

Pharmacokinetics of Drugs Used in Critically Ill Adults

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Summary

Critically ill patients exhibit a range of organ dysfunctions and often require treatment with a variety of drugs including sedatives, analgesics, neuromuscular blockers, antimicrobials, inotropes and gastric acid suppressants. Understanding how organ dysfunction can alter the pharmacokinetics of drugs is a vital aspect of therapy in this patient group. Many drugs will need to be given intravenously because of gastrointestinal failure. For those occasions on which the oral route is possible, bioavailability may be altered by hypomotility, changes in gastrointestinal pH and enteral feeding. Hepatic and renal dysfunction are the primary determinants of drug clearance, and hence of steady-state drug concentrations, and of efficacy and toxicity in the individual patient.

Oxidative metabolism is the main clearance mechanism for many drugs and there is increasing recognition of the importance of decreased activity of the hepatic cytochrome P450 system in critically ill patients. Renal failure is equally important with both filtration and secretion clearance mechanisms being required for the removal of parent drugs and their active metabolites. Changes in the steady-state volume of distribution are often secondary to renal failure and may lower the effective drug concentrations in the body. Failure of the central nervous system, muscle, the endothelial system and endocrine system may also affect the pharmacokinetics of specific drugs. Time-dependency of alterations in pharmacokinetic parameters is well documented for some drugs. Understanding the underlying pathophysiology in the critically ill and applying pharmacokinetic principles in selection of drug and dose regimen is, therefore, crucial to optimising the pharmacodynamic response and outcome.

This review is targeted at the pharmacokinetics of drugs in critically ill patients in the intensive care unit (ICU). The definition of a 'critically ill' patient may vary widely and is difficult to quantify in the published literature. In this review we have tried to focus on studies of critically ill patients in the ICU setting. However, in many cases we have found it prudent to include studies on patients with major organ dysfunction, but who were not necessarily treated in an ICU. The first section of this review discusses mechanisms by which organ dysfunction may affect pharmacokinetic parameters (fig. 1). Subsequent sections will deal with selected groups of therapeutic agents and the alterations in their pharmacokinetic profiles seen in critically ill patients.

Critically ill patients present to the ICU with a range of organ dysfunction related to severe acute illness which may complicate long term illness. ICU patients include representatives of all age groups. All of these factors may impact on the pharmacokinetic aspects of drug administration in the

ICU. Additional factors that may impact on drug pharmacokinetics include drug interactions (e.g. warfarin and aminophylline) and other therapeutic interventions (e.g. dialysis).

The management of critically ill patients encompasses: (i) specific treatment of the disease process; (ii) general support of failing organs during natural healing and repair, including nutrition and maintenance of fluid and electrolyte balance; and finally, (iii) the avoidance and treatment of complications (e.g. sepsis). Many of these processes require the administration of drugs. The ultimate aim of drug administration in the critically ill patient is to achieve a safe and effective concentration of the drug in the target tissue.^[1,2] The ability to achieve this aim will depend on drug-related factors, such as the dose administered and disposition characteristics, as well as patient-specific factors such as drug delivery to the site of action (e.g. cardiac output).

In the ICU environment attention to detail is required with regard to drug administration. As many

drugs are given on a dose per bodyweight basis it is important to weigh patients if at all possible. Serial weights will also help determine the loss of body mass or the gain in body water, both of which will affect the pharmacokinetics of drugs administered to these patients. Also the timing of drug doses, the compatibility of drugs coadministered via infusion lines, rate of drug infusion and complete administration of the required dose all require attention.

Pharmacokinetic parameters which require consideration are the absorption, distribution, metabolism and excretion of the drug.^[3] All of these parameters may be affected by disease processes.

Drug administration in critically ill patients mandates specific titration of drugs to effect (i.e.

the avoidance of average therapeutic regimens) and the measurement of both physiological response and drug concentrations where appropriate to avoid unnecessary drug interactions and adverse reactions. This approach will help identify the causes of poor or non-response to medication as well as 'unexplained' adverse reactions.

1. Organ Systems Responsible for Drug Disposition in Critically Ill Patients

1.1 Gastrointestinal Failure

Gastrointestinal (GI) failure in the critically ill patient may affect drug pharmacokinetics in several ways. Firstly, there is frequent loss of the most common and convenient route of drug administra-

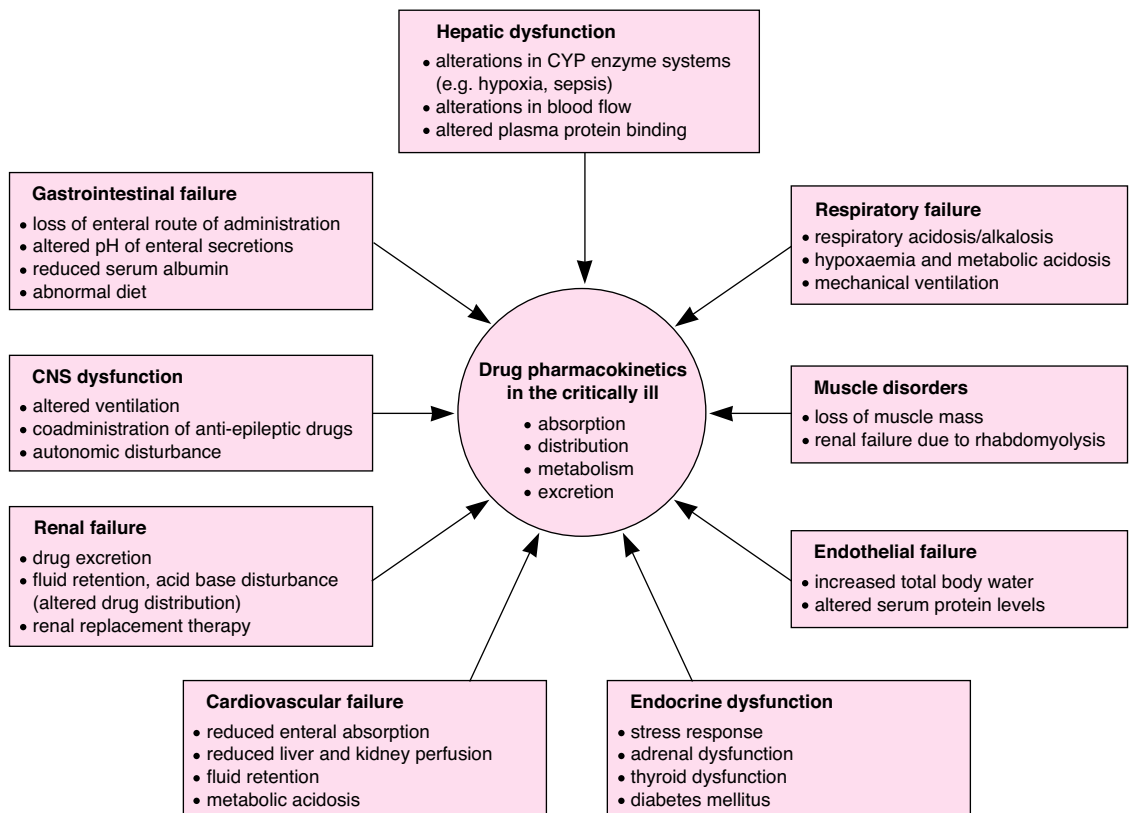


Fig. 1. Schema for the alterations in function of various organs/body systems that may impact on the pharmacokinetics of drugs used in critically ill patients. *Abbreviation:* CYP = cytochrome P450.

tion in the ambulant patient (i.e. the enteral route). This is usually due to gut hypomotility in the critically ill patient following surgery, caused by the constellation of organ failure associated with sepsis or as a result of the administration of opioids for analgesia. Hypomotility and the resultant reduction in drug absorption improve as the patient recovers, allowing enteral administration of drugs. In the acute phase of critical illness the concomitant administration of promotility agents may overcome stasis, in particular gastric stasis, and improve GI absorption of drugs. The large number of variables which influence gut motility make the enteral route of drug administration unreliable in the acute phase of critical illness and thus the intravenous route of administration is preferred. The plasma drug concentrations obtained following enteral administration of the drug may vary widely between individuals in this setting. In most cases, the intravenous route of administration, with its associated invasiveness and cost, is required to ensure reliable plasma drug concentrations. Gut hypermotility can also occur in the critically ill and may reduce the absorption of enterally administered drugs by decreasing mucosal contact time in the small intestine.

Secondly, the pH of the GI tract secretions may be altered by a number of factors.

- The acid environment in the stomach may be lost due to the administration of H₂ receptor antagonist drugs given to reduce 'stress' ulceration. This effect is less likely to be a problem because of the increasing use of sucralfate as a cytoprotective agent.
- Exocrine pancreatic dysfunction may result in a lower pH of intestinal secretions. These alterations in pH might cause variability in both the rate of and extent of bioavailability of drug absorption via alterations in the proportion of the uncharged species which controls absorption for most drugs or in the rate of drug delivery to the intestine.

Thirdly, a reduction in the level of serum albumin because of reduced dietary protein intake, haemodilution, and/or reduced hepatic synthesis may in-

crease free concentrations of some highly protein bound drugs and enhance their effects. These effects have been well demonstrated for phenytoin, where the free fraction of drug is increased in patients with hypoalbuminaemia and hepatic or renal impairment.^[4] It has been suggested that free concentrations of phenytoin are routinely measured in this setting to avoid adverse effects from high free fractions of phenytoin.^[4]

Fourthly, feeding may be intermittent and may interfere with drug absorption. The practice of administering crushed tablets via a nasogastric tube may alter the chemical stability and bioavailability of drugs. Diet in the ICU patient is frequently abnormal with vitamin deficiencies, changes in the ratio of carbohydrate, fat and protein intake or starvation. These changes may affect the way in which drugs are handled by the liver, usually via effects on cytochrome P450 (CYP).^[5]

1.2 Hepatic Dysfunction

Metabolic clearance in the liver is the major route for detoxification and elimination of a wide variety of drugs. Hepatic dysfunction is present in up to 54% of critically ill patients^[6] and this is associated with hypothermia, hypotension and sepsis and may result in decreased drug clearance via reduced hepatocellular enzyme activity, reduced hepatic blood and/or bile flow.^[3] Oxidation by the various isoforms of CYP and conjugation with glucuronide, sulphate or glutathione are the dominant reactions in humans, although a range of phase I and II metabolic reactions can be important for individual drugs.^[5]

The CYP system has recently been shown to be greatly affected in critical illness.^[7-9] Figure 2 shows data reported for midazolam metabolism to 1-hydroxy midazolam in a patient with septic shock.^[10] The 1-hydroxy metabolite concentration in blood appears to increase and decrease in concert with the severity of the patient's condition. Presumably hepatic metabolism is limited by factors such as the organ perfusion rate, intracellular oxygen tension and cofactor availability. Both CYP and conjugation pathways could be involved.

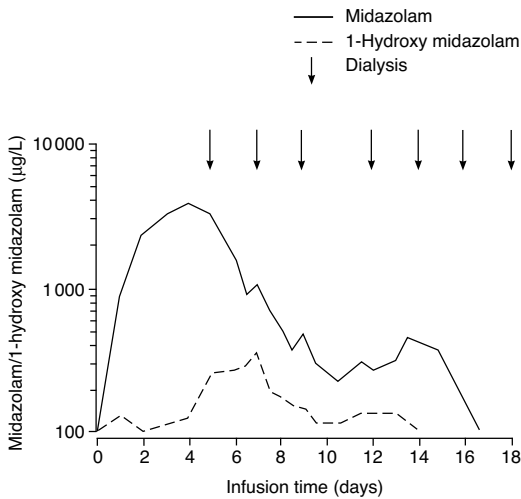


Fig. 2. Time-related metabolism of midazolam to 1-hydroxy midazolam in a critically ill patient with septic shock. Metabolism (and 1-hydroxy concentration) is low on days 0 to 4, improves between days 5 and 8 and deteriorates again from day 13 onwards. Infusion stopped on day 16 (from Shelly et al.,^[10] with permission).

Hypoxaemia results in reduced enzyme production in the liver, reduced efficiency of the enzyme present and decreased oxygen available for drug oxidation.^[5] In addition, hepatic drug metabolism is reduced in sepsis by the inhibition of CYP-dependent drug metabolism.^[9] This inhibition of CYP has recently been suggested to be mediated via endotoxin-induced nitric oxide production which in turn damages the CYP enzymes.^[11]

Interaction processes with coadministered drugs are important and CYP enzyme systems are affected by drugs that cause enzyme inhibition (e.g. ketoconazole, erythromycin and fluoxetine) or enzyme induction [e.g. carbamazepine, phenytoin and phenobarbital (phenobarbitone)]. For example, erythromycin inhibits CYP3A4 and may reduce the clearance of warfarin, methylprednisolone and cyclosporin. A full discussion of drug interactions is beyond the scope of this review (however, 2 recent reviews can be consulted^[12,13]). Diet, or lack of it, in the critically ill, as well as the stress response, may impact on hepatic metabolism.

Liver blood flow may vary widely in the critically ill and will influence the metabolism of drugs with flow-dependent clearance. McNab et al.^[14] has shown that hepatic blood flow may be reduced more than 3-fold in patients with septic shock. Chronic liver disease must be included in any assessment of hepatic drug clearance. Disease states such as cirrhosis will predominantly affect drugs with high extraction ratios (ER) [e.g. lidocaine] because of the reduction in hepatic blood flow caused by the abnormal hepatic architecture. Drugs with a low ER (e.g. phenytoin) rely more on hepatocellular integrity and clearance will be sensitive to hepatocellular injury (e.g. ischaemic or viral hepatitis).

The bioavailability of enterally administered drugs which undergo extensive first-pass metabolism (e.g. propranolol and metoprolol) in patients with hepatic dysfunction may be markedly increased. Critical illness may cause increased concentrations of acute phase reactant proteins such as α_1 -acid glycoprotein and reductions in plasma albumin concentrations. Alterations in acute phase reactants are often variable and may alter the clearance of drugs which have significant binding to these proteins (e.g. alfentanil).^[15] When hepatic dysfunction is severe, extrahepatic sites of drug metabolism, such as the gut and the lung, may become more important in drug clearance.

1.3 Cardiovascular Failure

Acute cardiovascular failure impacts on pharmacokinetics by several mechanisms and these are listed below.

(i) Reduced perfusion of the liver and kidneys resulting in decreased drug clearance. Homeostatic mechanisms (increased sympathetic drive) will attempt to maintain blood flow to the heart, brain and muscle at the expense of renal and splanchnic blood flow. This effect is seen most dramatically when a bolus dose of a sedative drug is administered intravenously to the shocked patient. Cardiac output, and therefore the drug, is directed preferentially to the brain and the heart, resulting in exaggerated effect (e.g. sedation and cardiac depres-

sion), followed by prolonged action due to reduced clearance of the drug.

(ii) Reduced enteral absorption of drug. This is due to the decreased forward flow (reduced organ perfusion) and occasionally increased back pressure (venous congestion) on the gut. Gut hypoperfusion and poor absorption of drugs theoretically may be worsened by the presence of mucosal oedema caused by hypoproteinaemia. A reduced skin blood flow will also cause erratic absorption for drugs given by the subcutaneous route.^[1]

(iii) Fluid retention, as part of the homeostasis, in response to the failing heart and because of fluid administered during resuscitation of the critically ill. This may increase the volume of distribution (V_d) of drugs, altering both the clearance and effect.^[16]

(iv) Reduced perfusion may cause anaerobic metabolism and metabolic acidosis which may then alter the distribution of ionisable drugs.

1.4 Respiratory Failure

The lung is not usually a major pathway for drug clearance, although it may be important for specific drugs (e.g. catecholamines).^[17] However, respiratory failure may impact on the pharmacokinetic profiles of drugs by several mechanisms:

- Hypoxaemia may have a profound effect on the ability of hepatic enzymes to metabolise drugs (see section 1.2).
- Respiratory failure may be accompanied by acidosis or alkalosis which will affect the pH of renal tubular fluid. In turn, this could alter the disposition of drugs whose renal clearance is pH sensitive [e.g. decreased half-life ($t_{1/2}$) for methadone and increased $t_{1/2}$ for salicylate in metabolic acidosis].
- Mechanical ventilation may be complicated by reduced cardiac output. The increase in intrathoracic pressure occasioned by the use of mechanical ventilation results in homeostatic mechanisms that increase intra- and extravascular water and, therefore, V_d .^[18,19]
- Extracorporeal membrane oxygenation (ECMO) is used in a small number of patients with severe

respiratory failure. The use of an extracorporeal circuit may significantly alter the pharmacokinetics of drugs [e.g. drugs may bind to the circuit increasing clearance, extravascular water may increase and thereby alter the apparent volume of distribution (V_z)].^[20] The effects of ECMO on specific drugs have been well described.^[21,22]

1.5 Renal Failure

Acute renal failure (ARF) or acute on chronic renal failure (ACRF) have profound effects on many aspects of drug pharmacokinetics, including drug excretion and distribution.

1.5.1 Excretion

The kidneys are responsible for the excretion of both the parent drug and metabolites produced by the liver and other tissues, and in renal failure both the parent drug and metabolites [some of which are pharmacologically active, e.g. 1-hydroxy midazolam glucuronide and morphine-6-glucuronide (M6G)] may accumulate.^[23-25]

1.5.2 Distribution

Fluid retention is a feature of both ARF and ACRF with consequent changes in total body water and the V_z for many drugs. In addition, metabolic acidosis and respiratory alkalosis are common in ARF and ACRF. The resulting pH differential between the plasma and tissue compartments may result in variability in the tissue distribution of ionisable drugs, depending on their pKa values.

Renal replacement therapy (RRT), including dialysis, will remove variable amounts of drugs usually cleared by the kidneys (see specific drugs in sections 2 to 6). The most common modes of RRT employed in the critically ill are intermittent haemodialysis, continuous arteriovenous haemofiltration or haemodiafiltration (CAVHD), continuous venovenous haemofiltration or haemodiafiltration and slow continuous ultrafiltration. All use an extracorporeal blood circuit in which blood flows through a filter.

Drug clearance by RRT may be calculated by measuring the plasma and filtrate drug concentra-

tions and the volume of filtrate, by using this equation:

Clearance = (filtrate drug concentration \times filtrate volume/unit time) over average plasma drug concentration

Pharmacokinetic studies in patients with renal failure requiring RRT are extensive and provide information on clearance and dose modification for a wide range of drugs.^[20] In the case of antibiotics, the loss of drug during RRT may require additional loading doses.^[26-37]

1.6 Central Nervous System Dysfunction

Central nervous system (CNS) failure does not directly affect drug pharmacokinetics. However, hypo- and hyperventilation, common in CNS failure, will result in acid-base disturbances (see section 1.4). The effect of drugs on the brain of patients with associated organ failure also needs to be considered in critically ill patients (e.g. the use of morphine with subsequent CNS depression in the patient with ARF). Cerebral 'irritation' in head injured patients results in a high sympathetic outflow and increased cardiac output, which in turn may increase hepatic and renal blood flow and alter elimination of drugs. Antiepileptic agents, some of which are potent inducers of CYP isozymes (e.g. carbamazepine and phenytoin), are commonly used in this group of patients. The addition of these agents to the therapy of a patient may cause the increased clearance of other concomitantly administered drugs which are cleared by the induced CYP isoforms.

Maintaining therapeutic concentrations of phenytoin in this group of patients is difficult and may require frequent measurement of plasma concentrations and dose adjustment. It is suggested that the low plasma phenytoin concentration in critically ill patients with head injuries is due to the increased clearance of phenytoin, particularly in those patients receiving long term enteral feeding.^[38] The maximum rate of metabolism by an enzyme-mediated reaction (V_{max}) was significantly higher (709 vs 394 mg/day) and Michaelis-Menten constant (K_m) significantly lower (2.5 vs 3.9

mg/L) in patients receiving enteral feeding for less than 5 days and more than 5 days, respectively.

1.7 Muscle Disorders

Skeletal muscle is profoundly affected by critical illness with hypercatabolism and associated myopathies and neuromyopathies. Drugs such as pancuronium and corticosteroids may have a reduced rate of elimination (and, therefore, prolonged duration of action) in the critically ill patient which may exacerbate neuromyopathy and muscle wasting. Renal failure arising from rhabdomyolysis may indirectly alter drug excretion. Algorithms for estimation of creatinine clearance (CL_{CR}) and lean body mass may be unreliable in ICU patients.^[39]

1.8 Endothelial Failure

Burns and systemic inflammatory response syndrome (SIRS) have a widespread effect on the endothelium, with resultant increases in total body water and interstitial fluid, which may affect both the V_z and clearance of drugs (due to hepatic and renal oedema). In the case of patients with burns, serum protein levels may be reduced because of the seepage of protein-rich fluid from the burn site. In addition, the associated stress response in burns and SIRS may impact upon water and salt homeostasis and serum protein levels, affecting drug protein binding and V_d . Hypovolaemia and cardiac dysfunction (see section 1.3) are encountered in patients with burns or with SIRS. Respiratory dysfunction and its attendant problems are also common in these patients. Endothelial injury, therefore, affects many organ systems and is likely to alter drug disposition by a variety of different mechanisms.

