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REVIEW ARTICLES

Recent developments in the perioperative management of adult patients with chronic kidney disease

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The complications of chronic kidney disease (CKD) present the anaesthetist with a number of clinical challenges related in part to altered drug handling and to difficulties with vascular access and fluid balance. Safe anaesthetic management requires an understanding of CKD pathophysiology to prevent aggravation of pre-existing disease. This review will consider some recent changes in the management of adult patients with CKD as they affect the anaesthetist. It will consider medical problems associated with CKD together with new developments in perioperative management.

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Chronic kidney disease (CKD) is defined as either a glomerular filtration rate (GFR) of <60 ml min^{-1} 1.73 m^{-2} for 3 months or more, irrespective of cause, or kidney damage leading to a decrease in GFR, present for 3 months or more.[73] The damage may manifest as abnormalities in the composition of blood or urine, on radiological imaging, or in histology. It is classified into five stages depending on GFR (Table 1).[63]

Prevalence

The *2006 UK Renal Registry Report* documented the UK annual incidence of new patients accepted for renal replacement therapy (RRT) as 108 per million population.[3] The prevalence of UK adult patients alive on RRT at the end of 2005 was 694 per million. From 2001 to 2005, there was a 7.3% rise in the number accepted for RRT, due to an ageing population and an increase in type 2 diabetes mellitus.[89] In the USA in 2005, 43.8% of all incident cases of established renal failure were due to diabetes mellitus.[137] The number of patients with Stages 1–4 CKD (Table 1) is likely to exceed the number with established renal failure by as much as 50 times.[89] Most individuals with CKD do not develop established renal failure, in part due to an increased mortality secondary to cardiovascular disease, the advanced age at onset of many renal diseases, and the slow rate of decline of renal function, especially if treated.[73]

Assessment of renal function

Estimation of the GFR is used to assess, define, and classify renal function in CKD (Table 1). A quantitative assessment of GFR involves measurement of the plasma clearance of an exogenous marker, such as inulin,[124] I-iothalamate, or ^{48}Cr-EDTA. This is time-consuming and often impracticable in the clinical setting. Creatinine clearance may be used clinically to estimate GFR, but this usually requires a 24 h urine collection, which is inconvenient for the patient and prone to collection errors. A shorter time period for urine collection, e.g. 2 h, may be used in catheterized patients.[129] In general, creatinine clearance does not improve the estimate of GFR over that provided by creatinine-based prediction equations (see below), but it may still be useful in individuals with exceptional dietary intake (patients on creatinine supplements) or low muscle mass (amputees).[80] The serum creatinine concentration is influenced by factors such as age, sex, muscle mass, and diet; it should not be used alone to assess kidney function. It is insensitive to mild–moderate decreases in GFR, which may be reduced by as much as 50% with serum creatinine still in the normal range.[126] To overcome these limitations, a number of creatinine-based prediction equations have been developed, and provide a more accurate assessment of renal function. The most widely used are the four-variable Modification of Diet in Renal Disease (MDRD) equation and the Cockcroft–Gault formula (Table 2). The MDRD equation estimates the GFR with surface area adjustment whereas the Cockcroft–Gault formula estimates the unadjusted creatinine clearance. These formulae have been validated in patients with CKD.[53] Both formulae are imprecise at high values of GFR, and in patients with a grossly abnormal muscle mass, patients with a very low BMI, pregnant patients, and where renal function is changing rapidly.

GFR may also be estimated using cystatin C-based equations, for example, the Filler equation (Table 2). Cystatin C is a protein (cysteine protease inhibitor) produced at a constant rate by all nucleated cells. It is freely filtered by the kidney and catabolized in the proximal tubule. The serum cystatin C concentration was thought to be independent of body composition, but it has now been shown to be affected by lean mass.[79] A recent study of renal transplant recipients compared the GFR measured using radio-labelled diethylenetriamine pentaacetic acid (^{99m}Tc-DTPA) to estimated GFR using cystatin C-based and creatinine-based equations.[143] The Filler equation correctly classified the stage of CKD in 76% of patients, compared with only 65% with the four-variable MDRD equation and 69% with the Cockcroft–Gault formula.

Patients on dialysis may have a degree of residual renal function. The presence of any residual renal function is associated with a lower mortality risk, reduced intradialytic weight gain, and improved solute clearance in haemodialysis (HD) patients.[127] Residual renal function, defined as a 24 h urine volume >100 ml, is associated with an adjusted odds ratio for death of 0.35 (95% CI: 0.18–0.68).[127]

Aetiology

Table 3 indicates the primary cause of established renal failure as reported in the *2006 UK Renal Registry Report*.[3]

Table 1 Classification of CKD.[63] Adapted from: Joint Specialty Committee on Renal Medicine of the Royal College of Physicians and the Renal Association, and the Royal College of General Practitioners.[63] Copyright © 2006 Royal College of Physicians. Adapted with permission

Stage 1: Normal GFR; GFR ≥90 ml min^{-1} 1.73 m^{-2} with other evidence of chronic kidney damage*

Stage 2: Mild impairment; GFR 60–89 ml min^{-1} 1.73 m^{-2} with other evidence chronic kidney damage*

Stage 3: Moderate impairment; GFR 30–59 ml min^{-1} 1.73 m^{-2}

Stage 4: Severe impairment; GFR 15–29 ml min^{-1} 1.73 m^{-2}

Stage 5: Established renal failure: GFR <15 ml min^{-1} 1.73 m^{-2} or on dialysis

*The 'other evidence of chronic kidney damage' may include: persistent microalbuminuria; persistent proteinuria; persistent haematuria, after exclusion of other causes, e.g. urological disease; structural abnormalities of the kidneys demonstrated on ultrasound scanning or other radiological tests, e.g. polycystic kidney disease, reflux nephropathy; biopsy-proven chronic glomerulonephritis

