In My Opinion

Thoughts on tolerance, hyperalgesia, and short-acting opioids

By Jennifer Schneider, MD

The recent article published in *Practical Pain Management*, "Appropriate Opioid Dosing for Activities of Daily Living," by Drs. Forest Tennant and Jeffrey Reinking,1 made several important points with can never be said too often. One is that the goals of opioid treatment for chronic pain, in addition to reduced pain, are improved activities of daily living, decreased time in bed or on a couch, improved mental functioning and improved quality of life. The second is that "the notion that there should be a ceiling or restricted dose of opioids is nonsensical, unscientific, and inhumane." Despite the belief of some researchers and some regulatory agencies that there is an arbitrary upper limit of opioid that should not be exceeded, there is in fact no clinical evidence of the validity of such a belief.

Also as pointed out by Tennant and Reinking, animal studies have clearly shown that there are genetic differences in the ability of different opioids to provide pain relief in different subjects. Additionally, there are documented differences in the metabolism of the various opioids. For example, persons who are deficient in the enzyme that metabolizes the prodrug codeine to morphine, need much higher doses of codeine in order to get pain relief. There are also differences among subjects in the penetration of various opioids through the blood-brain barrier, and differences among people in absorption of transdermal opioids. The result is that people given the same dose of an opioid can vary in the resulting blood level and in the degree of pain relief so that people can vary widely in the opioid dose they require for adequate pain relief. That opioid-tolerant chronic pain patients can function well, and even drive safely, in the presence of serum levels that may be considered lethal in opioid-naïve patients was shown clearly in Tennant's ground-breaking study of opioid blood levels.[2] When pain is not well-controlled, the limiting factor in further increasing the dose, or alternatively adding a second opioid, is the development of adverse effects such as sedation or constipation. What matters is the patient's pain relief and functioning, not the dose.

Tolerance

However, there are some points in Tennant's study that I feel require clarification. When Tennant writes that "chronic pain patients become tolerant to opioids after about 7-10 days," I believe he means to say that patients become tolerant to the sedative effects of opioids within 7-10 days, which of course is a very good thing. Tolerance generally means getting less effect from a given dose, so it is important to specify which effect you mean. Opioids have several effects on the body – pain relief, sedation, constipation, and nausea (as well as euphoria). It is well recognized that within days of starting an opioid, people develop tolerance to its sedating, nauseating, and euphoria-producing effects. Unfortunately people do not develop tolerance to the constipating effect of opioids, which is why it is important to discuss the need for a pre-emptive bowel program when initiating opioid therapy.

There is controversy in the literature about whether tolerance to pain relief develops. In my clinical practice, which includes many patients treated with opioids for up to 15 years, quite a few have been on stable doses of opioids for years. Other opioid-prescribing clinicians have observed the same thing. Unfortunately there is a dearth of outcome reports in the medical literature. Recently, Tennant3 reported on a series of cases in his practice in whom long-term opioid doses were stable. When patients report increased pain after months or years of opioid treatment, their physician frequently attributes this to the development of tolerance to the pain-relieving effect of the opioids. But, remember, tolerance to all the other effects of opioids develops within days! What is much more likely is that the patient's disease has progressed or that a new pain-producing problem has appeared.

It is also common for patients to require upward titration when opioids are first initiated. There are usually two reasons for this, and neither one is related to tolerance to the analgesic effect of the drug. First, opioids must be initiated at a very low dose because of the sedation and nausea they may produce. Over a few days, as these effects abate due to tolerance, the dose is then gradually increased until adequate analgesia obtains. It is quite common for the patient to return a short time later and say that their pain level has risen again. At this point, the most likely reason is increased activity. As the pain level diminishes, the patient (hopefully!) begins to spend less time horizontal and engages in more physical activities. Naturally their pain level will then increase, requiring additional upward titration. Within

weeks, however, the patient will reach an equilibrium between their level of functioning and the opioid dose. At this point, the dose is likely to stabilize. Clearly, we need more published outcome studies to confirm this common clinical observation.

