Nephrotoxins and drugs in renal insufficiency

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Abstract
The kidneys eliminate most drugs and their metabolites from the body. Inappropriate dosing of drugs in the setting of renal insufficiency is therefore a major hazard for patient safety. Moreover, drugs can be the cause of kidney disease, and nephrotoxicity manifests in a number of ways.

Keywords Chinese herbal nephropathy; nephrotoxicity; pharmacodynamics; pharmacokinetics; sick day rules; tubulointerstitial nephritis

Key points

- Many drugs are cleared from the body by the kidneys, and even drugs that are primarily metabolized by other organs can have active, renally cleared metabolites
- It is essential to consider a patient's kidney function when prescribing drug therapy
- A comprehensive enquiry into past and current drug use, including over-the-counter, herbal or illicit drug use, should be undertaken for anyone presenting with acute or chronic kidney disease
- The manifestations of nephrotoxicity are diverse, ranging from mild and asymptomatic tubular dysfunction to kidney stones and dialysis requiring kidney failure

Introduction

The quote 'All things are poison, and nothing is without poison; the dosage alone makes it so a thing is not a poison', attributed to Paracelsus, is never more true than in patients with impaired kidney function. Incorrect dosing of drugs represents one of the greatest risks to safety in patients with renal insufficiency and has the potential for significant harm. Not reducing the dose or increasing the dosing interval appropriately can lead to the development of adverse, toxic effects. Alternatively, inappropriately reducing the dose to a 'renal dose', especially for antibiotics, risks undertreating the patient. Furthermore, the drugs an individual is prescribed, or that they use for self-treatment, can directly or indirectly result in renal injury, with a variety of manifestations from calculi to transient or permanent reductions in glomerular filtration rate (GFR).

Drug dosing and renal impairment

In general, drugs or their active metabolites that are excreted by the kidney require a dose adjustment in renal impairment. The degree and extent of this depends on a number of factors, for example the degree of renal impairment, whether the patient is receiving renal replacement therapy (RRT), the degree of elimination of the drug and/or its metabolites by the kidney, and pharmacokinetic changes and toxicity related to the drug, especially if the drug has a narrow therapeutic index.

Laboratories report estimated renal function in adults normalized to a body surface area of 1.73 m^2, using either the Chronic Kidney Disease Epidemiology (CKD-EPI) or Modification of Diet in Renal Disease (MDRD) equation. In addition, the Cockcroft and Gault equation can be used to estimate GFR. There is no definitive guidance on which formula to use when dosing drugs; most drug-dosing recommendations are based on estimated GFR (eGFR), and for many drugs this is sufficient. However, for drugs that are considered to have a narrow therapeutic range or of high toxicity, it is recommended to calculate the creatinine clearance using the Cockcroft and Gault equation and the patient's ideal body weight.

Pharmacokinetics and pharmacodynamics

The relationship between a drug and the body can be described in terms of pharmacokinetics, i.e. the effect the body has on a drug, and pharmacodynamics, i.e. the effect of the drug on the body. When prescribing medications for patients with kidney disease, it is important to understand how kidney disease can affect the pharmacokinetics of drugs, and also how the pharmacodynamics of drugs can be altered in renal impairment.

Pharmacokinetic changes typically observed include reduced absorption of a drug as a result of uraemia, changes in distribution caused by hydration status and altered drug clearance including removal by dialysis. Many drugs that are metabolized by the liver have active metabolites that are excreted via the kidney; kidney disease therefore leads to an accumulation of metabolites, which can result in toxic adverse effects. For example, morphine is metabolized by the liver to morphine-3-glucuronide and morphine-6-glucuronide, which can accumulate in renal insufficiency, resulting in opiate toxicity and respiratory depression.

Renal excretion of drugs depends on three processes: glomerular filtration, renal tubular secretion and reabsorption. As kidney function declines, the amount of drug that is eliminated declines in proportion. This results in an increase in half-life of the drug, which has significance when deciding on the optimal drug-dosing regimen.

