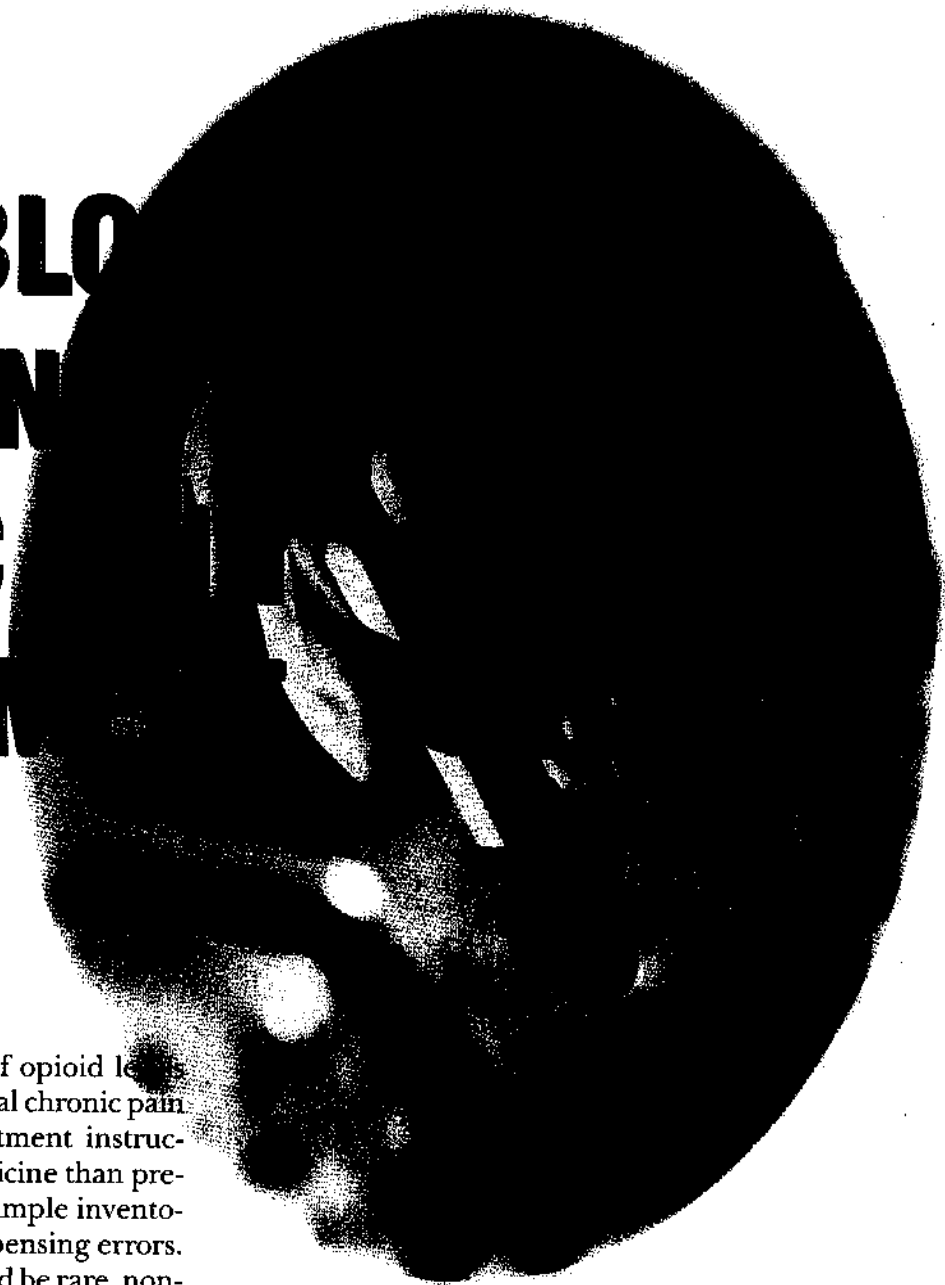


OPIOID BLOOD LEVELS IN CHRONIC MANAGEMENT



By Lawrence M. Probes, M.D.

