Nephropathy

Hyperkalaemia as a result of angiotensin-converting enzyme-inhibitor treatment

Colin Close, Consultant Physician & Endocrinologist, Associate Medical Director – Division of Medicine, Taunton & Somerset Hospital.

The development of hyperkalaemia is of concern when angiotensin-converting enzyme (ACE)-inhibitor treatment is started, but how common is it in clinical practice? The landmark trials of ACE-inhibitor and angiotensin II receptor blocker therapy in diabetic nephropathy reported very low adverse event rates for hyperkalaemia – below 2% – which may have been due in part to the widespread prior use of diuretics in these cohorts (Lewis et al, 1993; 2001; Brenner et al, 2001). The impression from clinical experience, however, suggests that it may be a more frequent occurrence. A number of factors might be expected to increase the likelihood of hyperkalaemia: the degree of renal impairment (I still find myself struggling with "CKD") and older age, as well as, more predictably, the concurrent use of potassium-sparing diuretics and potassium salts, the latter particularly in over-the-counter formulations, such as LoSalt (Klinge Foods, East Kilbride).

Johnson et al (summarised alongside) studied over 5000 people starting the ACE-inhibitor lisinopril in the Kaiser Permanente Northwest healthcare system, and found an overall incidence of hyperkalaemia of around 3%. They investigated the contribution of a variety of potential risk factors for the development of hyperkalaemia, and ascribed them scores in an attempt to quantify an individual's overall likelihood of developing hyperkalaemia.

Interestingly, risk was greatest at the extremes of the age range studied, below 50 and above 80 years, rose progressively as estimated glomerular filtration rate (using the Modification of Diet in Renal Disease Study [Klahr, 1989] equation) fell below 45 mL/min, and was greater in those with diabetes and heart failure. Over one-third of those developing hyperkalaemia had diabetes, although they comprised only a quarter of the participants. The overall incidence of hyperkalaemia in the individuals with diabetes was 4%. Risk was also greater with higher starting doses of lisinopril.

The main messages seem to be: be vigilant with regard to other medications, start at a low dose and increase gradually if risk factors are present, treat all age groups the same, beware people with heart failure, and monitor. Amelioration with thiazide and loop diuretics can help offset minor degrees of hyperkalaemia to enable continuation of renoprotective therapies in diabetic nephropathy. The potential contribution of "spurious" factors, such as tourniquet, application, fist clenching and the samples resting on cells before assay, may need to be considered.

Brenner BM, Cooper ME, de Zeeuw D et al (2001) *N Engl J Med* **345**: 861–9
Klahr S (1989) *N Engl J Med* **320**: 864–6
Lewis EJ, Hunsicker LG, Bain RP, Rohde RD (1993) *N Engl J Med* **329**: 1456–62
Lewis EJ, Hunsicker LG, Clarke WR et al (2001) *N Engl J Med* **345**: 851–60

INT J CLINICAL PHARMACOLOGY AND THERAPEUTICS

Efficacy of HCTZ and telmisartan combined

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 A total of 60 adults with stages 2–3 chronic kidney disease who had not achieved target blood pressure on high-dose angiotensin II receptor blockers were tansferred to a hydrochlorothiazide and telmisartan combination.

2 Mean systolic blood pressure decreased from 153 to 133 mmHg and diastolic from 89 to 78 mmHg (both, $P<0.0001$).

3 Urinary protein excretion was significantly reduced ($P<0.0001$).

4 Telmisartan and hydrochlorothiazide combined may be more efficacious in reducing blood pressure and urinary protein excretion than high-dose angiotensin II receptor blockers.

Abe M, Okada K, Maruyama T et al (2010) Blood pressure-lowering and antiproteinuric effect of switching from high-dose angiotensin receptor blockers to normal-dose telmisartan and low-dose hydrochlorothiazide in hypertensive patients with chronic kidney disease. *Int J Clin Pharmacol Ther* **48**: 206–13

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY

Risk predictor for hyperkalaemia

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓✓

1 Angiotensin-converting enzyme (ACE) inhibitors are recommended for people with chronic kidney disease (CKD) but high doses may not be prescribed due to adverse effects including hyperkalaemia.

2 The authors of this study aimed to predict the risk of hyperkalaemia by developing a prognostic risk score based on known hyperkalaemia predictors.

3 The cohort was retrospectively selected from records at Kaiser Permanente Northwest serving the Portland, Oregon, Vancouver and Washington Metropolitan areas.

4 Inclusion criteria were adults with possible CKD (estimated glomerular filtration rate [eGFR], <60 mL/min/1.73m^2) who commenced ACE-inhibitor therapy between 1998 and 2006.

5 Records were analysed for the incidence of hyperkalaemia defined as a potassium value >5.5 mmol/L or a diagnosis code for hyperkalaemia.

6 Out of a total of 5171 people, 145 experienced hyperkalaemia, with a 90-day risk of 2.8%. Predictors included age, eGFR, diabetes, heart failure, potassium supplements, potassium-sparing diuretics and a high-dose ACE inhibitor (lisinopril).

7 The risk score separated high-risk (top quintile observed risk, 6.9%) from low-risk (bottom quintile observed risk, 0.7%) people.