1.9 Endocrine Dysfunction

In the critically ill patient there may be marked changes in hormonal function.^[5] This may be as a result of a critical illness, the so-called stress response, or the cause for the admission to ICU, such as hypoadrenalism or hypothyroidism. The stress

response, associated with high circulating concentrations of catecholamines and cortisol, is able to influence the pharmacokinetics of drugs by increasing cardiac output, by redistributing the cardiac output (less splanchnic flow) and by fluid retention and increase in circulating volume (changes in V_d).

Stress also causes complex changes in circulating plasma protein levels (see section 1.3) which can affect the free fraction of the drug. These changes can also be induced by the administration of drugs such as catecholamines or exogenous steroids to patients in the ICU.

Marked plasma volume changes are associated with hypoadrenalism, resulting in responses to drugs as described for shock (see section 1.3). The effects of diabetes mellitus, thyroid disease and changes in glucagon levels on pharmacokinetics have recently been reviewed by Park.^[5]

2. Sedatives and Analgesics

Critically ill and mechanically ventilated ICU patients often require prolonged sedation and analgesia. An ideal sedative agent would be inexpensive, have rapid predictable onset and be readily cleared by the body without accumulation. While sedatives and analgesics are sometimes given by intermittent bolus injections, infusions are commonly used. The duration of these infusions can be days or weeks. Because some of these drugs and/or their active metabolites show multicompartmental behaviour, the pharmacokinetic values derived from short term administration may not be predictive of pharmacokinetic descriptors following long term infusion. Time-related changes in hepatic metabolism and in the V_d may also complicate steady state concentrations. The drugs most commonly used to maintain sedation are propofol and the benzodiazepines, often supplemented by opioids.

2.1 Benzodiazepines

Benzodiazepines are the agents most commonly used to maintain sedation in ICU. They provide reliable amnesic action with the adverse effects of cardiovascular and respiratory depression. Their

clinical effects result from reversible binding with the γ -aminobutyric acid – benzodiazepine receptor complex. Differences in the clinical response to benzodiazepines are related to both pharmacodynamic and pharmacokinetic variability. These differences are most marked in critically ill patients when these agents are given for prolonged periods by infusion.

All benzodiazepines undergo metabolism and then elimination in the urine. All undergo oxidative metabolism save for lorazepam which is metabolised by conjugation with glucuronic acid. Metabolites may have variable clinical action. Changes in the pharmacokinetics may result from changes in oxidative drug metabolism. Other important factors altering pharmacokinetics in the ICU are: age, renal dysfunction, V_d changes in critical illness and genetic variations.

2.1.1 Midazolam

Midazolam is water soluble at a low pH, allowing administration in a nonlipid carrier, but once it enters the body its closed imidazole ring structure renders it lipophilic and it becomes readily able to penetrate cell membranes.^[40] Midazolam infusion in intensive care may allow prolonged sedation without evidence of adrenal suppression.^[41,42] Midazolam is 94 to 98% protein bound, has a short distribution $t_{1/2}$, a large steady-state V_d (V_{ss}) [0.68 to 1.77 L/kg],^[43-45] an intermediate plasma total body clearance (CL) [means 18 to 39 L/h]^[43,44,46-48] and a short terminal elimination half-life ($t_{1/2z}$) [1.5 to 5 hours].^[40,48]

Midazolam is cleared almost exclusively by metabolism (hepatic ER = 0.3 to 0.5),^[40,45,46] and less than 1% is excreted unchanged in the urine.^[43,46] The initial metabolite (1-hydroxy midazolam) has a potency similar to that of midazolam,^[47,49] while the glucuronide metabolite of 1-hydroxy midazolam has a potency one-tenth of the parent compound.^[25] The latter may accumulate to extremely high plasma and tissue concentrations in the presence of renal failure and is responsible for prolonged sedation in the critically ill.^[25]

The pharmacokinetics of midazolam following bolus doses^[43,47] and short term infusions^[50] have

been studied in healthy individuals and in various age and disease state groups, including the elderly,^[44,51] hypoproteinaemia,^[52] major surgery,^[44] renal failure^[53] and chronic liver disease.^[54-56]

Although midazolam is the most predictable and easily titrated benzodiazepine, its duration of action can vary greatly in critically ill patients. Its disposition is also subject to wide interpatient variability.^[57,58] Although Michalk et al.^[59] did not find midazolam accumulation in ventilated ICU patients without significant organ dysfunction, sporadic case reports of prolonged $t_{1/2}$ in critically ill patients^[60,61] ($t_{1/2}$ from 4.3 to 53 hours) emerged soon after the general introduction of this drug for sedation in ICU patients. Within the ICU, prolonged sedation has been seen in mechanically ventilated patients,^[57,62-64] in septic shock,^[10] acute renal failure^[65] and following cardiac surgery.^[66]

The major reasons for the accumulation of midazolam in critically ill patients appear to be changes in V_z , protein binding and hepatic metabolism. The most dramatic changes in the pharmacokinetics of midazolam in the critically ill may result from altered hepatic metabolism. Shelly et al.^[10] demonstrated accumulation in critically ill patients at the peak of their illness with low or absent concentrations of 1-hydroxy midazolam, suggesting the failure of liver metabolism. Metabolite concentrations subsequently increased as the patient recovered.

The decrease in metabolism was postulated as due to either a reduced liver perfusion or an enzyme defect. Park et al.^[8] has demonstrated that serum from critically ill patients inhibits CYP3A4 which is responsible for the 1-hydroxylation of midazolam. Putative mechanisms by which this is thought to be mediated include the presence of an enzyme inhibitor and secondly by a tumour necrosis factor α (TNF α)-stimulated production of NO^[11] that reduces in the expression of CYP.^[5,7]

Marked variation in the V_d of midazolam has been seen in healthy individuals and may be responsible for the prolonged $t_{1/2}$ (>8 hours) in these patients since they have normal clearance values. Obesity is the commonest cause of this increased V_d .^[48] The increased V_z for midazolam in critical

illness (3.1 vs 0.9 L/kg) is probably responsible for the prolonged elimination of midazolam seen in many ICU patients.^[10,62] After correction for changes in V_d and changes in plasma protein binding, there was no change in metabolism due to renal failure.^[53] Maitre et al.^[66] has shown a prolonged $t_{1/2}$ (10.6 hours) and decreased metabolic clearance (15 to 18 L/h) in patients recovering from cardiac surgery.

2.1.2 Diazepam

Diazepam was used as the predominant sedative agent in ICUs in the 1970s but was associated with significant accumulation ($t_{1/2} = 2$ to 4 days) and prolonged action if appropriate dose adjustments were not made.^[67] Midazolam has now replaced diazepam as the most commonly prescribed benzodiazepine in the ICU setting. Diazepam has a much lower hepatic clearance than midazolam and longer mean $t_{1/2}$ of 44 and 72 hours^[68] in young and elderly healthy individuals, respectively. There is a large interpatient variation in $t_{1/2}$, even in healthy individuals. The mean plasma clearance is low (means 0.0162 to 0.0222 L/h/kg)^[68] and is independent of liver blood flow.

The metabolites desmethyldiazepam and oxazepam are both pharmacologically active.^[69] Both contribute significantly to the prolonged sedative action of diazepam. Desmethyldiazepam $t_{1/2}$ is twice that of diazepam^[68] in healthy individuals and $t_{1/2}$ ranges from 4 to 8 days in the critically ill.^[67]

Liver cells again provide the major metabolic pathway for diazepam removal. In the presence of hepatic cellular dysfunction the $t_{1/2}$ of diazepam is prolonged from a mean of 33 to 108 hours.^[70] Desmethyldiazepam has an even larger prolongation of its $t_{1/2}$ leading to accumulation in this setting. Increased V_z also contributes to this change. Renal failure is not associated with significant changes in the clearance of unbound drug.^[71]

2.1.3 Lorazepam

Lorazepam is recommended by the American College of Critical Care Medicine (ACCM) and the Society of Critical Care Medicine (SCCM) as the agent of choice for prolonged anxiolysis in the

ICU.^[72] Although it has a slow onset of action due to slow brain penetration, it has an intermediate to prolonged action. It is metabolised by hepatic glucuronidation and indeed has been used as a marker of this enzyme activity.^[73] This is of importance as this metabolic pathway seems to be better preserved with age and is less disturbed during the liver disturbance of critical illness. With prolonged infusion, Boucher et al.^[74] found a 9 to 130% increase in lorazepam clearance at day 14. The increase was independent of changes in hepatic blood flow and protein binding, and suggested to be because of the increased hepatic oxidative and conjugative metabolism.

2.2 Propofol

Propofol (2,6-diisopropylphenol) is an intravenous sedative agent that produces dose dependent depression of the CNS. It is water insoluble and is administered in a 1% oil in water emulsion containing 10% soya bean oil, 2.25% glycerol and 1.2% purified egg phosphatide.

The pharmacokinetics of propofol in healthy individuals undergoing surgery are characterised by a rapid distribution phase ($t_{1/2} = 1.3 \pm 0.8$ minutes; mean \pm SD), a rapid redistribution phase ($t_{1/2} = 30 \pm 16$ minutes) and a $t_{1/2}$ of 3.9 ± 2.8 hours.^[75,76] Propofol is metabolised primarily by conjugation in the liver to inactive glucuronide and sulphate metabolites which are then cleared by the kidney. Therefore, liver disease might be expected to most significantly affect clearance although clearance in healthy individuals is higher than hepatic blood flow, suggesting extrahepatic clearance ($CL \approx 1.5$ L/min). This has been confirmed during liver transplantation where clearance continues during the anhepatic phase.^[77,78] Raoof et al.^[79] has suggested that this extrahepatic glucuronidation may occur in the small intestine and the kidney.

