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Drug-Dosing Strategies for Renal Patients

MODIFYING DRUG DOSING FOR PATIENTS WITH RENAL INSUFFICIENCY

How do you adjust drug doses in your patients with kidney disease? Two methods, their equations in particular might come to mind – the Cockcroft-Gault equation or the modified diet in renal disease equation. Is one more applicable to your patient or the patients in general? You are listening to ReachMD, the Channel for Medical Professionals. Welcome to Focus on Pharmacy. I am your host, Dr. Charles Turck, PharmD. Our guest is Dr. Luke Probst, pediatric pharmacy specialist and a clinical assistant professor in the Department of Pediatrics and Medicine at the State University of New York Upstate Medical University. Dr. Probst is the author of the recently published article in the Journal Hospital Pharmacy on drug dosing modifications for patients with renal impairment.

DR. CHARLES TURCK:

Welcome Dr. Probst.

DR. LUKE PROBST:

Thanks very much, Dr. Turck.

DR. CHARLES TURCK:

We are going to be discussing strategies for drug dosing in patients with renal insufficiency. There are a number of different methods out there for the estimation and measurement of renal function. I was wondering if you could describe some of the more common ones.

DR. LUKE PROBST:

Sure, as you said the Cockcroft-Gault equation has been around since 1976 when a population of 200 subject was analyzed and the investigators characterized an equation that was useful in estimating renal functions in adult patients who were otherwise healthy and since that point forward, it's really been the calculation of choice for estimating renal function in adult patients for the purpose of drug dosing. There are a few others – the Jelliffe method name 1 that are some times used in certain subsets of population, but generally speaking pharmacists and other healthcare professional and even pharmaceutical manufacturers have used the Cockcroft-Gault

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equation for nearly the past 30 years for this purpose of estimating renal function in a person that accounts for not only their serum creatinine as a marker of renal function, but also their specific body habitus as it refers to height and weight normalization. More recently, the MDRD equation was published first in 1999 as somewhat of an offshoot of a previous study investigating the effect of diet on renal disease and from a subset of this very large study, approximately 2000 patients, I believe it was 1700 patients, were sub-analyzed and the operation tended to identify a more reliable method of estimating renal function, particularly in this case glomerular filtration rate as compared to the goal standard iothalamate analysis, which is very precise, but certainly cumbersome and precludes common use. These authors came up with a fixed variable equation that they found to be about 91% sensitive or 91% correlated with the iothalamate-derived GFR value for most of their patient in this study. From that point forward, the MDRD equation became useful in estimating GFR for the patient. However, it really has not been applied to drug dosing and there are a few limitations to using this equation. Even though it is more sensitive predictor of renal function, it's not an automatic substitute for the Cockcroft-Gault when talking about drug dosing.

DR. CHARLES TURCK:

You had mentioned a little bit before about how the MDRD equation hasn't necessarily been studied for the modification of drug dosages, at least not in the published literature. It hasn't been used in practice to modify drug doses.

DR. LUKE PROBST:

Well, I think it has by a number of clinicians who are now in the past year and a half or so seeing the reporting of estimated GFR using the MDRD equation automatically reported a long list of serum creatinine assay that may be drawn through the clinical laboratory system where the patient has the labs performed, our institution similar to many others that have accepted the recommendation of the National Kidney Disease education program to report GFR derived from MDRD with every serum creatinine value so that clinicians can better stage their patient as a characterization of their renal disease, but a lot of people have taken that as a reliable indicator of renal function from the standpoint of drug dosing as well and we pretty much discussed that aspect of it not completely validated use in the article that we published.

DR. CHARLES TURCK:

And would you tell us a little bit about what you found in the article that you published?

DR. LUKE PROBST:

This goes back to early 2007. At about the time that our clinical laboratory system accepted the recommendations as the NKDEP (National Kidney Disease Education Program) and pretty much on an arbitrary, they started reporting a GFR value immediately next to the serum creatinine value for any of our inpatients, and we started identifying situations in which the pharmacist in our institution were having dialogue with prescribers about renal dosing adjustments of medication and the prescribers were reporting back to us that you know by their information, this patient actually has good renal function and they disagreed with our recommendations for dosing adjustments in patients such as the elderly or patients with elevated serum creatinine because of the dichotomy of the derived renal function values from the 2 equations. So, we sought to clarify that on an evident-based level and ultimately brought this through to multidisciplinary group of nephrologist and Infectious Disease specialist and it ultimately went through our Pharmacy And Therapeutics Committee where we clearly showed situations in which the misapplication of the MDRD was putting patients at risk for possibly higher than necessary doses, which could certainly increase the risk of medication errors and toxicity.

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DR. CHARLES TURCK:

So, you found that in some cases there was in fact a dichotomy between values from the 2 different equations.