Pharmacodynamic changes include increased sensitivity to centrally acting agents, reduced sensitivity to endogenous

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Risk factors for contrast-induced nephropathy (NICE guidance)

- CKD (adults with an eGFR <40 ml/minute/1.73 m^2 are at increased risk)
- Diabetes mellitus, but only with CKD (adults with an eGFR <40 ml/min/1.73 m^2 are at particular risk)
- Heart failure
- Renal transplant
- Age 75 years or over
- Hypovolaemia
- Increasing volume of contrast agent
- Intra-arterial administration of contrast agent

Table 1

hormones (e.g. insulin, vitamin D) and an increased risk of bleeding associated with anticoagulant therapy.

Drug dosing in renal impairment

The aim of prescribing medications to a patient with impaired kidney function is to use doses that will achieve therapeutic levels similar to those seen with normal renal function. There are several approaches to dosing drugs in renal impairment: use the same dose but extend the dosing interval, reduce the dose and keep the same dosing interval, use a combination of these, administer a loading dose if a rapid response is required, or simply start with a low dose and titrate the dose upwards according to the response and/or adverse effects.

Because of the increased half-life of drugs, a loading dose is recommended if a rapid response is required, for example with an antibiotic. If no other drug parameters are affected by renal impairment, this will be the same loading dose used in normal renal function. If any other parameters are, however, affected, the dosage should be altered; for example, the volume of distribution of digoxin is decreased in renal impairment, therefore a reduction in loading dose is needed.

Effects of renal replacement therapy

Different renal replacement modalities, for example continuous veno-venous haemofiltration, haemodialysis or peritoneal dialysis, differentially affect the clearance of a drug. The dialysis prescription (i.e. dialyser surface area, duration of dialysis blood, dialysate flow rate), and drug characteristics such as molecular weight, volume of distribution, lipid solubility and protein binding, also affect clearance by RRT.

Drug dosing in acute kidney injury (AKI)

Drug dosing in AKI is more complicated than in chronic kidney disease (CKD) because of the concomitant dysfunction or failure of other organ systems, fluctuating GFR, changes in hydration status and possible use of RRT. In these critically ill patients, antibiotic therapy is often underdosed in the first 48 hours.

The dosing principles applied in CKD cannot be directly translated to the setting of AKI, but can help to inform dosing decisions. Changes in plasma creatinine concentration, which often lag behind actual changes in GFR and drug clearance, must be taken into account to avoid under- or overdosing patients with AKI. In practical terms, any adjustments to drug dose should be based on clinical judgement and a consideration of what drugs are essential to use in the context of AKI; similarly, when AKI starts to resolve, the doses should be increased accordingly.

Mechanisms of drug toxicity

Drugs may exert their nephrotoxic effects directly or indirectly.

Direct toxic effects

Contrast: ***Iodinated radiocontrast*** – radiocontrast media contain iodine. The antiseptic properties of iodine have been known for centuries, and contact with iodine solutions rapidly kills bacteria. Similarly, mammalian cells suffer cell membrane damage, and the high redox potential of iodine is also thought to interfere with the electron transport chain, resulting in acute tubular necrosis. Additionally, physiochemical properties of iodinated radiocontrast such as viscosity, osmolality and ionic strength can also play a role in nephrotoxicity. In recent years, much effort has gone into modifying these properties to reduce nephrotoxicity. Iso-osmolar contrast agents (e.g. iodixanol) are probably less nephrotoxic and are recommended for at-risk individuals, such as those with diabetes mellitus or heart failure.

However, possibly the greatest contribution to the development of meaningful disturbance in kidney function can be attributed to the clinical context in which the contrast study is being performed. Large observational studies have failed to demonstrate a difference in incidence of AKI in the setting of a liberal or a restricted policy for the administration of contrast. Despite extensive study, the only preventive measures currently recommended by the UK National Institute for Health and Care Excellence (NICE) are volume expansion with either sodium bicarbonate solution or 0.9% sodium chloride, and avoidance of other nephrotoxic medication in individuals deemed to be 'at risk' (Table 1).

