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Modifying Drug Dosing for Patients with Renal Insufficiency

What is the best method for modifying drug doses in your patients with renal insufficiency. You are listening to ReachMD XM-157, the channel for medical professional.

Dr. CHARLES TURCK:

Welcome to **Focus on Pharmacy**. I am your host, Dr. Charles Turck, pharm M.D. Our guest is Dr. Luke Probst, pharm M.D., a pediatric pharmacy specialist and clinical assistant professor in the Department of Pediatrics and Medicine at the State University of New York UpState Medical at University.

Dr. Probst is the lead author of a recently published article in the Journal of Hospital Pharmacy on drug dosing modifications for patients with renal impairment. Welcome Dr. Probst.

Dr. LUKE PROBST:

Thanks very much Dr. Turck.

Dr. CHARLES TURCK:

We are discussing modifications of drug dosing for patients with kidney disease. You recently published an article in Hospital Pharmacy and before we go into discussing the article, I kind of wanted to get you to tell us a little bit about what inspired the article.

Dr. LUKE PROBST:

The inspiration for the article was really our identification of a number of similar situations with myself and other pharmacists who are having more frequent discussions with our prescribers about the appropriateness dosing for renal-eliminated drugs in our adult inpatient population here at University Hospital. As these interactions became more and more frequent, we realized that there was a change in information that was available to the prescribers, namely their awareness of the estimated GFR as a result of that information now being reported by our clinical laboratory system that was predicated on the MDRD equation. So we ended up having to dialogue with them and with a collective group of people to clarify the issue of when the MDRD is appropriate to use and when it is not an optimal source of information for renal function assessment.

Dr. CHARLES TURCK:

What has the ledger in the past suggested and what kind of guidance does it give as far as modification of drug dosing is concerned?

Dr. LUKE PROBST:

Well you know the MDRD equation came out in 1999. I think a lot of pharmacists were actually excited that Oh! we have a great, newer, more robust estimation of renal function for the purpose of drug dosing, but we all quickly realized that there is no validation behind that to justify the use of that equation for the purpose of drug dosing. In recent years, there have been a number of published articles that have described clinical experience with both the use of Cockcroft-Gault and the MDRD for the purpose of drug dosing and the dichotomy that does exist there and one of the earlier ones was by Virgo and Colleagues in Annals of Pharmacotherapy in 1996 where they evaluated antibiotic drug dosing in 409 patients and they found that based on which calculation was used to assess renal function, a clinician may have chosen a different dose that was clinically significant anywhere from 21% to 37% of patients, depending on which calculation was used. There have been a number of other citations more recently than that. There is a study by Gill and Colleagues from Vancouver describing the dichotomous application or <_____> interpretation of the MDRD Cockcroft-Gault equation as it pertained to digoxin and dosing of amantadine in elderly patients and again they found that there would be overestimation of renal function in about 60% of those patients and that there could certainly be some important adverse sequelae from the misapplication of the MDRD in that regard. Back in 2006 as well, this issue of the utilization of the MDRD equation was evaluated by Delimos and Colleagues with regard to carboplatin dosing for oncologic disorders. These authors interestingly found that the MDRD tended to underestimate the dose of carboplatin that would be used when it was compared to the standard of the Calvert equations for estimating carboplatin dosing. So, again there is not only dichotomy, but in some situations inconsistency of how people would interpret the findings that they have when they use the MDRD equations for drug dosing.

Dr. CHARLES TURCK:

Is there a difference in kinetics associated with these different equations?

Dr. LUKE PROBST:

There had been some analysis of what the implications would be when using concentration sensitive or pharmacokinetically-based drug therapies. Truong and Fremao published a poster presentation last year at one of the National Hospital Pharmacy meetings and they showed not unexpectedly that the application of the MDRD equation as the basis for determining vancomycin dosing would have caused somewhat of an overshoot in the vancomycin dosing of a patient compared to the standard of using the Cockcroft-Gault and that furthermore, the Cockcroft-Gault was more closely associated with doses that were previously determined. They described that if they had proactively applied the Cockcroft-Gault that would have given a more reliable similar result as far as vancomycin levels go and for us, one of the first cases that really pointed out the presence of the problem for us was exactly a patient who was receiving gentamicin in whom we had a detailed dialogue with prescribers to discuss this dichotomy.