8 People with high risk for hyperkalaemia were successfully separated from those with low risk using this risk score.

Johnson ES, Weinstein JR, Thorp ML et al (2010) Predicting the risk of hyperkalemia in patients with chronic kidney disease starting lisinopril. *Pharmacoepidemiol Drug Saf* **19**: 266–72

JAMA

B-vitamins decrease GFR but increase vascular events

Readability	✓✓✓✓
Applicability to practice	✓✓
WOW! factor	✓✓✓

1 People with nephropathy are often found to have hyperhomocysteinaemia so the authors hypothesised that B-vitamin therapy would lower homocysteine levels and slow the progression of diabetic neuropathy.

2 This multi-centre, randomised, double-blind, placebo-controlled DIVINe (Diabetic Intervention with Vitamins to Improve Nephropathy) trial conducted in Canada between May 2001 and July 2007, included 238 participants who had either T1D or T2D and were diagnosed with diabetic nephropathy.

3 The main outcome measure was change in radionuclide glomerular filtration rate (GFR) from baseline to 36 months. Secondary outcomes were dialysis and a composite of myocardial infarction, stroke, revascularisation and all-cause mortality.

4 Radionuclide GFR decreased by a mean of 16.5 mL/min/1.73m^2 in the B-vitamin group compared with 10.7 mL/min/1.73m^2 in the placebo group.

5 The B-vitamin group experienced the composite outcome more often (hazard ratio, 2.0; 95% confidence interval [CI], 1.0–4.0; P=0.04).

6 The mean decrease of plasma homocysteine levels was 2.2 µmol/L in the B-vitamin group compared with a mean increase of 2.6 µmol/L in the placebo group.

7 High doses of B vitamins reduced levels of homocysteine and GFR but increased vascular events in people with diabetic nephropathy.

House AA, Eliasziw M, Cattran DC et al (2010) Effect of B-vitamin therapy on progression of diabetic nephropathy: a randomized controlled trial. *JAMA* **303**: 1603–9

AMERICAN JOURNAL OF KIDNEY DISEASES

CKD-EPI equation reclassifies low-risk individuals

Readability	✓✓✓✓
Applicability to practice	✓✓
WOW! factor	✓✓✓

1 The authors aimed to assess the accuracy of two equations at predicting chronic kidney disease (CKD) in an Australian population.

2 The two equations investigated were those given by the CKD Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD) study.

3 A total of 11 247 participants had their serum creatinine and urinary albumin, protein and creatinine measured on a random spot morning urine sample.

4 A total of 266 participants with CKD according to the MDRD study equation were reclassified as having no CKD according to the CKD-EPI equation (estimated prevalence 1.9%; 95% confidence interval, 1.4–2.6).

5 The reclassification of low-risk individuals results in a lower estimated prevalence of CKD using the CKD-EPI equation.

White SL, Polkinghorne KR, Atkins RC, Chadban SJ (2010) Comparison of the prevalence and mortality risk of CKD in Australia using the CKD Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) Study GFR estimating equations: the AusDiab (Australian Diabetes, Obesity and Lifestyle) Study. *Am J Kidney Dis* **55**: 660–70

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

CKD reduces clopidogrel treatment effects

Readability	✓✓✓✓
Applicability to practice	✓✓
WOW! factor	✓✓✓

1 This cross-sectional, observational study looked at the impact of renal function on platelet reactivity in people with diabetes and coronary artery disease on aspirin and clopidogrel therapy.

2 A total of 306 participants were classified into two groups according to presence or absence of moderate to severe chronic kidney disease (CKD).

3 Compared with people without, those with moderate to severe CKD (n=84) had significantly higher adenosine diphosphate- and collagen-induced platelet aggregation (P=0.001 and P=0.004, respectively).

4 In this cohort, impaired renal function is associated with reduced clopidogrel-induced antiplatelet effects.

Angiolillo DJ, Bernardo E, Capodanno D et al (2010) Impact of chronic kidney disease on platelet function profiles in diabetes mellitus patients with coronary artery disease taking dual antiplatelet therapy. *J Am Coll Cardiol* **55**: 1139–46

AMERICAN JOURNAL OF KIDNEY DISEASES

AER and NAG predict nephropathy

Readability	✓✓✓✓
Applicability to practice	✓✓
WOW! factor	✓✓✓

1 This nested, case-controlled study tested urinary markers as predictors of micro- or macro-albuminuria in people with T1D.

2 Participants were from the Diabetes Control and Complications Trial and urinary N-acetyl-beta-D-glucosaminidase (NAG), advanced glycation end product (AGE) and albumin excretion rate (AER) were measured when micro- or macro-albuminuria first occurred.

3 AER levels at baseline independently predicted microalbuminuria (adjusted odds ratio [aOR], 1.83) and macroalbuminuria (aOR, 1.82).

4 Baseline NAG excretion independently predicted macroalbuminuria (aOR, 2.26) and microalbuminuria (aOR, 1.86).

5 Measuring AER and NAG early in the natural history of T1D may help to predict diabetic nephropathy.

Kern EF, Erhard P, Sun W et al (2010) Early urinary markers of diabetic kidney disease: a nested case-control study from the Diabetes Control and Complications Trial (DCCT). *Am J Kidney Dis* **55**: 824–34

"Measuring albumin excretion rate and N-acetyl-beta-D-glucosaminidase early in T1D may help to predict diabetic nephropathy."