Dofetilide Dose Calculation Errors in Elderly Associated with Use of the Modification of Diet in Renal Disease Equation

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OBJECTIVE: To report 2 cases of drug dosage calculation errors that occurred when the Modification of Diet in Renal Disease (MDRD) equation was used for initiating drug therapy with dofetilide in elderly patients with chronic kidney disease.

CASE SUMMARY: An 83-year-old woman and a 92-year-old man were admitted for dofetilide treatment initiation and cardioversion for atrial fibrillation. The estimated glomerular filtration rate (eGFR) determined with use of the MDRD equation was significantly higher than the estimated creatinine clearance (eCrCl) determined with use of the Cockcroft-Gault equation for both cases (85 vs 43 mL/min for the man and 40 vs 24 mL/min for the woman). Initial dofetilide dosages calculated by the MDRD equation were 2-fold higher than those calculated by eCrCl in both cases. Initiation of dose based on the MDRD in the first patient led to a 32% increase in the QTc interval from baseline. Dofetilide therapy was adjusted for QTc interval prolongation based on eCrCl and reinitiated at a lower dose, and the patient did not develop further significant increases in the QTc interval. In the second patient, the lower dose based on eCrCl was initiated and the QTc interval remained within an acceptable range.

DISCUSSION: The initial dosing of dofetilide is based on eCrCl as specified by the drug manufacturer. Recent widespread use and automated reporting of the eGFR by clinical laboratories has tempted some clinicians to consider using eGFR for calculating drug doses. However, recent data suggest that the eGFR, calculated by the MDRD equation, consistently overestimates eCrCl, leading to dose discrepancies, particularly in the elderly. The cases reported here illustrate the drug dose calculation errors that may occur when using the MDRD equation for initiating doses of dofetilide.

CONCLUSIONS: Use of the eGFR or MDRD equation for calculation of doses in renal dysfunction has not been validated, and significant drug dose errors have been reported. The use of eGFR to calculate doses of dofetilide should be avoided.

KEY WORDS: creatinine clearance, dofetilide, MDRD equation, renal dosing.

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Dofetilide is a class III antiarrhythmic drug that is excreted primarily by the kidney, with approximately 80% of a dose appearing in urine in the unchanged form.[1,2] Dose reductions are therefore required in patients with impaired kidney function based on estimated creatinine clearance (eCrCl), using the Cockcroft-Gault (CG) equation.[2,3] Lack of appropriate dose reduction may lead to excessive drug exposure and subsequent QTc interval prolongation and torsade de pointes, a potentially fatal ventricular tachycardia.[4] Many clinical laboratories now automatically report the estimated GFR (eGFR) calculated by the Modification of Diet in Renal Disease (MDRD) equation in the electronic medical record for the purpose of detecting and staging chronic kidney disease (CKD).[5] Use of eGFR and MDRD for renal drug dosing has recently been endorsed by the National Kidney Disease Education Program, based largely on a retrospective analysis of patients enrolled in the original MDRD study.[6,7] However, these results have not been validated outside the MDRD study group, and

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extending the use of the MDRD equation for the purpose of dose calculations beyond its intended use of CKD classification is controversial, based on reported dosing errors and lack of validation in patients with CKD.[8-13] We describe 2 cases where dose calculation errors occurred using the MDRD equation, with 1 patient developing QTc interval prolongation after starting therapy on dofetilide, based on eGFR.

Case Reports

CASE 1

An 83-year-old woman (168 cm, 64 kg) presented with symptomatic atrial flutter with malaise, fatigue, diaphoresis, and heart pounding. Her history included arrhythmias, paroxysmal atrial fibrillation and flutter, asymptomatic coronary artery disease, type 2 diabetes, and dyslipidemia. Atrial fibrillation was documented in 2003. Pulmonary vein ablation was performed in 2006; however, recurrent atrial fibrillation necessitated therapy with sotalol 40 mg twice daily. Following a repeat ablation procedure in 2008, the patient experienced postprocedural atypical atrial flutter and intermittent breakthrough tachyarrhythmias. Because of recurrent fatigue and dizziness related to sotalol, treatment was switched to dronedarone 400 mg twice daily. The patient presented to the emergency department 1 week later with recurrent atrial flutter. A 12-lead electrocardiograph (ECG) showed atrial flutter with a 3:1 block, with a ventricular rate of 94 beats/min. Electrical cardioversion was performed; the patient's QTc interval was 440 msec postcardioversion. No acute change in the interval was observed when her 12-lead ECG was compared with a previous ECG. Results of serum chemistry testing included a low serum sodium concentration of 129 mEq/L, but were otherwise normal, with serum potassium 3.9 mEq/L, blood urea nitrogen 12 mg/dL, creatinine 0.7 mg/dL (non-isotope dilution mass spectrometry), and magnesium 1.9 mg/dL. The patient's calculated eGFR was 85 mL/min by MDRD and eCrCl was 43 mL/min by CG calculation.[6] Dronedarone was discontinued 24 hours prior to beginning dofetilide. Drugs taken concurrently with dofetilide included sitagliptin, insulin (Lispro), and warfarin. Dofetilide was initiated at 500 µg twice daily based on an eGFR greater than 60 mL/min. After the patient's first dofetilide dose, her QTc interval was prolonged to 580 msec, which was an increase of approximately 31.8% from baseline. Dofetilide doses were withheld and then adjusted for QTc interval prolongation by the critical care pharmacist to a dose of 250 µg twice daily the next morning. QTc intervals following the second, third, and fourth doses were 430, 480, and 460 msec, respectively. No further dose adjustments were required, and the QTc interval remained stable. The patient's ECG showed sinus rhythm with occasional atrial ectopy and first-degree atrioventricular block at the time of her discharge. After the patient was confirmed to be in stable condition for at least 12 hours, she was discharged with a maintenance dofetilide dose of 250 µg twice daily.

CASE 2

A 92-year-old man (168 cm, 62 kg) returned to the emergency department as the result of increasing dyspnea with acute-on-chronic congestive heart failure (CHF) 2 months after his previous admission. He had a longstanding history of multiple cardiac problems including aortic stenosis postaortic valve replacement, coronary artery disease postbypass surgery, chronic atrial fibrillation, dyslipidemia, hypertension, chronic CHF, and sick sinus syndrome with permanent pacemaker implantation. Four months prior to this admission, the patient experienced cardiac arrest believed to be secondary to bradycardia caused by sotalol. His medications prior to admission included fluticasone, lorazepam, tamsulosin, furosemide, omeprazole, simvastatin, and warfarin. On admission, the patient was found to have pleural effusion related to a degenerating bioprosthetic aortic valve, with stenosis and insufficiency. He also had a newly discovered systolic dysfunction, with estimated ejection fraction of 35%. His serum creatinine value was stable at 1.7 mg/dL (non-isotope dilution mass spectrometry) and baseline QTc interval was 443 msec. The calculated eGFR was 40 mL/min (MDRD) and eCrCl was 24 mL/min (CG). The physician's initial dofetilide prescription was 250 µg twice daily based on eGFR in the range of 40-60 mL/min. However, the dose was adjusted by the critical care pharmacist to 125 µg twice daily based on eCrCl of 20-39 mL/min prior to the patient receiving the first dose. After the 125-µg dose was administered, the first QTc interval was 468 msec, an increase of less than 6% from baseline. Further dose adjustments were not required and the patient spontaneously converted to sinus rhythm. Five days after dofetilide initiation, dofetilide therapy was held and ultimately discontinued after subsequent worsening of kidney function likely related to diuresis with intravenous furosemide. Carvedilol, hydralazine, and isosorbide mononitrate were initiated, and the patient remained in sinus rhythm on discharge.

Discussion

These cases illustrate the potential for significant dose calculation discrepancies for dofetilide when using the MDRD equation in place of the eCrCl, especially in elderly individuals. Both patients had eGFR (MDRD) values that were significantly higher than eCrCl values. In the first patient, the initial dose calculations using the eGFR value suggested that dofetilide 500 µg twice daily would be equivalent to a dose indicated for individuals with eCrCl

greater than 60 mL/min. However, when considering this elderly patient's low serum creatinine generation and using the CG equation, the eCrCl value was in the range of 40-60 mL/min; the appropriate starting dose with that low level is 250 µg twice daily (half of what the patient received).[12] The subsequently administered 500-µg dose was excessive as indicated by QTc interval prolongation, necessitating a dose reduction to 250 µg. In the second patient, although dofetilide is contraindicated for patients with a baseline QTc interval above 440 msec and this patient's baseline QTc interval was 443 msec, dofetilide was chosen based on resistance to prior therapy. The starting dose was calculated appropriately based on the patient's eCrCl (24 mL/min), despite the higher value for kidney function calculated by the eGFR equation (40 mL/min).

Problems with the MDRD equation overestimating eCrCl have been reported in over 20,000 patients with chronic kidney disease, leading to growing concern that automated reporting of eGFR in the patient's medical record will lead to inappropriate use of the MDRD equation and critical dose calculation errors.[9-14] Although there is some agreement regarding the need for renal dosage adjustment between the MDRD and CG equations, the doses of many drugs were higher in up to 40% of patients when the MDRD equation was used.[9-12] This difference is most striking in the elderly population, where use of MDRD-derived eGFR in lieu of eCrCl leads to higher dose calculations for nearly 50% of patients receiving enoxaparin, digoxin, and amantadine.[10,11] For gentamicin dosing, the MDRD equation overestimated gentamicin clearance by 29% in an elderly population, with differences of up to 69% in patients over 80 years of age.[12] In a study of 180 elderly patients in a long-term care facility, average eGFR values were 40% higher than CG estimates (72.9 vs 52.1 mL/min/1.73 m^2).[10] In this study, use of the MDRD equation resulted in amantadine dose recommendations that were more than 35% higher than those based on the CG equation, and 32% of these patients would have received higher initial doses of digoxin with MDRD versus CG equations.

