The requirement for therapeutic drug monitoring (TDM) in cardiothoracic transplant recipients is virtually universal. According to the 2011 ISHLT Registry for adult heart and lung transplant recipients, over 90% of all patients are maintained on calcineurin inhibitor (CNI) therapy at one-year post-transplant.\(^1\)\(^2\) Despite the immunosuppressive protocol pursued, the need for accurate and appropriate TDM is essential considering the pursuit of balancing efficacy with potentially toxic side effects. In many cases TDM occurs on a daily basis in the inpatient setting and remains a constant focus of an individual’s care throughout the remainder of their lives regardless of their current state of health. Considering the regularity in which immunosuppressive therapies are monitored, we as practitioners often do so without fully understanding the pharmacokinetic theories upon which they’re based.

The pharmacokinetic measurement most closely related to efficacy is the area under the concentration curve (AUC). A patient’s AUC is a direct representation of total drug bioavailability and exposure during the time it takes for a drug to be excreted (t\(_\infty\)), and is calculated by dividing the amount of unchanged drug in circulation by the rate of clearance.\(^3\) A more simplified version of AUC known as abbreviated AUC, which only requires TDM during the first four hours after administration of a dose can be used to simplify the monitoring requirements (AUC\(_{0-4}\)). Factors directly impacting AUC include the total dose, route of administration and variability in absorption, distribution, metabolism and elimination. Although measurement of AUC is considered the gold standard for correlating TDM with efficacy, consistently coordinating such a strategy is complicated, time consuming, and difficult to coordinate.

Peak concentration (C\(_{\text{max}}\)) has been described as a reliable marker of efficacy and a more easily attainable measurement compared to AUC. Data suggesting that CNI drug levels observed two-hours post-administration (C\(_2\)) have a strong relationship with AUC\(_{0-4}\) are robust.\(^4\) This specific model for TDM can be consistently attained if multiple aspects of patient care are coordinated including timely drug delivery, medication administration, and blood draws two hours post-administration. The feasibility of monitoring C\(_2\) becomes more uncertain in regards the outpatient arena, requiring that the patient play a larger roll in ensuring that drug levels are drawn precisely two hours after they self-administer a dose. Considering that all patients are generally instructed to take their CNI therapies at a predetermined time (e.g., 09:00, 21:00), this method may be more burdensome to accurately pursue as patient load increases.

The most frequently implemented TDM strategy in transplant recipients is the trending of trough levels (C\(_0\)), defined as the lowest concentration of medication a patient is exposed to, immediately prior to the next dose. All too often, we as practitioners accept and pursue C\(_0\) “goals” without fully understanding that they are based on a poor correlation to AUC. Monitoring C\(_0\) offers a simple and consistent marker for guiding therapy, but is the most unreliable marker of total medication exposure and efficacy. Due to the lack of coordination involved in ensuring
Regardless of the TDM plan chosen for the patient, major limitations exist in ensuring accuracy, and are often overlooked. Practitioners are forced to assume that patients are taking medications at the prescribed dose at the prescribed times, and that the levels are drawn exactly 12 hours after the previous dose if monitoring C₀. Drug levels can be influenced by multiple factors including deviation in diet or eating habits, taking additional over-the-counter or prescription medications without practitioner awareness, self-prescribing with herbal remedies and teas, or converting between brand name to generic formulations without prescriber knowledge. Monitoring levels without recognition of external influences may result in unnecessary reductions or increases in dose, potentially producing an ineffective or toxic drug regimen.

A sound understanding of the pharmacokinetics related to the most frequently used medications are required to ensure optimal monitoring. Several strategies for TDM of CNIs have been validated, each displaying benefits and pitfalls. Despite an individual program’s preference for TDM strategy, constant evaluation of the accuracy and appropriateness of levels is a necessity. It is the responsibility of all members of the multidisciplinary team to remain vigilant in ensuring appropriate TDM to maintain the highest level of pharmaceutical and patient care.

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References: