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Narrative Review

Blood Testing in Chronic Pain Management

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Blood testing is quickly becoming a useful laboratory tool for opioid prescribers who wish to document and assess patient tolerance, more objectively monitor patient safety, and evaluate patient compliance using information that is not available with traditional urine drug testing (UDT). Blood testing does not need to be performed as frequently as UDT but provides extremely valuable information which can be used to more accurately evaluate patient compliance and assist with interpreting blood toxicology results commonly used in impairment or overdose cases.

This narrative review presents the current evidence supporting the use of blood testing within the chronic pain management setting. In addition, this review aims to introduce and discuss the role of routine blood testing within the chronic pain management setting.

Blood testing for the purpose of documenting opioid tolerance is a relatively novel tool for pain physicians and as such this review is not intended to be a comprehensive or exhaustive review of the scientific or medical literature. Prescribers must also be aware that this type of laboratory testing need only be administered to chronic pain patients receiving daily opioid therapy. Patients taking infrequent, low dose, or as needed medications are not anticipated to benefit from this type of test.

Based on the complexity of both achieving acceptable outcomes with opioid treatment and the legal and societal issues at hand, we feel that the addition of blood concentration levels will become the standard of care in the near future.

Key words: Chronic pain, blood testing, opioids, opioid tolerance, patient compliance, opioid overdose

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In recent years, the use of controlled substances to treat disorders causing chronic pain has become a normal part of the patient treatment algorithm. This increase in utilization has also been directly correlated with an increase in morbidity and mortality from the use of these agents and an increasing need to scrutinize for both diversion and proper use. This monitoring process has consisted of physician surveillance by direct exam, pill counts, pharmacy monitoring, and in most practices, urine toxicology. While urine testing is valuable, it does have some limitations that make additional information desirable. Blood testing is quickly becoming a popular tool for opioid prescribers who wish to more objectively monitor patient safety, document opioid tolerance, and round out a comprehensive compliance program. There has long been a need for a tool which allows prescribing physicians to quantify opioid tolerance due to the emphasis placed on these drugs in impairment and overdose death investigations. In addition to providing crucial information pertaining to opioid tolerance, blood testing also improves patient safety and provides a level of compliance monitoring not possible with traditional urine drug testing (UDT).

Once the patient has achieved a steady state of medications with a routine dose, the use of blood screening will give insight into the patient's metabo-

lism, average range of blood levels, and concomitant levels of other agents. These levels may be critical in the event of a complication, intentional overdose, or unintentional complication. An initial baseline level, followed by blood levels at semi-annual visits, or with dose adjustment or significant health issues will be a critical point in the equation of improving health care in those undergoing opioid-based medical management.

Optimizing Patient Outcomes

Routine blood testing provides physicians with objective data that not only provides insight into how the prescribed medication is being taken but also identifies patients who may benefit from pharmacogenetic testing. Optimizing medication regimens and identifying patients who would benefit from pharmacogenetic testing greatly improves patient outcomes by ensuring patients are provided with the most suitable and effective therapy in a timely manner.

Steady State Blood Testing

Pharmacokinetic modeling provides a mathematical basis for quantifying the administration, distribution, metabolism, and excretion (ADME) of drugs in the body (1-3). It is these 4 processes (ADME) that determine the concentration of a medication in a patient's system following a prescribed dose. A fundamental understanding of these parameters allows for the accurate determination of

1. The dose(s) required to achieve a desired blood level of drug; or
2. The approximate dose(s) ingested to produce the observed drug concentration.

Pharmacokinetic modeling has been employed for many years for the purpose of designing appropriate dosing/drug regimens for a given patient and is most commonly employed to optimize dosing regimens for medications that exhibit narrow therapeutic ranges (examples include gentamicin, digoxin, lidocaine, theophylline, phenytoin, phenobarbital, carbamazepine, and lithium) as well as potent anesthetics (1,2,4-12). It is the authors' opinion that these same modeling principles should be used to evaluate dosing compliance in chronic pain patients receiving daily opioid medication.

Steady state blood testing is the only way to determine if a patient's opioid level is consistent with the prescribed dose. Unlike UDT, steady state blood testing provides valuable information about how a medication is being taken. Following repeated administration of a drug at given time intervals, a "steady state" is reached at which time the rate of drug administration is equal to the rate of drug elimination. Steady state is reached after approximately 3 – 5 half lives and at this the time the plasma concentration of the drug (at any time during any dosing interval), as well as the peak and trough concentrations, remain steady. The time required to reach steady state and the resulting blood concentrations depend on the drug, the dose, and the individual patient. If certain information about the drug in question (half-life, dose, dosing interval, absorption rate coefficient, elimination rate coefficient, etc.) and the patient (body weight, gender, etc.) is known, it can be used to calculate the expected steady state level in that patient for a given dose. If a patient is taking the prescribed medication accordingly, their blood level should fall within the expected range. If, however, the patient is frequently missing doses or abusing the medication, the patient's level will fall outside the expected steady state range. Pharmacokinetic assessments such as this are becoming necessary in the chronic pain setting due to the inability of traditional UDT to identify patients who are taking too much or too little medication.

