Current Management of Opioid-Related Side Effects

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The optimal management of opioid-related side effects is hampered by a lack of comparative studies of management strategies. The prevalence of such side effects is influenced by the extent of disease, the patient's

The management of opioid-related side effects in advanced cancer patients remains a challenge, and the problems involved are well described by O'Mahony et al in their article. The authors provide us with an excellent review of the current literature and, based also on their own experience, offer recommendations for dealing with opioid-related side effects. We strongly concur with the points presented by Dr. O'Mahony and his colleagues. In the following comments, we will emphasize a number of important issues sometimes overlooked in clinical practice, and will provide examples of our approach to managing adverse effects in the McGill Palliative Care Program.

Many of the common side effects of opioids are also common symptoms caused by the underlying cancer. In an attempt to simplify this complex situation, it is useful to distinguish the well-recognized adverse effects, such as nausea, vomiting, constipation, drowsiness, and respiratory depression, from the less well-recognized neuropsychiatric adverse effects, such as myoclonus, hallucinations, cognitive failure, delusion, and delirium. The well-recognized side effects usually occur at the start of the opioid regimen and/or with incremental doses; the neuropsychiatric adverse effects are more frequently related to long-term use, high-doses, and general metabolic abnormalities (notably, renal disease).

Evaluating Symptoms

Nausea, vomiting, drowsiness, and respiratory depression tend to resolve quickly after the initiation and titration of opioid analgesia; however, tolerance to constipation does not. We recommend evaluating symptoms using a visual analog or categorical scale prior to initiating therapy with an opioid analgesic medication and documenting the effects on the chart. Too often, patients are not asked before starting opioids if they are experiencing gastrointestinal symptoms, and the addition of an opioid may then exacerbate a previously tolerable gastrointestinal problem. Consequently, a patient’s nausea and vomiting may increase, and the patient may undergo unnecessary studies.

For patients seen in the outpatient clinic, we usually prescribe an antiemetic to be used as needed. Because gastroparesis is common in advanced cancer patients,[1] we feel that the antiemetic metoclopramide is probably the best choice. A placebo-controlled trial has shown metoclopramide to be effective in this patient population.[2] Of note, metoclopramide, like haloperidol, can be administered subcutaneously every 4 hours or in a continuous infusion over 24 hours.[3] The usual recommended dose is 60 mg in 24 hours, although higher doses may be required. When nausea and vomiting persist for more than a week after initiation of opioid therapy, another cause should be investigated.

Constipation and Nausea and Vomiting

The most common cause of nausea and vomiting with chronic use of opioids is probably underrecognized constipation. The authors present the standard definition of constipation; however, this definition has many limitations. It is probably more reasonable to look for a change in the bowel habits of cancer patients taking opioids. Noteworthy signs include decreased frequency or increased difficulty passing stool. Because constipation remains difficult to assess, we usually perform an abdominal x-ray when we are unsure of the degree of stool retention.

Starreveld et al described a very simple scoring system for evaluating constipation. The colon is divided into four segments, with a score of 0 to 3 assigned to each segment for a possible total score
of 12.[4] The patient who presents with a score higher than 7 should be considered constipated and requires more aggressive assessment. The main limitation of this scoring system is that a patient may have a score lower than 7 and yet have a large fecaloma limited to one segment. Such patients also need an increased bowel regimen to alleviate the risk of a stool-induced intestinal blockage.

Undeniably, the best approach to constipation is prevention. Patients with advanced cancer have a propensity for developing constipation, and in the absence of a contraindication, we usually start therapy with sodium docusate and senna. A clinical nurse specialist instructs patients on how to adjust the dose according to their bowel habits. The use of psyllium remains risky because cancer patients may have difficulty drinking enough fluid to make this medication effective, and in some situations, this may lead to increased constipation.

**Respiratory Depression**

As well described in the article by O'Mahony et al, respiratory depression remains a transitory problem following the initiation of opioids, and tolerance develops rapidly. The risk of respiratory depression, however, may recur when patients are switched from one opioid to another or from the oral route to the parenteral route. In the latter case, mistakes may occur because of a lack of understanding of equianalgesia as well as partial cross-tolerance of the opioids.

Physicians must familiarize themselves with published opioid equivalency tables.[5] These are useful guides, although individual patient variation is common and some tables are misleading with respect to methadone. Of note, dangerous respiratory depression often develops when patients are switched from high-dose opioids to methadone. This is especially important because many published tables suggest that morphine and methadone are equianalgesics when, in fact, the analgesic ratio of these agents more likely exceeds 10:1.[6] Methadone is an inexpensive analgesic with inhibitory NMDA effects and exhibits limited cross tolerance with other opioids. We anticipate that it will be a widely used opioid in the future. Clinicians should be trained in its use.[7]

**Cognitive Failure**

While drowsiness is common at the start of opioid treatment and usually resolves, true cognitive failure—a component of delirium—is very common in advanced cancer and almost the rule at the end of life.[8] Delirium in advanced cancer patients is characterized by an acute onset of cognitive failure, hallucinations, delusions, sleep-awake cycle reversal, psychomotor retardation, and/or agitation.

Physicians caring for advanced cancer patients should actively look for the onset of cognitive failure using objective testing such as the Folstein Mini-Mental Status Questionnaire.[9] This test is only a rough guide, and patients at risk should be asked regularly if they are experiencing hallucinations (visual or tactile), delusions (mainly paranoia), insomnia, or fearful nightmares. When the patient’s clinical picture meets DSM-IV criteria, the diagnosis of delirium should be recorded on the chart.[10] Delirium requires a prompt, complete investigation to rule out such causes as sepsis, liver and renal failure, hypoxia, hypercalcemia, and dehydration. Reversible etiologies should be treated.

In some patients, dehydration associated with renal failure results in drug accumulation, including opioids and their metabolites. Adverse drug effects are among the principle causes of delirium. Simple measures to manage this situation include reducing the opioid dose or switching opioids, initiating moderate hydration (1,000 to 1,500 mL of normal saline per 24 hours), and discontinuing other potentiating drugs.[8] Patients should also be treated symptomatically using neuroleptics (eg, haloperidol, methotrimeprazine) when delirium is irreversible and death is soon anticipated, benzodiazepines such as midazolam may also be employed.

**References:**


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