CKD as a risk factor for perioperative complications

CKD is a risk factor for serious postoperative complications, such as acute renal failure and cardiovascular complications which are associated with an increased morbidity and mortality.[58 59 70 98 102] In a systematic review of preoperative risk factors for postoperative renal failure,[102] preoperative renal dysfunction was repeatedly found to be predictor of postoperative renal failure. Howell and colleagues[58] conducted a case–control study of risk factors for cardiovascular death after elective surgery under general anaesthesia. Patients were diagnosed as having renal failure if their serum creatinine concentration on admission was >150 μmol litre^{-1}. Conditional logistic regression was used to calculate adjusted odds ratios. The adjusted odds ratio associated with renal failure was 3.56 with a 95% confidence interval of 1.04–12.10. A similar study by the same authors examined risk factors for cardiovascular death after urgent or emergency surgery and found that an association between renal impairment and cardiovascular mortality was evident on univariate analysis, but not after adjustment for confounding factors.[59] This may have been due to a lack of statistical power. Lee and colleagues[70] conducted a prospective cohort study to develop an index able to identify patients at higher risk of cardiac complications after non-cardiac surgery. A preoperative serum creatinine >176.8 μmol litre^{-1} (2 mg dl^{-1}) was found to be an independent predictor of cardiac complications, and was associated with major cardiac complications in 9% of cases. The Euroscore is a scoring system for the prediction of early mortality in cardiac surgical patients in Europe. A serum creatinine >200 μmol litre^{-1} is considered an objective risk factor, and contributes an added 2% to the predicted mortality.[98]

Pathophysiology

CKD is associated with pathophysiological changes in many systems, which have implications for the safe conduct of anaesthesia (Table 4).

Cardiovascular system

CKD is associated with an increased risk of cardiovascular disease. Myocardial infarction, heart failure, and stroke are

Table 2 Equations to predict GFR using creatinine and cystatin C[23 63 143]

The four variable or abbreviated MDRD equation

$$\text{GFR (ml min}^{-1}\text{ 1.73 m}^{-2}) = 186 \times [\text{s-creatinine}(\mu\text{mol litre}^{-1})/88.4]^{-1.154} \times \text{age (yr)}^{-0.203} \times 0.742 \text{ if female} \times 1.21 \text{ if African American}$$

Cockcroft–Gault equation

$$\text{Creatinine clearance (ml min}^{-1}) = (140 - \text{age}) \times \text{weight (kg)}/[72 \times \text{creatinine (mg dl}^{-1})] \times 0.85 \text{ if female}$$

serum creatinine levels in μmol litre^{-1} can be converted to mg dl^{-1} by dividing by 88.4

Filler equation

$$\text{Log (GFR in ml min}^{-1}\text{1.73 m}^{-2}) = 1.962 + [1.123 \times \log(1/\text{cystatin C in mg litre}^{-1})]$$

Table 3 Aetiology of established renal failure in the UK.[3] The data reported here have been reproduced with permission from the UK Renal Registry of the Renal Association (http://www.renalreg.com/reports.renal-registry-reports/2006/). The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the UK Renal Registry or the Renal Association

Aetiology	% total	Male:female ratio
Diabetes mellitus	19.8	1.6
Glomerulonephritis	10.3	1.9
Pyelonephritis	8.2	1.7
Renovascular disease	7.6	1.8
Polycystic kidneys	6.1	1.1
Hypertension	4.8	2.4
Uncertain aetiology/glomerulonephritis unproven	28.0	1.6
Other	15.2	1.4

Table 4 Complications of CKD

Cardiovascular system
Salt and water retention, hypertension, and LVH
Cardiomyopathy, congestive cardiac failure, and subclinical pulmonary oedema
Accelerated atherosclerosis and stiffening of large capacitative arteries
Altered lipoprotein metabolism
Complications of AVF/shunts, e.g. heart failure, limb ischaemia, steal syndrome, pulmonary atheroembolism
Uraemic pericarditis
Cardiovascular autonomic neuropathy with reduced baroreceptor sensitivity, sympathetic hyperactivity, and parasympathetic dysfunction
Calciphylaxis and vascular calcification resulting in valvular heart disease and calcified atherosclerotic lesions
Anaemia
Haemostasis and coagulation
Uraemic thrombocytopathy
Prothrombotic tendency/hypercoagulation and reduced fibrinolysis
Vascular access thrombosis
Metabolic acidosis
Bone resorption
Negative nitrogen balance, muscle wasting, growth retardation
Musculoskeletal system
Renal osteodystrophy
Rhabdomyolysis after major surgery
Endocrine system
Secondary and tertiary hyperparathyroidism, vitamin D deficiency
Diabetes mellitus
Gastrointestinal system
Delayed gastric emptying
Anorexia, vomiting, reduced protein intake, malnutrition
Reduced calcium absorption
Immune system
Immunosuppression due to uraemia or drugs
Fluid and electrolyte homeostasis
Hyperkalaemia
Volume overload
Dehydration

the leading cause of death in patients with established renal failure.[77]

Left ventricular hypertrophy (LVH) occurs due to a combination of pressure and volume overload. Volume overload may be due to sodium and water retention, the presence of an atrioventricular (AV) fistula, or chronic anaemia with increased stroke volume and heart rate.[77] Pressure overload is related to hypertension and arteriosclerosis. LVH is associated with myocardial fibrosis and abnormalities of myocardial relaxation both of which contribute to diastolic dysfunction and arrhythmias.[77] Reduced LV compliance may result in increased sensitivity to volume changes with a small increase in LV volume precipitating pulmonary oedema.

Accelerated atherosclerosis is a feature of CKD (Table 4).[119] This may be explained by impaired endothelial function, low grade inflammation, and dyslipidaemia. Lipoprotein metabolism is altered in CKD, in particular high-density lipoprotein levels fall and intermediate density lipoprotein accumulates.[119] Activation of the renin–angiotensin system (RAS) may also contribute. Angiotensin II, acting on the AT_1 receptor, stimulates the production of reactive oxygen species. This contributes to endothelial dysfunction and vascular remodelling.[119]

Vascular calcification with calcified, stenotic atherosclerotic lesions, and valvular heart disease is another cardiovascular complication of CKD and calcium supplements may enhance this process.[76] Calciphylaxis is a specific dialysis-related type of vascular calcification characterized by diffuse calcification of the media of small to medium arteries and arterioles with intimal proliferation and thrombosis. It results in skin ulcers and can lead to life-threatening skin necrosis or acral gangrene.

Conduction abnormalities: Myocardial fibrosis and calcification involving the conduction system results in an increase in the prevalence of second- and third-degree AV block in patients with CKD and an increase in the incidence of permanent pacing in dialysis patients.[71] Hyperkalaemia and calcium channel blockers may contribute to the development of complete AV block, as may epidural anaesthesia, with its attendant reduction in sympathetic activity.[41]

Hypertension may be the primary cause of kidney disease or the result of renal parenchymal or renovascular disease. Arterial pressure control and block of the RAS are important in preserving residual function in patients with both diabetic and non-diabetic renal disease.