Metabolism of propofol does not appear to be significantly altered by hepatic or renal disease. However, in critical care populations, clearance is generally slower than in the general population, probably reflecting a decreased hepatic blood flow.^[80,81] The clearance of propofol is flow, rather

than enzyme, limited. Thus Frenkel et al.^[81] found an increased V_{ss} ($0.5 \pm 0.15L$) and decreased CL (60 ± 9 L/h) in ventilated critically ill patients compared with healthy general surgery patients undergoing short term infusions (V_{ss} means 0.22 to $0.38L$ and CL means 1.77 to 2.3 L/min).^[75,76,82,83] They did not find significant accumulation of propofol. Similar mild reductions in clearance have been seen in other patient populations,^[80,84] but not all critically ill patients^[85] receiving prolonged infusions.

Elderly patients have decreased clearance and prolonged $t_{1/2}$ and thus maintenance infusions are best reduced in an age-related fashion. Long term infusions of propofol may result in accumulation within body lipids, and a prolonged elimination phase. Albanese et al.^[84] maintained sedative steady-state concentrations in critically ill patients for 42 hours. The observed mean $t_{1/2}$ of 31.3 hours was far in excess of values in studies using shorter infusion periods. Eddleston et al.^[86] has reported decreased plasma concentrations of propofol in patients undergoing haemodiafiltration, but it is uncertain whether this is due to haemodilution or to the adsorption of drug onto the dialysis membrane.

2.3 Narcotic Analgesics

Opioid narcotics are used extensively in the critically ill, both to provide analgesia and as sedative sparing and neuromuscular-blockade sparing agents. Many opioids are now available and they have considerable differences in onset and duration of action. In the ICU, these agents are often given by intravenous infusion over a prolonged period. Pharmacokinetic and pharmacodynamic differences are important, especially where prolonged action may lead to delayed ventilatory weaning.

2.3.1 Morphine

Morphine may have prolonged action in the critically ill, especially in the presence of renal dysfunction. Although this was attributed by some to impaired metabolism or reduced elimination of the morphine parent compound,^[87] the persistence of narcosis has now been shown to be because of an accumulation of the active metabolite M6G.^[23,88]

Both M6G and M3G metabolites have delayed excretion in the presence of renal failure.^[23,24,88] Milne et al.^[88] have defined the pharmacokinetics of M6G and M3G in critically ill patients. In the presence of renal failure, they found a linear relationship between the renal clearance of morphine, M3G, M6G and the measured CL_{CR} .

Shelley et al.^[23] has demonstrated rapid clearance of morphine to M3G and M6G even in the presence of hepatic failure. However, these findings are contradicted by those of McNab et al.^[14] who has demonstrated a 3-fold increase in the $t_{1/2z}$ and a 53% reduction in the clearance of morphine in shocked ICU patients with inadequate hepatic perfusion compared with nonshocked ICU patients.

2.3.2 Pethidine (Meperidine)

Pethidine (meperidine) is hepatically metabolised by hydrolysis to pethidinic acid and by *N*-demethylation to norpethidine which is then renally excreted. Norpethidine is of interest because it is both pharmacologically active and can cause CNS toxicity including myoclonus, tremors and seizures not reversed by naloxone.^[89] The $t_{1/2z}$ of norpethidine ranges from 15 to 20 hours in patients with normal renal function to 30 to 40 hours in patients with renal failure.^[90] Accordingly, pethidine is not recommended for use in the critically ill.^[72]

2.3.3 Fentanyl and Related Derivatives

The phenylpiperidine opiate opioid fentanyl and its derivatives alfentanil, sufentanil and remifentanyl have similar chemical structures and possess typical opioid characteristics. They are highly lipid soluble and all except remifentanyl are metabolised by the liver to inactive metabolites (except for desmethyl fentanyl, which is a metabolite of sufentanil) that are then excreted in bile and urine. Remifentanyl is metabolised by ubiquitous tissue and plasma non-specific esterases to an inactive metabolite. Despite the above similarities, there are significant pharmacokinetic and pharmacodynamic differences between these agents. Only fentanyl has achieved common use as a long term

narcotic agent in the critically ill although the others are used in specific patient groups.

Fentanyl is highly lipid soluble with a V_z of 3.2 to 5.9 L/kg^[91] in healthy individuals and an intermediate clearance rate of 0.48 to 1.26 L/h/kg^[91] reflecting its rapid hepatic metabolism by dealkylation, hydroxylation and amide hydrolysis to inactive metabolites which are then excreted in bile and urine with only 2 to 15% being excreted unchanged in the urine.^[92] It has a high intrinsic hepatic clearance ($ER = 0.62$) with estimates of clearance ranging from equivalent to hepatic blood flow to one-third of hepatic blood flow. Pharmacokinetics are not significantly disturbed in patients with cirrhosis undergoing general anaesthesia.^[93]

Fentanyl is metabolised by the CYP3A enzyme system.^[5] There is little information on its pharmacokinetics in the critically ill. Alazia et al.,^[94] in a small series of ICU patients without hepatic disease, found a markedly prolonged $t_{1/2z}$ and enlarged V_z , but normal clearance. In paediatric ICU populations^[95] there is a great age-dependent variation in pharmacokinetic parameters including the V_d ($V_{ss} = 5$ to 30 L/kg) and total body clearance is highly variable in this group with a tendency to accumulate. The V_d is typically increased and the $t_{1/2z}$ is prolonged in this group.

Alfentanil has a lower lipid solubility and V_{ss} (0.86 L/kg) which is one-quarter that for fentanyl.^[96] Its $t_{1/2z}$ of 1.53 hours is shorter than that of fentanyl (3.67 hours) despite a slightly lower hepatic ER (0.30 to 0.50).^[97] Bower et al.^[15] has shown that liver dysfunction causes greater alterations in alfentanil disposition than its congeners fentanyl and sufentanil.^[98] In hepatic dysfunction, decreased metabolism may be balanced by increased free drug where there is a reduction in plasma albumin and α_1 -acid glycoprotein. Frenkel et al.^[81] found wide interpatient variation in the pharmacokinetics of alfentanil in critically ill patients but there was no clinical evidence of accumulation. Yate et al.^[99] also found wide variability in pharmacokinetics and significant accumulation in 1 of 15 patients requiring overnight sedation following cardiopulmonary bypass (CPB). Human

liver CYP3A4 contributes significantly to alfentanil metabolism and alteration in the activity of this enzyme in the critically ill is expected to alter the pharmacokinetics.^[100]

Sufentanil ($V_z = 3.3 \pm 0.7$ L/kg)^[98] is more lipid soluble than fentanyl but has a similar clearance (0.678 ± 0.15 L/h/kg)^[98] and $t_{1/2}$ (3.5 ± 0.9 hours)^[98] because of its high hepatic clearance (ER = 0.72).^[96] While sufentanil should have a V_d many times larger than that of fentanyl this is not so, because of extensive binding to plasma proteins with a consequent decrease in tissue penetration.

Remifentanyl is a new opiate with pharmacodynamic responses similar to those of fentanyl. However, its methyl-ester linkage is susceptible to metabolism by blood and tissue esterases, with metabolites being renally excreted. Derschwitz et al.^[101] found no differences in pharmacokinetics between healthy individuals (a control group) and patients with chronic liver disease severe enough to require transplantation. This suggests that this agent may be the first true short-acting opiate.

3. Neuromuscular Blockers

Neuromuscular blocking drugs are ionised, water-soluble quaternary ammonium compounds, used to facilitate mechanical ventilation and reduce respiratory muscle oxygen consumption, for the control of raised intracranial pressure and the treatment of specific conditions, such as tetanus and status epilepticus. Although still used frequently in the ICU, there is a trend to use them less often and to use shorter-acting agents.^[102] Nondepolarising neuromuscular blockers, such as pancuronium, vecuronium and atracurium, are the most commonly prescribed agents and are as often administered by intermittent bolus or by continuous infusion.^[102]

Prolonged administration of neuromuscular blockers in the critically ill may be associated with prolonged weakness due to drug accumulation. Regular twitch monitoring is useful here in guiding the administration of such agents. Of particular concern following the repeated or continuous infusion of large doses of neuromuscular blocking

agents is prolonged weakness and wasting because of a pharmacodynamic action at the neuromuscular junction, even in the absence of high ongoing drug concentrations. Although such weakness was initially reported with the aminosteroid neuromuscular blocking agents,^[103,104] it has now been suggested to occur with similar incidence following the administration of atracurium.^[105] Simple bedside neuromuscular monitoring is again useful here in reducing this severe complication.^[106]

Clinically significant accumulation of neuromuscular blocking agents in ICU patients results predominantly from delayed elimination. Elimination can be considered in terms of agents that are excreted: (i) solely by the kidney (e.g. gallamine); (ii) predominantly by kidney but also by the liver (e.g. pancuronium); (iii) mainly by the liver but also by the kidney (e.g. vecuronium, rocuronium); and (iv) removed by other metabolic pathways (e.g. atracurium, mivacurium).

3.1 Pancuronium

Pancuronium is suggested by the ACCM and SCCM as the preferred neuromuscular blocking agent for most critically ill patients,^[107] although vecuronium will be preferred by many where muscarinic adverse effects are to be avoided. Pancuronium is largely excreted unchanged in the urine, but a small percentage is metabolised to 3-desacetylpancuronium which may accumulate after prolonged infusion^[108] and is poorly cleared by haemofiltration. Pancuronium also accumulates in fulminant hepatic failure.^[109] Prolonged infusion of pancuronium with renal or hepatic failure is relatively contraindicated and certainly clinicians should use bedside muscle twitch monitoring if possible.

3.2 Vecuronium

Vecuronium, a steroid-based compound derived from pancuronium, is cleared predominantly by the liver but is also renally excreted. In the presence of normal hepatic and renal function, the $t_{1/2}$ of vecuronium is 1.33 to 1.8 hours.^[110] Vecuronium, like pancuronium, is deacetylated in the liver to

produce 3-desacetyl, 17-desacetyl and 3,17-desacetyl derivatives which are respectively 2 times, 17 times and 35 times less potent than the parent vecuronium compound.^[111]

Only 3-desacetyl vecuronium has been documented to accumulate.^[112] Segredo et al.^[112] has shown that significant accumulation of the parent drug and its metabolites can occur in critically ill patients with renal dysfunction following prolonged infusion. More extensive data on the pharmacokinetics of 3-desacetyl vecuronium in the critically ill is not available. Of importance, vecuronium and the 3-desacetyl vecuronium metabolite are poorly cleared by haemodialysis.^[112]

3.3 Atracurium

Atracurium is of pharmacokinetic interest for 2 principal reasons. Firstly, it is metabolised primarily by ester hydrolysis with a small amount excreted unchanged in the urine. Ward and Weatherley^[113] thus found that isolated renal, hepatic and combined renal-hepatic failure were not associated with altered pharmacokinetics of atracurium itself in patients following bolus doses. Pharmacokinetics of the parent atracurium compound following infusion^[114] are unaltered in ICU patients by the presence of acute renal failure and by combined renal and fulminant hepatic failure.^[115]

Secondly, metabolism of atracurium results in the production of laudanosine which is potentially neurotoxic and has been shown to accumulate in renal failure. Thus, Parker et al.^[114] have shown that although ICU patients with renal failure have similar rapid atracurium clearance rates to those without renal failure, laudanosine clearance is delayed (23.6 vs 6.25 hours) and laudanosine concentrations in these patients may be 3-fold higher. Yate et al.^[116] found similar elevations of laudanosine in the critically ill, however concentrations were still considerably lower than those associated with seizures in dogs. The toxicity profile of this metabolite in humans is not determined.^[115,116] Bion et al.^[115] noted that laudanosine was not cleared by haemofiltration and that in the presence of severe hepatic and renal failure, $t_{1/2z}$ was up to 38.5 hours.

