ROLE OF SR OPIOIDS IN TREATING CHRONIC PAIN

A Practical Guide

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In the November/December 2007 issue of *Practical Pain Management*, Dr. Forest Tennant presented a thoughtful and detailed assessment of the role of sustained-release (SR) opioids in a primary care practice, describing when and how he recommends that PCPs transition chronic pain patients from immediate-release drugs such as hydrocodone/APAP to SR opioids.[1] Given the critical importance of sustained release opioids in ambulatory pain treatment, I present my methods and experience in this article. Physicians who prescribe sustained release opioids should study the various methods used by other physicians to develop an optimal procedure for safety and effectiveness that fits their practice.

The subjects that need to be understood regarding the transition from short- to long-acting opioids are:

- Why it is desirable to treat round-the-clock pain with SR opioids.
- The pharmacologic properties of long-acting and sustained-release opioids.
- How to transition from short-acting to SR opioids.

Why Make the Switch?

There are both safety and efficacy reasons for preferring SR opioids for chronic pain. The most commonly used short-acting opioids are combinations of hydrocodone or oxycodone with acetaminophen (and sometimes aspirin). The most frequently prescribed opioid analgesic is a combination of hydrocodone and acetaminophen (Vicodin, Lorcet, Norco). Regular Vicodin contains 5mg hydrocodone and 500mg acetaminophen. Pure mu opioid agonists (such as the drugs discussed in this article) have no ceiling analgesic effect and may be titrated as needed to achieve analgesia.[2] There is no absolute upper limit of how much of an opioid is safe to take (as long as it's titrated slowly to decrease the risk of respiratory depression)—but there is definitely a maximum dose of acetaminophen, above which liver toxicity may ensue. This maximum is generally accepted as 4 grams per day (that's eight regular Vicodin or four Extra-strength Tylenol), but for patients who already have liver damage or who drink alcohol, it is lower. Patients who take more than the maximum safe daily dose of acetaminophen risk liver damage. In contrast, SR opioids are single-entity drugs containing only the opioid element.

Short-acting opioids typically have a plasma half-life of 2-3 hours, with a duration of action of 4-6 hours. At night, this often results in nocturnal awakening due to a resurgence of pain. Taking a sustained-release opioid in the evening is more likely to provide better sleep at night, as compared with repeated dosing of a short-acting opioid.[3] When multiple doses are given, plasma levels of the drug follow a sine curve, going up and down several times over the 24 hours. At the peak, patients will get good pain relief but, at the trough, the pain is likely to return. Then the patient takes the next dose and the cycle continues. Rather than preventing pain, the patient is "chasing the pain" all day. Sustained-release opioids provide a more consistent blood level and more uniform pain relief. This can result in a lower 24-hour opioid dose than when the same drug is given in a short-acting form requiring multiple dosing.[3] As pain specialists Drs. Richard Payne and Russell Portenoy wrote in 2002, "Short-acting opioids are characterized by a rapid rise and rapid decline in serum levels, which may be beneficial for the treatment of acute pain and breakthrough pain, whereas long-acting drugs or sustained-release formulations provide a more effective means of controlling chronic pain. Opioids with long half-lives or extended-release formulations are preferred for the management of chronic pain. These drugs may facilitate patient adherence with treatment regimens, increase convenience for caregivers, provide consistent levels of analgesia, and allow the patient to focus less on pain and pain medications."[4]

Another potential problem with short-acting opioids relates to the mechanism of CNS euphoria. What causes a person to feel a "buzz" is not the concentration of a drug in the blood stream, but rather the rate of increase of the drug's concentration in the brain. The faster the drug level rises, the more euphoria the person may feel. This is the reason that addicts and abusers like to crush a sustained-release opioid tablet and then inject it, which will get the drug into the brain more quickly. This, of course, is also the reason that recreational cannabis users prefer to smoke a marijuana cigarette than to eat a marijuana brownie. Marijuana smoke gets into the capillaries of the lung within seconds, and goes right up to the brain; marijuana in the stomach has to proceed throughout the digestive tract and only gradually gets into the blood stream. Some chronic pain patients, who are neither drug addicts nor abusers, report that when they take a short-acting opioid, they get not only some pain relief but they also feel better. Pain and addiction specialist Dr. Seddon Savage explains, "Some addiction researchers believe that the use of short-acting, acute-onset opioids may increase the risk of addiction, possibly as a result of enhanced reward stimulation, perceived by users as a rush or high. For this reason, when pain

is more constant than episodic, use of long-acting medications may be preferred."[2]

Finally, the goals of treating chronic pain consist primarily of reducing pain and improving function. Part of improving function is to decrease the patient's focus on his or her chronic pain and on the medications. The ideal is to have the patient consider their pain pill the same way they consider, for example, their blood pressure pill—a medication to take once or twice a day and then get on with one's life. This is the opposite of the relationship patients have with the short-acting opioids that they take multiple times a day, often watching the clock while waiting for the opportunity to take the next pill. The pain pills should not be the center of the patient's life. Long-acting opioid preparations go a long way towards aiding in this goal.