Hyperalgesia

There are other assertions in Tennant's article with which I respectfully disagree. These have to do with (1) hyperalgesia and (2) initiation of opioid therapy in opioid-naïve patients. Hyperalgesia, which means increased sensitivity to painful stimuli, is used in two difference contexts in pain medicine. In one context, hyperalgesia refers to the excessive pain often induced by neuropathies or certain chemicals. It is used in this sense in a recent paper describing the hyperalgesia and allodynia produced by injections of capsaicin.4 Another context is the unfounded assertion that some patients who chronically take high-dose opioids develop increased pain with increased doses, or increased sensitivity to noxious stimuli. This is based on studies of laboratory animals, and of people given intrathecal opioids or studied under other unusual conditions.[5,6] I am unaware of any studies supporting the existence of this phenomenon in clinical practice with respect to patients chronically on oral or transdermal opioids. The assertion of opioid-induced hyperalgesia has found its greatest usefulness by physicians and regulators looking for justification to limit opioid prescribing and by some cost-conscious insurance companies seeking a medical reason to deny payment for high doses of opioids. Tennant and Reinking write in their article, "Hyperalgesia. . . can clinically exist if a physician overprescribes opioids to a mild pain patient or a person who doesn't have pain. This situation almost always exists because the physician is unfamiliar with the Controlled Substance Act Schedules." This statement is not evidence-based; it's an opinion without a clinical or published basis.

Initiating Opioid Therapy

Tennant and Reinking write, "Legitimate chronic pain patients must be started on a weak (Schedule III or IV) opioid rather than a stronger Schedule II) opioid. Ambulatory chronic pain patients must be initially treated with a short-acting Schedule III or IV opioid used on an as-needed basis." In fact, there are many different ways to initiate opioid therapy, and there is no standard of care on this. I agree that it's smartest to begin an opioid-naïve patient on a short-acting opioid. This is because some people are more sensitive than others to the nauseating effect of opioids. If they develop severe nausea after ingesting the lowest available dose—for example, 20mg of a 12-hour formulation such as Kadian (morphine extended release)—that drug's effect and associated nausea may persist for a whole day. In contrast, if nausea develops following ingestion of Vicodin (5mg hydrocodone + acetaminophen) or Percocet (5mg oxycodone + acetaminophen), serum levels of the opioid will drop within several hours and the nausea will abate that much sooner. Beginning with a low dose of an immediate-release opioid and increasing as needed is a good way to determine the patient's opioid requirement. My recommendation at that point is to convert to a similar dose of a sustained-release opioid product, which will give smoother blood levels, a longer duration of action with fewer doses, and will avoid concern about excessive quantities of acetaminophen.[7]

However, I disagree with the recommendation to initiate opioid therapy specifically with a Schedule III product (such as Vicodin) rather than Schedule II (such as Percocet). The DEA's schedules for controlled substances were arbitrarily conceived on the basis of the supposed abuse-potential of the drug formulation. Hydrocodone, which is at least as strong as morphine, is a Schedule III whereas morphine is Schedule II. Why? Because all currently available hydrocodone formulations include aspirin or acetaminophen which are dangerous when taken in high doses. The idea may have been that people would be less likely to take large quantities of those drugs (which, in fact, is not true). Currently, abuse-deterrent opioid formulations are the hottest products in development. Classifying Vicodin in lower schedule than morphine and therefore making Vicodin easier to prescribe (it can be phoned in, whereas morphine requires a written prescription) was apparently the DEA's early effort at abuse deterrence. There is no medical basis for initiating opioid therapy with hydrocodone rather than oxycodone. Similarly, there is no medical basis for the statement in Tennant's article that "If potent Schedule II or long-acting opioids are used in a new or opioid-naive patient, physical signs of opioid excess and/or hyperalgesia will likely occur" to any greater extent (if at all!) than if the patient is begun on a Schedule III opioid such as hydrocodone. ■

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