3.4 Mivacurium

Mivacurium, a short-acting nondepolarising competitive muscle relaxant, is metabolised by hydrolysis by plasma pseudocholinesterase and, as such, its action may theoretically be prolonged in the presence of atypical plasma cholinesterases and hepatic dysfunction. Thus, Cook et al.^[117] have demonstrated decreased clearance (mean 1.998 L/h/kg vs mean 4.224 L/h/kg in the control group) in patients undergoing liver transplantation compared with anephric and normal patients. Clearance showed a strong correlation with plasma cholinesterase concentrations. Mivacurium exists as 3 stereoisomers, and although 2 are rapidly metabolised by cholinesterase, the *cis-cis* isomer has a prolonged renal-dependent clearance. However, when prolonged infusions are used, accumulation of this isomer does not result in prolonged blockade.^[117,118]

4. Antibiotics

Serious infections require prompt diagnosis and treatment. Shock and multiple organ dysfunction in patients with sepsis are associated with mortality greater than 50%. Patient survival is influenced by accurate diagnosis, prompt resuscitation and treatment which includes administration of the appropriate antibiotics.^[119] Therapeutic drug monitoring (TDM) and the application of pharmacokinetic principles enable the clinician to maximise antibacterial treatment. Attempts have been made to relate pharmacokinetic variables to clinical and microbiological outcomes. For example, the area under the inhibitory curve (AUC) has been used to compare antibiotics in treatment of ventilator associated pneumonia.^[120] At comparable AUC's, ciprofloxacin eradicated pathogens from the respiratory tract in 2 days, compared with 6 days for eradication using cefmenoxime. Another study of ciprofloxacin showed that the ratio AUC/minimum inhibitory concentration (MIC) was the best predictor of clinical and microbiological cure including time to bacterial eradication.^[119,121]

Antibiotics often need to be given intravenously to critically ill patients. The rate of delivery may be important in order to optimise blood drug concentrations and to minimise toxic effects. Enteral administration should be considered for some patients because of its merits of simplicity, tolerability and reduced cost. For example, nasogastric fluconazole is well absorbed in ICU patients, with a bioavailability of 97%.^[122] Similarly, good absorption of nasogastric trimethoprim and sulphamethoxazole has been demonstrated in AIDS patients with respiratory failure.^[123] In mechanically ventilated patients, intravenous erythromycin accelerates gastric emptying,^[124] but the role of this drug in increasing enteral absorption of other antibiotics is not known. Gastrostomy or jejunostomy administration of ciprofloxacin results in 27 to 67% bioavailability, in the presence of enteral tube feeding.^[125] Rectal metronidazole is well absorbed in the presence of abdominal sepsis.^[126]

Delivery by inhalation can produce high concentrations in bronchial secretions and minimal systemic absorption, but the clinical efficacy of this route of administration still has to be confirmed.^[127,128] In ventilated patients with nosocomial pneumonia, endotracheal and aerosol ceftazidime resulted in bioavailability of 0.47 and 0.08, respectively, and achievement of therapeutic concentrations in bronchial secretions for up to 24 hours.^[128] Prophylactic intratracheal gentamicin in ventilated patients reduced secondary pneumonia from 70 to 18%, and gentamicin 40mg did not result in therapeutic serum concentrations.^[127]

Colistin can be given by inhalation for Gram-negative chest infections with no measurable blood concentrations.^[129] Pentamidine isethionate also may be given by inhalation for *Pneumocystis carinii* pneumonia, with achievement of blood concentrations up to 10% of those following parenteral administration.^[130]

Antibiotics diffuse rapidly into most tissues, although penetration to the lung, heart and brain can be variable.^[131] Blood and tissue concentrations are in dynamic equilibrium and should be greater than the MIC for the suspected microbe. Free or

non-protein bound drug concentration in the blood determines the extent of diffusion to the tissues. Aminoglycosides are minimally bound to protein (0 to 10%) and consideration of plasma protein binding is not relevant. Protein binding of cephalosporins is variable (20 to 90%) and low albumin levels have been associated with an increased level of free drug.^[132]

Vancomycin is bound to albumin and IgA, and in patients with IgA myeloma, binding of vancomycin to IgA may result in subtherapeutic concentrations.^[133] Although it has been suggested that drug displacement interactions at protein binding sites may enhance efficacy,^[133] there is no firm evidence for this statement.

The clearance of antibiotics in the critically ill depends upon the degree of impairment of hepatic and/or renal function.^[134,135] Reduced doses may be needed for penicillins and cephalosporins, which are largely excreted by the kidney, and for clindamycin which is largely metabolised by the liver. Clearance may be altered by drug-induced changes in hepatic enzyme activity (see section 1.2).^[136]

4.1 Dose Prediction

Target concentration monitoring strategies are often appropriate in critically ill patients. TDM for antibiotics is particularly useful when therapeutic response and toxic effects are difficult to assess, such as in severe sepsis.^[137] Nomograms and algorithms have been used to adjust the dosage of cefotaxime in multiple organ failure^[138] and ceftazidime in impaired renal function.^[139]

Computer-assisted infusion regimens have been developed on the basis of population pharmacokinetic analysis using different models and covariates (e.g. age, bodyweight and CL_{CR}). Comparison of 1- or 2-compartment open models for amikacin showed that the 2-compartment model provided additional information about average tissue accumulation and thereby enabled earlier identification of abnormal accumulation.^[140] Inclusion of covariates in the model explained part of the interindividual variability and provided the best prediction of amikacin dosage in patients in the

ICU.^[141-143] Selected models and monitoring strategies have been applied to other aminoglycosides and glycopeptides^[144-146] and Bayesian algorithms provide an accurate prediction of dosage requirements.^[147,148] Bioelectric impedance analysis^[149] has also been discussed in order to optimise gentamicin dose in critically ill patients. Jelliffe et al.^[150] have published an excellent review of the various models and fitting strategies that can be used in optimising aminoglycoside dosage.

Although computer-assisted individualisation of antibiotic dose in critically ill patients is technically feasible, it requires dedicated pharmacokinetic advisory staff and for this reason is often not as widely practised as might be desirable.

4.2 Individual Antibiotics

Information on the pharmacokinetics of individual drugs is summarised alphabetically by group in table I with selected individual drug groups also discussed in the following sections. Data have been drawn from individual studies and from readily available reference texts.^[196-198]

4.2.1 Aminoglycosides

Gentamicin, tobramycin and amikacin are given parenterally. Tobramycin was found to penetrate alveolar lining fluid and macrophages so that single daily dose administration (SDD) was satisfactory for susceptible respiratory pathogens.^[199] Amikacin concentrations in bronchial secretions of ventilated patients reached a maximum 3 hours after infusion, and SDD achieved tissue concentrations more than 2-fold higher^[200] than those found after a conventional twice daily regimen.

In meningitis, systemic gentamicin can be combined with intrathecal gentamicin.^[198] Cell penetration is limited by the polarity of the molecule and distribution to the lung, eye and CNS may be inadequate.

TDM for aminoglycosides is important because of their narrow therapeutic index and potential for renal and ototoxicity. Previously, gentamicin and tobramycin peak concentrations of 10-12 mg/L have been recommended, with trough concentrations <2 mg/L, and amikacin and kanamycin con-

centrations of 20 to 35 mg/L, with a trough of <10 mg/L. In recent years bacterial killing by aminoglycosides has been found to be concentration-dependent, and SDD of gentamicin and tobramycin 5 to 7 mg/kg is now widely recommended.^[18,201,202]

Figure 3 illustrates the time-dependence of change in Vd for single dose gentamicin in critically ill patients using pharmacokinetic descriptors from Trigner et al.^[155] At day 2 after admission, Vd is significantly increased (0.43 L/kg) and the peak concentration is decreased to 14 mg/L, by comparison with a Vd of 0.25 L/kg in non-critically ill patients.^[202] Note that the elimination rate constant was similar in critically ill and non-critically ill patients. Single daily dose regimens also have the potential to optimise the 'post antibiotic effect' which has been demonstrated *in vitro*.^[203] Meta-analysis has been used to show that SDD aminoglycoside administration is as effective and about 25% less toxic than the traditional twice- or thrice daily regimens.^[204] However, a recent review of 28 clinical trials of SDD aminoglycosides showed no significant differences in either efficacy or toxicity.^[205] From a pharmacodynamic point of view, it should be remembered that in many infections, gentamicin acts synergistically with β -lactams and vancomycin.

