

Case Report: Adverse drug reactions in unrecognized kidney failure

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Mild kidney failure is common and frequently unrecognized in elderly people.¹⁻³ In this case report, a change of medications improved a patient's quality of life and possibly decreased risk of adverse drug reactions. The report demonstrates the importance of calculating creatinine clearance, the relevance of adjusting medication in renal impairment, and the value of having a clinical pharmacist help care for elderly patients.

Case report

Ms L., a 96-year-old woman with many medical problems, was sent for medication review to a pharmacist at a geriatric day hospital. Her chief complaint was diarrhea of sudden onset every few days over the past several years. The diarrhea occurred at any time during the day or night, and

daytime episodes caused her great distress. She could not identify aggravating or alleviating factors, and investigations and referrals to internists failed to find the cause of her diarrhea.

Ms L.'s medical history included diabetes, atrial fibrillation, congestive heart failure, recurrent urosepsis, hypomagnesemia, previous cerebrovascular accident, hypertension, incontinence, and falls. Her medication list included 1000 mg of metformin at breakfast and 500 mg at lunch and supper; warfarin and digoxin, 0.125 mg daily; furosemide, 40 mg daily; fosinopril, 10 mg daily; amlodipine, 5 mg daily; sotalol, 80 mg twice daily; magnesium glucoheptonate, 45 mL (3 tbs) three times daily; potassium, 16 mEq three times daily; nitrofurantoin, 100 mg daily; and loperamide as needed.

On examination, Ms L.'s blood pressure was normal (120/70 mm Hg), with an occasional irregular heart rate at 72 beats/min. She had a normal jugular venous pulse and clear chest. Her potassium (4.1 mmol/L) and glucose (7.0 mmol/L) levels were normal, her serum creatinine level was 60 mmol/L, and her magnesium level was low at 0.58 mmol/L.

A pharmacist used the Cockcroft and Gault formula to calculate her creatinine clearance and found substantial renal impairment with an estimated glomerular filtration rate of 36 mL/min.⁴⁻⁶ The following medication changes were recommended to her family doctor to minimize risk of adverse reactions due to drug accumulation:

- metformin was switched to a low dose of glyburide (to determine whether metformin was contributing to the diarrhea and because of the potential risk of lactic acidosis); (Note: when elderly patients switch to glyburide, starting with

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a low dose and monitoring glucose is believed to prevent hypoglycemia);

- nitrofurantoin was switched to low-dose ciprofloxacin (because nitrofurantoin is unlikely to be effective in renal impairment); and
- digoxin dose was decreased (to reduce risk of toxicity with concomitant hypomagnesemia, interaction with metformin, and possible contribution to diarrhea).

Following these medication changes, Ms L.'s diarrhea stopped, her magnesium and potassium levels remained normal without supplementation, and her glucose was controlled with glyburide.

Discussion

Ms L. had been taking metformin for many years. Because her diabetes was well controlled, and her serum creatinine levels were within the normal range, her family physician had not considered that she might be experiencing toxicity due to reduced renal function. Her calculated creatinine clearance (36 mL/min), however, was clearly abnormal. Reduced renal function, we speculate, might have caused increased serum levels of metformin and led to the development of diarrhea, a documented adverse reaction to metformin.^{7,8} The patient's diarrhea, electrolyte imbalances, and risk of lactic acidosis were addressed with the medication changes. With cessation of her chronic diarrhea, Ms L. felt less isolated and was able to move about freely in public.

Cockcroft and Gault formula

Conventional units

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)} \times (0.85 \text{ [for female patients]})}{\text{Cr (mg/dL)} \times 72}$$

or

International system of units

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)} \times 1.2 \times (0.85 \text{ [for female patients]})}{\text{Cr } (\mu\text{mol/L})}$$

EDITOR'S KEY POINTS

- Normal results of serum creatinine assessment in elderly patients might be misleading. This case illustrates the value of calculating creatinine clearance with the Cockcroft and Gault formula, a simple exercise.
- This case also demonstrates the benefit of involving a clinical pharmacist in evaluating complicated medication regimens for elderly patients.

