Kidney Function Monitoring: Pathway to the Future

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Kidney injury and disease is a major health care concern worldwide as well as a major health care economic concern. Acute kidney injury (AKI) affects upwards of 20 percent of hospitalized patients and upwards of 70 percent of patients in the intensive care units (ICU), with ~5 percent of those in the ICU requiring renal replacement therapy (RRT)— such as dialysis.[1]

Chronic kidney disease (CKD) affects 26 million Americans with ~44 percent of new cases each year caused by diabetes. The World Health Organization (WHO) estimates ~200 million people worldwide have diabetes and 10 to 20 percent of those will die of kidney failure.[2] Furthermore, there are 93,000 patients in the United States on the waiting list for a kidney transplant, with a typical five to 10 year wait.[3]

The assessment of kidney function is a critical part of patient care. Real-time measurement is essential for detecting and monitoring AKI. Accurate measurement is essential for monitoring, and choice of therapeutic pathway for CKD. Glomerular filtration rate (GFR), which is the volume of plasma filtered by the glomeruli of the kidney per unit time, is now accepted as the best index of kidney function.[4] Current clinical guidelines of the National Kidney Foundation (NKF) advocate the staging of kidney disease by GFR.[5]

The optimum measure of GFR is the plasma clearance of exogenous filtration agents such as inulin, iothalamate, iohexol, and 99mTc-DTPA.[6] However, the measurement process for all these agents is complex, involving laborious sample collection and analysis with laboratory based instrumentation. Thus, these measured GFR techniques are often employed in a research setting and infrequently in the clinical setting.

Clinicians routinely use a serum creatinine assay and one of several empirically constructed equations to estimate GFR in patients.[7] Creatinine is endogenously produced by muscle and mainly eliminated by the kidney. The concentration of creatinine in the serum can easily and cheaply be measured from a blood draw and a laboratory analysis. Thus for a normally functioning kidney, the serum creatinine concentration is stable with a low "normal" value. For an impaired functioning kidney, this value may be much higher since the kidney no longer excretes as much as is being produced by the muscle mass. However, the serum creatinine concentration change from a normal value to an abnormal value following a kidney insult or injury may take 24 hours or longer. Furthermore, the serum creatinine value is affected by variables other than renal clearance. Age, gender, hydration, muscle mass, dietary intake, and more affect the creatinine concentration in the blood. In addition, the empirical equations for conversion of the serum creatinine concentration to an estimated GFR have their own limitations.[8] Thus, the current clinical methodology is not a real-time measurement and also is often not an accurate measure of GFR.[9,10]

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in the clinic has been an on-going effort since the early 1990s. Rabito et al developed an arm-band radioactivity detector to measure plasma clearance of 99mTc-DTPA.[11] Refinements to this instrumentation and technique exist to date. However, translation to clinical use, such as in the ICU, never occurred due to the necessity of processing and handling radioactivity as a routine part of this methodology.

The logical next step taken by researchers in this field was development of an exogenous optical GFR agent. Such an agent would be easily measurable with simple detectors, similar to the Rabito arm band device, but without the associated complications of radioactivity.

The rational design of an ideal fluorescent GFR tracer agent would require characteristics of extreme hydrophilicity, little to no protein plasma binding, no in vivo metabolism, clearance exclusively by glomerular filtration in a timeframe appropriate for the clinic, inherent fluorescence that is easily detectable through the skin, and extreme non-toxicity. In addition, secondary attributes such as photo and chemical stability, as well as ease and low cost of synthesis are important. Most known dyes are either lipophilic, non-biocompatible, excrete mainly via the hepatobiliary system, and thus do not have the required properties for a fluorescent GFR tracer agent.

One approach to development of such, from research at Covidien/Mallinckrodt over the last 10 years, resulted in the invention of many fluorescent GFR tracer agent compounds.[12,13] This technology is now being commercialized by MediBeacon, LLC.[14] A combination product is being developed which employs a novel fluorescent tracer agent and a noninvasive fluorescence detection system (somewhat similar to a pulse oximeter detection system). The agent is administered by IV, excitation light is delivered to the skin and emission light is collected. The emission light intensity is correlated to the tracer agent concentration in the body. GFR is calculated from the time dependence of this emission light as the fluorescent agent is cleared from the body by the renal system.

Successful results employing this combination product system in two animal models have been obtained. Translational research now on-going should yield a robust real-time accurate GFR measurement that could be done at the bedside and/or point-of-care in the hospital and clinic. RBT

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