Neurotoxicity of Opioids: Are We Responding?

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Opioid analgesics are one of the most effective treatment modalities for cancer pain. In the past, several studies have revealed mismanagement of cancer pain, and under-utilization of opioids. As a result, the last ten years have seen an enormous educational drive by various international organizations to reverse the needless suffering. These educational drives have resulted in a healthy and appropriate increase in the availability and use of opioids, as well as a general increase in dose and length of exposure to the opioids. Clinicians are gradually becoming more acquainted with the general principles of cancer pain management and more knowledgeable regarding the common opioid adverse effects such as nausea, constipation and sedation.

With this increased utilization, has come an increased detection of "newer" adverse effects. These adverse effects are primarily neuro-psychiatric in nature and include myoclonus, grand-mal seizures, hallucinosis and delirium, hyperalgesia and allodynia. Myoclonus presents as generalized muscular twitching and if severe enough, can go onto develop grand-mal seizures. Hyperalgesia and allodynia, in which normally non painful stimuli become very painful, are one of the more dramatic toxicities described. Several authors have reported patients experiencing visual or tactile hallucinations. Cognitive impairment, delirium and late-onset sedation have also been noted. Most of the commonly utilized opioids, including morphine, hydromorphone, oxycodone, and fentanyl, have been implicated.

The accumulation of various active opioid metabolites has been postulated to be the main underlying cause of these "newer" toxicities. Metabolites of various opioids are generated by the liver and eliminated by the kidneys. Studies have shown that morphine-3-glucuronide (M-3-G) cause severe central nervous system excitation, whereas morphine-6-glucuronide can result in a spectrum of classically related opioid side effects. Other metabolites, as well as the parent opioid, may also be involved. Since these opioid metabolites are eliminated by the kidneys, renal impairment will result in their accumulation, giving rise to toxicity. Patients at risk for developing these neuro-toxicities are those with borderline cognition, those on high doses of opioids and for prolonged periods, patients with neuropathic pain, patients with renal impairment and dehydration, and patients taking psychoactive medications such as benzodiazepines.

It must be emphasized that these newer toxicities should not be a deterrent to clinicians and physicians utilizing these effective drugs in their efforts to control cancer pain. Various very effective strategies have been described to prevent, control and reverse these toxicities. The most successful strategies are opioid rotations, hydration and the discontinuation of other aggravating drugs. In recent years an increasing number of authors have reported successes using these strategies. An opioid rotation involves the switching over to an alternative agonist opioid at an equianalgesic dose, less 20-50%, when these toxicities emerge. This allows for the elimination of

the offending drug while maintaining adequate analgesia with the new one. Our group utilizes switches between morphine, hydromorphone, oxycodone, fentanyl and methadone. We have found methadone a very useful opioid: with the caveat that chronic administration of methadone results in it being approximatley is approximately ten times more potent than morphine. This is very different to most commonly reported equi-analgesic dose tables. Hydration allows for the elimination of the offending opioid metabolites. Discontinuation of other drugs that may aggravate delirium etc , such as benzodiazepines, is prudent if delirium presents. The symptoms of delirium can be controlled with other drugs such as haloperidol. In countries where alternative agonist opioids are not available, the overall opioid dose can be reduced or circadian modulation, with decreased nocturnal doses, that can be employed. Where severe sedation persists despite opioid rotations, dose reductions, and the elimination of other psychoactive drugs, a psychostimulant may be useful. Various other drugs for the treatment of such toxicities as myoclonus have been reported in the literature. These include clonazepam, lorazepam, baclofen, barbituates, etc. However, none of these have been studied in well-controlled trials, the evidence for their effectiveness is occasionally contradictory, many of them are themselves associated with central nervous system adverse effects, and ultimately, they do not remove the underlying cause of the problem.

As clinicians, we should be more attentive to these toxicities. We should be monitoring cognition in these patients regularly, we should be inquiring about the presence of hallucinations and hyperalgesia, and we should be identifying patients at risk. These toxicities should not deter us from utilizing opioids in cancer pain. Rather, we should be aware of them, we should be knowledgeable of the various strategies to manage them, and in our education efforts, we should be emphasizing the need for regular, thorough multidimensional assessments of our patients, we should emphasize the recognition of these toxicities and teach other caregivers on how to manage these toxicities appropriately. We should continue to promote the use of opioids, but the time has also come for greater finesse when utilizing these excellent medications.