Management of opioid tolerability and related adverse effects

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Abstract

Aims: Adverse effects associated with opioid use are numerous and can be treatment limiting, but a variety of management strategies and tactics exists. The aim of this study was to review opioid use adverse effects and their treatment options.
Methods: We reviewed the recent literature and highlighted the most common adverse effects associated with opioid use and the suggested treatment options and tactics.
Results: Adverse effects of opioids range from common ones (constipation, nausea) to the less common (hiccups, lower leg edema), from the relatively mild (dry skin, runny nose) to the severe (respiratory depression). The adverse effects of opioids may be classified into inhibitory and excitatory, although they sometimes occur simultaneously. Ultra-low doses of opioid antagonists can reduce excitatory effects which, in turn, can heighten the inhibitory response (and possibly potentiate analgesia).
Conclusions: Patients on opioid therapy may benefit from a change in drugs (ideally to a non-opioid altogether, but possibly to a lower dose or different opioid) or combination therapy. Specific medications or therapies have been shown to be effective in managing some adverse effects of opioid therapy, but there is considerable intra-patient variability. Opioid therapy confers analgesic benefits to well-selected patients, but adverse effects of this therapy are common and may require physician management.

***Keywords**: Opioids, opioid adverse effects, opioid adverse events, opioid antagonists.*

Introduction

Opioid tolerance can be defined as the need to take increasing amounts of the opioid agent in order to effectively maintain the same level of analgesic relief (1). However, the relationship between opioid tolerance and addictive mechanisms is unknown. While opioid rotation can often be useful to strike this appropriate balance, the adverse effects of different opioids may create new or worsened side

effects. Opioid rotation can be limited by the fact that there is not always sufficient evidence available to guide equianalgesic ratios (2). The most straightforward approach to management of opioid-related side effects starts with dose reduction, followed by changing to a different opioid or route of administration (3,4). However, many adverse effects (AEs) are systemic and central in nature, so opioid rotation may not abate the symptoms; changing routes of administration may be impractical. Thus, prescribing additional medications to manage side effects has become common, although it often leads to patient inconvenience and potentially hazardous polypharmacy.

Classification of opioid adverse effects

Excitatory and inhibitory effects may occur simultaneously, producing bimodal action (5). Ultra-low doses of opioid antagonists block the excitatory effects, such as hyperalgesia, while potentiating the inhibitory effects, such as analgesia, and may improve the side-effect profile (6,7). A recent study of low-dose nalbuphine and morphine in humans (n=174) found that low-dose nalbuphine with morphine in patient-controlled anesthesia reduced the rate of nausea without adversely affecting analgesic benefit (8). In the aforementioned study, 1 mg nalbuphine was added to 100 mg preservative-free morphine and saline to make a total volume of 100 mL solution for patient-controlled analgesia. Another human study of analgesia (n = 112) combined 100 ng (1 mL) of naloxone with 100 ìg of fentanyl and 34 mL of lidocaine 1.5% for the active agent arm of the study, finding that the addition of low-dose naloxone prolonged axillary brachial plexus blockade – that is, time to first postoperative pain – in patients undergoing elective forearm surgery (9).

Managing opioid-related adverse effects

Many patients who take opioids may discontinue them and restart. Tolerance to opioids can build quickly, but it is also lost quickly.

Table 1. Management of opioid-related adverse effects

1.	If possible, use non-opioids.
2.	Use combination therapy (opioid and a non-opioid pain reliever) rather than increasing the dose of the single opioid.
3.	Periodically convert to non-opioids, decrease and/or discontinue opioids to see if the patient tolerates the change.
4.	Consider opioid rotation (changing from one opioid to another opioid) if you are unable to circumvent side effects (10).
5.	Consider social and family history in relation to opioids.
6.	Exercise caution when combining opioids with other CNS depressants.
7.	If opioids are decreased or discontinued and then reintroduced, slow titration is preferred to give the body time to adjust.
8.	Watch for CYP P-450 medications interactions.

Opioid-related adverse effects

Respiratory AEs: Respiratory AEs are so important that they belong in a special category. This action decreases the brain stem's response to CO_2 and directly affects the cough center in the medulla, even at sub analgesic levels. Morphine and fentanyl have higher rates of respiratory depression than buprenorphine, which in one study was found to exhibit a plateau effect with respect to respiratory depression (11). Doubling the dose of buprenorphine increased analgesia but did not increase the rate of respiratory depression. General principles of airway management and managing inhibitory symptoms may be utilized including naloxone 0.4 mg to 2 mg intravenously in emergencies.

Intracranial AEs: All opioids, particularly short-acting opioids, are known to induce headaches in chronic headache patients. A severe headache induced immediately after opioid initiation usually subsides spontaneously and may respond, at least partially, to acetaminophen and non-steroidal anti-inflammatory drugs. Severe headaches may require discontinuation of the opioid.

Musculoskeletal AEs: Musculoskeletal AEs are mainly excitatory and may be a part of opioid-induced hyperalgesia. Muscle weakness with a decrease in deep tendon reflexes may be a result of opioid-induced central nervous system inhibition. Muscle relaxants in usual doses can be used; antispasmodic medications, including alpha blockade from tizanidine, can be beneficial in treating muscle twitching and myalgia. Dopaminergic anti-Parkinson medications, such as pramipexole dihydrochloride and ropinirole extended release, may be beneficial but must be used with caution because of their potential to depress the central nervous system. Buprenorphine has less excitatory effects on the muscles than other similar agents.