DR. LUKE PROBST:

Yes and actually to ease that out a little bit more, we sampled after we recognized a few key cases and realized that there was some query that was going to be needed regarding this MDRD data piece. We analyzed 30 of our adult inpatients, who were not in the ICU, who didn't have acute renal failure, so relatively clean subset of patients and we actually applied the Cockcroft-Gault creatinine clearance dosing rule that we use on a daily basis and compared that to what was reported in our lab system corresponding to the same serum creatinine we used for the Cockcroft-Gault equation and we found a pretty significant number of patients, which the determination of renal function based on either of those 2 equations was a clinically important distinction. We have a policy in our institution whereby a pharmacist can automatically adjust the dose of a renally cleared medication based on the published information and based on that pharmacist's determination of patient's renal function by the Cockcroft-Gault equation and we found again that a number of patients crossed the threshold between acceptable renal function and renal dysfunction that would warrant dosing adjustment and clearly the differences became what we felt to be clinically important. There were a few cases of patients who were receiving aminoglycoside in whom the empiric dose would have been much higher in a patient whose renal function was assessed by the MDRD compared to the Cockcroft-Gault in a number of other patients with different dosing regimen who would have had their therapy changed and who actually did have their therapy changed based on the Cockcroft-Gault, but in whom if you relied on the MDRD equation, the therapy would not have been adjusted downward again which most people believe could predispose patient to some of the unwanted adverse effects or toxicities of the drug.

DR. CHARLES TURCK:

I am your host, Dr. Charles Turck and our guest is Dr. Luke Probst, PharmD, pediatric pharmacy specialist and a clinical assistant professor in the Department of Pediatrics and Medicine at the SUNY Upstate Medical University.

Dr. Probst, you had been talking about areas where there has been a dichotomy between estimations of glomerular filtration rate in between the same patient wherein a lot of the same values are used to get the 2 entirely different estimations of renal clearance depending on which equation is used. Are there always differences for the same patient?

DR. LUKE PROBST:

There are not always differences for the same patient. Most of the differences do occur at the extremes of either age or renal function and it's important for clinicians to remember that the MDRD equation that was derived was actually derived in relatively healthy adults between the ages of 18 and 65, who did not have renal dysfunction of an appreciable extent at the time that they were evaluated. It was only studied in Caucasians and African-Americans and there were very few diabetic patients in the study group for which the MDRD equation was derived. So, as always, there is element of caution that people have to remember that the application of the MDRD equation though has not been studied in a number of patient groups, especially in the hospital settings, but even in the ambulatory care setting, any person over the age of 70, this formula really has not been validated and we found a significant number of patient with probably the most drastic difference in estimates of renal function between their Cockcroft-Gault and the MDRD in the older population. For example, we had a 92-year-old lady with a serum creatinine of 0.5 who according to the Cockcroft-Gault equation that we used had an estimated creatinine clearance of 20 mL per minute. In that same 92-year-old lady, the MDRD equation reported that her creatinine clearance was greater than 90 mL per minute. That was the high end of measurability that they used, so one doesn't know exactly what that calculated value was, but clearly very few 92-year-old ladies have renal functions with GFRs or creatinine clearances approaching the 100 mL per minute and so we did find a significant number of patients that we were reviewing especially with advanced age having these over-estimations of renal function with the MDRD equation. Similarly, in those patients, who had elevated serum creatinine

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values, who had significant renal disease, there was still some difference in the compared values of MDRD and Cockcroft-Gault derived renal function and actually in a few cases, the MDRD started to underestimate renal function compared to the Cockcroft-Gault, so there was a little inversion of the estimations there, but certainly those were at the extremes. Again, advancing age and the extremes of serum creatinine did tend to provide some inconsistency with what one would expect as an estimate of renal function before applying those to calculation.

DR. CHARLES TURCK:

You had mentioned a little bit earlier that the MDRD equation had only been derived fairly recently within the last decade. I was wondering if you could speak for a moment about the role that the Cockcroft-Gault equation has played historically in determining drug dosage adjustment.

DR. LUKE PROBST:

Sure, as I had said previously, the Cockcroft-Gault equation was derived in 1976 and has since been used for drug dosing purposes by clinicians and as well as most pharmaceutical manufacturers who are required to evaluate their pharmaceuticals for the existence of renal elimination and if there is renal elimination present for that drug therapy, then they need to characterize the impact of renal function or dysfunction on drug dosing and make recommendations. Most package inserts that are provided by pharmaceutical manufacturers suggest or recommend the use of the Cockcroft-Gault equation for the purpose of assessing drug-dosing adjustments in patients with renal dysfunction.

DR. CHARLES TURCK:

We had been speaking with Dr. Luke Probst about strategies for drug dosing in patients with renal insufficiency. Thank you so much, Dr. Probst for joining us.

DR. LUKE PROBST:

Thank you Dr. Turck, it's been a pleasure.

I am Dr. Charles Turck, you have been listening to Focus on Pharmacy on ReachMD, The Channel for Medical Professionals. Be sure to visit our web site at www.reachmd.com featuring on-demand pod casts of our entire library. For comments and questions, please call us toll free at (888-MD XM157) and thank you for listening.

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