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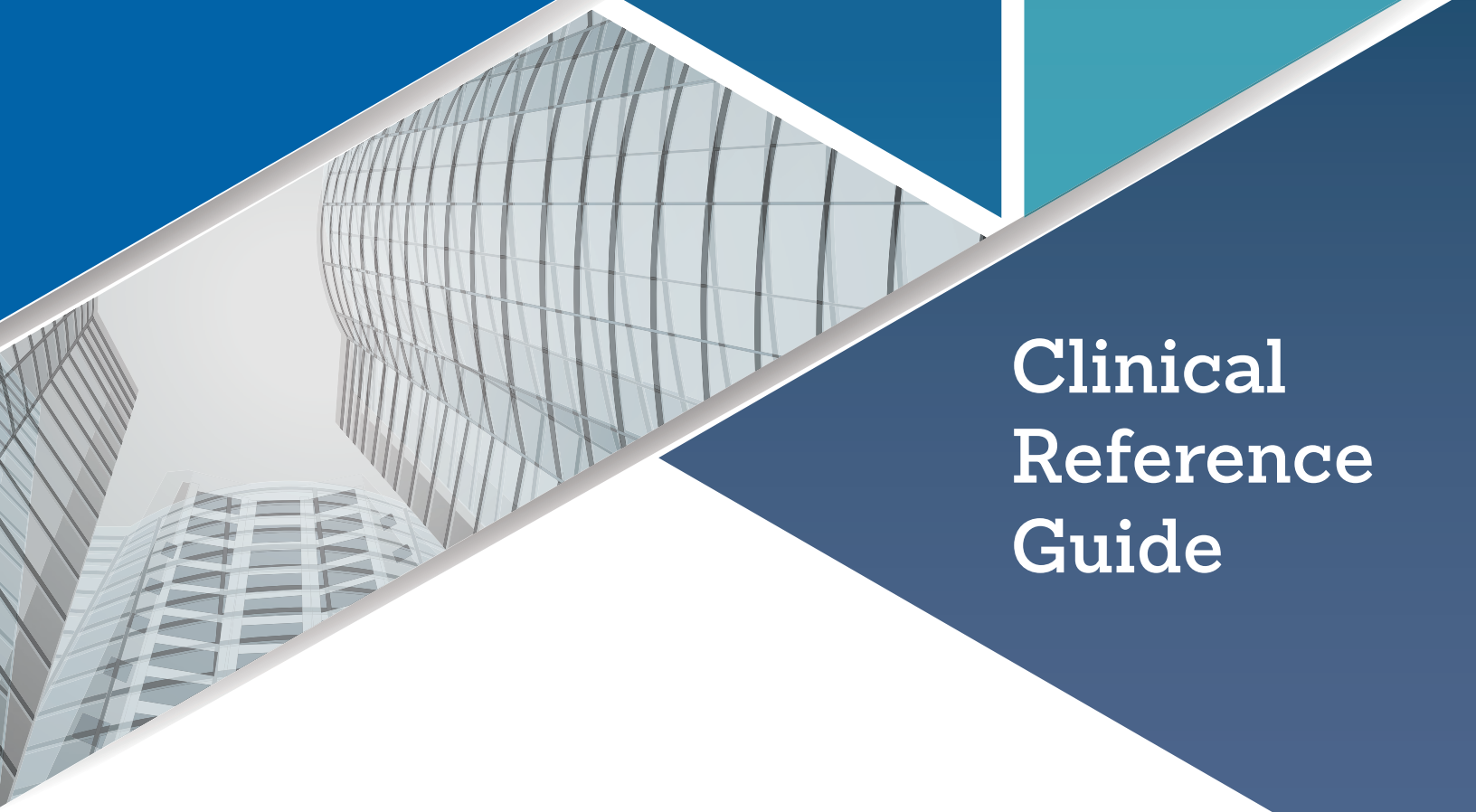

Clinical Reference Guide

Interpretation of Drug Test Results to Decipher Dose Adherence

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Interpretation of Drug Test Results to Decipher Dose Adherence

At this time, there is no validated approach to determine dosing adherence using drug testing in any matrix (blood, urine, oral fluid, etc.).

