Correct interpretation of biochemical test results will help pharmacists make rational medicines decisions

In our continuing series that aims to refresh our basic pharmacy skills Daniel Greer reminds us of the frequently requested biochemical tests, such as 'U and Es'. Understanding how these fundamental electrolytes and urea are kept in balance and the effects of altering the balance is particularly important for pharmacists when reviewing patients who are not handling their medicines well or who are suffering symptoms arising from a potential iatrogenic cause

This article will the look most common biochemical tests requested — those for urea and electrolytes — often referred to as 'U&Es'.

Treat the patient not the number

When a test result is sent out from the laboratory a reference range is quoted for each test (see Table 1 for examples) — and this may vary between laboratories. The reference range is based on a sample of healthy population, and is normally the mean +/- 2 standard deviations, which includes 95% of the population. This does mean that 5% of the healthy population will have values outside the reference range. It is important, therefore, not to use an isolated test value as a sole indicator of disease. Results should always be interpreted in the context of supporting symptoms, co-existing disease and drug therapy, and in many cases with consideration to weight, age, sex and height. Errors in sampling and testing do occur, so it always better to look at trends of results rather than a single test result.

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Urea and electrolytes

A request for urea and electrolytes (U&Es) will result in tests for serum sodium, potassium, urea and creatinine.

Sodium

Sodium is the major extracellular cation, and is responsible for 90% of serum osmolality. In the kidney sodium is filtered by the glomerulus and 95% is re-absorbed in the renal tubules. Normal intake is approximately 150mmol per day, which roughly matches the sodium content of a 1L bag of a 0.9% (145mmol) solution of sodium chloride .

Homeostasis of sodium is closely related to water balance. Homeostasis of sodium and water is controlled by antidiuretic hormone (ADH) and aldosterone.

Hypernatraemia. This can be caused either by water depletion or excess sodium. Clinical symptoms include peripheral and pulmonary oedema. Cerebral dehydration can result in symptoms ranging from thirst to confusion and coma.

The most common cause of hypernatraemia is water depletion, which will occur if there is inadequate intake or excessive loss, such as occurs during fever or diarrhoea. Water loss will normally be compensated for by increased thirst, and therefore, by water intake. However, thirst may not be responded to in those with impaired consciousness, mental function or those unable to drink independently. The very young and old are most often at risk. Excessive water loss may sometimes occur through the kidneys because of diabetes insipidus (iatrogenic causes include lithium and demeclocycline), or by an osmotic diuresis seen in hyperglycaemia.

Excess sodium will be caused by either sodium retention or excess intake. Mineralocorticoid drug therapy, such as hydrocortisone and fludrocortisone, causes sodium retention in the distal tubules of the kidney by stimulation of aldosterone

Table 1. Reference ranges for urea, creatinine and electrolytes

Laboratory test	Reference range
Sodium	135–145 mmol/L
Potassium	3.5–5.0 mmol/L
Urea	3.0–8.0 mmol/L
Creatinine	50–110 micromol/L

Table 2. Possible drug causes of the syndrome of inappropriate antidiuretic hormone secretion

Monoamine oxidase inhibitors
Phenothiazines
Tricyclic antidepressants
Serotonin reuptake inhibitors
Cytotoxics, including cisplatin, cyclophosphamide, melphelan, vinblastine and vincristine
Carbamazepine
Chlorpropamide
Haloperidol
Vasopressin and analogues
Nicotine

receptors. Excess sodium intake can have iatrogenic causes, such as overuse of intravenous sodium chloride, effervescent tablets (soluble KAPAKE tablets, for example, contain 16.9mmol of sodium per tablet).

Hyponatraemia. This can be caused by either an excess of water, or sodium loss. Clinical symptoms are unusual above 120mmol/L, though this does depend somewhat on how rapidly the change in sodium levels has occurred. Sudden hyponatraemia poses a much higher risk of cerebral oedema. Symptoms include nausea, cramps and weakness through to confusion and convulsions.

Excess intake of water can be caused by excess prescribing of intravenous dextrose, sometimes seen in surgical patients requiring intravenous fluids. Retention of fluid causing hyponatraemia can be seen in patients with congestive cardiac failure or cirrhosis with ascites because of activation of the renin and angiotensin system. In these cases although serum sodium is low there is an underlying increase in total body sodium.

An important drug-related cause of hyponatraemia is the syndrome of inappropriate antidiuretic hormone secretion (SIADH). This is the commonest cause of low sodium in hospital. The action of ADH increases reabsorption of water in the collecting ducts of the kidney. A low plasma osmolality is seen together with a high urine osmolality — an inappropriately concentrated urine. Causes include malignancy, CNS disorders, such as stroke, subarachnoid haemorrhage or head injury, chest diseases like tuberculosis or pneumonia, and drugs. Table 2 contains some known drug causes.

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Hyponatraemia caused by sodium loss can be drug related. Diuretics, in particular thiazides and potassium sparing diuretics, can cause hyponatraemia. This can be a particular problem in the treatment of cirrhotic ascites, where dilutional hyponatraemia can be worsened by the diuretic spironolactone, which would normally be first-line therapy. Addison's disease will cause hyponatraemia by the same mechanism as potassium sparing diuretics, the lack of adrenal hormone aldosterone resulting in a decrease in sodium/potassium exchange in the distal tubules.

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Sodium loss is also seen when there are gastrointestinal fluid losses, for example in vomiting, diarrhoea and fistulae.

Potassium

Potassium is a predominantly intracellular cation, 98% is found in intracellular fluid. Normal intake is around 1–2mmol/kg/day. Potassium is essential for muscle and myocardial function, and derangements will affect these functions. Homeostasis of potassium is controlled by renal excretion and cellular shift — the movement of potassium between and intracellular and extracellular spaces.

Hyperkalaemia

Hyperkalaemia can be caused by excess potassium intake, decreased renal excretion, or extracellular shift, though it is rare for excess potassium to result in hyperkalaemia without impairment of renal excretion. Hyperkalaemia can result in potentially fatal arrhythmias.

A pseudohyperkalaemia can result if there is haemolysis of the blood sample — this is often reported on the laboratory result with no potassium result given. A false high reading by the same mechanism can also occur from excessive fist clenching during blood sampling.

Severe tissue damage, such as haemolysis, burns, crush injury and tumour lysis will result in potassium moving into the extracellular fluid. Acidosis also cause the release of potassium from cells. Excess potassium often has an iatrogenic cause, where oral or intravenous potassium supplements are not stopped after the cause of depletion has been resolved.

There are several drug causes of hyperkalaemia, all causing decreased excretion of potassium through the sodium/potassium exchange mechanism in the distal renal tubules. ACE inhibitors and spironolactone reduce aldosterone activity, which decreases sodium/potassium exchange, while amiloride blocks sodium channels and prevents sodium being

Most drug dosage recommendations are based on Cockcroft and Gault estimations, with different recommendations for doses according to whether renal impairment is mild (20–50ml/min), moderate (10–20ml/ min) or severe (<10ml/min).

absorbed in exchange for potassium excretion. Combined use of ACE inhibitors and potassium sparing diuretics will increase the risk of hyperkalaemia. A deficiency of aldosterone in Addison's disease will also cause decreased potassium excretion.

Hypokalaemia

Hypokalemia can result from excess potassium loss, intracellular shift or increased renal excretion.

Potassium loss can occur through gastrointestinal losses. Examples include vomiting, nasogastric suction, diarrhoea, and fistulae.

Intracellular shift of potassium can occur with certain drug therapies. Insulin and beta-adrenergic agonists cause an intracellular shift of potassium, and these effects are used therapeutically to treat hyperkalaemia. Hypokalemia and hypophosphataemia occurs by the same mechanism in refeeding syndrome, where the re-introduction of carbohydrate in malnourished patients results in increased levels of insulin.

Renal loss of potassium is a common side-effect of all non potassium-sparing diuretics, because of the increased presentation of sodium to the distal renal tubules. Renal loss also occurs in hyperaldosteronism. The mineralocorticoid effects of administered steroids, liquorice and carbenoxolone also produce this effect.

Table 3. Cockcroft and Gault equation

$$\text{CrCl (ml/min)} = \frac{(140\text{-age}) \times \text{Wt (kg)} \times F}{\text{Serum Cr (micromol/l)}}$$

F(female) = 1.03
F(male) = 1.23

Table 4. MDRD and classification of kidney disease

Stage	Description	eGFR
1	Normal GFR	>90mL/min/1.73m^2 with other evidence of chronic kidney damage
2	Mild impairment	60–89mL/min/1.73m^2 with other evidence of chronic kidney damage
3	Moderate impairment	30–59mL/min/1.73m^2
4	Severe impairment	15–29mL/min/1.73m^2
5	Established renal failure	<15mL/min/1.73m^2 or on dialysis

GFR (mL/min/1.73m^2) = 175 x [serum creatinine (mmol/L)/88.4]$^{-1.154}$ x age (years)$^{-0.203}$ x 0.742 if female and x 1.21 if African Caribbean or African American

To convert to actual GFR:

$$\text{Actual GFR} = \text{eGFR} \times \frac{\text{Actual body surface area}}{1.73}$$

Renal function tests — urea and creatinine

Urea

Urea is often grouped with creatinine as an indicator of renal function, but there are many other factors that can affect urea levels, which make it a less useful test of renal function. Levels of production are increased by a high protein diet, increased catabolism (starvation), tissue damage or sepsis. An acutely raised urea level can be a useful sign in those who present with a suspected upper gastrointestinal bleed, because the digestion of blood results in high urea levels.

Urea is an osmotic diuretic, and is reabsorbed in dehydrated states, so can be used with the clinical picture as an indicator of fluid status. A serum creatinine ratio of <15 supports a picture of dehydration, while a ratio of >25 supports fluid overload.

Creatinine

Creatinine is a product of muscle breakdown, and is excreted almost exclusively by glomerular filtration. The relatively constant rate of production in individual patients together with almost exclusive glomerular filtration, means that creatinine clearance should reflect glomerular filtration rate (GFR). GFR is a measure of the efficiency with which the kidneys remove waste products, including drugs, and is therefore an important tool for pharmacists when advising on drug dosing adjustment in patients with renal impairment.

Estimating creatinine clearance and GFR

Creatinine clearance can be measured by 24-hour urine collection, but this method is often inaccurate because of the difficulties of collection and the need for maximal patient co-operation. The most common method of estimating GFR is to use a prediction equation that adjusts for differences in creatinine production rates between patients of different age, sex and weight.

Cockcroft and Gault equation

Historically, the Cockcroft and Gault formula is the most well established formula for estimating creatinine clearance (Table 3). Most drug dosage recommendations are

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based on Cockcroft and Gault estimations, with different recommendations for doses according to whether renal impairment is mild (20–50ml/min), moderate (10–20ml/min) or severe (<10ml/min).

There are limitations to this equation. Calculations are based on steady state so are less useful in acute renal failure. The equation is inaccurate at extremes of body weight (some suggest using ideal body weight); has only been validated in caucasians; and tends to overestimate GFR in more severe impairment, where tubular secretion of creatinine can contribute significantly to creatinine clearance.

MDRD equation and reclassification of kidney disease

In the UK in 2003 the classification of kidney disease changed, and with it a new prediction formula was introduced (see Table 4). The modification of diet in renal disease (MDRD) equation differs from the Cockcroft and Gault in that it only requires the patient's age and creatinine and not body weight. It gives a GFR estimate normalised for a body surface area of 1.73m^2. An online calculator for the MDRD can be found at http://www.renal.org/eGFRcalc/GFR.pl.

In line with the *National Service Framework for Renal Services*,[1] most laboratories are now reporting eGFR values in parallel with serum creatinine values. The MDRD equation is inaccurate at extremes of body weight and tends to underestimate GFR, particularly in those with normal renal function.

Which equation to use?

Pharmacists and other health care professional should be aware that MDRD eGFR estimates are not the same as Cockcroft and Gault equations. Current advice is that for adjusting drug doses Cockcroft and Gault should remain the gold standard.[2] If eGFR is used, it should be converted to an actual non-normalised GFR using the patient's body surface area (Table 4).

Pharmacists should also take care which classification of kidney disease is being referred to when the terms mild, moderate and severe renal impairment are used. Most doses quoted in standard reference sources are still based on Cockcroft and Gault.

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