Aminoglycosides are excreted largely unchanged by glomerular filtration. Biliary excretion also is significant and gentamicin concentration in the bile is approximately 30% of that in the plasma. Impaired renal function with variations of CL_{CR} can partially explain variability in aminoglycoside clearance, although some studies have shown a poor correlation between the 2 clearances in critically ill patients.^[156,206] Vd is increased in the critically ill^[155] and population-specific dose administration nomograms may be used to estimate the increased loading doses which are necessary in these patients.^[207] The increased Vd has been shown to decrease as the patient recovers^[155] and for this reason subsequent dosages are best guided by patient-specific Bayesian pharmacokinetic optimisation. Another study of gentamicin and

Table 1. Pharmacokinetic values for antimicrobials in non-critically ill and critically ill patients^a

Drug	PB (%)	V _{ss} (L/kg)			t _{1/2} (h)			CL (ml/min/kg) ^b			A _{0c} (% dose)		
		not crit	crit	renal	hepatic	not crit	crit	renal	hepatic	not crit	crit	renal	hepatic
Aminoglycosides													
Amikacin ^[29,141,142,152-154]	4	0.25	0.36-27.9	0.21-0.50	↔	2.3	29.7	1.1-2.2 17-150	1.17		0.3- 0.6		98
Gentamicin ^{[[32,155,156]}	10	0.25	0.14-0.67	↔	1.1-69.3	1.2-17.8	20-60	1.52		0.05-3.35	0.3		90
β-Lactams including cephalosporins, monobactams and carbapenems													
Cefazolin ^[157]	90	0.14	↑	↔	1.8		47-70	↓	0.95		↓	↔	80
Cefotaxime ^[138]	36	0.23	0.22-0.56		1.1	4.48	15	↔	3.7	16	0.2	↔	55
Cefotetan ^[158]	85	0.14	↔	↔	3.6		13-25		0.53		↓		67
Ceftazidime ^[30,128,132,159]	21	0.23	0.35	↔	1.6	1.6-6.0	13-25		1.92	1.0	0.3		84
Cefiprone ^[160]	10	0.29	↔	↔	2.0		9.2						85
Ceftriaxone ^[32,161]	90	0.16	↔	↔	7.3	5.3-13.7	12-24	↑	0.24		0.03	↓	49
Aztreonam ^[162]	56	0.16	↔	↔	1.7		6-8	↔	1.3		0.1	↑	68
Impenem ^[27,35,163]	20	0.23	0.36 ^c	↑	0.9	1.7	2-4		2.9	3.6	0.3-1.5		69
Cilastatin ^[27,35,163]	35	0.2	0.3 ^c	↔	0.8	1.4	13.8		3.0	2.7	0.2-0.4		70
Chloramphenicol													
Chloramphenicol ^[164]	53	0.94		↔	4.0		3-7	↑	2.4		0.2	↓	25
Glycopeptides													
Teicoplanin ^{[[65-168]}	90	1.0	1.0		40-60	99	62-289		11.4		0.07	↓	77
Vancomycin ^[147,169]	30	0.39	↔	↔	5.6		200-250		1.57		0.2		79
Macrolides													
Azithromycin ^{[[70,171]}	7-50	31		↔	40		↔	↔	9		↔	↔	12
Erythromycin ^[157]	84	0.78	↑	↑	1.6		5.5	↑	9.1		0.06		12
Lincosamides													
Clindamycin ^[172]	94	1.1	↔	↔	2.9		4	↑	4.7		0.03	↓	13
Penicillins and β-lactamase inhibitors													
Amoxicillin ^[157]	20	0.21	↔	↔	1.7		5-20		2.6		0.3		86
Flucloxacillin ^[198]	90	0.09			1.0		↑		2.2		↓		90
Benzylpenicillin (penicillin G) ^[157]	60	0.35			0.5		6-20				0.1	↓	60

Piperacillin ^[173,174]	30	0.18	↔	0.9	3-5	3.83	0.3	↓	71	
Ticarcillin ^[157]	65	0.21		1.2	11-16	1.6	0.1	↓	77	
Tazobactam ^[173,174]	22	0.21		1.0	7			↓	80	
Clavulanic acid ^[157]	22	0.21	↔	0.9	3.5	3.6	0.3		43	
Quinolones										
Ciprofloxacin ^[68,119,175,176]	40	1.8	1.1-1.5	4.1	↑ 8-609	↔	6.0	5.54	0.2 ↔	65
Ofloxacin ^[19]	25	1.8	↑	5.7	↑ 15-60		3.5	↓	0.3	64
Sulphonamides										
Sulphamethoxazole ^[123,177]	62	0.21	0.5	10.1	15.5	20-50	0.32	0.4	0.1	14
Trimethoprim ^[123,177]	37	1.6	1.6	10	10.9	20-49	1.0	1.88	0.2	63
Tetracyclines										
Doxycycline ^[157]	88	0.75 (V _z)		16	18-25		0.53		↔	41
Tetracycline ^[78]	65	1.5		10.6	57-108	↑	1.67		↓	58
Others										
Metronidazole ^[179,181]	11	0.74		↔	7-21	↑	1.3		0.3	10
Rifampicin (rifampin) ^[182]	89	0.97 (V _z)		3.5	9.2	↑	3.5		0.04	7
Antifungals										
Amphotericin B ^[183]	90	0.76		18	24		0.46		0.04	3
Fluconazole ^[122,184,186]	11	0.60 (V _z)		32	↑	↑	0.27		0.3	75
Itraconazole ^[187,189,196]	99.8	14		21	25		23		↔	1
Ketoconazole ^[196]	99	2.4		3-8	3.3		8.4			2
Antivirals										
Aciclovir ^[190-193]	15	0.69	4.8°	2.4	20-25		6.19		0.3	75
Ganciclovir ^[193,195]	2	1.1		4.3	29	30	4.6		0.3	73

a Mean values or range of means from different studies representing patients who are not critically ill (not crit), critically ill (crit), and critically ill patients with renal dysfunction (renal) equivalent to creatinine clearance of <30 ml/min, or with hepatic dysfunction (hepatic).

b Conversion factor from ml/min/kg to L/h/70kg = 4.2. 'Renal' column includes studies of extracorporeal circuits with CL_{CR} of 25ml/min.^[1,40] Values are normalised for bodyweight of 70kg.

c normalised assuming an average bodyweight of 70kg.

Abbreviations: A_∞ = % dose excreted unchanged in urine; CL = plasma clearance; crit = critically ill; not crit = not critically ill; PB = protein binding; t_{1/2β} = elimination half-life; V_{SS} = volume of distribution at steady state except as otherwise specified; ↑ = increased; ↓ = decreased; ↔ = unchanged.

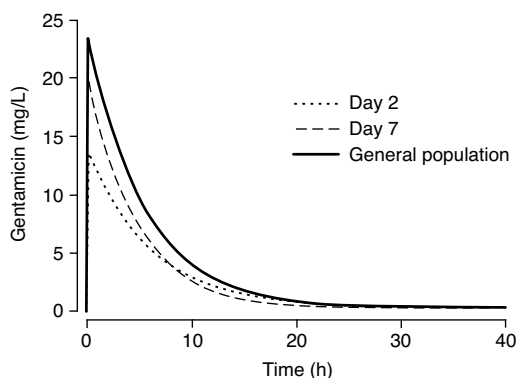


Fig. 3. Simulation of a single dose of gentamicin 6 mg/kg (infusion over 20 minutes, using pharmacokinetic descriptors from Trigriner et al.^[155]) in intensive care patients on days 2 and 7 after admission, compared with a general population of non-critically ill patients.^[202]

tobramycin in critically ill surgical patients showed that cardiovascular variables, such as left atrial pressure, cardiac output and peripheral vascular resistance, could not reliably predict V_z , $t_{1/2}$ and clearance.^[2]

Initial dosages of amikacin 11 mg/kg thrice daily can be given to patients in the ICU.^[208] In 42 critically ill patients the V_z for amikacin correlated well with illness severity measured by APACHE 2 score.^[152] With anuria, 6 mg/kg every 2 days may be suitable, but dose modification should be guided by measuring plasma concentrations. In critically ill patients, haemodialysis removed an average of 21% of amikacin and resulted in a 27% fall in amikacin plasma concentrations.^[33]

Extracorporeal circuits (e.g. ECMO) may decrease plasma concentrations of antibiotics by binding of drug to the circuit materials. In humans, ECMO decreases gentamicin concentrations^[20,22] and animal studies have shown that tobramycin concentrations are also decreased with an apparent increase in V_{ss} .^[21] Haemodialysis in critically ill patients with acute renal failure is often poorly tolerated, especially in those patients with multi-organ failure and haemodynamic instability. Intermittent or continuous haemofiltration or haemodiafiltration is more widely used than intermittent haemodialysis in this group of unstable

patients. Therapeutic measures such as CPB can profoundly affect drug pharmacokinetics^[209] (e.g. a reduction in teicoplanin concentrations because of drug redistribution during CPB.^[210]). By contrast, a study of the V_z , $t_{1/2}$ and CL of ciprofloxacin showed little change during CPB compared with pre-operative values.^[211]

4.2.2 Cephalosporins and Related β -Lactams

Cephalosporins are widely used in the critically ill. Tissue penetration is variable, with good penetration into cerebrospinal fluid (CSF) by the third generation drugs cefotaxime and ceftriaxone.^[212] Intermittent bolus doses of ceftazidime in patients in the ICU result in a large interpatient variability in plasma concentrations with no clinical predictor of those with low plasma concentrations.^[213] Ceftazidime delivery by continuous infusion has been shown to produce serum concentrations which remain greater than MIC.^[213] β -Lactam antibiotics do not exhibit any post-antibiotic effect and infusions may be of benefit with relatively resistant organisms such as *Pseudomonas*.^[213] Continuous infusion of ceftazidime was also found to be more efficacious in an *in vitro* pharmacokinetic model, when high sustained concentrations were required for killing of *Pseudomonas aeruginosa*.^[214]

Cephalosporins undergo variable degrees of metabolism prior to excretion in the urine or bile. Most are excreted unchanged in the urine. Clearances of ceftriaxone and ceftazidime are similar in ICU and other groups of patients.^[161,215] In a study of high dose ceftazidime in ICU patients with *Pseudomonas* chest infections, $t_{1/2z}$ was 2.1 and 2.2 hours at the start and end of treatment, respectively. V_z was similar at 0.5 L/kg.^[159] There was no evidence for accumulation. Low plasma albumin concentrations are often seen in critically ill patients. For highly protein bound third generation cephalosporins, the resulting increased free fraction may result in altered microbiological kill, as well as in increased drug clearance by the liver and kidneys and an increased V_z .^[132,216]

Dosage adjustment is necessary in severe renal impairment. In acute renal failure following surgery, plasma and renal clearance of ceftriaxone

were closely related to CL_{CR} ^[161] and nonrenal (hepatic) clearance was decreased.^[161] In another study of severe renal dysfunction, ceftriaxone $t_{1/2}$ increased only moderately from 14.4 to 17 hours, and this was associated with significant nonrenal elimination which may be facilitated by the increased free fraction often present in these patients.^[217]

Hepatic disease does not affect the disposition of most third generation cephalosporins except cefotaxime, cefoperazone and ceftriaxone.^[215] In concurrent renal and hepatic failure, the $t_{1/2}$ of ceftriaxone is significantly prolonged.^[215]

In patients with sepsis with renal failure requiring continuous haemodiafiltration, the V_z of ceftazidime was 31.3L, $t_{1/2}$ was 14.7 hours and CL was 1.488 L/h.^[30] By contrast, the mean V_z , $t_{1/2}$ and CL of ceftazidime were 18.2L, 2.2 hours and 5.31 L/h, respectively, in critically ill patients with normal renal function.^[213] Haemodialysis removes a variable amount of most cephalosporins, but ceftriaxone and cefoperazone were not significantly eliminated.^[30,134]

4.2.3 Penicillins

The target blood concentration following intravenous infusion depends upon the nature and severity of the infection. With the selection of the appropriate dose and dosage interval, plasma concentrations are likely to exceed MIC for most of the time. Renal impairment results in a $t_{1/2}$ of benzylpenicillin (penicillin G) rising to 2 hours at a CL_{CR} of 1.8 L/h and up to 10 hours with anuria.^[198] Hepatic inactivation then accounts for 10% of the antibiotic each hour.