It is well established that there is no correlation between drug dose and urine drug concentration.[1-10] A general association between dosage and blood concentration exists, as an increase in dose will generally cause an increase in plasma drug concentrations. However, there are no established therapeutic ranges for opioids in blood. Oral fluid concentrations may correlate to blood concentrations with a few drugs (such as ethanol); however, this is not the case with most drugs as only free, unbound drug enters into saliva. pH also has a major influence upon saliva drug disposition.[11]

A. Urine

Urine concentrations do not correlate with drug dose, blood concentration, or clinical effects. Studies have repeatedly demonstrated that urine drug concentrations may not be interpreted to determine the amount of drug taken, when the last dose was administered, or the source of exposure to the drug.[1-10]

There has been extensive discussion in the drug testing industry regarding the normalization of urine concentrations by patient sex, height, weight, urine specific gravity, and pH in an attempt to correlate a normalized urine drug concentration with dose. Algorithms which purportedly relate normalized urine drug concentrations to dose were developed on the basis of patents and publications by Dr. Michael Kell which were published in 1994 and 1995 in the Journal of Addictive Diseases.[12,13] Dr. Kell developed the equations while attempting to correlate urine concentrations of methadone to plasma concentrations for use in therapeutic drug monitoring; however, the drug testing method employed in the study did not provide accurate concentrations and only detected parent drug, not EDDP (primary methadone metabolite). Several other authors have demonstrated that methadone urine concentrations do not correlate with plasma concentrations. Other studies have demonstrated that correcting for sex, urine pH, and daily dosage explains only 32% of the total variance of methadone's urinary excretion.[14-18]

Limited data from two additional studies of hydrocodone and OxyContin® (oxycodone) urine concentrations have been released.[19,20] The authors of these studies claim to use urine drug concentration ranges to distinguish between dosage regimens. However, these publications were limited to small (n=20 in the hydrocodone study and n=36 in the OxyContin® study), healthy populations and showed significant overlap of urine concentrations between administered dosages. The algorithm does not take into account the many sources of pharmacokinetic variability in absorption, distribution, metabolism, or excretion. Subjects were not allowed to ingest medications or foods that interfere with metabolism and were genotyped to ensure they were all CYP2D6 normal metabolizers. Consequently, study results cannot be accurately extrapolated to the general pain management population.[21]

McCloskey et al. have published two studies reanalyzing the data from the original hydrocodone and Oxycontin® studies by Couto et al. These authors have criticized the original studies' statistical analyses for their irrelevancy to the clinical question at hand, i.e. whether or not ingestion of different dosages produced ranges of urine concentrations that may be used to discriminate between adherence to a therapeutic regimen.[22,23] Through a receiver-operating characteristic (ROC) analysis, the authors sought to determine if a subject's urine drug level could indeed identify the correct dosage group for OxyContin®. The authors concluded that even in such a tightly controlled study, adjusted urine drug levels could not reliably be used to identify a subject's oxycodone administration rate.[22] The authors also extrapolated reference range data to determine which dosages would exhibit less overlap with urinary concentration ranges published in the hydrocodone study. Though this exercise primarily serves an academic curiosity (rather than providing concrete clinical guidance), the authors hypothesized that dosages would theoretically need to be as much as 9-fold lower or 4-fold greater than the dosages used to yield urinary concentration ranges with less than 5% overlap. The authors cautioned that these values would

be underestimates for clinical populations, reiterating that the populations studied were unique in that they were highly uniform. They also reference a previous single-dose study in which hydrocodone 10 mg yielded urine concentrations in the range of values reported for chronic dosing of hydrocodone 20 mg/day.[23] In conclusion, the authors have advised that the use of such testing algorithms be approached "with great caution."[22,23] In addition, recent guidelines released by the American Association for Clinical Chemistry (AACC) and cosponsored by the American Academy of Pain Medicine (AAPM) state "quantitative definitive urine testing should not be used to evaluate dosage of administered drug or adherence to prescribed dosage regimen." The guidelines do, however, state that quantitative definitive urine testing is useful to identify abnormal drug metabolism, presence of pharmaceutical impurities, minor metabolism, and specimen adulteration with prescribed drugs, as well as to rule out unexpected sources of exposure (e.g. poppy seeds).[21]

B. Blood

Drug concentrations in blood cannot be used reliably to determine if patients are under- or over-medicating. Correlations between blood concentrations and dosage are not reliable for medications metabolized by CYP450, as much variability exists. Aside from changes to dose, a full host of pharmacokinetic factors may influence blood concentrations. Changes in absorption, distribution, and metabolism may all affect drug clearance from the blood compartment. These may vary substantially in patients from day to day, dependent on factors such as whether the drug was taken with food, alcohol, or interacting medications (such interactions may affect plasma protein binding or rates of metabolism by specific enzymes). Even during prolonged constant rate infusions, changes in drug plasma concentrations as large as 50% have been reported within a 24-hour time frame.[24-26] Using a blood concentration to determine adherence to a specific dosing regimen has not been scientifically validated or accepted, and such over-interpretation is not recommended.[27-30]

Establishing a "baseline" plasma level of prescribed opioids has been suggested in the pain management community as being helpful in litigious situations, such as a wrongful death or medical malpractice lawsuit. The thought is that a blood concentration taken after or during an opioid overdose may be compared to a level when the patient was not overtly intoxicated, or was sufficiently medically managed. However, obtaining a baseline plasma level and comparing the drug concentration to subsequent measurements will not necessarily establish dosage adherence or abuse if overdose occurs. Pharmacokinetic parameters may vary in the same patient over time, especially in the presence of illness (which may affect absorption or distribution), changes in organ function, interacting drugs or foods, and other factors.

The timing of collection relative to dose may significantly impact measured blood concentration. Short-acting opiates, such as hydrocodone and oxycodone, exhibit elimination half-lives of 3 to 4 hours; therefore, it is likely that a peak plasma concentration measured immediately after ingestion of a dose could be twice as high as a plasma concentration measured 6 to 8 hours after ingestion. Even after steady-state blood concentrations are achieved, variability associated with dosage intervals has a large effect on observed drug concentrations. An individual's personal elimination half-life is not likely to match up with a population average, and without monitoring peak and trough concentrations or performing a timed excretion study under direct observation, a patient's elimination half-life cannot be determined. Additionally, patients have varying levels of opioid tolerance; for instance, one patient may have a particular fentanyl blood concentration and be fully functioning, while another patient with the same concentration may be deceased.

C. Oral Fluid

Recently, a study has attempted to develop a proprietary algorithm to allow for therapeutic drug monitoring based on oral fluid testing results. This study assessed the potential for determination of dosing adherence in patients prescribed oxycodone. Unfortunately, the limitations of the study were very similar to others mentioned regarding the ability to determine dose adherence based on a drug concentration. Similar to Couto et al., complex exclusion criteria was applied in order to find favorable results and greatly limits the applicability of this practice to a general patient

population. Despite attempts to control for numerous factors which may affect oral fluid drug concentrations, favorable results were only found in about 75% of patients, meaning that utilization of this algorithm would not be beneficial in 1 in 4 patients.[31] Another study in a less homogenous population describes utilizing a "near-Gaussian distribution" of hydrocodone concentrations normalized by height, weight, gender, prescribed dose, and calculated values (e.g. calculated blood volume). This study was reportedly validated by a sample population of 55 random patients having a similar distribution to the population used to develop the model (n=3,944). This validation is insufficient to validate the use of an algorithm or distributions to determine dose adherence. The authors of this study note that "this comparison alone is not definitive for adherence with a treatment regimen."[32] At this time, establishment of a steady state oral fluid drug concentration in order to monitor dose adherence is not a scientifically supported practice.

D. Therapeutic Drug Monitoring in Pain Management

Therapeutic drug levels in plasma have not been established for opioids or benzodiazepines for clinical use in pain management, largely due to the complex interplay of pharmacokinetics (what the body does to the drug) and pharmacodynamics (how the drug affects the body) for these drug classes. Attempts to establish a “therapeutic” range for these drugs are meaningless, because blood level does not correlate with patient response.[29] The sites of action for opioids and benzodiazepines reside in the central nervous system (CNS), and serum drug concentrations do not correlate with CNS concentrations. In addition, each patient’s response to opioids or benzodiazepines depends on other factors such as: genetic variation in receptor subtype, P-glycoprotein efflux transporter activity, and drug tolerance.[33,34]

Individuals who advocate plasma monitoring at steady state ignore a major flaw of such an assumption: drug dosing in chronic pain management is dynamic and therefore an uncontrolled variable. Assessment of true steady state is based on the patient’s own generalization of an "average" pattern of use. For example, a patient may assert that he or she takes a drug “every six hours,” but in reality may take a drug after eight hours, then four hours, skip the occasional dose, and so on. Such generalizations will drastically affect the achievement of a true steady-state, particularly for short acting, immediate-release medications.[35]

Many laboratories who advocate dosage adherence monitoring in blood reference the Tennant Blood Study.[36-38] The author, Dr. Forest Tennant, addressed the problem that “toxic” levels published in common toxicology references do not necessarily apply to opioid tolerant patients. This is quite problematic, especially when interpreting medical examiner reports. The Tennant Blood Study published demographic data and blood levels for patients on different drug regimens. However, these were chronic pain patients treated in an outpatient setting, and there is no assurance that any of the patients included in the study were actually adherent to prescribed regimens. One cannot assume that reported concentrations correlate to a particular dose with reliability. In addition, the timing of blood collection relative to dose varied from patient to patient, a factor which would significantly alter measured concentrations. Finally, testing was performed by different laboratories, a variable of uncertain yet potentially significant magnitude. Differences would arise from calibrator concentration variance, hydrolysis efficiency, extraction efficiency, or even major reporting practices such as reporting “total” versus “free” plasma levels. The Tennant Blood Study is useful to demonstrate that ambulatory patients may be relatively unimpaired with high blood concentrations, but it does not create a therapeutic range for opioids.

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