

Opioid Induced Neurotoxicity

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GOAL

To educate the pharmacist on opioid induced neurotoxicity (OIN) and its management.

INTRODUCTION

The pharmacist plays a key role in monitoring the effect and adverse effects of medications that are taken by patients. Many patients taking opioids over extended periods of time may have chronic progressive pain secondary to cancer. Many of their treatments will be for palliation rather than cure. Opioid induced neurotoxicity is a term used to describe symptoms of cognitive impairment, severe sedation, hallucinations, myoclonus, seizures and hyperalgesia.^{(1) (2)} These are some of the signs and symptoms that we as pharmacists should instruct the patient and families to watch for.

DEFINITIONS

Pain is a subjective condition. Pain is what the patient tells you it is. Acute pain is sometimes easier to visualize on a patient's face. There may be signs of grimacing, the patient may groan and cry out loud. The autonomic nervous system may show signs of hyperactivity (sweating, pallor, tachycardia, and hypertension) during an acute episode of pain. Chronic pain is harder to detect at first glance. The patient doesn't show any of the autonomic signs. Long term pain that is not relieved will cause a patient to be tired, and depressed. The patient's face looks sad, quiet and sleepy.⁽³⁾ Assessing pain by visualization alone can be deceiving. The visual analogue scale (VAS) is a useful tool that can provide a record of the patient's pain history and may help to show response to medication. The scale is traditionally 10cm long with numbers from 1-10. The patient grades his pain at a particular time and the measurement is the patient's present pain intensity.

Palliative care has many different definitions depending on the reference. In 1995 the Canadian Palliative Care Association defined it as "the combination of active and compassionate

therapies intended to comfort and support individuals and their friends and families who are living with, or dying from, a progressive life threatening illness, or are bereaved."⁽³⁾ Comfort care is also one of the terms used to describe palliative care. When patients are enrolled on a palliative care program it usually means that the goals of treatment are aimed at palliation of symptoms and not cure. Palliative care does not mean that "we do nothing". Many patients will want treatment of acute reversible conditions (eg. antibiotics, blood transfusions) if they are still experiencing good quality of life. This often depends where they are in the trajectory of their illness.

Neuropathic pain is an area that is currently being evaluated for its relation to N-methyl-D-aspartate (NMDA)

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receptors that may be involved in the pain mechanism. This type of pain is due to a peripheral neurological lesion and may be described as: burning or radiating pain, sudden episodes of shooting pain, or pain with light touch. This type of pain is often less responsive to typical opioids. When the dose of opioid starts to escalate in the treatment of pain one should consider that this type of pain may be involved. Methadone can sometimes be useful in treating this type of pain, along with anticonvulsants and steroids.⁽¹⁾ Treatment of neuropathic pain is beyond the scope of this article.

Hyperalgesia is a term to describe a lowering of the pain threshold. It can be a paradoxical pain where the pain becomes overwhelming and ceases to be relieved or is actually worsened by further administration of the opioid.⁽⁴⁾
⁽⁵⁾ The patient may tell you, "I have pain all over."

Allodynia is a condition where stimuli that are not normally painful precipitate pain in the patient. For example a bed sheet resting on the patient's leg causes a significant amount of pain where normally it wouldn't even be consciously noticed.

Myoclonus is a sudden, brief, shock-like, involuntary movement that are caused by muscle contractions. The jerks can occur singly or repetitively, small (hard to detect contractions) or gross contractions where the limb movement can be visibly detected. Myoclonus can involve a single region or multiple regions of the body. It normally occurs during periods of drowsiness and light sleep, but is not limited to these situations.⁽⁶⁾

SIGNS AND SYMPTOMS

Signs and symptoms of OIN are not always obvious. Confusion is a side effect that may be encountered for the first few days-weeks when started on an opioid. This is normally mild and self-limiting once tolerance to the opioid occurs. Delirium in cancer is not always easily linked to one identifiable cause. Opioids may be the cause of the toxicity but other potential causes should be ruled out. (See section on investigations). Delirium may present clinically either with agitated, hyperactive symptoms or be hypoactive. Sometimes both symptoms will coexist.⁽¹⁾

Myoclonus may be an early indicator that the patient is starting to develop OIN. Mild myoclonus that occurs during sleep may be normal, but if the myoclonus becomes noticeable during waking hours treatment options should be considered. If not treated myoclonus can escalate into seizures. Mild myoclonus may be observed and treated with clonazepam. However,

Acute delirium
Myoclonus
Seizures
Hyperalgesia
Hallucinations

Table #1
Signs and symptoms

when a patient is on high doses of opioids or has been on the same opioid for a long period of time, consider rotating the opioid that the patient is taking.⁽¹⁾

Hyperalgesia, or paradoxical pain, can be misdiagnosed as inadequate pain control. This may lead to increasing the dose of opioid. This pain is actually caused by the opioid (a neurotoxic side effect), and other treatments should be considered. (See section on treatment)

Hallucinations, either visual or tactile, can occur with opioids. Patients may be reluctant to relate these concerns to health care professionals for fear they will be considered psychiatrically ill.⁽¹⁾ If the patients do not verbalize their hallucinations, they may be seen to pick at the air. Often the only signs may be a change in a patient's mood.⁽¹⁾ Family or nurses who have more contact with the patient will often be the source of information on changing mood. The hallucinations can be managed by changing or reducing opioids, or treating with medications like haloperidol.