Pharmacogenetic Assessment

Steady state blood testing is also a cost effective way of identifying suitable candidates for pharmacogenetic testing. By first performing a steady state blood test, providers can identify patients whose opioid blood levels fall outside their expected steady state range. If a patient's opioid blood level is below the expected steady state range it can indicate that the patient is taking less medication (lower dose or infrequent doses) than prescribed or that the patient is capable of ultra-rapid metabolism. Ultra-rapid metabolizers exhibit an increased metabolic capacity which results in lower circulating levels of the parent drug (and elevated levels of the respective metabolite) (13). If a patient's opioid blood level is above the expected steady state range it indicates that either the patient is taking more medication than prescribed or that the patient is a poor metabolizer. Poor metabolizers exhibit a decreased metabolic capacity which results in higher circulating levels of the parent drug (and decreased levels of the respective metabolite) (13). Routine steady state blood testing will allow physicians to make informed decisions about which patients may benefit from subsequent pharmacogenetic testing.

Improving Patient Safety

Documenting a patient's steady state opioid concentration prior to increasing a daily dose allows health care providers to objectively evaluate the safety of increasing the dose. By obtaining a steady state blood level, physicians can determine whether or not an increase in dose is appropriate and also discuss possible risks with the patient. The decision to increase an otherwise stable opioid dose is a clinical decision that is wrought with potential consequences if not done with some objective guidance. Since pain complaints are subjective, blood testing is an objective way to evaluate the patient's levels and to consider any trend that has occurred since the initial stable blood level was collected and analyzed. This is very important in the chronic treatment of these complex individuals since the constant need to escalate often leads to higher doses over time. Patients receiving higher doses of opioids are at an increased risk of serious adverse events which puts them in a high risk group requiring close supervision. The use of blood testing can assist in this goal by assessing several factors:

1. Are they taking the medication as prescribed? Blood testing can correlate the steady state serum level and analyze the consistency with the dose prescribed.
2. Are they taking any concomitant medications that may increase the risk of an overdose? Analysis has shown that drugs such as benzodiazepines can greatly increase the risk of overdose when compared to opioids alone.
3. Are they developing tolerance to the drug prescribed? A high serum level with lack of efficacy and no adverse side effects could suggest tolerance and may suggest the need to rotate to another method of pain treatment, or in some settings it may indicate that additional increases are clinically relevant options.

In addition to the increased importance of patient safety, blood testing can add to accuracy in analyzing socially important questions. Blood levels are often used to evaluate legal and socially important questions in the United States. In the area of investigation a serum blood level is often drawn to assess whether a medication, prescribed or taken illicitly, played a role in an accident. These blood results are often used with no comparator to evaluate whether the level of the drug played a role in a motor vehicle collision, an accidental overdose, or a suicide. The decisions made from the toxicology leads to both legal and societal conclusions regarding the cause of death or injury that may be inaccurate. In the setting of a level with no baseline level, a normal range may be compared to someone who is stable on a steady state of medication. Having a baseline blood level may be very helpful in better understanding these issues. If blood testing becomes a common component of the standard of care it will be very helpful in understanding the current importance of these drugs in both public statistics and in public policy for interested parties such as the Center for Disease Control and the State Boards of Medicine. Without a standard of baseline blood levels a coroner or medical examiner will most likely attribute any death or accident to the opioid unless there is a normal steady state level to compare with at the time of the evaluation. It is this consideration that will improve public health in the setting of routing blood testing for all chronic opioid patients.

Documenting Opioid Tolerance

Many chronic pain patients build significant tolerance to opioid medications through repeated administration. Tolerant pain patients often require higher doses of opioid medication in order to achieve the desired analgesic effects. As opioid dosages increase over time due to tolerance or worsening medical conditions, so too do the circulating levels of opioid in the patient's blood. Documenting steady state opioid concentrations in tolerant pain patients provides physicians and forensic investigators with a crucial piece of information in the event of a patient's unexpected death.