Gadolinium – gadolinium-containing contrast agents for magnetic resonance imaging (MRI) studies are not in themselves nephrotoxic. However, concerns regarding their use in patients with renal insufficiency began to emerge after a report of 14 cases of a systemic fibrosing condition (subsequently known as nephrogenic systemic fibrosis) occurring in patients with poor kidney function exposed (usually repeatedly) to gadolinium through radiological investigations. Newer gadolinium-based contrast agents e.g. macrocyclic ionic, macrocyclic non-ionic present a lower risk of nephrogenic systemic fibrosis; therefore renal insufficiency (eGFR <30 ml/minute/1.73 m^2) should no longer be seen as an absolute contraindication to a gadolinium-enhanced MRI scan, but repeated exposure should still be avoided.

Aminoglycosides: widely used and highly effective, aminoglycoside antibiotics (especially gentamicin) are also highly nephrotoxic, with evidence of nephrotoxicity occurring in 10–25% of treatments.[1] A number of different mechanisms of toxicity have been identified, with triggering of tubular epithelial apoptosis and necrosis being the most important. As an extended duration of treatment and split dosing have been shown to be risk factors for nephrotoxicity, once-daily dosing is preferred.

Cisplatin: first licensed in 1978, cisplatin is an efficacious chemotherapeutic agent that continues to be widely used in the treatment of several malignancies including of the head and neck, oesophageal, bladder, testicular, ovarian, uterine, cervical, breast, stomach and lung cancers. Cisplatin induces cross-links between purine bases, thus interfering with DNA synthesis and impairing cell division. All rapidly dividing cells are vulnerable to cisplatin-induced injury so myelosuppression and gastrointestinal toxicity are relatively common complications. However, the most frequently encountered adverse effect of cisplatin treatment is nephrotoxicity.

There are a wide range of manifestations of cisplatin nephrotoxicity. AKI is reported to complicate up to 30% of treatments, and before measures to limit nephrotoxicity were introduced, the incidence of AKI associated with cisplatin treatment was estimated to be almost 100%. Tubular dysfunction manifesting as hypomagnesaemia is the most frequent evidenceof nephrotoxicity, with an estimated prevalence of 40–100%. Other features include distal renal tubular acidosis, a concentrating defect and a Fanconi-like syndrome.

The incidence of AKI can be reduced by prehydration and osmotic diuresis using mannitol, although it is essential to avoid hypovolaemia when inducing an osmotic diuresis.

Crystal nephropathies: several drugs are known to precipitate out of human urine, leading to crystal formation resulting in microtubular obstruction and acute tubular injury. Factors predisposing to crystal nephropathy include the degree of supersaturation of the drug in the urine (which in turn is influenced by volume status), intratubular pH, drug dosage and route of administration (intravenous administration favouring crystal formation). The most common causes of drug-related crystal nephropathy are aciclovir, indinavir, sulfadiazine and methotrexate.

Altered haemodynamics: ***Tolvaptan*** – is a selective vasopressin (V2) receptor antagonist used for the treatment of hyponatraemia and autosomal dominant polycystic kidney disease. Tolvaptan has been shown to lead to a small, reversible fall in GFR, although this effect appears less marked in patients with more advanced CKD (GFR <30 ml/minute/1.73 m^2) (Box 1).

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) – renal blood flow is under the control of a number of factors including prostaglandin E2 (PGE2) and angiotensin II. PGE2 mediates vasodilatation of the afferent renal arteriole, increasing blood flow into the glomerulus to maintain GFR. Angiotensin II mediates vasoconstriction of the efferent renal arteriole (carrying blood away from the glomerulus), constriction of which increases intraglomerular pressure and also acts to maintain GFR. Both these systems contribute to autoregulation of renal blood flow in the kidney. They are particularly important if there is a reduction in circulating blood volume caused by dehydration, or an effective decrease in blood volume caused by redistributed blood flow, as can occur in the setting of septic shock (Box 2).