In an ideal world, measurement of opioid levels rarely would be necessary. The ideal chronic pain patient always would follow treatment instructions exactly and never use more medicine than prescribed. Pharmacies would maintain ample inventories of all opioids and never make dispensing errors. Addiction and pseudoaddiction would be rare, non-existent, or someone else's problem. No patients would have personality disorders or create angry and unpleasant situations with office staff and clinicians. The fear of lawsuits over any possible adverse event would not cast a shadow over daily practice, and defensive medicine would not be necessary. Patients would have textbook pharmacokinetics without problems of swallowing, absorption, digestion, drug-drug interactions, enzyme inhibition or induction. Allergic reactions to medications would be rare. Insurance companies would approve of first-choice and brand-name medication without prior authorizations. Since these conditions do not exist, clinicians should take advantage of opioid blood levels to complement other forms of monitoring in our "real-world" patients.

Determination of opioid levels in the blood is emerging as an important tool for ensuring the safety, effectiveness and integrity of opioid analgesic therapy in the treatment of chronic pain.

Safety of Treatment

Safety at the start of treatment relies principally on clinical evaluation and patient selection, and measurement of blood opioid levels is not a routine need when starting opioid therapy. However, in the elderly, the young, the debilitated, and those at higher risk for misuse, abuse and diversion of drugs, opioid blood level monitoring early in treatment might be indicated.

The most immediate safety concerns with opioids are ventilatory depression and hypotension, which primarily are acute risks upon initiating the drugs or raising the dose. They are managed by careful evaluation of the patient before starting the opioids, education of the patient and family about the side effects and risks of treatment, and clinical monitoring.

When evaluating a patient with chronic pain for opioid therapy, it is important to consider cardiopulmonary functioning and any disorders that might increase the risk of ventilatory suppression. Patients with diagnosed or suspected sleep apnea might require evaluation in a sleep disorders clinic and/or overnight polysomnography, and — if indicated — treatment with continuous positive airway pressure (CPAP) or other interventions. One approach is to prescribe lower doses of short-acting drugs for use only during the daytime when the patient is awake and active. This reduces the risk of a long-acting drug suppressing respiration and ventilation during sleep at night, when the risks are greater. Around-the-clock opioid therapy and treatment with controlled-release and long-acting opioids can be delayed until the patient is evaluated more completely and any indicated treatment started. Patients with chronic obstructive pulmonary disease (COPD) and asthma may require consultation with a pulmonologist to optimize respiratory management prior to initiating chronic opioids.

Fortunately, tolerance to most of the undesired effects of opioids develops rapidly after reaching a stable dose, including effects on respiration and blood pressure — which usually return to normal levels. The only two effects to which tolerance does not develop routinely are constipation and analgesia itself. Most patients on chronic opioids require bowel management plans. True tolerance to analgesia in long-term therapy is uncommon, and a much more likely explanation

for loss of analgesia is pseudotolerance: increased pain caused by disease progression or pharmacokinetic factors of ingestion, absorption and metabolism that lower blood levels.

In order to minimize the risk of hypotension, patients should be advised to maintain good hydration, eat regular meals and carefully manage treatment for diabetes, hypertension and other problems. In patients at increased risk for hypotension, the prescribing physician should consider additional cardiovascular evaluation (electrocardiogram, cardiology consultation).

Sedation may occur with opioids both acutely and during chronic administration. All patients should be cautioned about drowsiness, cognitive dulling and motor slowing, and they should be instructed not to drive, operate machinery,

text of chronic pain management. A more useful term is “intoxication.” When opioids reach a dose that is too high or when the blood levels are rising very quickly upon acute administration, the most reliable signs of excessive medication are the behaviors of intoxication. Signs of intoxication due to alcohol, sedative-hypnotics and opiates are familiar to clinicians and the public alike and include slurred speech (dysarthria), unsteady gait with staggering or swaying (ataxia), rambling speech, decreased coordination, and drowsiness (appearing sleepy or actually falling asleep).