Tolerant pain patients are often able to function with opioid blood concentrations that are well above what is considered "therapeutic" or even "toxic" for a naïve patient. Steady state blood testing provides physicians with a way of documenting what is normal or expected for a given patient and while opioid tolerance is well understood in a clinical setting, obtaining steady state blood levels may be the only way to objectively document this phenomenon. It should be clearly stated that the need for such testing is due to the emphasis that is put on opioid blood concentrations in postmortem investigations. In most cases, forensic death investigation involves postmortem toxicology testing which is performed using blood from the decedent. The significance of positive drug findings are often times determined by comparing the drug concentration found in the decedent to "therapeutic" or "toxic" levels published in textbooks, package inserts, or forensic

handbooks. Pain physicians need to be aware of the fact that tolerant patients are often able to function with opioid levels that would be considered "toxic" or even "lethal" if found in a postmortem investigation. In such cases, the cause of death will most likely be attributed to the elevated opioid concentration unless there is proof that this concentration was normal for the decedent in question. While "therapeutic" or "toxic" levels for a given drug may provide some insight into possible drug effects for a naïve, non-tolerant patient, these levels should not be used to interpret postmortem findings in patients with a history of opioid therapy. If such ranges are used to interpret postmortem findings in decedents with a history of opioid use, it is extremely likely that the significance of the opioid with respect to cause of death will be grossly overstated. Routine steady state blood testing in patients on moderate to high doses of opioid medication provides us with extremely important information which can greatly impact the interpretation of postmortem toxicology results. The understanding of clinicians on these issues has been lacking. In many settings, physicians teach of limiting dosing based on morphine equivalent dosages (MED), but there is seldom any discussion or understanding that the MED may not correlate to the circulating blood levels. This concept is easy to understand if you consider 2 patient vignettes. Patient 1 is an 84-year-old woman with severe scoliosis and multiple compression fractures who is on 100 MED. She weighs 90 pounds and she has both liver and renal disease. Her medication list includes oral agents to treat cholesterol, hypertension, and rheumatoid arthritis. Patient 2 is a 35-year-old man who suffers from pain secondary to failed back surgery syndrome and is on 100 MED. He weighs 240 pounds and has no other health issues and takes no medications. When considering these 2 patient scenarios, it is not surprising that a blood concentration may be very different in them despite the same MED. In the legal and post mortem setting any decisions on their wellbeing or cause of death would be based on the actual blood concentrations. The lack of any reference in the clinical medial record leaves any conclusions purely up to the reference chosen by the evaluating party. This can put an otherwise compliant well-meaning physician at risk for miscommunications and poor conclusions that could adversely impact the determination of cause of death or injury. Based on the consideration of these important points, it is very important for the medical community to consider using blood concentration levels as a guide to proper prescribing instead of MED as a sole consideration.

Comprehensive Compliance Monitoring

Steady state blood testing is also a component of any comprehensive compliance monitoring program as it affords information which is not attainable with traditional UDT. While urine testing provides an effective means of identify drugs which have been used in recent days, blood testing provides a snapshot of drugs and/or metabolites that are circulating in the patient's system due to very recent use. Evaluating the presence or absence of prescription medications in the blood can be a very useful tool for identifying patients who may be attempting to cheat a urine drug test. Due to the extended window of detection offered by urine testing drugs/metabolites are often detectable in the urine for 1 – 5 days following use. While this aspect of UDT can be very advantageous in the case of illicit or non-compliant drug use, it can also be a disadvantage when monitoring the presence or absence of the prescribed medication. Regardless of how much medication a patient is prescribed, they only need to be taking a single dose every other day in order to test positive on a urine drug test at any point in time. Unfortunately if a patient is savvy enough to participate in this behavior, it can be extremely difficult to identify. Steady state blood testing is one way in which this type of aberrant behavior can be identified as patients on "around the clock" opioid therapy should have detectable levels of medication in their blood at any time (this is not the case for PRN {sp} medications or in patients who have missed a recent dose). A negative blood test accompanied by consistently positive urine tests would indicate that the patient is taking some of the medication but certainly not enough in recent hours to be present in the blood. If the medication in question is a PRN medication then this finding is perfectly acceptable as it may have been some time since the last dose. If, however, the medication in question is the primary analgesic which is prescribed multiple times daily, the result would indicate that the patient may be only taking isolated, infrequent doses in order to pass the urine drug test.

Conclusion

In this paper we have given an overview of the importance of blood testing in the clinical setting of prescribing opioids in chronic pain treatment. In most current practices monitoring has consisted of patient interviews and random urine testing. Based on the complexity of both achieving acceptable outcomes with opioid treatment and the legal and societal issues at

hand, we feel that the addition of blood concentration levels will become the standard of care in the near future. A baseline steady state level should be considered after the patient has been on a stable dose for the amount of time required to achieve steady concentration levels. The patient should be retested at a preset regular interval such as an annual or semi-annual visit to assess changes in metabolism, health, or compliance. Consideration should also be given to retesting in the setting of dose adjustments, consideration of drug escalation, or with the addition of concomitant medications that may impact metabolism or drug effect. The use of blood testing will not replace patient-physician visits, random urine testing for immediate confirmation of compliance, or physician and staff vigilance. The use of blood testing will be an additional tool to improve clinical decision-making, improve patient safety, and to give more accurate information in the legal and public health arena.

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