ACE inhibitors and ARBs inhibit the production of angiotensin II or block its action on vascular smooth muscle cells in the efferent arteriole, thereby leading to a reduction in intraglomerular pressure and a fall in GFR.

Diuretics – are not inherently nephrotoxic. However, they can lead to volume constriction, leading to reduced renal blood flow and consequently reduced GFR. In common with many drugs, they may cause an allergic tubulointerstitial nephritis.

Non-steroidal anti-inflammatory drugs (NSAIDs) – short-term use of NSAIDs invariably results in reduced GFR as a consequence of afferent arteriole vasoconstriction, but this is reversible upon discontinuation of the NSAID. However, prolonged use, as commonly employed for the treatment of rheumatoid arthritis, in the pre-disease-modifying drug era, has long been believed to result in chronic ischaemia and the development of irreversible damage to the renal parenchyma, leading to reduced GFR, hypertension and variable degrees of proteinuria – so-called analgesic nephropathy. Causality has not been established, but the incidence of analgesic nephropathy has fallen in the industrialized world from a peak of 15–20% of cases of end-stage kidney disease in the 1980s to the current level of 1%. This fall in the incidence of analgesic nephropathy appears to mirror the reduced use of NSAIDs as a means of managing many conditions in the era of biologic therapies.

Metformin

Metformin is not nephrotoxic. There is a widespread misconception among medical professionals and patients alike that metformin damages the kidney. This is not true, and mounting evidence suggests the opposite – that among the pleiotropic effects of metformin are renoprotective properties. By convention, metformin is stopped once the glomerular filtration rate falls to <30 ml/minute/1.73 m^2, based on fears of an increased risk of lactic acidosis. Large observational studies have, demonstrated that lactic acidosis occurs with the same frequency in diabetic patients whether or not they are treated with metformin.

Box 1

'Sick day' rules for ACE inhibitors and ARBs

Controversy exists over whether to advise patients prescribed diuretics and ACE inhibitors or ARBs to stop these medications when they become acutely unwell, especially if they experience diarrhoea or vomiting. Although avoiding these medications might theoretically help the kidneys to withstand the physiological stress of volume constriction, there is a paucity of evidence to support the advice. Among other concerns, it has been suggested that providing this advice might reduce concordance with therapy, and there appears to be evidence for this.

Box 2

Sodium glucose co-transporter 2 (SGLT-2) inhibition – SGLT-2 blockade increases sodium and glucose delivery to the cells of the macula densa at the end of the thick ascending loop of Henle. This leads to increased tone in the afferent arteriole, which reduces renal blood flow. This could be the mechanism by which SGLT-2 inhibition affords the renal protection that has been observed in clinical trials.

Indirect toxicity

Rhabdomyolysis: drug-induced rhabdomyolysis is commonly seen, with statins being most frequently implicated drugs (Table 2).[2] Impaired kidney function may also increase the risk of statin-induced rhabdomyolysis. Estimates of the frequency of AKI complicating rhabdomyolysis vary from 15% to 50%. Neuroleptic malignant syndrome is one of the best-described causes of severe drug-induced rhabdomyolysis and AKI. Drugs of abuse, including heroin, methadone and cocaine, are also associated with rhabdomyolysis, both through direct myotoxicity and via the induction of a stuporous state in which long periods of lying down leads to muscle necrosis.

Glucose-6-phosphate dehydrogenase (G6PD) and haemoglobinuria: G6PD deficiency is the most common enzyme deficiency known, with upwards of 400 million people affected worldwide. The gene encoding the G6PD enzyme, is located on the long arm of the X chromosome, thus men are more commonly affected than women. Many drugs that cause oxidative stress can produce intravascular haemolysis in the setting of G6PD deficiency. This can be severe enough to cause haemoglobinuria with tubular injury and microtubular obstruction, similar to the mechanism of injury caused by myoglobin in rhabdomyolysis.

