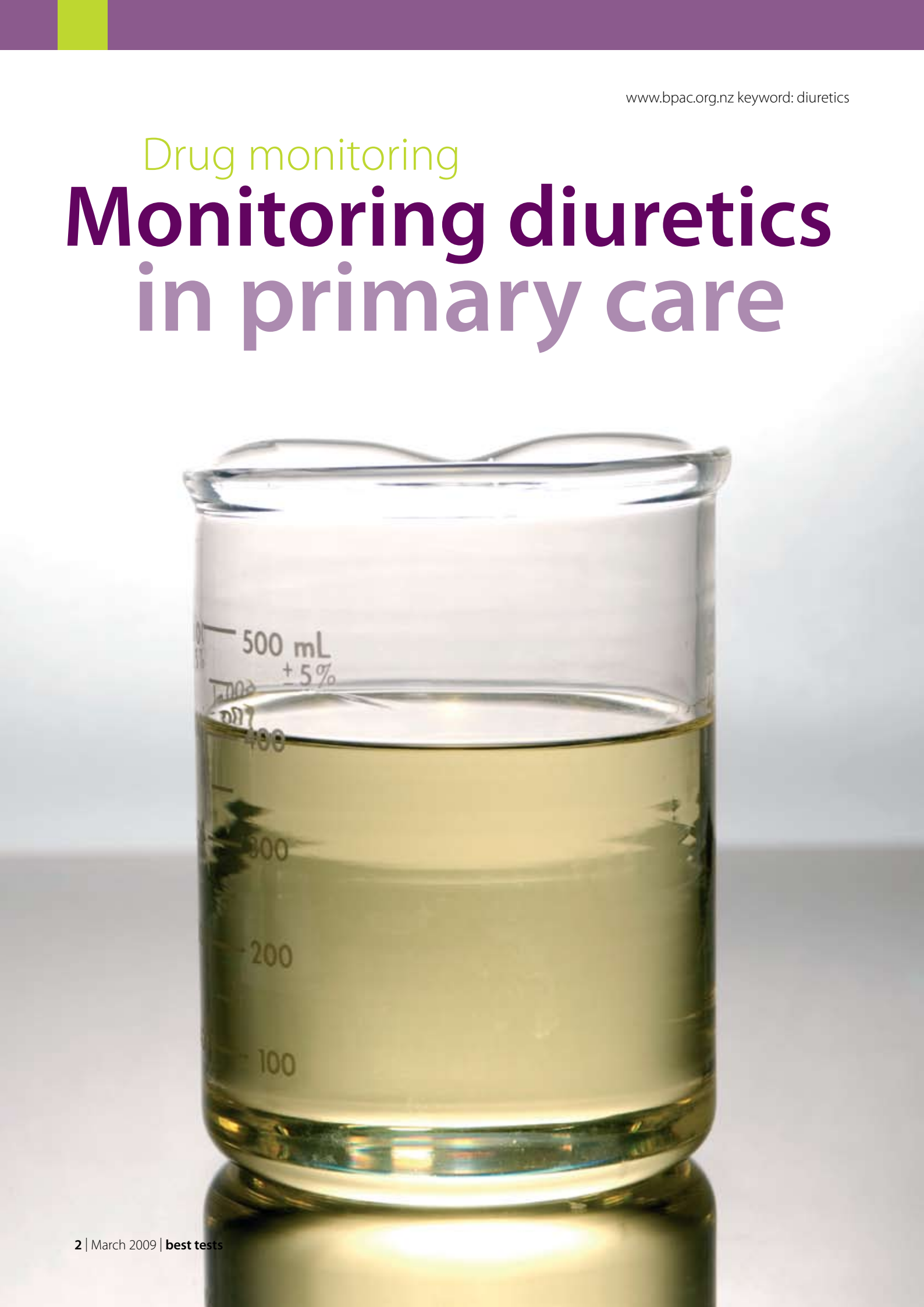
Drug monitoring

Monitoring diuretics in primary care



Why do we monitor patients taking diuretics and what do we monitor?

Monitoring a person on diuretics is necessary to assess response to treatment and to prevent adverse events, particularly electrolyte imbalances and decline in renal function (see Tables 1 and 2).

People with hypertension should have their blood pressure measured every six months and more often if uncontrolled or unstable. People with heart failure should be assessed at least six monthly and more often if clinical condition or medication is changed.

The following is assessed:[1]

- clinical assessment of functional status (e.g. using the NYHA classification to grade severity of functional impairment, see box 2 at end of article)
- fluid status (e.g. body weight, JVP, peripheral oedema, postural hypotension)
- cardiac rhythm (ECG may be required if arrhythmia is suspected), heart sounds, chest crepitations
- cognitive and nutritional status

Box 1: Patients at higher risk of adverse effects:[2]

- Those with existing renal dysfunction (e.g. stage 3 or above chronic renal disease – GFR = 30–59 mL/min/1.73m^2)
- Those aged 60 years or over
- Those receiving combination therapy (e.g. ACE inhibitors and diuretics or potassium sparing drugs)
- Those with concomitant medical conditions such as peripheral vascular disease, diabetes

When do we monitor?