So, this was a 77-year-old gentleman who had a urinary tract infection and prescribers chose to use gentamicin and they prescribed the dose of 5 mg/kilo, in this case 350 mg intravenously every 24 hours. When the pharmacist reviewed that order before it was prepared, he was concerned that that was too high of a dose and had actually recommended based on an assessment of the patient's renal function using the Cockcroft-Gault, a much lower dose around the range of 150 mg every 24 hours and the reply of the prescriber at the time was that well the patient had a serum creatinine of 1.1 and GFR was 65 mL/minute at least that is what the GFR was reported in the hospital system, that was the basis for essentially using a relatively normal dose of gentamicin in this patient. The pharmacist at the same time estimated the patient's creatinine clearance to be about 47 mL/minute in which case a smaller dose at a less frequent dosing interval of 24 hours was advised. Now the long and short of it that the 350 mg dose was given and a drug level drawn subsequent to that showed that the anticipated gentamicin level was higher than it should have been nor than we would have wanted it to be and so we changed the regimen to the pharmacist recommended 150 mg every 24 hour regimen and with the next dose, we sampled peak and trough levels which were quite therapeutic and one could argue possibly still higher than necessary with regard to the peak level, but

certainly nontoxic. We believe that if the original order of 350 mg was perpetuated, we certainly would have gotten into far higher peak levels, which may have contributed to some toxicities or adverse affects and everyone is concerned with nephrotoxicity and ototoxicity for gentamicin therapy. So, we believe we may have prevented significant adverse event from occurring.

DR. CHARLES TURCK:

In the article that you have published in Hospital Pharmacy, you also describe another patient's case. I was wondering if you could give some details about that as well.

Dr. LUKE PROBST:

Yes the second case that we chose to highlight was that of an 86-year-old woman who to summarize during her hospital stay developed a bout of atrial fibrillation for which she was decided to initiate sotalol therapy and the dose was chosen as the usual dose for most adults at 80 mg twice daily and again the pharmacist reviewing that order prior to the drug being administered had concern because that pharmacist's assessment of patient's renal function was that the creatinine clearance for the patient was 39 mL/min and the package labeling recommends reducing the dosing interval of sotalol to once daily not twice daily in patients with creatinine clearances less than 60 mL/minute. So this patient was far below that threshold value. At the same time, this patient again 86-year-old with a relatively one would think normal serum creatinine of 0.7. The MDRD based GFR reported in our lab system suggested that this patient had a GFR of 89 mL/minute, which is a drastic difference from the 39 that we had estimated. Soon in to our dialogue with prescriber, there was agreement to change that patient's regimen from 80 mg twice daily to 80 mg once daily and again since we did intervene, we do not know the sequelae of this event, but we proposed that we may have helped to avoid some of the toxicities of sotalol which included QT prolongation and torsades de pointes which have been fatal in certain situations.

Dr. CHARLES TRUCK:

I was wondering if you could just briefly summarize the findings in aggregate.

Dr. LUKE PROBST:

Sure. Our findings were that in a lot of patients that we see in our hospital setting, the application of the MDRD equation for the purpose of determining what an optimal dosing regimen is for renally adjusted medications often overestimate that patient's renal function in comparison to the application of the Cockcroft-Gault equation and in many cases, that overestimation would have led to the prescribing of a renally eliminated drug at a dose or a dosing interval more generous than what we as pharmacists evaluating that patient's renal therapy would determine and automatically change. A number of drugs were known to have risks for these patients. Some patients were receiving as already stated gentamicin and sotalol, dalteparin which is an anticoagulant that has bleeding risk issues for excessive dosing and a number of antibiotics which even though they may be less toxic than say gentamicin, cefazolin, still may have been prescribed in a higher dose than is necessary according to the policies that we prepared and practiced by that are all based on the evidence and the literature and package inserts from the various manufacturers.

Dr. CHARLES TURCK:

Did the findings of your study lead to any changes on the institutional level?

Dr. LUKE PROBST:

Yes they did. What we actually did was that since we were finding a number of these interactions to be occurring with greater frequency, the Clinical Pharmacists Group convened and we prepared essentially a white paper that we thought would be a good education piece for prescribers, nurses, and everyone else, all the medical professionals in the hospital. To more clearly understand the role of and the

differences between the MDRD and the Cockcroft-Gault equation and ultimately the final piece of that document was the recommendation that medical professionals solely use the Cockcroft-Gault and not use the MDRD for the purpose of drug dosing adjustments. We then took that to our pharmacy and therapeutics community who approved it and that was integrated into one of our hospital policies, so that the ongoing practice that allows pharmacists to automatically adjust the doses of renally-eliminated medications in adults allowed us to do that based on the evidence that we know presently to be most reliable and it also provided clear guidance for those prescribers who may not be familiar with this information to know that this information was truly evaluated in a thorough fashion and had the full support of the academic side of the medical staff.

Dr. CHARLES TURCK:

We have been speaking with Dr. Luke Probst about alterations of drug dosing for patients with renal impairment. Dr. Probst thank you so much for joining us.

Dr. LUKE PROBST:

Thank you Dr. Turck, it has been a pleasure.

I am Dr. Charles Turck, you have been listening to Focus On Pharmacy on ReachM XM-157, the channel for medical professionals. Please be sure to visit our web site at reachmd.com featuring on-demand podcasts of our entire library. For comments and questions, please feel free to call us toll free at 888-MDX-M157 and thank you for listening.