Numerous case reports describe haemolytic crises in individuals with G6PD deficiency complicated by AKI. The clinical picture tends to be an individual (often male) heralding from a region in the world where G6PD deficiency is common and who presents with severe anaemia.

Tubulointerstitial disease: this can be acute or chronic.

Acute tubulointerstitial nephritis – is most often the result of an idiosyncratic, allergic (type 4) reaction. It can occur shortly after initiation of a new medication, on re-exposure to a previously used medicine or secondary to a medication that has been taken without problems for a number of years. Numerous drugs have an appreciable risk of acute tubulointerstitial nephritis, the most common culprits being antibiotics (35%), proton-pump inhibitors (35%) and NSAIDs (20%). Extra-renal manifestations include the classical triad of fever, eosinophilia and rash.[3] Eosinophiluria (eosinophils accounting for >2% of urinary white cells) can also be present.

The mainstay of treatment is to withdraw the offending drug. Corticosteroids (e.g. prednisolone 1 mg/kg body weight to a maximum of 60 mg daily) can accelerate the recovery of kidney function, but there is a paucity of evidence to support this; for 2–3 weeks followed by a tapered withdrawal.

Chronic tubulointerstitial nephritis – numerous drugs can result in chronic tubulointerstitial nephritis leading to progressive loss of kidney function.

Calcineurin inhibitors (ciclosporin, tacrolimus): these immunosuppressants, which prevent T cell activation and proliferation, are widely used in both haemopoietic and solid organ transplantation, as well as in the treatment of other autoimmune conditions. Evidence for their nephrotoxicity is best demonstrated outside the context of kidney transplantation. Calcineurin inhibitors can cause acute reversible reductions in GFR, largely mediated through haemodynamic effects and usually associated with high blood levels of tacrolimus or ciclosporin.

Calcineurin inhibitor nephrotoxicity leads to irreversible injury to the kidneys and represents a significant barrier to the long-term success of renal transplantation. However, the potential nephrotoxicity of calcineurin inhibitors should be balanced against their efficacy in preventing both acute and chronic immunological injury to the kidney transplant. Chronic CNI toxicity is characterized on light microscopy by the presence of 'striped' interstitial fibrosis. This striped appearance is caused by a release of vasoconstrictors, including endothelin, which results in ischaemia, particularly of the medullary rays.

Calcineurin inhibitors also, rarely, cause a thrombotic microangiopathy that can produce acute or chronic reductions in GFR. This is most commonly seen as an idiosyncratic reaction in the early post-transplant period and is suggested by the presence of elevated LDH, falling haemoglobin concentration and falling platelet count with evidence of red cell fragments (schistocytes) on a blood film. Conversion to an alternative calcineurin inhibitor or withdrawal of calcineurin inhibitors is the most commonly employed management strategy.

Lithium: this is among the best-described causes of chronic, drug-induced, tubulointerstitial nephritis. Lithium is a highly effective mood stabilizer and continues to be one of the first-line pharmacological agents offered for the treatment of bipolar affective disorder.

Lithium is freely filtered at the glomerulus and reabsorbed by sodium channels in the tubules. The central triggering event behind the development of the progressive interstitial fibrosis associated with lithium exposure appears to be a disturbance of glycogen synthase kinase 3 (GSK-3) signalling in the principal cells of the collecting duct. Microcyst formation in the cortex and medulla, which can progress to overt cystic disease detectable by ultrasonography and other imaging modalities, is characteristic. In addition to the induction of tubulointerstitial fibrosis, lithium

The 10 most frequently implicated drugs causing rhabdomyolysis

- Simvastatin
- Atorvastatin
- Rosuvastatin
- Ezetimibe
- Gemfibrozil
- Risperidone
- Propofol
- Ciclosporin
- Olanzapine
- Fenofibrate

Table 2

exposure results in nephrogenic diabetes insipidus, usually within 6 weeks of the initiation of treatment.