The threshold for initiating treatment with antihypertensive medication in patients with renal impairment is an SBP $\geq$140 mm Hg, DBP $\geq$90 mm Hg, or both, unless the urine protein:creatinine ratio is $>$100 mg mmol^{-1}, when a threshold of 130/80 mm Hg is advocated. An arterial pressure of $<$130/80 mm Hg is required for optimal control and an arterial pressure of $<$125/75 mm Hg may produce additional benefits in patients with proteinuria of $\geq$1 g/24 h.[63 147]

Despite the fact that angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARBs) may precipitate a deterioration in renal function, for instance, in the presence of bilateral atherosclerotic renal artery stenosis, the majority of patients with CKD and hypertension will benefit from such treatment. Blocking the RAS may have renoprotective benefits beyond that of arterial pressure control alone.[47] ACEI and ARBs have a major prognostic benefit in proteinuric renal disease.[63] There is

also evidence that a combination of ARB and ACEI may be more effective than ARB or ACEI alone in protecting renal survival.[96] Other antihypertensives that are commonly used include thiazide and loop diuretics, the dihydropyridine calcium channel blockers, α-adrenoceptor blockers, hydralazine, moxonidine, and minoxidil.

Erythropoietin increases blood viscosity and vascular resistance. This may aggravate hypertension.[112] Calcineurin inhibitors such as ciclosporin and corticosteroids may also induce hypertension in renal transplant recipients.

Haemostasis and coagulation

Patients with CKD are often considered to have a bleeding tendency characterized by platelet dysfunction (uraemic thrombocytopathy or thrombasthenia). There is, however, evidence indicating a prothrombotic state in these patients.[109 116 135 136] The evidence of platelet dysfunction is based upon laboratory findings and a prolonged bleeding time. A number of abnormalities of platelet function have been demonstrated including defective interaction of von Willebrand factor with platelet glycoprotein IIb–IIIa receptors, reduced platelet ADP content, and reduced thromboxane A_2.[111] Platelet count is generally normal, but anaemia may contribute to the bleeding tendency. A low haematocrit has been associated with prolonged bleeding time: patients subjected to a red cell transfusion programme showed a normalized bleeding time once haematocrit was $>26\%$.[40] Despite the haemostatic defect, there is also a tendency towards hypercoagulation.

Thromboelastographic indices in patients with CKD show that all aspects of coagulation are increased, including initial fibrin formation, fibrin–platelet interaction, and qualitative platelet function.[109] There is also a reduction in fibrinolysis. Vascular access thrombosis is of particular importance in patients with Stage 5 CKD on HD as it is associated with an increased mortality.[1] Numerous studies have attempted to identify factors associated with vascular access failure[46 52 56 61 81 92 130] (Table, see Supplementary material available at *British Journal of Anaesthesia* online).

Neuraxial block

The combination of platelet dysfunction and the residual effects of heparin given during dialysis have raised concerns of an increased risk of epidural haematoma formation. Despite this, there are a number of studies reporting the use of epidural anaesthesia in patients with various stages of CKD. The use of hypotensive epidural anaesthesia in 50 patients, with CKD Stage 3 or more undergoing total hip replacement,[125] did not result in any acute deterioration of renal function or other complications from epidural anaesthesia. Beneficial effects in terms of respiratory function and quality of analgesia were reported in 13 patients who received combined epidural and general anaesthesia for renal transplantation, when compared with a control group who received general anaesthesia and systemic analgesics.[31] This study of only 25 patients was not adequately powered to detect differences related to haemodynamic stability, graft function, or other safety issues.

There may be an association between HD and spontaneous epidural haematoma formation.[124] HD is associated with a rise in intracranial pressure that may play a role in its pathogenesis. Epidural anaesthesia in poorly controlled hypertensive patients may result in haemodynamic instability that could potentially compromise renal perfusion and increase the likelihood of acute kidney injury. Although there may be patients with CKD for whom the benefits of epidural anaesthesia outweigh the risks, a careful analysis of the individual case is required.

Metabolic acidosis

A reduction in ammonia synthesis and the ability to excrete hydrogen ions results in metabolic acidosis in patients with CKD. The potential for sodium bicarbonate to exacerbate hypertension and volume overload has caused concern. However, there was no evidence of this in a recent systematic review.[114] The effect of metabolic acidosis on the perioperative management of CKD patients relates to their reduced ability to compensate for respiratory acidosis, and altered drug distribution and efficacy. Preoperative assessment should include measurement of plasma bicarbonate.

Autonomic neuropathy

Autonomic neuropathy is common in patients with CKD and may have significant effect on arterial pressure perioperatively. A prevalence of 65% in non-diabetic predialysis CKD patients has been noted, whereas studies of patients with CKD on HD have revealed a prevalence between 38% and 87.5%.[15 117 118]

The aetiology may be multifactorial, with uraemia, diabetes mellitus, and hyperparathyroidism[82] contributing to the pathogenesis. A significant association between the radiological signs of osteodystrophy and the presence of autonomic neuropathy[132] has been shown, but not a link between the biochemical measures of secondary hyperparathyroidism and autonomic neuropathy. Symptoms of peripheral sensory and motor neuropathy correlate with cardiovascular autonomic neuropathy.[118] Delayed gastric emptying may be present in up to 69% of patients.[2] The autonomic dysfunction associated with CKD is characterized by reduced baroreceptor sensitivity, sympathetic overactivity, and parasympathetic dysfunction,[10 66] and may predispose to the development of arrhythmias perioperatively.[62] Elevated levels of angiotensin II and deafferentation of the baroreceptors may be responsible for the increase in sympathetic tone. Treatment with ACE inhibitors corrects this sympathetic overactivity.[74] The parasympathetic dysfunction results in reduced heart rate

variability and a reduced heart rate response to atropine.[10] Of the numerous tests described to assess the cardiac autonomic reflexes, the heart rate variation during deep breathing and arterial pressure response to hand grip exercise have the best positive predictive value and are of use in preoperative assessment.[117] The ECG may provide evidence of autonomic neuropathy in the form of reduced heart rate variability (reduced R-R interval variation). A simple ECG rhythm strip may not detect this with great sensitivity. However, heart rate variation is easy to quantify by recording the ECG during deep breathing at 6 bpm (5 s inspiration:5 s expiration) for 1 min. The mean of the difference between maximum and minimum heart rates for each of the six measured cycles is calculated from the R-R interval. A value of 15 beats min^{-1} or greater is considered normal.[37]

