Cases in primary care laboratory medicine

Monitoring renal function in hypertension

Una Martin, Jamie J Coleman

Several classes of antihypertensive drugs can cause a fall in glomerular filtration rate and a rise in serum potassium and creatinine concentrations. Appropriate monitoring during treatment of hypertension allows potentially serious underlying conditions to be identified and adverse events avoided.

This is the sixth article in this series

Department of Clinical Pharmacology, Division of Medical Sciences, University of Birmingham, Birmingham B15 2TH
Una Martin
senior lecturer in clinical pharmacology
Jamie J Coleman
specialist registrar in clinical pharmacology

Correspondence to:
U Martin
u.martin@bham.ac.uk
Series coordinator:
W S A Smellie

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We present two typical cases seen in a hospital hypertension clinic that illustrate the role of measurement of electrolytes and renal function in patients treated with angiotensin inhibitors (angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists) or potassium sparing diuretics. Both cases highlight the need to identify patients at increased risk of developing difficulties when taking such antihypertensive drugs and the need to target increased monitoring in at-risk patients.

Case 1

A 64 year old woman was referred to a hypertension clinic with a blood pressure of 180/110 mm Hg. Her biochemical profile was normal (serum creatinine concentration 102 $\mu\text{mol/l}$, urea 6.4 mmol/l, potassium 4.2 mmol/l, sodium 139 mmol/l). Treatment started with amlodipine 5 mg, and when she was reviewed, six weeks later, her blood pressure was 165/95 mm Hg. Perindopril 4 mg was added, and one week later her blood pressure was 144/70 mm Hg. However, her renal function showed some deterioration, with slight rises in serum creatinine concentration (110 $\mu\text{mol/l}$) and urea concentration (9.3 mmol/l). A month later the patient's blood pressure control remained good (140/70 mm Hg), but there was further deterioration in renal function (creatinine of 143 $\mu\text{mol/l}$, urea 10.4 mmol/l). A further month later, she was normotensive (139/71 mm Hg) with no further change in renal function (creatinine 143 $\mu\text{mol/l}$, urea 11 mmol/l).

In view of the deterioration in her renal function, she was investigated with a renal ultrasound scan followed by enhanced renal magnetic resonance angiogram. A short tight stenosis of the left renal artery was diagnosed. A nuclear medicine renal scan showed that the left kidney was contributing 15% of overall function, so angioplasty of the left renal artery was performed. After the procedure, the patient's blood pressure decreased further and stabilised at 138/83 mm Hg, and her treatment was reduced to amlodipine monotherapy.

Summary points

Monitoring of renal function and electrolytes before and during treatment of hypertension may provide an alert to underlying problems and help to prevent serious adverse effects

Early changes in biochemical parameters may be important and indicate the need for more frequent monitoring

The evidence base for the effectiveness of monitoring strategies is still limited

Case 2

A 72 year old obese woman with type 2 diabetes was referred with hypertension. She was taking lisinopril 10 mg, felodipine 5 mg, and bendroflumethiazide 2.5 mg. Her blood pressure in the clinic was 170/100 mm Hg, and her mean ambulatory daytime blood pressure was 168/74 mm Hg. Other antihypertensive drugs were added sequentially, but the patient developed unacceptable side effects—including nasal stuffiness and nosebleed with doxazosin, nausea with moxonidine, and bronchospasm with atenolol. Spironolactone 12.5 mg once daily was prescribed. The patient's blood pressure was 190/100 mm Hg, and blood biochemistry showed a serum potassium concentration of 4.0 mmol/l, creatinine 123 $\mu\text{mol/l}$, sodium 137 mmol/l, and urea 7.7 mmol/l.