Management of lithium-associated tubulointerstitial disease typically consists of discontinuation of treatment, but the risks of this must be carefully balanced against the potential adverse effects on the individual's mental health. If withdrawal of lithium or replacement by an alternative agent is not felt to be possible, the use of amiloride to block uptake of lithium via the epithelial sodium channel has been shown in animal models to prevent lithium-induced renal damage. Amiloride (unlicensed indication) can potentially alter plasma levels of lithium, and a period of enhanced monitoring is prudent.

Secondary glomerular disease:

Membranous nephropathy — the drugs classically associated with membranous nephropathy are gold and penicillamine, both of which have been historically used in the treatment of rheumatoid arthritis. NSAIDs have also been associated with this condition.

Focal segmental glomerulosclerosis — bisphosphonates (e.g. pamidronate), sirolimus, interferon-α, lithium and heroin have all been associated with the development of focal segmental glomerulosclerosis, predominantly the collapsing variant.

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis — a link between exposure to a number of drugs and the development of ANCAs directed against myeloperoxidase has long been recognized. In addition, some patients are reported to have also experienced systemic vasculitis with the characteristic renal histological appearances of pauci-immune necrotizing glomerulonephritis. Drugs reportedly associated with ANCA-associated vasculitis include hydralazine, propylthiouracil and carbimazole.

Drug-induced lupus (DIL) — is a well-recognized entity.[4] Exposure to various drugs (Table 3) over an extended period of time results in a loss of self-tolerance and development of autoimmunity. In contrast to idiopathic systemic lupus erythematosus, DIL demonstrates an equal sex distribution and is typically associated with older age at onset. It is also less commonly associated with double-stranded DNA antibodies and renal involvement.

Anti-vascular endothelial growth factor (VEGF) therapy — anti-VEGF therapy has been a significant step forward in the treatment of a number of malignancies including colorectal, breast, ovarian and lung cancers. VEGF and its receptors are expressed in the kidney, predominantly in and on podocytes. VEGF inhibition and VEGF receptor blockade have been linked to a variety of glomerular pathologies, including proliferative glomerulonephritis and the development of hypertension.

Herbal medicines: traditional herbal medicine has been practised widely throughout the world and by many cultures, Chinese and Ayurvedic traditions being among the best known. In recent decades, interest in traditional forms of medicine has become popular in industrialized nations. Individuals also often falsely assume that a herbal remedy is less toxic and less likely to produce adverse effects than allopathic ('Western') medicine. Nephrotoxicity can result from incorrect storage or processing, the intrinsic toxicity of herbs, incorrect dosing, adulteration or contamination, especially by heavy metals, and interactions between herbal medicines and other prescribed or over-the-counter medications.

Aristolochic acids are the main and best described nephrotoxic compounds found in traditional medicinal remedies; others include plant alkaloids, anthraquinones, flavonoids and glycosides.[5] A case-series of rapidly progressive CKD was first described in Belgium in the early 1990s in association with the use of Chinese herbal slimming pills. Aristolochic acid was identified as the causative agent.

Clinical manifestations of herbal nephropathy are diverse, ranging from AKI and rhabdomyolysis to nephrolithiasis and progressive CKD. Aristolochic acid nephropathy is typified by proximal tubular dysfunction (glycosuria, low-molecular-weight proteinuria), hypertension, severe anaemia, metabolic acidosis, small kidneys on kidney ultrasonography and a high risk of urothelial malignancies.

A history of herbal or traditional remedy use should be sought in any patient presenting with unexplained AKI or CKD.

Environmental toxins: *Balkan endemic nephropathy (BEN)* — BEN, a cause of slowly progressive CKD, was first described in the 1950s affecting individuals living, or having spent a substantial portion of their lives, in rural areas located along the tributaries of the Danube river. There is familial clustering of cases but a pattern of Mendelian inheritance is not seen. BEN typically results in slowly progressive CKD, with individuals typically reaching end-stage kidney disease during the fifth or sixth decade of life. The condition is characterized by anaemia and tubular proteinuria. Histologically, the features of BEN are of progressive tubular atrophy with interstitial fibrosis and minimal glomerular change. BEN is strongly associated with urothelial cancers of the upper renal tract (renal pelvis, upper ureter).