The main concern with overestimating kidney function is dosing errors that can contribute to toxicity and adverse drug reactions. For drugs with a wide therapeutic range, toxicity may not be measurable or associated with doses commonly used in clinical settings. For cardiovascular drugs with a narrow therapeutic range, such as dofetilide, pharmacokinetic studies have shown that QTc interval prolongation is closely related to dose and plasma concentration.[1,4] Here, increasing drug plasma concentrations lead to changes in QTc interval from baseline in a predictable, linear manner. Overdoses of dofetilide can lead to QTc interval prolongation, complete heart block, and torsade de pointes.[15]

It is widely accepted that the authoritative reference for dosing a drug based on kidney function is the FDA-approved package label. These recommendations are based on pharmacokinetic studies conducted in patients with kidney disease in accordance with the FDA *Guidance for Industry: Pharmacokinetic Studies in Patients with Impaired Renal Function*.[16] For nearly all drugs on the market today, CrCl is the index used in the mathematical algorithm for dose calculations, and many FDA-approved product labels (ie, package inserts) specifically indicate use of the CG equation, including dofetilide.[2,17] Therefore, dose adjustments for dofetilide must be based on eCrCl, and newer equations for eGFR developed for other purposes, such as the MDRD and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation,[18] should not be used for renal dosing until the relationships between these equations and pharmacokinetic/pharmacodynamic outcomes are firmly established.

The cases reported here illustrate the critical need for clinicians to be aware of the differences in dose calculations that result from using the MDRD and CG equations. This is especially important for drugs such as dofetilide, where exposure has been directly linked to toxicity, as well as for patient populations such as the elderly, that are vulnerable to adverse drug events. Although the eGFR and eCrCl equations provide estimation of kidney function, they are not equivalent and should not be used interchangeably for drug dose calculations. The MDRD or other eGFR equations should not be used for renal dosing until the relationships between these new indices of renal function and pharmacokinetic outcomes have been firmly established through additional studies.

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References

1. Allen MJ, Nichols DJ, Oliver SD. The pharmacokinetics and pharmacodynamics of oral dofetilide after twice daily and three times daily dosing. Br J Clin Pharmacol 2000;50:247-53.
2. Product information. Tikosyn (dofetilide). New York, NY: November 2006.
3. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.
4. Jonker DM, Kenna LA, Leishman D, et al. A pharmacokinetic-pharmacodynamic model for the quantitative prediction of dofetilide clinical QT prolongation from human ether-a-go-go-related gene current inhibition data. Clin Pharmacol Ther 2005;77:572-82.
5. Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction

equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461-70.

6. Bailie GR, Uhlig K, Levey AS. Clinical practice guidelines in nephrology: evaluation, classification, and stratification of chronic kidney disease. Pharmacotherapy 2005;25:491-502.
7. Stevens LA, Nolin TD, Richardson MM, et al. Comparison of drug dosing recommendations based on measured GFR and kidney function estimating equations. Am J Kidney Dis 2009;54:33-42.
8. Golik MV, Lawrence KR. Comparison of dosing recommendations for antimicrobial drugs based on two methods for assessing kidney function: Cockcroft-Gault and Modification of Diet in Renal Disease. Pharmacotherapy 2008;28:1125-32.
9. Spruill WJ, Wade WE, Cobb HH 3rd. Continuing the use of the Cockcroft-Gault equation for drug dosing in patients with impaired renal function. Clin Pharmacol Ther 2009;86:468-70.
10. Gill J, Malyuk R, Djurdjev O, Levin A. Use of GFR equations to adjust drug doses in an elderly multi-ethnic group—a cautionary tale. Nephrol Dial Transplant 2007;22:2894-99.
11. Melloni C, Peterson ED, Chen AY, et al. Cockcroft-Gault versus Modification of Diet in Renal Disease: importance of glomerular filtration rate formula for classification of chronic kidney disease in patients with non-ST-segment elevation acute coronary syndromes. J Am Coll Cardiol 2008;51:991-6.
12. Roberts GW, Ibsen PM, Schioler CT. Modified Diet in Renal Disease method overestimates renal function in selected elderly patients. Age Ageing 2009;38:698-703.
13. Hermsen ED, Maiefski M, Florescu MC, et al. Comparison of the Modification of Diet in Renal Disease and Cockcroft-Gault equations for dosing antimicrobials. Pharmacotherapy 2009;29:649-55.
14. Péquignot R, Belmin J, Chauvelier S, et al. Renal function in older hospital patients is more accurately estimated using the Cockcroft-Gault formula than the Modification of Diet in Renal Disease formula. J Am Geriatr Soc 2009;57:1638-43.
15. Aktas MK, Shah AH, Akiyama T. Dofetilide-induced long QT and torsades de pointes. Ann Noninvasive Electrocardiol 2007;12:197-202.
16. Food and Drug Administration. Guidance for industry: pharmacokinetic studies in patients with impaired renal function—study design, data analysis, and impact on dosing and labeling. Rockville, MD: US Department of Health and Human Services, May 1998.
17. Dowling TC, Matzke GR, Murphy JE, Burckart GJ. Evaluation of renal drug dosing: prescribing information and clinical pharmacist approaches. Pharmacotherapy 2010;30:776-786.
18. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604-12.