POINTS DE REPÈRE DU RÉDACTEUR

- Des résultats normaux d'une évaluation de la créatinine sérique chez les patients plus âgés peuvent induire en erreur. Le présent cas démontre l'utilité du calcul de la clairance au moyen de la formule Cockcroft et Gault, un exercice bien simple.
- Ce cas fait aussi valoir les avantages de solliciter la participation d'un pharmacien clinique dans l'évaluation d'une médication complexe chez des patients âgés.

This case illustrates several key issues in caring for elderly people. Physicians should calculate creatinine clearance rather than rely on serum creatinine levels, and medications should be adjusted accordingly. Adverse drug reactions and drug interactions should be considered when there are troublesome signs and symptoms.^{9,10} Renal function often decreases with age.¹¹⁻¹³ Unfortunately, serum creatinine assessment underestimates renal function in patients of advanced age and decreasing muscle mass.¹⁻³ A better estimation of renal function is calculated creatinine clearance. The modified Cockcroft and Gault formula is one method commonly recommended.⁴

This estimation of renal function can be used as a guide when choosing medications and medication doses for patients. Lactic acidosis related to metformin, although rare, might be more common with reduced renal function and renal hypoperfusion due to congestive heart failure. While a recent meta-analysis showed little evidence to support a causal role for metformin in development of lactic acidosis, the possible causal role remains controversial, and manufacturers continue to recommend avoiding use of metformin for elderly patients who have substantial renal impairment.^{14,15}

Conclusion

The case of Ms L. reinforces the importance of monitoring calculated creatinine clearance in

elderly patients (ie, older than 65). Once impaired renal function is identified, family physicians should adjust medication doses appropriately, monitor drug levels, and avoid nephrotoxic drugs. Clinical pharmacists can play an important role in assisting family physicians in the often complex care of elderly patients. ❁

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References

- Swedko PJ, Clark HD, Paramsothy K, Akbari A. Serum creatinine is an inadequate screening test for renal failure in elderly patients. *Arch Intern Med* 2003;163:356-60.
- Duncan L, Heathcote J, Djurdjev O, Levin A. Screening for renal disease using serum creatinine: who are we missing? *Nephrol Dial Transplant* 2001;16:1042-6.
- Papaioannou A, Ray JG, Ferko NC, Clarke JA, Campbell G, Adachi JD. Estimation of creatinine clearance in elderly persons in long-term care facilities. *Am J Med* 2001;111:569-73.
- National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;39(2 Suppl 1):S1-S266.
- Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31-41.
- Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. 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(6):461-70.
- Foss MT, Clement KD. Metformin as a cause of late-onset chronic diarrhea. *Pharmacotherapy* 2001;21(11):1422-4.
- Raju B, Resta C, Tibaldi JT. Metformin and late gastrointestinal complications. *Am J Med* 2000;109(3):260-1.
- Atkin PA, Veitch PC, Veitch EM, Ogle SJ. The epidemiology of serious adverse drug reactions among the elderly. *Drugs Aging* 1999;14(2):141-52.
- Ratnaik RN, Jones TE. Mechanisms of drug-induced diarrhoea in the elderly. *Drugs Aging* 1998;13(3):245-53.
- Clase CM, Garg AX, Kiberd BA. Prevalence of low glomerular filtration rate in nondiabetic Americans: Third National Health and Nutrition Examination Survey (NHANES III). *J Am Soc Nephrol* 2002;13:1338-49.
- U.S. Renal Data System, USRDS 2001 Annual Data Report. *Atlas of end-stage renal disease in the United States*. Bethesda, Md: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Disease; 2001.
- Jungers P, Chauveau P, Descamps-Latscha B, Labrunie M, Giraud E, Man NK, et al. Age and gender-related incidence of chronic renal failure in a French urban area: a prospective epidemiologic study. *Nephrol Dial Transplant* 1996;11(8):1542-6.
- Salpeter S, Greyber E, Pasternak G, Salpeter E. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2002;(2):CD002967.
- Jones GC, Macklin JP, Alexander WD. Contraindications to the use of metformin. Evidence suggests that it is time to amend the list [editorial]. *BMJ* 2003;326:4-5.