Cutaneous AEs: Cutaneous AEs are mostly excitatory in nature and include itching, flushing, sweating, rash, ecchymosis, petechiae, and facial wrinkles. Inhibitory cutaneous AEs include dry skin as well as brittle hair and nails. Hypoventilation is associated with pallor or grayish skin color and is a direct sign of developing hypoxia and encephalopathy. Some cutaneous adverse effects are related to the release of histamine and may diminish over time in chronic opioid therapy. Sweating may be treated with a variety of measures: hydroxyzine 25 mg to 100 mg every 6 to 8 hours; terazosin 2 mg to 4 mg orally per day; scopolamine patch and atropine; aluminum chloride 20% topically; calcium supplementation; and micro-doses of naltrexone. Anticholinergic biperiden also may be used, but care must be taken since anticholinergic agents may increase constipation, urinary retention, or other adverse effects. For inhibitory AEs, simple measures, such as 3 g to 6 g a day of Omega III fatty acids (fish oil, flaxseed oil) and liberal use of creams and topical ointments, may suffice.

Circulatory AEs: The inhibitory AEs associated with opioids on the circulatory system include orthostatic hypotension due to vasodilatation; a decrease in cardiac output; bradycardia or tachycardia; and QT-segment prolongation on the electrocardiogram. The excitatory AE is mainly peripheral edema, especially lower leg edema due to histamine release and cAMP induction. For inhibitory AEs, vasoconstrictors and hydration can be used. For excitatory AEs, diuretics and terazosin 1 mg to 10 mg by mouth at bedtime can be considered. Compression stockings and sequential circulation may be used in cases of lymphedema.

Visual AEs: The mechanism behind visual problems is not clearly understood, but one suggestion is that MOR-3 activation releases nitric oxide, which, in turn, causes intraocular hypertension and miosis, resulting in blurred vision (12,13). Another theory proposes even opioid-tolerant patients may have miosis with sudden or marked increases in dose. Mydriasis is more likely to occur in patients with opioid-induced hypoventilation and hypoxia. Pulsating pupils under penlight exam suggest adrenal fatigue. Visual disturbances, like other side effects, may be dose related.

Gastrointestinal AEs: When released from enteric neurons, it is likely that opioid peptides play a mediator role in the regulation of propulsion and secretion (16-20). Stool softeners are commonly used to treat opioid-induced constipation, but this is not usually as effective as a laxative or laxative-stool softener combination, since opioid-induced constipation is caused by poor gut motility. Patients who had GI spasm prior to opioid therapy will likely find their abdominal pain exacerbated by opioids. To manage excitatory GI AEs, decrease opioid dose and consider the use of promethazine, prochlorperazine, and ondansetron. Micro-doses of naltrexone can be considered as well. Inhibitory AEs, specifically constipation, are treated by laxatives (possibly in combination with a stool softener) as well as metoclopramide and dicyclomine. Methylnaltrexone 12 mg by subcutaneous injection can block opioid-inhibitory GI AEs in the gut. Erythromycin-related motilides, ghrelin analogues,

the mixed 5-HT4 receptor agonist/ 5-HT3 receptor antagonist renzapride and the CCK1 receptor antagonist dexloxiglumide represent further prokinetic drug candidates that are in clinical development (14,15).

Endocrine AEs: There is a dose-dependent relationship with respect to opioids and AEs involving the endocrine system. Curiously, there are no reports in the literature of decreases in follicular-stimulating hormones and prolactin blood levels as AEs of opioids. Thyroid-stimulating hormone (TSH) may be suppressed or stimulated by opioids and can mask hypothyroid symptoms. Hypoadrenalism is related to suppression of adrenocorticotropic hormone (ACTH), and some opioid patients may require steroid supplementation because of cortisol suppression and clinical Addison's disease. Prolactinemia has been reported, including gynecomastia, weight gain, and infertility. The use of bromocriptine 5 mg to 7.5 mg by mouth every day may be used to treat prolactinemia along with decreasing the opioid dose.

Urinary AEs: Urinary AEs are primarily excitatory and involve urinary retention caused by an increase in the sphincter's tonus. There is a higher prevalence of hypogonadism in male opioid patients than in females, which has led to the speculation that prostatic hypertrophy may owe to inhibitory effects of opioids suppressing more testosterone than estrogen. Clinical management of urinary AEs may include conservative approaches with hydration or one of the pharmacological measures, such as dicyclomine 10 mg to 20 mg up to 4 times daily, oral bethanechol 10 mg to 30 mg 2 to 4 times daily, 1 mg to 10 mg oral terazosin at bedtime, or 0.5 mg oral dulasteride daily. Meperidine, in particular, should not be used in patients where renal toxicity might be an issue.

Conclusions

Opioids represent a challenge in clinical practice due to their wide-ranging clinical, side effect, and end-organ effects. The complex properties of opioid analgesics and their potential interactions with other medications present a significant clinical challenge to even seasoned pain specialists. It is not unheard of that chronic opioid patients choose to discontinue opioid therapy (and give up pain relief) rather than endure intolerable adverse effects. Nevertheless, opioid analgesia offers tremendous benefits to well-selected chronic pain patients when resulting AEs can be managed. In addition to the previously described strategies, further research needs to be carried out to address specific opioid AE management strategies that will optimize analgesia while lessening concerns about tolerability, serious adverse events, and chronic end-organ concerns.

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