What do you need to know about sustained-release and long-acting opioids? First, it is crucial to understand that a distinction needs to be made between methadone and the other commonly used SR opioids, such as sustained-release oral morphine, oxycodone, oxymorphone, and fentanyl patches. All except methadone are drugs with a short half-life, but which are packaged in a delivery system that releases them over an average of 12 hours (OxyContin, MSContin, Opana ER), 24 hours (Avinza, Kadian), or 3 days (Duragesic patches). Once they are released into the body, these drugs are metabolized over a several-hour period, the same as when given in a short-acting formulation—meaning they do not accumulate in the body when dosed every 12 hours, 24 hours, or 3 days as directed. If the dose of such drugs is increased every two days (three days for the fentanyl patch), the plasma concentration of the drug will not rise. From a safety perspective, therefore, the drug can be titrated upwards fairly quickly.

In contrast, the methadone molecule has a plasma half life which is quite variable, but is significantly longer than most other opioids. Analgesic effect, on the other hand, is short, which may result in the patient taking several doses per day. If the drug is titrated upwards quickly, the concentration in the blood stream will rise, and the results can be fatal. This is why reported deaths from prescribed methadone have often occurred during the first few days of its use. In November 2006 the Food and Drug Administration issued an alert called "Methadone Hydrochloride: Death, Narcotic Overdose, and Serious Cardiac Arrhythmias." In this document they explained, "Methadone's elimination half-life (8-59 hours) is longer than its duration of analgesic action (4-8 hours). Methadone doses for pain should be carefully selected and slowly titrated to analgesic effect in patients who are opioid-tolerant."[5] High doses of methadone can also cause Q-T prolongation on the EKG and a potentially fatal arrhythmia, torsades de pointes.

Methadone is unique in another way that makes it difficult to transition to it safely. Whereas other drugs can be converted from one to another using an accepted conversion ratio, methadone doesn't have a linear conversion ratio: When converting from another drug to methadone, the higher the daily dose of the other drug, the more conservative the dose of methadone needs to be. For example, a conversion table might state that methadone and morphine are equipotent, meaning that 10mg of morphine is equivalent to 10mg of methadone (a ratio of 1:1). But if a patient has been chronically taking 100mg of morphine day, the bioequivalent dose of methadone is quite variable, more like only 20mg of methadone per day (a ratio of 5:1). At higher doses of morphine, the conversion ratio may be as high as 10-15:1. As a result, I do not recommend that primary care providers undertake converting patients to methadone without first consulting a knowledgeable colleague. The conversion should be gradual and extremely conservative, and titration upwards should not be done more often than weekly. The remaining discussion will describe conversion to sustained-release opioids rather than methadone.

How do you transition from short-acting to sustained-release or long-acting opioids safely and effectively?

As stated above, a sustained-release opioid is in fact an immediate-release opioid in a slow-release delivery system. The only reason an SR drug might be less safe than the same total dose of a short-acting drug is if the SR drug is misused by tampering with the delivery system so that the entire dose is released at once. Additionally, when dissolved in alcohol or even water, some SR opioids release all the active opioid, again risking overdose if the entire dose is taken at once. All SR opioid package inserts advise against drinking while taking the drug.

Conversion of one short-acting opioid to a SR formulation of a different opioid (for example, hydrocodone/APAP converted to an equianalgesic dose of SR morphine) is facilitated by consulting conversion tables. A typical conversion ratio between hydrocodone and morphine is 1:1.5. That is, 10mg of hydrocodone is equivalent to approximately 15mg of morphine. It is easy to calculate what will be the final dose of the SR opioid. However, one cannot safely assume that the conversion in the table applies precisely to an individual patient. Patients differ in their cross-tolerance. Some patients may be genetically resistant to some opioids while being very sensitive to others.[6,7] The package inserts of the SR opioids recommend, in general, to calculate the target dose of the SR opioid but then begin with only half that dose, while supplementing as needed with the patient's prior short-acting drug. Every few days, one can increase the dose of the new SR drug while decreasing the short-acting drug until the patient reaches a level of adequate pain relief.

