we have limited data on efficacy and safety of both approaches. Traditional treatment remains symptomatic and not targeted on a real cause of the symptoms. So we are on the beginning of the road that should give a positive answer to the question. But we have also the privilege to be part of development in this fascinating area that not only opens up a new chapter in the science but above all has a clear positive impact on patients' quality of life.

References

1. Ueberrall MA, Mueller Schwefe G (2006) Opioid-induced constipation-- a frequent and distressing side effect in daily practice affecting oral and transdermal opioid applications. *Eur J Pain* 10:S172.
2. Bell TJ, Panchal SJ, Miaskowski C, Bolge SC, Milanova T, et al. (2009) The Prevalence, Severity, and Impact of Opioid-Induced Bowel Dysfunction: Results of a US and European Patient Survey (PROBE 1). *Pain Med* 10: 35-42.
3. Reimer K, Hopp M, Zenz M, Maier C, Holzer P, et al. (2009) Meeting the Challenges of Opioid-Induced Constipation in Chronic Pain Management – a novel approach. *Pharmacology* 83: 10-17.
4. Davis MP (2005) The opioid bowel syndrome: a review of pathophysiology and treatment. *J Opioid Manag* 1: 153-161.
5. Holzer P (2007) Treatment of opioid-induced gut dysfunction. *Expert Opin Investig Drugs* 16: 181-194.
6. Thörn SE, Wattwil M, Lindberg G, Säwe J (1996) Systemic and central effects of morphine on gastroduodenal motility. *Acta Anaesthesiol Scand* 40: 177-186.
7. Bruera E, Brenneis C, Michand M, MacDonald N (1987) Continuous subcutaneous infusion of metoclopramide for treatment of narcotic bowel syndrome. *Cancer Treat Rep* 71: 1121-1122.
8. Larkin PJ, Sykes NP, Centeno C, Ellershaw JE, Elsner F, et al. (2008) The management of constipation in palliative care: clinical practice recommendations. *Palliat Med* 22: 796-807.
9. Klaschik E, Nauck F, Ostgathe C (2003) Constipation--modern laxative therapy. *Support Care Cancer* 11: 679-685.
10. Ahmedzai S, Brooks D (1997) Transdermal fentanyl versus sustained-release oral morphine in cancer pain: preference, efficacy and quality of life. *J Pain Symptom Manage* 13: 254-261.
11. Tassinari D, Sartori S, Tamburini E, Scarpi E, Raffaelli W, et al. (2008) Adverse effects of transdermal opiates treating moderate-severe cancer pain in comparison to long-acting morphine: a meta-analysis and systematic review of the literature. *J Palliat Med* 11: 492-501.
12. Rosti G, Gatti A, Costantini A, Sabato AF, Zucco F (2010) Opioid-related bowel dysfunction: prevalence and identification of predictive factors in a large sample of Italian patients on chronic treatment. *Eur Rev Med Pharmacol Sci* 14: 1045-1050.
13. Weschules DJ, Bain KT, Reifsnnyder J, McMath JA, Kupperman DE, et al. (2006) Toward Evidence-Based Prescribing at End of Life: A Comparative Analysis of Sustained-Release Morphine, Oxycodone, and Transdermal Fentanyl, with Pain, Constipation, and Caregiver Interaction Outcomes in Hospice Patients. *Pain Med* 7: 320-329.
14. Thomas J, Karver S, Cooney GA, Chamberlain BH, Watt CK, et al. (2008) Methylnaltrexone for Opioid-Induced Constipation in Advanced Illness. *N Engl J Med* 358: 2332-2343.
15. Ahmedzai SH, Nauck F, Bar-Sela G, Bosse B, Leyendecker P, et al. (2012) A randomized, double-blind, active-controlled, double-dummy, parallel-group study to determine the safety and efficacy of oxycodone/naloxone prolonged-release tablets in patients with moderate/severe, chronic cancer pain. *Palliat Med* 26: 50-60.
16. Slatkin N, Thomas J, Lipman AG, Wilson G, Boatwright ML, et al. (2009) Methylnaltrexone for treatment of opioid-induced constipation in advanced illness patients. *J Support Oncol* 7: 39-46.
17. Leppert W (2010) The role of opioid receptor antagonists in the treatment of opioid-induced constipation: a review. *Adv Ther* 27: 714-730.
18. McNicol ED, Boyce D, Schumann R, Carr DB (2008) Mu-opioid antagonists for opioid-induced bowel dysfunction. *Cochrane Database Syst Rev* 16: CD006332.
19. Candy B, Jones L, Goodman ML, Drake R, Tookman A (2011) Laxatives or methylnaltrexone for the management of constipation in palliative care patients. *Cochrane Database Syst Rev* 1: CD003448.
20. Dunlop W, Uhl R, Khan I, Taylor A, Barton G (2012) Quality of life benefits and cost impact of prolonged release oxycodone/naloxone versus prolonged release oxycodone in patients with moderate-to-severe non-malignant pain and opioid-induced constipation: a UK cost-utility analysis. *J Med Econ* 15: 564-575.