The frequency of monitoring depends on the clinical condition of the patient and which diuretic they are taking.

See Tables 1 and 2 for diuretic monitoring advice

Patients with heart failure require closer monitoring than those with hypertension

Patients with heart failure require more frequent monitoring than those with hypertension because they are more likely to be taking multiple medicines and their clinical condition is often less stable.

People with heart failure should have their electrolytes and creatinine assessed before initiation of diuretics and then at one week. Creatinine and electrolytes can be monitored annually in lower risk patients but up to every three to six months in higher risk patients (see box 1). Additional monitoring may be required after dose increases, if interacting drugs (Table 3) are added and during illness.

People with hypertension taking diuretics should have their electrolytes assessed within four to six weeks of initiating therapy and thereafter can be assessed every six to twelve months unless their clinical condition changes or a potentially interacting drug is added (Table 3).

Spironolactone can cause hyperkalaemia and requires close monitoring initially

Spironolactone carries the risk of hyperkalaemia which is asymptomatic and potentially hazardous.[2] Those at greatest risk of hyperkalaemia are elderly people, people with diabetes, and people who have impaired renal function. These people may already have reduced renal excretion of potassium.

Drugs taken concurrently with spironolactone may also increase the risk of hyperkalaemia. These include NSAIDs, ACE inhibitors and cyclosporin (see Table 3). Patients should be advised to avoid use of over-the-counter NSAIDs and herbal products that contain potassium and advised to avoid foods rich in potassium such as bananas, orange juice and melons and to avoid use of salt substitutes or other products that contain potassium.[3, 4]

Table 1: Recommended monitoring for diuretics in hypertension[2, 5]

Thiazide or loop diuretics in hypertension			
Monitor	**Frequency**	**What to look for**	**What to do**
Electrolytes	▪ Within 4–6 weeks of starting treatment ▪ Thereafter, every 6–12 months. ▪ If clinical condition changes or a potentially interacting drug is added (Table 3)	Potassium < 3 mmol/L (or < 4 mmol/L in high risk patients)	Review diuretic therapy Increase intake of potassium e.g., eat potassium rich food such as bananas, oranges, melons or consider potassium supplementation Consider elevated aldosterone (primary and secondary)
		Serum creatinine rises >20% or eGFR falls >15%	Re-measure within 2 weeks, if renal function continuing to worsen specialist advice may be required

Potassium-sparing diuretics in hypertension (e.g. amiloride)			
Monitor	**Frequency**	**What to look for**	**What to do**
Electrolytes	▪ Baseline (should not be initiated if potassium > 5 mmol/L) ▪ After 5–7 days with dose titration if required ▪ Every 5–7 days until potassium values are stable ▪ Thereafter, every 6–12 months for low risk patients ▪ High risk patients (older people, renal or cardiac dysfunction), every 4–8 weeks	Potassium > 6 mmol/L or a significantly rising trend	Stop diuretic and seek specialist advice

Close attention to medication regimens, particularly for patients with heart failure, is required in situations where blood volume changes or electrolyte disturbances occur

One example is vomiting and diarrhoea due to gastroenteritis or food poisoning. In this situation,

- Blood volume is depleted, impairing renal function
- Potassium level can be low because of diarrhoea or high because of renal failure from volume depletion. Changes in potassium status can be aggravated by diuretics, ACE-inhibitors or spironolactone
- Digoxin levels will increase because of failed renal excretion and hypokalaemia can predispose patients to digoxin toxicity

A simple management strategy is to withhold medications with serial assessments including both volume status (weight, level of hydration) and blood results. This is particularly important for people with heart failure.

Table 2: Recommended monitoring for diuretics in heart failure[2, 5]

Thiazide or loop diuretics in heart failure			
Monitor	**Frequency**	**What to look for**	**What to do**
Renal function (electrolytes + creatinine)	Baseline then at 1 week after initiation, then: ▪ 1–2 weeks after each dose increase/relevant drug addition (Table 3) in low risk patients ▪ 5–7 days after each dose increase/relevant drug addition (Table 3) in high risk patients (e.g. those receiving spironolactone, or combination therapy, those with existing renal dysfunction) ▪ During illness ▪ Thereafter, every 3–6 months in stable higher-risk patients up to annually in stable lower-risk patients	Potassium < 3 mmol/L (or < 4 mmol/L in high risk patients)	Review diuretic therapy Increase intake of potassium e.g., eat potassium rich food such as bananas, oranges, melons or consider potassium supplementation
		Serum creatinine rises >20% or eGFR falls >15%	Re-measure within 2 weeks, if renal function continuing to worsen specialist advice may be required