Fluid and electrolytes

Traditional teaching is that extracellular fluid volume and electrolyte composition remain normal until the development of dialysis-dependent renal failure.[140] However, there is evidence that patients with CKD develop fluid overload early and this may be a stimulus for inflammation and accelerated progression of renal disease.[106] It is possible that oedema is associated with altered gut permeability and an associated inflammatory response.[106]

Patients with CKD are unable to adapt to large variations in salt intake and have an impaired ability to concentrate and dilute urine. Maximum sodium excretion is a function of GFR.[104] The impaired ability to excrete a sodium load predisposes these patients to volume overload, especially when large volumes of saline solutions are administered. This propensity becomes more marked as CKD progresses. Infusion of large volumes of saline will also result in hyperchloraemic metabolic acidosis. The deleterious effects of metabolic acidosis include depression of myocardial contractility, reduced cardiac output, and reduced renal blood flow.[105] Furthermore, hyperchloraemia can reduce renal blood flow and GFR.[146] If access to free water is restricted in the perioperative period, the inability to concentrate urine will result in hypernatraemia and hypertonicity (Table, see Supplementary material available at *British Journal of Anaesthesia* online).

In managing patients on dialysis, the anaesthetist should establish the patient's dry weight and compare it with their weight immediately before coming to theatre. Failure to achieve dry weight with dialysis is a common problem, particularly with short duration dialysis prescriptions.

Plasma potassium concentration usually remains normal until the onset of Stage 5 CKD. This is due to an increase in the excretion of potassium per functioning nephron and increased output in the stool.[103] Nevertheless, patients with CKD are at risk of developing hyperkalaemia if challenged with excessive exogenous potassium or transcellular potassium shifts. In this respect, acidaemia, insulin deficiency, hypertonicity, and acute beta-adrenergic receptor block should be avoided.[104] The American College of Cardiology/American Heart Association 2007 guidelines on perioperative cardiovascular evaluation includes renal insufficiency, defined as a serum creatinine >200 μmol $litre^{-1}$, as a clinical risk factor.[43] The guidelines recommend that the presence of one or more clinical risk factors, in patients having vascular- or intermediate-risk surgery, should prompt the anaesthetist to consider beta-blocker therapy. However, there is a risk of hyperkalaemia associated with the i.v. administration of beta-blockers.[54] This is likely to be of greatest importance for patients with Stage 5 CKD. Table 5 gives a list of drugs that may contribute to the development of hyperkalaemia. I.V. fluids containing hydroxyethyl starch have adverse effects on renal function in renal transplant recipients and in critically ill patients with severe sepsis or septic shock.[13 22 120]

Vascular access

Maintenance of vascular access patency is of vital importance in patients with Stage 5 CKD on HD. Vascular access may be either permanent or temporary. Options for permanent access include native arteriovenous fistulae (AVF), arteriovenous grafts (AVG), and long-term

Table 5 Drugs associated with hyperkalaemia

Drug	Comment
Succinylcholine	Transient increase in serum potassium concentration of 0.5–1 mmol $litre^{-1}$ under halothane anaesthesia May be used in patients with advanced renal disease provided that preoperative potassium level is normal. Avoid repeated administration[133]
Non-steroidal anti-inflammatory drugs	Inhibit aldosterone synthesis. Renal prostaglandins stimulate renin synthesis and increase the number of open high-conductance potassium channels in the distal tubular principal cells[107]
Beta-adrenergic receptor blockers	Reduced cellular uptake of potassium and inhibition of aldosterone secretion[86]
Heparin	Inhibits aldosterone synthesis.[107] Occurs within a few days of the initiation of therapy. Monitor potassium concentration if receiving heparin for more than 3 days
ACE inhibitors and ARBs	Inhibit aldosterone synthesis[107]
Digoxin	Inhibition of the NA^+-K^+-ATPase in the basolateral membrane of the principal cells[107]
Spironolactone	Potassium-sparing diuretic Blocks the intracellular mineralocorticoid receptor[107]
Amiloride and triamterene	Potassium-sparing diuretics Inhibit sodium transport channels in the luminal membrane of the principal cells of the distal tubule[107]
Ciclosporin	Inhibition of the NA^+-K^+-ATPase and apical secretory potassium channel activity in principal cells. Reduced aldosterone sectretion. Increased potassium efflux from cells[107]
Tacrolimus	Inhibition of the NA^+-K^+-ATPase and steroid-mediated sodium transport in the distal tubule[115]

catheters. Temporary vascular access includes: acute short-term non-cuffed catheters which may or may not be tunnelled; long-term tunnelled cuffed catheters; and s.c. port catheter systems.

Native AVF

A fistula-first approach is advocated as native fistulae have the best long-term patency rates, require fewer interventions, and are associated with fewer infective complications than catheters and grafts.[100] The mortality risk is also reduced in patients dialysing through fistulae.[110]

A period of maturation, characterized by an increase in blood flow and an increase in the size of the vein, is required before a newly created AVF can be used. This takes 1–4 months. The anaesthetist should protect potential fistula construction sites, especially the cephalic vein, perioperatively.

Arteriovenous grafts

AVG provide useful permanent access when superficial veins are not suitable or have been exhausted. AVG may be synthetic (e.g. polytetrafluoroethylene) or biological (e.g. bovine mesenteric vein).

Vascular catheters for HD

Factors requiring consideration before the placement of a central venous catheter for HD include: the duration for which the catheter is required, the insertion site, the ideal position of the tip of the catheter, and the method of insertion.

Duration

The *NKF K/DOQI Guidelines* state that acute short-term non-cuffed catheters should be used for $\leq$1 week because of the risk of infection.[100] If a non-cuffed catheter is required for longer, it should be converted to a tunnelled cuffed catheter using the same site provided that there is no evidence of infection.[39] With long-term use, cuffed central catheters are associated with a higher relative risk of death due to infection than AVFs.[32]

Insertion site

The right internal jugular vein is the preferred site as the risk of complications is lower.[100] In particular, it is the risk of stenosis of the vein that is reduced when using this route.[20] The left internal jugular site is associated with a poorer blood flow rate and a greater rate of stenosis and thrombosis.[100] The subclavian route should be avoided as the risk of stenosis after catheterization is unacceptably high, with 40–50% of patients demonstrating some degree of stricture on venography.[20] Subclavian vein stenosis can result in fistula dysfunction with elevated venous dialysis pressures and painful arm oedema.[121] In patients who are candidates for renal transplantation, the femoral route should be avoided to prevent stenosis of the external iliac vein, as the transplanted kidney is anastomosed to it.[100] The femoral route is also associated with the greatest risk of infection.