RISK FACTORS

Risk factors will differ for each patient. Some patients who have a terminal illnesses like cancer may be on high doses of opioids or may have been on them for a prolonged period of time. There is no ceiling dose for strong opioids (i.e. morphine, hydromorphone etc) which allows one to escalate the dose as needed. Sometimes this escalation may occur rapidly.⁽⁷⁾⁽⁸⁾⁽⁹⁾ The pattern of opioid use to treat pain has been changing over the years. The pain had been under-diagnosed /under-treated in the past. The changing pattern of increased use/escalating doses has resulted in the evolution of OIN as a major side effect.⁽¹⁾

Does the patient have an underlying condition other than the opioid that may be causing the delirium/cognition situation. The patient may have other disease states, such as, diabetes or Alzheimers that could play a role in their cognitive state.

Opioids are metabolized by the liver and excreted via the kidney thus renal and hepatic organ dysfunction may cause opioid concentrations to become elevated. The elevated concentrations may cause added central nervous system toxicity.⁽⁴⁾⁽¹⁰⁾ Systemic clearance of opioids is reduced in patients who are older than 50 years, and the elderly population are more susceptible to the beneficial and

adverse effects of narcotics. When choosing an opioid, those with shorter half-lives may be safer.⁽¹⁰⁾

Morphine is an opioid that has pharmacodynamic implications. It has two active metabolites; morphine-6-glucuronide (M6G) and morphine-3-glucuronide(M3G). M6G may contribute to both the analgesia and the adverse effects observed while on morphine.⁽¹³⁾ These active metabolites need to be considered when a patient is receiving morphine for pain relief, especially if the patient is elderly or has reduced renal function. Studies show in these populations that the ratios of M3G and M6G accumulate exponentially, making toxicity more likely.⁽¹⁴⁾ A case study article explains that elevated concentrations of the metabolites may play a role in the development of hyperalgesia, allodynia and myoclonus.⁽¹⁵⁾

Meperidine is an analgesic that we must look at for pharmacodynamic considerations. It is metabolized to normeperidine which is an active metabolite. Normeperidine is a strong convulsant and a weak analgesic. The problem arises because the half-life of normeperidine is three-four times longer than that of meperidine. When normeperidine starts to accumulate tremors, multi focal myoclonus and in severe cases seizures will develop. This opioid should not be used long term due to these risks.^{(10) (12)}

Nephrotoxic medications will exacerbate the renal dysfunction. NSAIDs, which are nephrotoxic, have been shown to be associated with increased risk of myoclonus.⁽¹¹⁾ Dehydration may also be a causative factor in the emergence of OIN.

When patients are taking a number of medications the risk for drug interactions increases. If patients are taking other CNS depressants, the sedation may be additive or synergistic with opioids. Constipation caused by anti-cholinergic medications may also be additive or synergistic with opioids.⁽¹⁰⁾

When one is dealing with issues of pain control, one must remember that there are many factors that can affect the experience of pain. One needs to consider the concept of "Total Pain". Besides the physical cause of pain, it is important to note that pain can be exacerbated by emotional, psychosocial and spiritual issues. Attention to all of these factors may play a role in our ability to treat someone in pain.

Palliative care is best delivered by a team of professionals who can help to address the many issues that this population of people deal with.⁽³⁾

INVESTIGATIONS

We want to investigate looking for possible underlying causes other than opioid toxicity. One needs to check for infection, dehydration, hypercalcemia, uremia or other metabolic changes. Metastatic disease to the brain or other organs can be ruled out by doing a bone scan, CT scan or MRI. In comfort care the patient's needs and goals of care must come first. Expensive tests and blood work are appropriate at times depending on the patient's quality of life and their wishes for how much investigation is to be done.

MANAGEMENT

1. Opioid Rotation

Opioid induced neurotoxicity can be a result of an opioid/active metabolites. If this is suspected then a rotation to a different opioid will allow the opioid/metabolites to be excreted and still maintain pain control with the new analgesic.⁽⁴⁾ There is no ideal opioid to rotate to. The first line agents include morphine, hydromorphone, fentanyl patch or oxycodone. Methadone is considered a second line agent because it has an unpredictable half-life and the equianalgesic dose is not well documented.⁽¹⁾ On the positive side methadone has the benefit of low cost, and no active metabolites have been identified yet. It is used especially when neuropathic pain is suspected. Methadone requires time and skill and can only be used by those licensed to prescribe it.

If opioid rotation is the management chosen, change from the current first line opioid to a different first line opioid by way of an equianalgesic conversion and reduce the dose by 30-

Infection
Dehydration
Metabolic abnormalities -hypercalcemia (total Ca conc>2.60mmol/L) -uremia -hepatic encephalopathy
Brain Metastasis
Hypoxemia-O ₂ and CO ₂ saturation levels
Medications-see if any can be discontinued or changed to medications that are less likely to cause problems

Table #2
Investigations

50% to account for incomplete cross-tolerance. The different opioids bind to different receptors (mu, kappa, delta) therefore tend to have less tolerance than expected by conversion tables.