Spironolactone in heart failure			
Monitor	**Frequency**	**What to look for**	**What to do**
Renal function (electrolytes + creatinine)	▪ Baseline (should not be initiated if potassium > 5 mmol/L) ▪ After 5–7 days with dose titration if required ▪ Every 5–7 days until potassium values are stable ▪ Thereafter, every 6–12 months for low risk patients ▪ High risk patients (older people, renal or cardiac dysfunction), every 4–8 weeks	Potassium between 5.5 and 5.9 mmol/L or creatinine rises significantly above baseline (but less than 200 µmol/L)	Reduce dose to 25 mg on alternate days, and monitor renal function frequently to ensure it is not worsening
		Potassium > 6 mmol/L or creatinine rises > 200 µmol/L	Stop diuretic and seek specialist advice

Table 3: Drug interactions with diuretics[6, 7]

Interacting drug	Thiazide or loop diuretics	Spironolactone
NSAIDs	NSAIDs cause fluid retention and antagonise the effects of diuretics. The nephrotoxic effect of NSAIDs is exacerbated by diuretics especially if also combined with ACE inhibitors – more frequent monitoring of renal function and blood pressure may be required	NSAIDs antagonise the effects of spironolactone and may increase the risk of hyperkalaemia and renal failure. Concurrent ACE inhibitor use would increase this risk further – avoid combination if possible
Digoxin	Thiazide and loop diuretics can cause hypokalaemia which may predispose patients to digoxin toxicity particularly if other electrolyte abnormalities are present (e.g. calcium, magnesium) – increased monitoring of potassium is recommended if these are used concurrently	Spironolactone may increase the plasma concentration of digoxin and lead to digoxin toxicity but because spironolactone and its metabolite may interfere with the digoxin assay methods, this interaction can be difficult to evaluate. Patients on this combination require close monitoring.
ACE inhibitors and angiotensin II receptor antagonists	First dose hypotension may occur, especially with high initial doses of diuretic Diuretics can potentiate ACE inhibitor-induced acute renal failure. This risk is further increased by concurrent use of NSAIDs – increased monitoring is warranted	Concurrent use increases the risk of severe hyperkalaemia particularly if renal impairment is present – regular monitoring of renal function and electrolytes is indicated. The dose of spironolactone is best kept below 25 mg daily.
Lithium	Thiazide and loop diuretics increase lithium levels. This combination should only be used when the patient and lithium levels are able to be closely monitored. Patients should be advised to report any signs of toxicity such as lethargy, muscle weakness, or lack of coordination	Lithium clearance may be reduced and toxicity is possible. Lithium levels and the patients clinical status should be monitored closely
Cyclosporin	Nephrotoxicity has been reported and there may be an increased risk of gout – monitor serum uric acid and renal function if these agents are to be used concurrently	Concurrent use may result in hyperkalaemia – monitor potassium levels

Thiazide and loop diuretics can cause hyponatraemia and hypokalaemia

Thiazide and loop diuretics both cause hyponatraemia and hypokalaemia, however thiazide diuretics are more often associated with hyponatraemia. Hypokalaemia may increase the risk of arrhythmias and is a particular problem for people also taking digoxin due to the increased risk of toxicity.[1]

Assess electrolytes and renal function in patients whose clinical condition changes

Hyponatraemia can occur even after prolonged treatment and more commonly occurs in elderly people. Lethargy, dizziness or vomiting may be a sign of hyponatraemia and it is recommended that any patient presenting with these symptoms should have their electrolytes and renal function measured.[2]

Note: sodium levels slightly below the reference range can occur in the absence of symptoms. It is more important to look for changes in sodium levels and symptoms rather than isolated measurements.

Other drugs may increase the risk of adverse effects

Additional monitoring may be required when other drugs are added to current diuretic therapy. Other medicines that effect renal function or electrolyte status may increase the risk of adverse events occurring. Diuretic drug interactions are described in Table 3.

Box 2: NYHA status: Severity based on symptoms and physical activity

Class I: No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnoea.

Class II: Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, or dyspnoea (symptomatically 'mild' heart failure).

Class III: Marked limitation of physical activity. Although comfortable at rest, less than ordinary physical activity results in fatigue, palpitation, or dyspnoea (symptomatically 'moderate' heart failure).

Class IV: Inability to carry out any physical activity without discomfort. Symptoms of congestive cardiac failure are present even at rest. With any physical activity, increased discomfort is experienced (symptomatically 'severe' heart failure).

References:

1. Clinical Knowledge Summaries. Heart failure. Available from: http://cks.library.nhs.uk/heart_failure (Accessed February 2009).
2. Smellie WSA, Forth J, Coleman JJ, et al. Best practice in primary care pathology: review 6. J Clin Pathol 2007; 60: 225-234.
3. Palmer BF. Managing hyperkalaemia caused by inhibitors of the renin-angiotensin-aldosterone system. N Engl J Med 2004; 351: 585-592.
4. Martin U, Coleman JJ. Monitoring renal function in hypertension. BMJ 2006; 333: 896-899.
5. Suggestions for drug monitoring in adults in primary care. Available from: www.nelm.nhs.uk (accessed February 2009).
6. Baxter K (ed). Stockley's Drug Interactions. [online] London: Pharmaceutical Press. http://medicinescomplete.com (Accessed February 2009).
7. BNF 56. British National Formulary 56th Ed. London: British Medical Association and the Royal Pharmaceutical Society of Great Britain; September 2008.