Complications

Problems relating to vascular access are a leading cause of hospitalization, morbidity and the need for anaesthesia in patients with Stage 5 CKD.[100] These include infection, stenosis, thrombosis, aneurysm, limb ischaemia, limb oedema, heart failure, pulmonary atheroembolism, steal syndrome, and recirculation.

Pharmacology

In patients with CKD, the effect of altered clearance, the production and accumulation of active metabolites, and the risk of aggravating pre-existing kidney disease on drug administration must be considered. Dose adjustment is not usually necessary until the GFR is $<$50 ml min^{-1} 1.73 m^{-2}. CKD may influence both the pharmacokinetics and the pharmacodynamics of a drug.

Pharmacokinetic changes

Absorption

Drug absorption may be altered by: gastroparesis causing delayed gastric emptying, raised gastric pH caused by gastric urease, converting urea to ammonia, and gut oedema.[101] Reduced intestinal P-glycoprotein, a transporter found on the apical cell surface of small and large intestine mucosal cells which protects the body against toxic compounds by transporting them into the intestinal lumen, activity in CKD may lead to increased intestinal absorption and bioavailability of certain compounds.[101]

Distribution

Volume of distribution may be increased or decreased by alterations in body composition, especially total body water, plasma protein binding, and tissue binding.[101] Time since the last dialysis session influences the volume of distribution of certain drugs, for example, remifentanil (Table 6).[30] A reduced volume of distribution after a dialysis session may result in increased steady-state drug concentrations for drugs administered by continuous infusion.

Plasma protein binding of acidic drugs, which bind mainly to albumin, is altered by the accumulation of organic acids, such as uric acid and lactic acid, which compete for binding sites on albumin. The albumin concentration is reduced in CKD and there is a change in its conformational binding site.[101] Basic drugs bind mainly to α_1-acid glycoprotein (AAG), an acute phase protein that is often elevated in CKD. A reduction in plasma protein binding with an increase in the free fraction of a drug may result in an increased volume of distribution and clearance with no significant change in drug exposure.[101]

Table 6 The influence of Stage 5 CKD on drug disposition

Drug	$T_{1/2}\beta$		Systemic clearance		Volume of distribution at steady state		Unbound fraction (%)		Reference
	Controls	*CKD*	*Controls*	*CKD*	*Controls*	*CKD*	*Controls*	*CKD*	
Opioids									
Morphine	186 min	185 min	21.3 ml min^{-1} kg^{-1}	17.1 ml min^{-1} kg^{-1}	3.7 litre kg^{-1}	2.8 litre kg^{-1} $P<0.05$	—	—	Chauvin and colleagues[18]
	286 min	290 min	741 ml min^{-1}	533 ml min^{-1}	241 litre	141 litre $P=0.002$	—	—	Sear and colleagues[123]
Fentanyl	405 min	594 min $P<0.05$	14.8 ml min^{-1} kg^{-1}	11.8 ml min^{-1} kg^{-1}	7.7 litre kg^{-1}	9.5 litre kg^{-1}	—	—	Duthie,[33] reproduced from Sear[122]
Alfentanil	83 min	58 min $P<0.05$	6.5 ml min^{-1} kg^{-1}	5.3 ml min^{-1} kg^{-1}	0.46 litre kg^{-1}	0.304 litre kg^{-1} $P<0.05$	—	—	Van Peer and colleagues[138]
	90 min	107 min	3.1 ml min^{-1} kg^{-1}	3.1 ml min^{-1} kg^{-1}	0.281 litre kg^{-1}	0.405 litre kg^{-1} $P<0.02$	11%	19% $P<0.05$	Chauvin and colleagues[17]
	120.2 min	142.4 min	211.8 ml min^{-1}	341.9 ml min^{-1} $P<0.05$	27.6 litre	40.5 litre	10.3%	12.4% $P<0.05$	Bower and Sear[11]
Remifentanil	16.3 min	18.86 min $P=0.045$	48.7 ml min^{-1} kg^{-1} $P=0.017$	29.9 ml min^{-1} kg^{-1}	0.566 litre kg^{-1}	0.358 litre kg^{-1} $P=0.002$	—	—	Dahaba and colleagues[30]
Oxycodone	138 min	234 min $P=0.028$	1100 ml min^{-1}	840 ml min^{-1}	2.39 litre kg^{-1}	3.99 litre kg^{-1} $P=0.034$	—	—	Kirvela and colleagues[64]
NMBAs									
Atracurium	20.6 min	23.7 min	6.1 ml min^{-1} kg^{-1}	6.7 ml min^{-1} kg^{-1}	0.182 litre kg^{-1}	0.224 litre kg^{-1}	—	—	Fahey and colleagues[38]
	19.3 min	20.1 min	5.5 ml min^{-1} kg^{-1}	5.8 ml min^{-1} kg^{-1}	0.153 litre kg^{-1}	0.141 litre kg^{-1}	—	—	Ward and colleagues[141]
Cisatracurium	30 min	34.2 min $P<0.05$	293 ml min^{-1}	254 ml min^{-1}	—	—	–	—	Eastwood and colleagues[34]
Mivacurium									
Cis–cis	68 min	80 min	3.8 ml min^{-1} kg^{-1}	2.4 ml min^{-1} kg^{-1} $P<0.01$	0.227 litre kg^{-1}	0.224 litre kg^{-1}	—	—	Head-Rapson and colleagues[57]
Cis–trans	2 min	4.3 min	106 ml min^{-1} kg^{-1}	80 ml min^{-1} kg^{-1}	0.278 litre kg^{-1}	0.475 litre kg^{-1}	–	–	Head-Rapson 1995[57]
Trans–trans	2.3 min	4.2 min	57 ml min^{-1} kg^{-1}	47 ml min^{-1} kg^{-1}	0.211 litre kg^{-1}	0.270 litre kg^{-1}	–	–	Head-Rapson 1995[57]
Pancuronium	100 min	489 min $P<0.05$	74 ml min^{-1}	20 ml min^{-1} $P<0.005$	0.148 litre kg^{-1}	0.236 litre kg^{-1} $P<0.05$	—	—	McLeod and colleagues[87]
Vecuronium	52.6 min	83.1 min $P<0.05$	5.29 ml min^{-1} kg^{-1}	3.08 ml min^{-1} kg^{-1} $P<0.05$	0.199 litre kg^{-1}	0.24 litre kg^{-1}	—	—	Lynam and colleagues[78]
Rocuronium	57 min	70 min	4.5 ml min^{-1} kg^{-1}	2.7 ml min^{-1} kg^{-1} $P<0.0001$	0.194 litre kg^{-1}	0.22 litre kg^{-1}	—	—	Robertson and colleagues[113]
	97.2 min	104.4 min	3.7 ml min^{-1} kg^{-1}	2.5 ml min^{-1} kg^{-1} $P<0.05$	0.207 litre kg^{-1}	0.212 litre kg^{-1}	—	—	Cooper and colleagues[25]
Induction agents									
Propofol	27.7 min	23.8 min	33.75 ml min^{-1} kg^{-1}	30.66 ml min^{-1} kg^{-1}	5.79 litre kg^{-1}	11.25 litre kg^{-1}	—	—	Ickx and colleagues[60]
							0.98%	1.11% before HD 0.87% after HD	Costela and colleagues[27]
Thiopental	611 min	583 min	3.2 ml min^{-1} kg^{-1}	4.5 ml min^{-1} kg^{-1} $P<0.05$	1.9 litre kg^{-1}	3.0 litre kg^{-1} $P<0.05$	15.7%	28% $P<0.05$	Burch and Stanski[14]
	588 min	1069 min	2.7 ml min^{-1} kg^{-1}	3.9 ml min^{-1} kg^{-1}	1.4 litre kg^{-1}	3.2 litre kg^{-1} $P<0.05$	11%	17.8% $P<0.05$	Christensen and colleagues[19]