Intoxication cannot be implied by a particular blood level. It is a clinical term based on clinical criteria that may be observed and described objectively. There are legal definitions of intoxication, such as a certain blood alcohol level, but for

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or engage in any other potentially hazardous activities if they do not feel fully alert and awake. Considering the prevalence of medical disorders (especially sleep apnea) and social situations (sleep deprivation, shift work sleep disorder) that cause excessive daytime sleepiness (EDS), all patients — even those not taking opioids or other sedating drugs — should be evaluated for possible disorders of arousal.

Opioids have a narrow therapeutic index upon acute administration, which means that blood levels progress from safe and therapeutic to potentially intoxicating and dangerous over a relatively narrow range. However, upon chronic administration, the therapeutic range widens, so that some patients require levels two to four times greater than patients treated for acute trauma or postoperative pain. Individuals with chronic chemical dependence disorders may have blood levels of various drugs five times greater or more than the laboratory reference range and yet show minimal or no clinical evidence of sedation or intoxication.

The terms “toxic” and “detoxification” often are applied incorrectly in the con-

clinical purposes these are not very useful. It is possible for a person to be intoxicated and grossly impaired with relatively low blood levels of an opioid after acute administration. Likewise, patients who take opioids chronically may have blood levels well above what the laboratory reports as a “toxic” level and yet show no signs of intoxication or impairment. Unfortunately, pain patients — experiencing opioid withdrawal after being unable to obtain their medication — are sometimes sent to a recovery program for “detox,” when in fact they show no signs of intoxication whatsoever. These patients need totally excellent pain and psychiatric treatment, possibly in a doctor’s office or perhaps in a pain program or inpatient psychiatric dual-diagnosis unit.

It is important at each office visit to document the overall behavior and mental status of opioid patients. Consider this excerpt from an office progress note:

“The patient appeared punctually, casually and neatly dressed and groomed, fully awake and alert with no signs of agitation, affective lability, irritability, depression, drowsiness or intoxication. Attention and concentration were normal

with no signs of cognitive dysfunction. Speech was clear, coherent, well-articulated, logical and spontaneous without slurring, rambling or pressure. Gait was steady without staggering or swaying. Posture was erect with good eye contact, well-modulated facial affective expression, good coordination and no adventitious movements."

If this same patient has a 2-hour serum oxycodone level of 219 ng/ml and reports good to excellent pain control and side-effect management on OxyContin 80 mg t.i.d., then despite a laboratory report indicating "toxic >200 ng/ml," the clinician may conclude that the patient shows no clinical evidence of intoxication and continue the same dose of medication.

For patients with major risk factors, the "start low, go slow" approach is best. Consider establishing baseline levels early in the course of treatment. Although the titration may be gentle, it is no less important to reach and maintain a therapeutic level that corresponds to good pain control.

Effectiveness of Treatment

Despite reference ranges for analgesia printed on laboratory reports for blood opioid levels, the true analgesic range for any opioid is not known. This is not because of limitations in laboratory assay methods but rather due to the subjective nature of pain assessment. Also, analgesic ranges mostly have been studied in patients with acute and postoperative pain, not studied in chronic pain patients with neuropathic pain and psychiatric illnesses. Therefore, the reference ranges provided by laboratories and textbooks should be used as broad guidelines in chronic pain patients.

Consider each opioid patient to represent a clinical investigation with an "N" of one. In each patient, the blood opioid levels establish a benchmark, a "ballpark" figure that supports (or casts doubt on) the safety, effectiveness and integrity of treatment. With continued treatment and monitoring, subsequent opioid levels can be interpreted primarily in the light of previous levels and patient reports of pain relief with a given medication and dosage. We can study and determine the therapeutic range for an individual patient.

In routine treatment settings, "standard" laboratory reference ranges should not be the sole reason or even a major reason for restricting treatment. If anything,

monitoring of blood opioid levels tend to lead to an increase in the dose of pain medications. Patients with a low risk profile who do well early in treatment probably do not need opioid level monitoring at all, although one still might order them simply to establish a baseline, in case some unexpected changes in their medical condition or adverse circumstances emerge.