As expected, conversion tables for the SR formulations state that when converting a short-acting opioid to a sustained-release formulation of the same drug, one can safely convert the total daily dose of a short-acting opioid to the same total daily dose of the sustained-release drug. For example, a patient who is on eight Percocet (5mg oxycodone/325mg acetaminophen) per day can be directly converted to Oxycontin, 20mg bid, which will give the same total daily dose of oxycodone. If you have tried this, you may have found that some patients resist the conversion, stating that the SR opioid, in the same total dose they were previously taking in a short-acting form, is not as effective.

One reason for this, of course, is that they are no longer taking the acetaminophen component, which in itself is an effective analgesic. The solution is to try adding some acetaminophen to their regimen. But another possibility is that the patient may have been receiving some CNS "reward" from the rapidly absorbed opioid, and the patient unknowingly considered the good feeling as a component of their pain relief. With the sustained-release preparation, they are less likely to

experience the CNS effect. This is why, in agreement with Dr. Tennant, I recommend a gradual conversion by putting the patient on a low dose of an SR opoid while continuing them on an equivalent lesser dose of the rapidly acting opioid they were previously on. Over a few weeks, increase the quantity of the SR dose while decreasing the IR. Readers who wish additional information on issues of equianalgesic dosing of different opioids are referred to the papers by Pereira et al,[8] Anderson et al,[9] and Ripamonti et al.[10]

Most patients will need a small quantity of immediate-release pain medication to deal with breakthrough pain. The level of pain in a patient with chronic pain can vary depending on the time of day, the patient's activities, mood, life stresses, the weather, and sometimes without an apparent explanation. This is why many patients need a combination of a timed, long-acting opioid prescription, and a second prescription for a short-acting opioid for breakthrough pain. If the patient ends up needing several doses of the breakthrough medication every day, consider increasing the long-acting dose.

Another property of these drugs that is useful for the prescriber to know is that for some patients the duration of action of SR drugs is less than in the package insert. For example, about 25% of patients on a Duragesic patch require every two-day dosing, and about 25% of patients on OxyContin require every 8-hour dosing (data from Janssen presentation). Similarly, about 50% of patients prescribed Kadian prefer to take it every 12 hours (data from Kadian presentation). So when you transition patients to SR drugs, be prepared to consider that the dosing interval may end up somewhat shorter in some patients than in others.

Maintaining a Chronic Pain Patient on Opioids

All chronic pain patients treated with ongoing opioids, whether with only short-acting opioids (which I don't generally recommend), only long-acting opioids, or a combination, need to be followed-up regularly, several times a year. My comfort level is every two months, longer for patients on low doses. On each visit, the following elements need to be discussed. Dr. Steve Passik[11] has summarized these as the "Four As", as follows:

- *Analgesia—the level of pain*. This is easily assessed by asking the patient, "On a scale of 1 to 10, where zero is no pain and 10 is the worst possible, how much pain do you have right now? In general?"
- *Activities of daily living*. How active are they? Are they walking the dog? Cleaning house? Working at a job?
- *Adverse effects*. Ask especially about constipation, since tolerance to the constipating effects of opioids does not develop. Recommend, and remind the patient, about the need for a bowel program.
- *Aberrant drug-related behaviors*. These can include needing an early refill, having lost a prescription, etc. Document any problems with the patient's compliance, and what your response was.

Many of us have now added a fifth *A*, which is:

- *Affect*. Is the patient depressed? Anxious? Stressed out? These feelings can exacerbate the patient's pain, and need to be addressed.

Be sure to document all prescriptions and explain any changes in writing. If the patient complains of increased pain, do not assume that he or she has developed tolerance to the pain-relieving effect of the opioid, which is uncommon in stable patients.[12,13] Dr. Russell Portenoy has written, "Contrary to conventional thinking, the development of analgesic tolerance appears to be a rare cause of failure of long-term opioid therapy."[14] More likely explanations for the increased pain include increased activity, disease progression, or situational factors. Focused physical exams should be done occasionally, but do not need to be done on every visit. Because chronic opioids of all types tend to decrease testosterone levels,[15,16] check testosterone levels early on in all male patients who are on moderate to high doses of chronic opioids and, unless there are contraindications, prescribe testosterone replacement.

Summary

Chronic pain patients with moderate to severe pain who require opioids for round-the-clock pain relief are best served by being transitioned early on to a sustained-release opioid regimen rather than being maintained indefinitely on as-needed doses of short-acting drugs. When used appropriately, sustained-release opioids are as safe as short-acting drugs, provide better sleep, are at least as effective as short-acting drugs, often provide better pain relief, and their ceiling dose is not limited by the acetaminophen content—in contrast to the short-acting combination drugs so popular now among primary care clinicians. PCPs need to become educated to increase their comfort level with SR opioids. ■

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