Haemodialysis decreases serum concentration of benzylpenicillin by about 50%, so that half the initial loading dose should be given after dialysis. There is no significant removal of flucloxacillin by haemodialysis.^[34] Hepatic impairment increases flucloxacillin $t_{1/2}$ by 25% and AUC by 40%. Piperacillin concentrations in bile are high and, in addition, the drug is removed by continuous arteriovenous haemodialysis and the dosage may need to be increased by 50%.^[218]

4.2.4 Quinolones

Ciprofloxacin is usually infused intravenously and distributes to all tissues with the highest concentrations in the liver, bile and kidney.^[131] In nosocomial pneumonia, ciprofloxacin concentrations in bronchial mucosa exceed that in plasma by a factor of 17.^[219] Between 20 to 40% is bound to serum protein and up to 70% is excreted unchanged by the kidney. Four metabolites, which have decreased microbiological action, are excreted in the urine and account for 12% of an intravenous dose. Bile concentrations are 3 to 4 times higher than the serum concentration and 15% of an intravenous dose is excreted in the faeces.^[198]

Ciprofloxacin inhibits the metabolism of theophylline and can raise its plasma concentrations.^[220] Dose reduction is necessary at $CL_{CR} < 1.8$ L/h.^[20] Studies in critically ill trauma patients have shown that Bayesian estimates of ciprofloxacin clearance gave good prediction compared with less severely ill patients.^[221] AUC during ciprofloxacin treatment was a good predictor of early recovery from ventilator-associated pneumonia^[120] and of clinical and microbiological cure.^[119] Oral ciprofloxacin was adequately absorbed in critically ill patients with Gram-negative intra-abdominal infections.^[222]

Nasogastric ciprofloxacin was also found to be well absorbed in healthy volunteers in the presence of enteral feeding,^[223] but a recent study showed that bioavailability was reduced to 72% by enteral feeding^[224] and to 50% by antacids.^[225] Pefloxacin and ofloxacin have actions similar to those of ciprofloxacin. Pefloxacin has $t_{1/2}$ of 8 to 13 hours and is extensively metabolised.^[226] Ofloxacin $t_{1/2}$ is 5 to 8 hours and 80% of a dose is excreted unchanged by the kidney within 24 to 48 hours.^[227] In renal failure the $t_{1/2}$ is 15 to 60 hours.^[227]

4.2.5 Carbapenems

The clearance of imipenem is linearly related to CL_{CR} and dosage reduction is indicated with $CL_{CR} < 3$ L/h and with haemofiltration.^[228] Binding of imipenem and cilastatin to serum proteins is 20% and 35%, respectively, and the drugs are distributed widely, with the exception of poor penetration

to the brain.^[229] With imipenem, 70% is recovered in the urine within 10 hours of administration, in contrast to 20% in the absence of the renal dehydropeptidase inhibitor cilastatin.^[198] Meropenem pharmacokinetics^[230] are similar to those of imipenem, except that 70% of the drug is recovered from the urine in the absence of cilastatin.^[231] Imipenem and cilastatin are both subject to significant clearance by haemodialysis and an additional loading dose is required after the procedure.^[27,34] Hepatic dysfunction does not require dose alteration.^[231]

4.2.6 Glycopeptides

In critically ill patients, vancomycin penetrates tissues well,^[232] including the epithelial lining fluid of the lower respiratory tract, and achieves concentrations well above MIC for most staphylococci and enterococci.^[233] Target peak and trough concentrations are 30 to 50 mg/L and <15 mg/L, respectively. CSF concentrations are 7 to 20% of plasma concentrations with inflamed meninges and vancomycin can also be injected into a ventricular drain.^[234] Oral administration is indicated for pseudomembranous colitis and little is absorbed from the gut. It is excreted unchanged by glomerular filtration. In renal impairment, $t_{1/2}$ may be prolonged (>24 hours). Hepatic impairment also results in delayed elimination.^[235] Haemoperfusion removes vancomycin, but clearance during haemodialysis is unpredictable.^[34,169,198] Therefore monitoring of plasma concentrations and renal function is important.^[34,235]

Teicoplanin has a similar antibacterial spectrum to vancomycin, but has a longer duration of action. After intravenous administration of teicoplanin 3 to 30 mg/kg/day, the $t_{1/2}$ was 33 to 130 hours with a mean renal clearance of 0.408 L/h.^[165,236] Trough serum concentrations of 10 to 25 mg/L have been suggested but there is little information on the relationship between plasma concentrations and toxicity.^[198] Dose reduction is required in renal impairment. Dose supplementation may be required after CPB due to a reduction in plasma concentrations.^[210]

4.2.7 Lincosamides

Clindamycin is widely distributed in the body, including high concentrations in bile, but there is no significant penetration into the CSF.^[172] Following hepatic metabolism into both active and inactive metabolites, excretion by the liver and kidney takes place over several days. Renal impairment prolongs $t_{1/2}$ [198] and severe hepatic failure also require dose reduction.^[237] There is no significant clearance by dialysis.^[198]

4.2.8 Macrolides

Erythromycin is widely distributed, although CSF concentrations are low. It is concentrated and demethylated in the liver and an active metabolite is excreted in the bile. Erythromycin may inhibit CYP enzymes and decrease the clearance of warfarin, theophylline and benzodiazepine drugs.^[238] Azithromycin does not have this effect. Only about 12% of an erythromycin dose is excreted in the urine and dosage reduction is not indicated in renal failure.^[239] Haemofiltration and haemodialysis remove only small amounts of erythromycin.^[34]

4.2.9 Sulphonamides

Sulphamethoxazole with trimethoprim (cotrimoxazole) may be used in critically ill patients with *Xanthomonas* and *Pneumocystis carinii* pneumonia. Plasma concentrations of sulphamethoxazole and trimethoprim are generally in the ratio 20 : 1, but in the tissues the ratio is 5 : 1, since lipophilic trimethoprim has a larger V_z .^[123] The aim of therapy should be to achieve optimal sulphonamide levels of 50 to 150 mg/L.

In trauma patients, sulphamethoxazole V_z and clearance were significantly greater and the $t_{1/2}$ significantly shorter than previously reported estimates in nontrauma patients; no significant differences in trimethoprim parameter estimates were found.^[177] The potential for nephrotoxicity demands monitoring of renal function and plasma sulphamethoxazole concentrations.

4.2.10 Tetracyclines

Tetracyclines may be indicated in rickettsia, chlamydia and mycoplasma sepsis, and, in particular, in atypical chest infection with *Mycoplasma*

pneumoniae or *Legionella pneumophila*. Up to 60% is excreted in the urine and renal impairment requires dose adjustment or cessation. Significant hepatic metabolism and concentration in the bile result in delayed clearance in the event of hepatic impairment or biliary obstruction.^[240] The $t_{1/2}$ of doxycycline is reduced from 16 to 7 hours during phenobarbital or phenytoin treatment.^[241,242]

4.2.11 Metronidazole

Metronidazole is well absorbed following oral and rectal administration, but intravenous administration is preferred if there is any doubt about enteral absorption. Renal excretion includes 10% metronidazole, 50% active hydroxy metabolite and 15% inactive glucuronide.^[243] $CL_{CR} < 1.8$ L/h is associated with increased $t_{1/2}$, but patients with obstructive jaundice showed the longest $t_{1/2}$ and lowest CL values.^[179,180]

4.2.12 Rifampicin

Rifampicin (rifampin) may be used in combination with β -lactam or vancomycin in the treatment of staphylococcal endocarditis or osteomyelitis. Its absorption following oral administration is variable, it is deacetylated in the liver and undergoes enterohepatic recirculation.^[198] Rifampicin is a potent inducer of CYP3A4^[244] and has a prolonged $t_{1/2}$ in hepatic disease.^[198] Up to 30% of a dose is excreted via the kidneys and dose reduction may be necessary in renal failure.^[245]

4.3 Antifungals

4.3.1 Azoles

The pharmacokinetics of fluconazole are similar following oral and intravenous administration with a 90% oral bioavailability.^[198] A loading dose of 800mg, which is twice the usual daily dose, produces plasma concentrations of 90% steady state by the second day of treatment. A wide concentration range of 1 to 20 mg/L has been reported for fluconazole using both microbiological and high performance liquid chromatographic assay procedures.^[246] Interpretation of plasma concentrations is also uncertain because MIC values may not always be determined using the species that infect

patients.^[246] The penetration of fluconazole into all tissues is good, including the brain.^[184,247] Impaired renal function may require reduced dose,^[185,198] as $t_{1/2}$ is inversely related to CL_{CR} . Haemodialysis reduces plasma concentration by 39%.^[246]

4.3.2 Amphotericin B

Amphotericin B penetrates tissues well, with the exception of CSF. Only small amounts are excreted in the urine.^[198] With prolonged administration, $t_{1/2}$ increases from 1 to 15 days.^[198] Haemodialysis does not remove amphotericin B.^[198] Compared with the colloidal form, lipid formulations at equivalent dose are associated with higher hepatic and renal concentrations and with lower toxicity.^[198,248]

4.4 Antivirals

4.4.1 Aciclovir and Ganciclovir

Aciclovir is excreted mostly unchanged by glomerular filtration and tubular secretion. In chronic renal failure patients requiring haemodialysis, both the loading and maintenance doses may need to be decreased so that therapeutic plasma concentrations can be achieved and the risk of neurotoxicity minimised.^[190] Haemodialysis removes 51% of aciclovir in the body, and an additional loading dose is indicated.^[191] The $t_{1/2}$ of ganciclovir increases from 3 to 29 hours in severe renal impairment, while haemodialysis reduces plasma concentration by 50%.^[34,193]

5. Inotropes

These drugs find wide application where there is a low cardiac output, despite adequate fluid replacement and correction of electrolyte imbalance. Both catecholamines (e.g. adrenaline, noradrenaline, dopamine, dobutamine and dopexamine) and inhibitors of the intracellular enzyme phosphodiesterase isozyme III (PDEs, e.g. amrinone and milrinone) are commonly used to stabilise and support the circulation and assist in prevention of secondary ischaemic injury (e.g. renal failure). The $t_{1/2}$ of both classes are short and their effects can be easily controlled by a variable rate intravenous infusion.