Methadone is an opioid where conversion is not straight forward. There are several ways to convert the patient to methadone. A detailed discussion of methadone is beyond the scope of this article, however there are references available that discuss conversion.⁽³⁾

The dose reduction may be more than the traditional 30-50% from one opioid to another if the patient was on very high doses of the analgesic. There have been reported cases where the patients were on very high doses of hydromorphone and they were switched to morphine at a dose that was equal to ~20% of the equi-analgesic hydromorphone dose.⁽⁷⁾ These patients gained good pain control and were even tapered down from that morphine conversion dose.

Another case describes a patient receiving an oral morphine equivalent daily dosage (MEDD) of 28,000 mg per day and switching to methadone. The patient's toxicity symptoms resolved, her pain was controlled and her cognitive function improved. This patient needed intensive psycho social counseling in addition to her medication changes.⁽⁸⁾ There are other case reports available that discuss dose reduction greater than the traditional 30-50% when patients are on very high analgesic doses.⁽⁹⁾

A consult to a palliative or pain specialist should be indicated if the patient is not being well controlled on current medications.

2. Hydration

If a patient is experiencing signs and symptoms of OIN and is dehydrated, hydration may be given in an attempt to remove metabolites faster. Hydration in palliative care is a controversial area. The decision about hydration may depend upon where the patient is in the trajectory of their illness. Opioid induced neurotoxicity can make a person appear close to death. At times the use of hydration and other suggested treatments can reverse the situation and patients may then return to a relatively good quality of life for a number of weeks or months. The decision should be made on a patient to patient basis, depending on the goals of care.⁽¹⁶⁾⁽¹⁷⁾⁽¹⁸⁾⁽¹⁹⁾⁽²⁰⁾

3. Myoclonus

The incidence of opioid induced myoclonus varies depending on the

study, and the perceptions of the symptom. It ranges from 2.7%-87%. Myoclonus in patients on chronic opioid therapy seems to be dose-related in an unpredictable manner.⁽²¹⁾ There are different views on the cause of myoclonus. A deficit in serotonin metabolism, an increase in release of serotonin and interactions with other neurotransmitter systems have been presented to explain some types of myoclonus.⁽²¹⁾ It has also been postulated that myoclonus could be caused thru an anti-glycinergic effect. Glycine is known to mediate inhibition on dorsal horn neurons. Morphine-related opioids and their metabolites may act via a spinal antiglycinergic effect to reduce post-synaptic inhibition at a non-opioid receptor site, resulting in hyperalgesia and/or myoclonus.⁽⁸⁾

If myoclonus is present, a switch or reduction of opioid should be considered. Symptomatic treatment may include using benzodiazepines, (i.e. midazolam, clonazepam) dantrolene, or baclofen.^{(6) (21)(22) (23) (24) (25)}

4. Psychostimulants

Sometimes patients on opioids can become sedated and drowsy. Some patients with cancer can have an underlying depression with or without sedation. Due to the limits of time with palliative patients, traditional antidepressants may take too long to show benefit. Psychostimulants like methylphenidate, and dextroamphetamine (Ritalin and Dexedrine) are useful because their onset of action is generally quick, they will aid the patient in remaining more alert, and help to reduce or reverse the depressed emotions.⁽²⁶⁾

Most studies available deal with methylphenidate and the dosage range is usually 2.5mg up to 80mg per day. Normally the medication is given twice daily, once in the morning and the second dose at noon. Some of the studies available have the limitation that they don't examine the duration of effect.⁽²⁵⁾ The study times are only weeks, due to patients in end stage disease or that the study is slated for that duration of time.^{(27) (28)}

Psychostimulants are not without side effects. They can cause insomnia, anorexia, nausea, sometimes even delusions and psychosis.

EARLY DETECTION

Mini-Mental Status Exam

This is an easy to administer questionnaire that involves simple memory and recall tests. It is approximately 30 questions and takes only about ten

minutes to administer. It could be an aid in the prevention and progression of OIN. One retrospective study looks at doing this exam twice a week in patients with advanced cancer. The study compares time periods where cognitive assessment was completed and when it was not. If determined by the exam that the patient's cognitive status was deteriorating, the opioid would be rotated and hydration would start. They concluded that routine cognitive monitoring, opioid rotation and hydration may reduce the incidence of impaired mental status (OIN).⁽²⁹⁾

CONCLUSION

The goal of the article is to educate pharmacists on opioid induced neurotoxicity and its management. One of the pharmacist's roles is to provide information on safe and effective use of medications. Opioids can treat patient's pain effectively but they can also cause serious side effects. Certain patients will be at higher risk for developing these side effects. If we are aware of the signs and symptoms and investigations that should be done then we can provide optimum care to our patients. The management of opioid induced neurotoxicity will vary depending on the cause. The awareness of the options will enable pharmacists to be a part of the patients care team. ■

References available upon request to MSP