When she was reviewed a week later, her blood pressure was unchanged, but her serum potassium was now 4.9 mmol/l, sodium 139 mmol/l, creatinine 129 $\mu\text{mol/l}$, and urea 8.3 mmol/l. Her blood pressure improved to 150/86 mm Hg over the next six weeks, during which time she was regularly reviewed. She had weekly renal function tests, and her serum potassium concentration increased progressively to a peak of 6.5 mmol/l, with an associated deterioration in serum creatinine to 143 $\mu\text{mol/l}$. Spironolactone and lisinopril treatments were stopped. Over the next few weeks the

patient's serum potassium gradually returned to the normal range (4.6 mmol/l) with a serum creatinine concentration of 124 µmol/l. Her blood biochemistry remained stable on reintroduction of the ACE inhibitor, but blood pressure control remained poor.

Discussion

The two cases show pitfalls in the management of hypertension and the potential for serious problems to be missed if appropriate monitoring of electrolytes and renal function is not observed in patients taking angiotensin inhibitors or potassium sparing diuretics.

Case 1

The first patient had considerable unilateral renal artery stenosis, which was suspected only when her renal function deteriorated after introduction of an ACE inhibitor. Renovascular disease should be suspected in patients with hypertension who have more than one additional cardiac risk factor or evidence of pre-existing vascular disease. In particular, patients with reduced or absent peripheral pulses are at high risk of renal artery stenosis (present in up to half of patients with extra-renal atherosclerosis¹) and may have an audible abdominal renal bruit with impaired renal function. Such patients should be evaluated for renal artery stenosis before starting an angiotensin inhibitor.

Renovascular disease is also suggested by a rise in previously normal serum creatinine concentration of $\geq 30\%$ after starting treatment with an angiotensin inhibitor. All hypertensive patients to be given such drugs should therefore have their renal function measured before and after one week of treatment. Patients at high risk of renal artery stenosis or renal impairment should have a further measurement within the next month.

Case 2

The second patient was unable to tolerate several second line antihypertensives, and a small dose of spironolactone was started. Despite an improvement in her blood pressure, this drug caused an unacceptable rise in serum potassium and was discontinued. Low dose spironolactone (12.5-25 mg) is increasingly used for patients with treatment resistant hypertension or in patients who do not tolerate standard drug regimens. These patients will often be normokalaemic, and the risk of hyperkalaemia with spironolactone is increased particularly in patients also taking an angiotensin inhibitor.

Electrolytes should be monitored to avoid serious hyperkalaemia. The guidelines for hypertension are the same as those for heart failure. Serum potassium and creatinine concentrations should be checked after five to seven days of low dose spironolactone (12.5-25 mg) and then repeated weekly until the potassium levels are stable, with dose titration to 25 mg spironolactone if necessary. A progressive rise in serum potassium or a single value of >6 mmol/l means that spironolactone should be stopped. Once the potassium concentration is stable and the blood pressure response has levelled off, electrolytes should be checked on a regular basis, and immediately if the patient becomes systemically unwell for any reason (see below).

Guidance on monitoring hypertensive patients receiving angiotensin inhibitors

How often should renal function be monitored?

- Before starting treatment
- One week after starting treatment and at any subsequent dose increase
- At 4 and 10 days after starting treatment or increasing dose in patients at high risk of developing hyperkalaemia or deteriorating renal function (such as those with peripheral vascular disease, diabetes, pre-existing renal impairment, increasing age)

When to consider seeking further advice

- Patient has renal impairment (serum creatinine concentration >200 µmol/l or glomerular filtration rate <30 ml/min) or confirmed or suspected renovascular disease before starting treatment
- Substantial rise in creatinine concentration ($\geq 30\%$) with large fall in blood pressure after starting treatment (may suggest renovascular disease that should be investigated)

Questions and answers: learning points

The questions and answers shown in the boxes summarise the key recommendations from the sixth review in best practice in primary care pathology published in the *Journal of Clinical Pathology*.²