Over the years, numerous environmental toxins have been proposed as the cause of BEN, and aristolochic acid exposure was first proposed in 1969 by Ivic. The evidence for this hypothesis has been strengthened by recent studies demonstrating aristolochic acid—DNA adducts in urothelial tumours from patients with BEN and the identification of aristolochic acid contamination of soil and crops from areas affected by BEN. The differing clinical course of BEN and aristolochic acid nephropathy is likely to be the result of a dose effect, with higher exposure over a shorter time frame occurring in individuals consuming Chinese herbal medicines (see above).

Mesoamerican nephropathy — this is an emerging cause of CKD seen predominantly in young, male sugar cane workers and occurring independently of traditional risk factors for CKD. It is estimated that it might have resulted in the deaths of thousands of young and middle-aged men. Environmental exposure to toxins such as heavy metals or agrochemicals has been postulated as a cause, but to date no association has been established. The preferred theory for its aetiology involves recurrent episodes of heat stress caused by strenuous physical exercise in a hot, humid environment. Nonetheless, there is a possibility that dehydration increases the urinary concentration of a yet unidentified environmental toxin.

Drugs associated with DIL

- High risk — hydralazine, procainamide
- Moderate risk — quinidine
- Low risk — isoniazid, minocycline, carbamazepine, sulfasalazine, tumour necrosis factor-α inhibitors

Table 3

Heavy metals – lead, arsenic and cadmium are all known to be nephrotoxic. High levels of these heavy metals can be found in some areas as a result of industrial pollution, with contamination of soil, crops and water. Clinical manifestations vary from asymptomatic tubular dysfunction and kidney stones to CKD with reduced GFR.

Air pollution – particulate matter from vehicle exhausts has been associated with an increased (although not statistically significant) risk of renal cancer. Studies are continuing to examine the effects of air pollution on renal function. ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 56-year-old man presented with a 3-day history of dark, cola-coloured urine, muscle pains and difficulty walking. He had recently had an acute myocardial infarction, since when he had been taking bisoprolol 5 mg daily, aspirin 75 mg daily, clopidogrel 75 mg daily, atorvastatin 80 mg daily and isosorbide mononitrate 30 mg daily.

Investigations

- Potassium 6.3 mmol/litre (3.5–4.9)
- Creatinine 465 micromol/litre (60–110)
- Corrected calcium 1.92 mmol/litre (2.20–2.60)

Which of the following is the most likely cause?

A. Aspirin
B. Atorvastatin
C. Bisoprolol
D. Clopidogrel
E. Isosorbide mononitrate

Question 2

A 67-year-old woman presented with dysuria, frequency and rigors. She had a history of type 2 diabetes, hypertension and hypercholesterolaemia. She was taking aspirin 75 mg daily, a losartan–hydrocholorothiazide combination tablet and metformin, and these had been continued. In addition, she was being treated with gentamicin (80 mg 8-hourly).

Investigations

- Creatinine 186 micromol/litre (60–110) (78 micromol/litre 3 days previously)

Which drug is most likely to have contributed to this development?

A. Aspirin
B. Gentamicin
C. Hydrochlorothiazide
D. Losartan
E. Metformin

Question 3

A 32-year-old woman presented with tiredness and breathlessness on exertion. She had a history of depression. She was taking citalopram and a Chinese herbal slimming remedy.
On clinical examination, she looked pale and had a body mass index of 32 kg/m^2.

Investigations

- Haemoglobin 87 g/litre (115–165)
- Creatinine 169 micromol/litre (60–110)

Which of the following is most likely to be the cause of her elevated serum creatinine level?

A. Aristolochic acid
B. Arsenic
C. Cadmium
D. Citalopram
E. Lead