

The Importance of Opioid Tolerance: A Therapeutic Paradox

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Surgeons appreciate that a responsibility to manage pain is an integral part of their practice. Multiple treatment modalities for optimally managing pain are frequently necessary, but knowledgeable use of analgesic drugs is the most essential because drug therapy is the mainstay of pain treatment. The most important analgesic drug group to understand is the opioids. Opioids are potent, versatile, and safe (except for meperidine and propoxyphene, which have toxic metabolites), but they are frequently underused in patients with chronic pain, such as cancer patients, who are commonly seen in a surgical practice.

Physicians are aware of the dangers of opioid use, particularly respiratory depression, but many have an incomplete understanding of the safety of opioids, particularly with longterm use. This leads to underprescribing and to inadequate pain relief. The safety of opioids is related to two unique pharmacologic properties and to the development of tolerance.

Unique properties of opioids

Opioid analgesics have two unique pharmacologic properties that are not thoroughly appreciated. These two properties are at the core of their safety as analgesics.

Opioids do not damage organs

Opioids at any dose do not cause visceral organ damage.¹ This cannot be said of any other analgesic drug group. Salicylates and other nonsteroidal antiinflammatory drugs (NSAIDs) can cause irreversible renal damage at high doses.² Acetaminophen can cause irreversible hepatic and (rarely) renal damage at doses greater than 4,000 mg/day.³ The dose-limiting factor in opioid use is not the risk of organ damage, but the development of intractable side effects, such as nausea, vomiting, som-

nolence, myoclonus, and cognitive failure, all of which are reversible with dose reductions or rotation to alternative opioids or use of adjuvant medications. There is a recent report describing hypogonadism in patients on longterm opioids.⁴

Opioids do not have a ceiling dose

The pharmacologic “ceiling” refers to a plateau on a drug’s dose-response curve beyond which additional dose increases produce no change in efficacy and only cause more side effects or toxicities;⁵ it is a property common to most pharmacologic agents. There is no plateau on the opioid dose-response curve, so there is no ceiling for opioids. Increases in an opioid dose most often advance drug efficacy, and increased analgesia is produced with each dose escalation.

There is pain that cannot be controlled with dose increases because of the persistence of moderate to severe opioid-related side effects. This has been termed pain that is “poorly responsive” to the opioid. This is related to mechanisms that can increase the potential for side effects such as metabolite accumulation and tolerance.⁶⁻⁹

These two properties—the lack of organ toxicities and lack of a ceiling—mean the development of tolerance to the analgesic effect of opioids is clinically irrelevant. An opioid dose can always be increased without concern about the total number of milligrams prescribed, and an increase in analgesia will be realized. The appropriate dose of an opioid is that which is required to control the pain.

Opioid tolerance

Pharmacologically, tolerance is defined as loss of drug effect with chronic dosing.¹⁰ The mechanism of opioid tolerance is partially understood in mammals.¹¹ Tolerance is a complex receptor-selective phenomenon. The glutamatergic receptor (GluR) system has been implicated in the development and maintenance of morphine tolerance; this in part mediated by *N*-methyl-D-aspartate (NMDA) receptors. Some common intracellular pathways are shared between pathologic pain states and opioid tolerance.¹²⁻¹⁵

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Development of tolerance to the analgesic effect of opioids with chronic use is widely known, and it is generally believed to be a negative aspect of opioid use because dose requirements to maintain analgesia must increase over time. But development of tolerance to opioid side effects, which also occurs with chronic use, is less well appreciated.¹⁶ Development of tolerance to opioid side effects is the other aspect of opioid pharmacology that contributes to opioid safety.

Tolerance to the analgesic effect of opioids can begin after a few weeks of around-the-clock dosing, as does tolerance to the respiratory depression effect of opioids (and other side effects except constipation). As tolerance develops, side effects usually resolve, and the respiratory depression effect of opioids disappears. Tolerant patients can receive steadily higher opioid doses without risk of respiratory depression as long as the dose increases are appropriate (25% to 50% increase with each dose escalation).

Clinical significance of opioid tolerance

Respiratory depression is the most feared complication of opioid therapy. It can be seen in opioid-naïve patients (those who are not opioid tolerant) as doses are escalated. Symptomatic respiratory depression with dose escalation is very unusual in patients on chronic opioid therapy because tolerance to the respiratory depression effect develops. Concern about causing a dangerous respiratory depression with chronic opioid use is generally unwarranted and can prevent adequate pain relief. This concern should not prevent aggressive opioid use in surgical patients with chronic pain. Even if a symptomatic respiratory depression occurs during opioid therapy, the patient can often be observed, but if necessary, it can be reversed with dose reduction, and if needed, the judicious use of an opioid antagonist.