Angiotensin inhibitors

Treatment of hypertension in patients with normal renal function does not generally cause renal dysfunction. It is not uncommon for serum creatinine concentrations to rise as blood pressure is lowered in patients with chronic renal insufficiency.³ Small (20-30%) and non-progressive rises in concentration usually indicate that intraglomerular pressure has been successfully reduced and are not an indication to decrease or stop the antihypertensive drug.⁴ An angiotensin inhibitor (ACE inhibitor or angiotensin II receptor antagonist) should be withdrawn only if the rise in creatinine exceeds 30% above baseline within the first two months of drug treatment or if hyperkalaemia (>6 mmol/l) develops. Conditions in which the use of angiotensin inhibitors may cause an exaggerated or progressive decline in renal function include bilateral renovascular disease or stenosis in the artery of a solitary functioning kidney.

Atheromatous renal artery stenosis is common, being present in 15-30% of otherwise unselected patients with coronary artery, cerebrovascular, or peripheral vascular disease. It often develops in patients with longstanding essential hypertension and should be considered in patients with extensive atherosclerotic cardiovascular disease, particularly those who smoke. Many patients will also have substantial parenchymal renal damage contributing to the hypertension. Although treatment with an angiotensin inhibitor may reduce the glomerular filtration rate in the affected kidney in unilateral renal artery stenosis, the serum creatinine concentration may not rise if the other kidney has good function. However, such treatment in bilateral renal artery stenosis normally produces a rapid, large rise in creatinine concentration from a normal or slightly elevated baseline. Another

clinical pointer to renal artery stenosis is sudden worsening of previously well controlled blood pressure in a patient known to have vascular disease.

Initial investigation is with ultrasound which may show renal asymmetry. Duplex scanning of the renal artery may have a role, but it is dependent on operator skill and is often impossible in obese subjects. The increasing refinement and availability of computed tomography and magnetic resonance angiography make definitive investigation simpler and safer than traditional angiography.⁵

Studies of revascularisation of atheromatous renal artery stenosis show relatively minor improvements in blood pressure, in contrast to the good results from revascularisation for fibromuscular hyperplasia (which accounts for 10% of renal artery stenosis and is commoner in younger female patients⁶). The largest ever randomised trial of intervention in renal artery stenosis is currently under way in Britain (www.astral.bham.ac.uk) and may provide evidence on the benefits of intervention on both hypertension control and renal function.

Diuretics

Spirolactone is a potassium sparing diuretic that blocks the interaction of aldosterone with the aldosterone receptor. The RALES study showed that low dose spironolactone improved outcome in patients with severe congestive heart failure.⁷ Based on this and other studies, guidelines have been produced for the use of spironolactone in heart failure.⁸ Recent British hypertension guidelines also recommend a role for spironolactone in resistant hypertension.⁹ The guidelines developed for use of spironolactone in

Useful websites

- Lab Tests Online (UK) (www.labtestsonline.org)—a comprehensive guide to laboratory tests and their use for patients
- Cochrane Library (www.nelh.nhs.uk/cochrane.asp)—information and systematic reviews on evidence based medicine. The Cochrane Collaboration is beginning reviews on laboratory diagnostic testing
- *Journal of Clinical Pathology* (www.jclinpath.com)—subscription website containing electronic access to the *Journal of Clinical Pathology*, with full content of the questions and answers examined in this article
- *Clinical Evidence* (www.clinicalevidence.com)—summaries of current evidence based management guidelines
- PRODIGY (www.prodigy.nhs.uk)—clinical decision making guidelines principally for general practitioners
- Joint Renal Association, Royal College Specialty Committee on Renal Disease. *Guidelines document. Chronic kidney disease in adults: UK guidelines for identification, management and referral.* www.renal.org/CKDguide/full/UKCKDfull.pdf

heart failure and hypertension are similar, as regular monitoring applies to both.² Eplerenone is an alternative aldosterone receptor blocker that has fewer hormonal side effects, but it is not currently licensed for treating hypertension in the United Kingdom.