Local anaesthetics have two plasma protein binding sites: a high affinity, low capacity site on AAG, and a low affinity, high capacity site on albumin.[88] The albumin binding site becomes increasingly important as the plasma concentration of the local anaesthetic increases. Metabolic acidosis increases the percentage of unbound drug, and this effect is more pronounced with bupivacaine.[97] The effect of these changes on the toxicity of local anaesthetics is unclear.

Elimination

The kidneys contribute up to 18% of total cytochrome P450 (CYP) activated drug metabolism and are also involved in conjugation reactions.[36] Interestingly, non-renal clearance of many drugs is reduced in patients with kidney disease.[101] Hepatic clearance may vary with changes in hepatic blood flow, the free fraction of a drug, and the metabolic capacity of the liver enzymes.[36] Animal studies of experimental CKD have demonstrated a 40% reduction in total microsomal CYP activity.[69] Severe kidney disease differentially affects hepatic CYP activity; in particular, the activity of CYP 3A4 and CYP 2C9 is reduced.[101] In contrast, elevated plasma urea concentration induces CYP 2E1 activity.[101] The mechanism of altered enzyme activity appears to relate in part to altered gene transcription, although depletion of cofactors may also be involved.[36 101]

Potent inhalation agents

Historically, *methoxyflurane* anaesthesia resulted in elevated serum inorganic fluoride levels and polyuric renal failure.[28] Serum fluoride levels >50 μmol litre^{-1} were associated with an increased risk of renal damage.

Sevoflurane metabolism also results in elevated fluoride levels, with peak levels >50 μmol litre^{-1}. Sevoflurane reacts with strong bases in CO_2 absorbents to produce Compound A, a dose-related nephrotoxin in rats.[48] A retrospective evaluation of pooled renal laboratory data from 22 clinical trials that compared sevoflurane with isoflurane, enflurane, or propofol found that the incidence of raised serum creatinine and blood urea nitrogen concentrations was similar after sevoflurane or the control agents.[84] There was no specific trend with respect to postoperative serum creatinine and fresh gas flow, type of CO_2 absorbent, or effect of concurrent treatment with nephrotoxic antibiotics when sevoflurane was used. The authors concluded that exposure to <4 MAC h of sevoflurane was not associated with an increased risk of renal toxicity. Serum fluoride kinetics after sevoflurane anaesthesia have been studied in patients with CKD and compared with a group with normal renal function.[99] In CKD patients, the serum inorganic fluoride level and its rate of elimination did not differ significantly from controls. Indices of renal tubular function, such as β2-microglobulin and *N*-acetyl-β-D-glucosaminidase, do not significantly change after anaesthesia with sevoflurane in either patients with CKD or controls.[99] Despite initial concerns, sevoflurane is a suitable choice of potent inhalation anaesthetic agent for patients with CKD (Table, see Supplementary material available at *British Journal of Anaesthesia* online).

Enflurane undergoes greater biotransformation to inorganic fluoride than either isoflurane or desflurane. It is known to cause vasopressin-resistant polyuria in rats, and in volunteers prolonged enflurane anaesthesia resulted in a 25% reduction in urine concentrating ability and a transient reduction in creatinine clearance of 35%.[4 85] Case reports of renal failure after enflurane anaesthesia in patients with renal dysfunction suggest that it is best avoided in this group, although studies of the effects of enflurane in patients with stable renal insufficiency found no deterioration in function.[24 35 144]

Desflurane and isoflurane are not associated with renal toxicity and appear safe to use in patients with CKD.[75 148]

I.V. anaesthetic agents

Propofol pharmacokinetics are unaltered by established renal failure (Table 6). The induction dose of propofol associated with a bispectral index value of 50 is significantly higher in patients with established renal failure compared with controls: 2.03 *vs* 1.39 mg kg^{-1}; $P<0.05$.[49] The time interval between cessation of a propofol infusion and eye opening is significantly shorter in renal failure patients than controls (474 *vs* 714 s; $P<0.05$), although blood propofol concentrations are not significantly different on waking.[60]

Thiopental has an increased volume of distribution and reduced plasma protein binding in renal failure (Table 6). The brain is exposed to a higher free drug concentration. The rate of administration should be reduced.[122]

Neuromuscular blocking and reversal agents

When selecting a neuromuscular blocking agent (NMBA) for use in patients with CKD, consider the impact of renal impairment on the elimination of the drug, the potential for drug accumulation with incremental doses, and the production of active metabolites. Other factors include the effect of acidaemia and drug interactions on the intensity and duration of block. In general, the initial dose required to produce neuromuscular block ($3\times ED_{95}$, which is the effective dose to produce 95% twitch depression) is larger in patients with CKD than in normal subjects. But, with the exception of atracurium and cisatracurium, the dose required to maintain block is reduced.[50 108] To prevent postoperative residual curarization (PORC), the anaesthetist should avoid using long-acting NMBA, or agents which are excreted in part in the urine, and make routine use of neuromuscular monitoring.

The problems of prolonged neuromuscular block and PORC were particularly pertinent to the use of D-tubocurarine and pancuronium, as both agents have a

reduced clearance and prolonged half-life in the presence of CKD. Furthermore, pancuronium has an active metabolite, 3-hydroxypancuronium, with half the neuromuscular blocking potency of the parent compound.