The effects of the catecholamines are limited initially by adverse effects, such as tachycardia, hypertension and vasoconstriction and later by tolerance to α_1 -adrenoceptor agonists and by adrenoceptor down-regulation. The catecholamines are cleared mainly by monoamine oxidase (MAO) and catechol-*O*-methyl transferase (COMT).^[249] MAO is widely distributed in neuronal and non-neuronal tissues while COMT is located mainly in the liver. Hence, systemic clearance of these agents is usually controlled by the liver. However, the lung may also play a substantial role clearing up to about 50% of drug in a single pass.^[17]

By contrast the PDEs act intracellularly to raise cyclic adenosine monophosphate (cAMP) and calcium concentrations, leading to improved cardiac contractility, reduced left ventricular afterload and improved diastolic relaxation. Understanding the pharmacokinetics of these drugs is useful both in appreciating the extent of interpatient variability in the dose required and the time delay which may occur before the effects of the therapy are fully functional.

5.1 Adrenaline and Noradrenaline

While these 2 catecholamines have been widely used in critically ill patients,^[250] there are no published pharmacokinetic studies in this population. Recommended infusion rates in critically ill patients vary from 0.01 to 0.15 $\mu\text{g}/\text{kg}/\text{min}$ for adrenaline and 0.06 to 0.15 $\mu\text{g}/\text{kg}/\text{min}$ for noradrenaline.^[251] It seems likely that hepatic dysfunction *per se* could lead to a lower dose requirement.

5.2 Dopamine

Literature reports on the disposition of dopamine in both adult^[252-254] and paediatric^[151,255-259] patients in the ICU suggest that there is a considerable interpatient variability in CL (0.01 to 0.45 L/kg/min) at the usual infusion rates of 0.5 to 20 $\mu\text{g}/\text{kg}/\text{min}$. Nevertheless, with one exception, this variability does not appear to be due to nonlinear kinetic behaviour and it has been suggested that much of the variability in clearance has resulted

from the use of nonsteady-state plasma concentrations in the calculation of this parameter. Several of these studies show that a biexponential function is necessary to describe the post-infusion plasma concentration-time profile for dopamine with apparent $t_{1/2}$ median values of 1.8 minutes and 22.1 minutes, respectively, and a V_{ss} of 1.58 L/kg. A carefully controlled study^[254] has shown that interpatient variability in CL is less (CV = 3.5 to 12%) than the literature suggests and highlights the fact that it may take 1 to 2 hours infusion times to achieve 90% of the final C_{ss} .

5.3 Dobutamine

Mean values for CL are 0.053 to 0.059 L/kg/min in adults^[260,261] and the disposition of the drug follows first-order kinetics over the usual range of infusion rates. Nevertheless, individual studies show a wide interpatient variability in CL (median CV = 37%). Klem et al.^[260] have shown that clearance was not correlated with bodyweight, age or estimated CL_{CR} . Importantly, they demonstrated a significant inpatient variability in clearance measured at different times after the start of the infusion, with most variation seen in the first 24 hours. The mechanism of this effect is not related to clearance across the lung,^[262] and, therefore, is most likely related to variability in hepatic clearance by COMT.

5.4 Dopexamine

This drug, which is a relatively recent introduction, is principally a dopamine (DA-1) and β_2 -adrenoceptor agonist with predominant splanchnic vasodilatory actions.^[263] Recent data in liver transplant patients (acute reperfusion stage) shows that clearance is predominantly hepatic and that the mean CL was 0.024 L/kg/min following a 2 $\mu\text{g}/\text{kg}/\text{min}$ steady-state infusion.^[264] Like other catecholamines, dopexamine is metabolised mainly by *O*-methylation and sulphation^[265] and hepatic dysfunction may lead to decreased clearance.

5.5 Amrinone

Amrinone was the first PDE inhibitor to be marketed. It is extensively metabolised in the liver with the principal metabolite being *N*-acetylamrinone.^[266] The pathway is genetically controlled by *N*-acetyltransferase 2,^[267] resulting in lower steady-state amrinone concentrations in rapid acetylators. The pharmacokinetics of amrinone in adults are different to those in children.^[268] Despite demonstrated beneficial cardiovascular actions,^[269] long term amrinone therapy causes thrombocytopenia in about 3% of patients^[270] by a non-immune toxic effect of the drug and/or its metabolite(s). Moreover, the drug is unstable in some intravenous fluids. These properties have limited the utility of amrinone.

5.6 Milrinone

Milrinone is excreted largely unchanged in the urine, and also has a number of glucuronide or sugar conjugates formed by the liver. The pharmacokinetics of milrinone in a variety of critically ill patients appear to be best described by a 3-compartment disposition model.^[271-273] Approximate volumes for compartments 1, 2 and 3 were 11.1, 16.9 and 363L, respectively, with corresponding clearances of 0.067, 1.05, and 0.31 L/min, respectively.^[271] Because of the multicompartmental nature of milrinone disposition, normal $t_{1/2}$ considerations are misleading and these authors have, therefore, calculated 'context sensitive' elimination times of 4.9, 108 and 188 hours for 50%, 80% and 90% drug elimination following a 1 minute 50 µg/kg bolus injection and a 24 hours maintenance infusion at 0.5 µg/kg/min. The underlying long $t_{1/2}$ for milrinone (80 hours) also suggests that caution should be exercised with long-duration infusions where accumulation and nonlinear behaviour are possible.

In adult cardiac bypass surgery patients, single doses ranging from 25 to 75 µg/kg/min were effective in significantly increasing cardiac index^[271] and a clinical efficacy threshold of 100 µg/L was proposed. Bailey et al.^[272] combined pharmaco-

kinetic and pharmacodynamic observations using a sigmoid E_{max} model (maximum effect the drug produces) to show that the concentration giving a 50% increase in cardiac index (C_{50}) for milrinone in cardiac bypass patients ranged from 100 to 235 µg/kg [confidence interval (CI) 95%]. The more recent study by Prielipp et al.^[273] has shown that milrinone (>100 µg/L) is effective in raising cardiac index by at least 0.4 L/min/m² in a range of medical-surgical ICU patients.

6. Gastric Acid Suppressant Drugs

6.1 H₂ Antagonists

These drugs have been widely used for the prophylaxis of stress-induced gastric ulceration in both critically ill adults and children. The major representative compounds include cimetidine, ranitidine, famotidine, nizatidine and roxatidine. All have high clearance rates and are eliminated primarily by a mixture of renal filtration and tubular secretion.^[274] Although the H₂ blockers are relatively nontoxic drugs, concerns about drug interactions (inhibition of various CYP isoforms primarily by cimetidine), CNS toxicity and adverse cardiovascular actions have been raised for some of these agents (mainly cimetidine and ranitidine),^[136,274] particularly in situations where renal clearance is compromised.

The effects of diminished renal function on the pharmacokinetics of H₂ antagonists in a broad spectrum of patient groups have been reviewed recently.^[275] Pharmacokinetic data for critically ill adult patients are sparse and only cimetidine^[276,277] and ranitidine^[278,279] have been studied. For both drugs, the V_{ss} was similar, CL lower and $t_{1/2z}$ longer for critically ill patients compared with healthy individuals. Nevertheless, renal function remained the major determinant of clearance in the critically ill.

6.2 Proton Pump Inhibitors

The substituted benzimidazole derivatives omeprazole, lansoprazole and pantoprazole are more recently developed agents with antiulcer activity

Table II. Pharmacokinetics of proton pump inhibitors

Drug	Healthy individuals			Patients with renal or hepatic failure			References
	$t_{1/2\beta}$ (h)	V_z/F (L/kg)	CL/F (L/h/kg)	$t_{1/2\beta}$ (h)	V_z (L/kg)	F (L/h/kg)	
Lansoprazole	1.4	0.45	0.26	1.6-4.1 ^a 6.1-7.2 ^b	0.37-0.85 ^a 0.35-0.55 ^b	0.13-0.43 ^a 0.04-0.07 ^b	270,280
Omeprazole	0.5-0.7	0.34	0.43	2.8 ^b	0.23 ^b	0.06 ^b	157,281-283
Pantoprazole	1.9	0.17 (V_{ss})	0.13 (CL)	5.1-12 ^b	0.09-0.21 ^b	0.012-0.024 ^b	157,284

a Renal failure.

b Hepatic failure.

Abbreviations: CL = total body clearance; F = fractional availability; $t_{1/2\beta}$ = elimination half-life; V_{ss} = volume of distribution at steady state; V_z = volume of distribution, including terminal exponential phase.

via an inhibition of the H^+ , K^+ -ATPase proton pump in the gastric parietal cells. In general these drugs are well tolerated and have few significant adverse effects. While there have been no studies of their pharmacokinetics in critically ill patients *per se*, there is a significant body of literature which has described their disposition in healthy individuals and in patients with renal or hepatic failure (table II). These data indicate that renal failure has little or no effect on clearance while severe hepatic failure can result in a marked reduction in clearance.^[157,281,284] Despite increased blood concentrations in hepatic failure, dose adjustment is not considered necessary, except possibly in very severe disease.^[157,28-286]

7. Practical Strategy for Dealing with Altered Pharmacokinetics in Critically Ill Patients

Critically ill patients often present complex problems. Diagnosis and treatment require detailed analysis, and pharmacokinetic considerations are an important consideration in overall patient management. While every case must be considered individually, the following headings may assist in defining appropriate drug treatment and dose regimens:

- consider the underlying pathophysiology
- seek out relevant previously published clinical experience
- specifically review the comparability of the patient populations studied. Exercise caution in drawing conclusions from populations with chronic organ dysfunction

- apply pharmacological principles in selecting the appropriate drug treatment and/or dose regimen
- consult with appropriate specialists (e.g. a pharmacologist or microbiologist)
- make use of TDM and computer-assisted target concentration monitoring when appropriate
- where possible, monitor pharmacodynamic response to assess outcome.

Application of these principles should assist in optimising drug therapy. Finally, it is important to review the outcome of therapy regularly and to promote understanding and education of the underlying pharmacokinetic principles to medical, nursing and allied health staff.

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