Patients at greatest risk of hyperkalaemia with spironolactone treatment include those who are elderly, diabetic, or have impaired renal function in whom a deficit in the excretion of renal potassium may already exist.¹⁰ Aldosterone production is decreased in patients receiving drugs that block the production or action of renin (β blockers) and angiotensin II (ACE inhibitors and angiotensin II receptor antagonists). Prostanoids facilitate renin release so non-steroidal anti-inflammatory drugs and related drugs suppress renin release. All of these agents will increase the risk of hyperkalaemia in patients taking spironolactone.¹¹ Patients should also follow a low potassium diet with specific counselling against the use of salt substitutes and some herbal remedies that contain potassium. Spironolactone should be stopped temporarily if diarrhoea or vomiting occurs.⁸ Thiazide diuretics may be continued to reduce the risk of hyperkalaemia, with substitution of a loop diuretic in patients with severe renal insufficiency.

If a potassium sparing diuretic is added to an angiotensin inhibitor particularly close monitoring is required. The incidence of serious hyperkalaemia (>6 mmol/l) in the RALES study was only 2%, although the average serum creatinine concentration of study participants was 102 μ mol/l and the spironolactone dose did not exceed 25 mg/day.⁷ Subsequent reports have described a higher frequency of hyperkalaemia in practice,¹² but these included patients with more severe renal function taking higher doses of spironolactone and more patients also taking potassium supplements or other drugs known to impair renal potassium excretion.

Angiotensin inhibitors are effective treatment in hypertension and are recommended as first line drugs in many patients.^{9 13} Addition of spironolactone is

Guidance on monitoring hypertensive patients receiving diuretics

How often should electrolytes or renal function be measured?

Thiazide or loop diuretics

- Within 4-6 weeks of starting low dose treatment
- Thereafter, every 6-12 months
- Whenever a patient's clinical condition changes or a potentially interacting drug is added to the treatment

Spirolactone or potassium sparing diuretics

- Before starting treatment (it should not be started if serum potassium concentration >5.0 mmol/l)
- After 5-7 days, with dose titration if required
- Every 5-7 days until potassium concentration is stable
- Thereafter, at regular intervals during chronic treatment, from 1-2 times a year up to every 4-8 weeks depending on risk factors (elderly, renal or cardiac dysfunction)

When to consider seeking further advice

- If potassium rises to >6.0 mmol/l, spironolactone or potassium sparing diuretics should be stopped and specialist advice sought
- Concomitant use of potassium sparing diuretics and angiotensin inhibitors should normally be reserved for practitioners experienced in such combinations and with increased monitoring as for high risk patients (see above)

potentially useful for patients with poor blood pressure control who are taking three or more drugs. Using the guidelines outlined in this article and restricting the use of spironolactone to 25 mg, we have found the incidence of serious hyperkalaemia and substantial renal dysfunction to be low. By careful monitoring, however, we have also identified occasional serious cases of hyperkalaemia and stopped treatment before adverse events occurred.

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Corrections and clarifications

Short cuts: What's new in the other general journals

In the "Redistributing wealth is good for health" item by Alison Tonks (*BMJ* 2006;333:643-4, 23 Sep), we omitted a vital dot in the "doi" (that's direct object identifier for those who're interested). This prevented people from linking to the original *Lancet* article or searching successfully for it. The correct doi is 10.1016/S0140-6736(06)69341-0.

Totally transforming Auchendreich

A currency conversion went awry in this Soundings piece by Colin Douglas (*BMJ* 2006;333:609, 16 Sep). In the third paragraph, the consultancy cost of £30m should have been converted to €44.7m and \$56.7m.

Sudanese health minister's advocacy of condoms sparks protest

In this article by Peter Moszynski (*BMJ* 2006;332:1233), we wrongly said that Sudan's health minister, Dr Tabitha Sokaya (who was appointed to the position in September 2005), was "the first woman to hold the post and the first Christian." In fact, we should have said "the first Christian woman to hold the post."

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Kieran Walsh *clinical editor, BMJ Learning*
(bmjlearning@bmjgroup.com)