Atracurium is not dependent upon renal or hepatic function for its elimination, as it undergoes spontaneous breakdown at body temperature and pH, a process known as Hofmann degradation, and metabolism by non-specific esterases. One of the products of Hofmann degradation, laudanosine, has been shown to be epileptogenic in animals.[16] The pharmacodynamics and pharmacokinetics of atracurium are not altered by CKD (Table 6).[38] Atracurium is less potent, results in greater histamine release, and has a shorter duration of action than cisatracurium.[12]

Cisatracurium, the 1R *cis*-1′R *cis* isomer of atracurium, is subject to Hofmann degradation and ester hydrolysis, albeit to differing degrees. As it is more potent, the plasma concentration of laudanosine after cisatracurium is lower than after an equipotent dose of atracurium. Although the laudanosine levels are significantly higher in patients with CKD who have received cisatracurium compared with healthy controls, these levels are still approximately 1/10th of those seen after atracurium.[34] Renal failure alters the pharmacokinetics, but has little impact on the pharmacodynamics of cisatracurium. The clearance is reduced by 13% and the terminal elimination half-life prolonged by 4.2 min (Table 6).[34] The only difference in onset or recovery variables is a longer mean time to 90% depression of the first twitch of the train-of-four response (T1/T0); 3.7 *vs* 2.4 min, probably due to a poorer cardiac output and slower delivery to the neuromuscular junction.[12]

Mivacurium consists of three isomers: *cis–trans* (37%), *trans–trans* (57%), and *cis–cis* (6%). Clearance of the *cis–cis* isomer, the least potent, is significantly reduced in patients with renal failure and it may accumulate (Table 6).[57] In renal failure, spontaneous recovery is slower and lower infusion rates are required.[108] There is an acquired decrease in plasma cholinesterase activity in CKD, and a negative correlation between cholinesterase activity and time to recovery after mivacurium has been demonstrated.[108]

Vecuronium undergoes predominantly biliary excretion, although up to 30% may be excreted by the kidney.[6] It is also metabolized in the liver to 3-hydroxyvecuronium which is active at the neuromuscular junction. Renal failure results in a reduced clearance, increased terminal elimination half-life, and prolonged duration of action (Table 6).[78] Accumulation occurs with repeat boluses or constant infusions resulting in prolonged neuromuscular block.[8 72]

Rocuronium is excreted primarily in the bile, although up to 33% may be excreted in the urine within 24 h.[145] A small fraction is metabolized in the liver producing a metabolite with very low neuromuscular blocking activity.[91] Renal failure reduces the clearance of rocuronium by 39% (Table 6).[113] The duration of action (25% recovery of T1/T0) and time to recovery of the TOF ratio to 0.7 are significantly prolonged in patients with renal failure compared with controls: 49 *vs* 32 min and 88 *vs* 55 min, respectively.[113] Importantly, inter-patient variability is increased in patients with renal failure.[25]

Neostigmine clearance is reduced and its half-life is prolonged in CKD. This may result in a parasympathomimetic response, including bradycardia and AV block, especially when used in combination with atropine rather than the longer-acting glycopyrronium.[142]

Sugammadex may prove useful in preventing PORC when patients have received an aminosteroid NMBA. It is a modified γ-cyclodextrin that selectively encapsulates steroid-based non-depolarizing NMBAs. The resulting guest–host complex is water soluble and exists in equilibrium but with a very low dissociation rate.[95]

Sugammadex is biologically inactive and does not bind to plasma proteins. Furthermore, it appears to have relatively few side-effects, although hypotension has been documented.[139] In individuals with normal renal function, sugammadex is excreted unchanged in the urine and it also enhances the renal excretion of rocuronium. Sorgenfrei and colleagues[131] showed that 59–77% of sugammadex is excreted unchanged in the urine within 16 h. But, its efficacy as a reversal agent does not appear to rely on renal excretion of the cyclodextrin-relaxant complex.[95]

Analgesic agents

In administering analgesic agents, the anaesthetist needs to consider: the impact of renal impairment on the distribution and elimination of the parent compound and hence the need for adjusting the dose or dose interval (Table 6); the formation of active metabolites; and the risk of compromising residual renal function.

Acetaminophen

Oral acetaminophen 40 mg kg^{-1} day^{-1} for 3 days in normal subjects and patients with CKD produced no demonstrable change in glomerular or tubular function in either group.[7] Prolonged use of acetaminophen is associated with analgesic nephropathy, but occasional or moderate use is safe.[67] Analgesic nephropathy is mainly associated with prolonged use of compound analgesics containing two antipyretic agents with caffeine or codeine. The use of acetaminophen in the perioperative period is safe and does not require dose adjustment.

Non-steroidal anti-inflammatory agents

The adverse effects of the non-steroidal anti-inflammatory drugs (NSAIDs) are likely to outweigh any potential benefit in the perioperative period. They exacerbate hypertension and precipitate oedema, hyponatraemia, and hyperkalaemia. There is an increased risk of gastrointestinal bleeding, which may be aggravated by the combined

effects of uraemic thrombasthenia and drug-induced platelet inhibition. Their use is associated with an increased risk of cardiovascular complications in this at risk population.[93] They are nephrotoxic agents that precipitate an acute decrease in GFR and may also cause acute interstitial nephritis as part of an idiosyncratic reaction. The renal effects of the COX-2 inhibitors are similar to those of the non-selective NSAIDs.[68]

Opioids

Opioids have no direct toxic effects on the kidney. They do, however, have an antidiuretic effect, and they may cause urinary retention. Very rarely, their use has resulted in rhabdomyolysis.[9]

Morphine

Morphine is metabolized in the liver to a number of metabolites of which morphine-3-glucuronide is the major one, accounting for 70% of the dose. Morphine-3-glucuronide antagonizes the analgesic effect of morphine, and is associated with irritability and a lower seizure threshold.[94] Approximately 5% of a dose of morphine is metabolized to morphine-6-glucuronide (M6G), which has potent analgesic properties and may result in delayed onset of sedation and respiratory depression. The elimination of M6G is dependent on renal function, and in patients with renal failure, its half-life is prolonged from 2 to 27 h.[94] The metabolite load from an equi-analgesic dose of morphine given by the oral route is greater than that from the parenteral route, due to extensive first-pass metabolism. In renal patients, the dose of morphine should be reduced and the patient carefully monitored for signs of delayed onset respiratory depression postoperatively (Table 6). A significant fraction of morphine will be removed by HD.[5]