One of the most common reasons to measure opioid levels is when a patient who has been titrated up to a robust dose of an opioid reports partial pain control and asks for an increase in the dose. For example, a patient with chronic low-back pain, a low-risk profile for aberrant behavior, and no history of substance abuse (except nicotine dependence) has been titrated on controlled-release oxycodone (OxyContin) up to 80 mg every 12 hours. Serum oxycodone levels collected 2 hours and 8 hours after the first morning dose of OxyContin 80 mg come back in the medium or low range, 50 nanograms per milliliter (ng/ml) and 25 ng/ml respectively. Some laboratories have reported a therapeutic oxycodone range of 10-40 ng/ml (Medtox Laboratories, St. Paul, MN; Spectrum Health, Grand Rapids, MI) with "toxic" levels >100. However, the therapeutic reference range that is becoming more widely reported is 10-100 ng/ml (National Medical Services, Willow Grove, PA; San Diego Reference Laboratory, San Diego, CA) and "toxic" >200.

Patients in the author's psychiatric chronic pain practice generally report the best relief of pain at levels greater than 40 ng/ml, and supports the view that 75 ng/ml as a threshold for "doing business with the CNS" in chronic pain patients, especially those with psychiatric comorbidities such as major depression, bipolar disorder and post-traumatic stress disorder.

Take, for example, a patient with chronic pain who reports partial pain control for 6, maybe up to 8 hours after the first morning dose of OxyContin 80 mg. Pain intensity falls from a 9 to a 6 on a 0-10 scale, but then pain is poorly controlled for 4-6 hours until after the next dose. Collections at 2 and 8 hours show that blood levels dropped by 50%, from 70 to 35 ng/ml. It is likely that this patient will respond better to q.8-hour dosing, rather than q.12-hour dosing as recommended in the package insert. A reasonable pre-

scription would be to add OxyContin 20-40 mg as one of the 3 daily doses for 3 to 7 days then, if desired and well-tolerated, increase by another 20-40 mg up to a new target dose of 80 mg t.i.d. (q.8 hours).

Treat the Patient, Not the Blood Level

When valproate (Depakote) was approved only for treatment of seizure disorders, the therapeutic range was considered 50-100 ng/ml. For the first few years after Depakote was approved for the treatment of Bipolar Disorder, it was assumed that the therapeutic range for mood disorders would be the same. However, experience showed that some patients required levels much higher, up to 150 ng/ml. Clinical experience led the way, but until the higher reference range was accepted nationally, clinicians would receive calls from the laboratory with a "critical" serum valproic acid level of 125 ng/ml.

Based on the upward revision of therapeutic levels for Depakote for mood disorders, it could be hypothesized that bipolar disorder is a "higher-demand" central nervous system diathesis compared to epilepsy. By way of analogy, the author's experience in treating chronic pain in psychiatric patients with major mood and anxiety disorders (especially major depression, bipolar disorder and post-traumatic stress disorder) suggests that comorbid psychiatric disorders intensify the experience and perception of pain. "Time after time after time" these dual-diagnosis pain-psychiatric patients have required higher blood opioid levels and a wider range of co-analgesic drugs. It is noteworthy that most classes of co-analgesic drugs are psychotropics, namely antidepressants, anticonvulsant mood stabilizers, psychostimulants, and antipsychotics.

The limbic system governs the experience and expression of emotional states, but it also processes the hedonic aspects of pain perception. Experience with dual-diagnosis chronic pain-psychiatric patients suggests that they suffer from a mutually-reinforcing set of negative conditions: emotional dysphoria (depression, irritability, fear) and psychiatric disorders create or intensify the perception of pain, while chronic pain originating in the periphery or the CNS tends to induce dysphoria, creating secondary psychiatric syndromes and exacerbating primary mental illness that preceded the pain disorder.