The following case report illustrates the safety of opioid therapy in a tolerant patient.

MK was a 56-year-old man who presented with abdominal pain, obstructive jaundice, and a mass in the head of his pancreas on abdominal CT scan. There was no evidence of liver involvement, and the mass was believed to be potentially resectable. But at the time of laparotomy the mass was found to be invading the portal vein and was determined to be unresectable. The biliary system and stomach were bypassed for palliation. MK opted for a trial of

chemotherapy, but it was discontinued because the tumor responded poorly.

The jaundice cleared, but the surgery and chemotherapy did not notably reduce his pain. He had constant, dull, midabdominal pain without descriptors suggestive of a neuropathic component. Initially, he was placed on oral extended-release morphine around the clock plus immediate-release morphine as needed for breakthrough pain. This controlled his pain well, but over the next few months his morphine requirement slowly increased as his disease advanced. The only opioid side effect he experienced was constipation, which was managed with stimulant laxatives. He was able to stay at home and eventually opted for hospice care. He did not want cardiopulmonary resuscitation.

Months later he still had constant midabdominal pain with occasional sharp exacerbations. He was taking 300 mg of oral extended-release morphine every 8 hours plus 50 mg of oral immediate release morphine 4 to 5 times per day for breakthrough pain. He developed ascites, peripheral edema, dyspnea, and his functional status had declined dramatically. He developed problems swallowing his medicines, and his morphine was changed to the IV route through his existing infusaport. Over the next few months, his IV morphine dose was escalated steadily. Each dose escalation relieved the pain for only a few weeks. He was seen by a pain consultant for a possible celiac plexus block, but the block was not believed to be feasible. At 18 months after operation he was on IV morphine 100 mg/hour plus 25 mg boluses every 10 minutes as needed for breakthrough pain. He continued to complain that he had severe, and at times unbearable, abdominal pain. He was seen by a psychiatric consultant who recommended an antidepressant, but the consultant found no evidence of substance abuse behavior.

Over the ensuing weeks the morphine was increased steadily. After another 6 weeks the patient was receiving 500 mg/hour morphine IV plus 60 mg IV boluses every 10 minutes as needed. He was bed-bound, alert without confusion, and his pain was moderately well controlled. There was no evidence of respiratory depression; respirations were 10 per minute. The next dose escalation was to 800 mg/hour of morphine IV plus 75 mg IV boluses every 10 minutes as needed. He was maintained on this dose for 3 weeks without developing notable opioid side effects, such as sedation.

The final dose escalation was to 1,100 mg/hour of morphine IV plus 100 mg IV every 10 minutes as needed. MK lived 3 days on this morphine dose. He was somnolent his last day, but he could be aroused to take fluids with gentle verbal stimulation. He had mild myoclonus. His respirations were 8 per minute without evidence of cyanosis. He died quietly at home.

Opioid tolerance is a good thing

The case of MK illustrates the points made above regarding the safety of opioid analgesics, morphine in this instance, when the doses are increased appropriately. MK received an incredibly high daily dose of intravenous morphine without serious complications. He was rendered pain-free in his last days. He died at home, as was his wish and he died without undue suffering. The safety of opioid analgesics made this possible. He was kept pain-free but not at the cost of marked respiratory depression or other opioid side effects.

Physicians generally believe that opioid tolerance is a bad thing because increasing opioid doses are required to maintain analgesia. Although tolerance to the analgesic effects of opioids can present a challenge to providing pain relief, the same capacity of developing tolerance to other opioid effects such as sedation and respiratory depression make the phenomenon of tolerance generally advantageous in the clinical setting. In many instances, the reason for an increasing opioid requirement clearly correlates with the progression of underlying disease. Fortunately, if either tolerance to the analgesic effect or the progression of disease is the reason for increasing opioid requirements, the dose can be safely increased because of tolerance to other opioid effects, as was done in this case. Other therapeutic approaches such as opioid rotation,^{17,18} coanalgesics,¹⁹ ketamine,^{20,21} and axial delivery²² should be considered in situations where escalation of the opioid dose is not effective. A dose escalation might not be effective if it is impractical, too costly, or associated with undesirable side effects, such as can occur in cases of unrecognized neuropathic pain or when opioid dose requirements continue to increase because of development of tolerance to the analgesic effect.

Appreciation of the positive aspects of opioid tolerance and understanding the conditions that mimic it can make a large contribution toward reduction of suffering in surgical patients.

Appendix

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