Fentanyl

Fentanyl undergoes extensive hepatic metabolism with no active metabolites. Approximately 7% is excreted unchanged in the urine.[68] Clearance is reduced in CKD, with a strong negative correlation between clearance and urea concentration.[65] HD has little impact on fentanyl plasma concentration.[5]

Alfentanil

Elimination half-life and plasma clearance are not altered in renal failure, although protein binding is reduced with an increase in the free fraction of alfentanil (Table 6).[17] There are no active metabolites. The dose required is reduced, but the dose interval remains unchanged.[94]

Remifentanil

Remifentanil is not dependent on renal function for elimination. It undergoes ester hydrolysis and its main metabolite is minimally active with 1/300–1/1000 the potency of the parent compound.[30] In patients on HD, remifentanil had a reduced clearance and prolonged elimination half-life (Table 6).[30] A lower infusion rate is required, but recovery is not significantly prolonged.[29]

Oxycodone

Oxycodone is metabolized in the liver to noroxycodone and oxymorphone. Oxymorphone has analgesic activity and both the parent compound and the metabolites accumulate in renal failure.[64] The elimination half-life of oxycodone is prolonged, from 2.3 h in controls to 3.9 h in established renal failure (Table 6).[64] The dose should be reduced and dose interval increased.

Tramadol

Thirty per cent of tramadol is excreted unchanged in the urine. *O*-Demethyl tramadol is an active metabolite which is excreted by the kidneys. Uraemia is associated with a lowered seizure threshold, and tramadol may be epileptogenic in these circumstances.[44] Tramadol is removed by HD.

Other opioids

Meperidine is metabolized to normeperidine which is dependent on renal function for elimination. The use of meperidine in patients with CKD has been associated with seizures, myoclonus, and altered mental state.[55] Codeine and dihydrocodeine are also best avoided as their elimination half-life is significantly prolonged, and conventional doses have resulted in central nervous system depression.[51 83]

Immunosupression therapy

Patients with Stage 5 CKD who have undergone renal transplantation require immunosuppression. These drugs are usually given by the oral route. If enteral administration is inappropriate, then i.v. administration with dose adjustment will be required. Traditional regimens include some form of triple therapy, consisting of a calcineurin inhibitor (ciclosporin or tacrolimus), an antiproliferative agent (azathioprine or mycophenolate mofetil), and a corticosteroid.[149] Newer regimens attempt to spare or eliminate corticosteroids and calcineurin inhibitors. Polyconal and monoclonal antibodies also form part of the armamentarium.

Calcineurin inhibitors

Ciclosporin and tacrolimus are calcineurin inhibitors which form the mainstay of immunosuppression therapy. They prevent cytokine mediated T-cell activation and proliferation by blocking the calcineurin phosphatase-dependent pathway involved in the transcription of several cytokines, interleukin-2 being the most important.[45] Both ciclosporin and tacrolimus are metabolized by CYP 3A4: drugs that either induce or inhibit this enzyme will alter the plasma concentration of these immunosuppressants. The oral bioavailability of ciclosporin is variable and is

influenced by the formulation used. The oral bioavailability of the unmodified formulation is 30%. The i.v. dose should be reduced accordingly and levels monitored.[149] The solvent in i.v. ciclosporin, cremophor EL, has been associated with anaphylactic reactions. Furthermore, i.v. ciclosporin may cause vasoconstriction and hyperkalaemia.[134] It should therefore be administered slowly as a continuous infusion.[45] Adverse effects include hypertension, hyperlipidaemia, hyperkalaemia, gum hypertrophy, and nephrotoxicity with renal fibrosis. Ciclosporin has been shown to increase the hypnotic effect of barbiturates and the analgesic effect of fentanyl in mice.[21] A retrospective study in humans found no evidence of clinically significant prolongation of anaesthetic effect.[90] Ciclosporin potentiates neuromuscular block. Its intraoperative use is associated with an increased risk of postoperative respiratory failure.[128]

Tacrolimus is similar to ciclosporin, but may have a better cardiovascular risk profile, with less hypertension and hyperlipidaemia, and although it is also nephrotoxic, it is associated with improved long-term post-transplant renal function.[42] Important adverse effects include disturbed glucose metabolism and diabetes mellitus, tremor, diarrhoea, neurotoxicity, and nephrotoxicity. Dose is adjusted according to monitored levels and an i.v. preparation is available.

Antiproliferative agents

Mycophenolate mofetil has replaced azathioprine. It acts by inhibiting *de novo* purine synthesis in lymphocytes. It is dosed empirically and adjusted when side-effects occur.[149] These include leucopaenia, diarrhoea, and infection. It is not nephrotoxic. The oral bioavailability is 94%. Azathioprine causes transient antagonism of neuromuscular block which is unlikely to be of clinical importance.[50]

Mammalian target of rapamycin inhibitors

Sirolimus and everolimus are used in some newer regimens to replace calcineurin inhibitors as they are less nephrotoxic. They act by blocking signal transduction in the interleukin-2 pathway. They are metabolized by CYP 3A4, with enzyme inducers and inhibitors affecting the level of immunsuppression. Side-effects include hyperlipidaemia, leucopaenia, thrombocytopaenia, pneumonitis, and, rarely, angioedema.[149]

Antibodies

Examples include antilymphocyte and antithymocyte antibodies (polyclonal), OKT3 which is a monoclonal mouse antibody directed against the CD3 protein complex, and anti-interleukin-2 receptor monoclonal antibody. OKT3 has been associated with non-cardiogenic pulmonary oedema, particularly in combination with pre-existing increased intravascular volume.[26] A biphasic response may follow administration with fever, hypertension, and tachycardia followed by hypotension and hypoxia.

Conclusions

In managing patients with CKD, the anaesthetist aims to minimize the risk of perioperative complications. This requires careful patient assessment and efforts to modify identified risk factors, for example, hyperkalaemia, to improve patient outcome. Recent developments in this regard include: a refined appreciation of the association between CKD and cardiovascular disease, knowledge of the importance of blocking the RAS to delay progression of the condition, and new insights into the complex prothrombotic and haemostatic abnormalities involved. It is clear that temporary vascular access for HD is to be avoided and subclavian HD catheters are associated with an unacceptably high risk of subclavian vein stenosis. The pharmacokinetic and pharmacodynamic changes must be taken into consideration: many drugs having reduced renal and non-renal clearance in CKD. PORC remains a risk.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

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