Pharmacokinetic considerations for drugs administered in the critically ill

Significant physiological changes are common among critically ill patients. This case-based review describes the consequences of these changes on the selection and dosing of medications.

The case below illustrates the presentation of a critical illness. Therapeutic success depends in part upon appropriate pharmacotherapy. Fluctuations in homeostasis resulting from the critical illness are often more extreme than presentations of lesser acuity, and as a consequence may be associated with unique alterations in the absorption, distribution, metabolism and excretion of drugs. This article reviews some pharmacokinetic and pharmacodynamic principles that should be considered by clinicians during the management of critically ill patients.

Fluid shifts and alterations in the volume of distribution

Trauma, sepsis or surgery generate a systemic inflammatory response syndrome (Hall, 2013) resulting in characteristic inflammation-induced alterations in vascular permeability (Stephens et al, 1988). The fluid required for resuscitation of these critically ill patients increases the degree of tissue fluid accumulation. As a consequence, critically ill patients often have increased total body water and interstitial fluid volumes compared to healthy individuals (Boucher et al, 2006; Smith et al, 2012). As total body water is an important parameter determining the distribution of hydrophilic medications, intensive care patients have been shown to exhibit increased volumes of distribution of beta-lactam antibiotics, aminoglycosides, vancomycin and linezolid (Boucher et al, 2006; Swoboda et al, 2010; Gonçalves-Pereira and Póvoa, 2011; Smith et al, 2012). Conversely, hydrophobic antibiotics such as fluoroquinolones and macrolides have more preserved volumes of distribution in critical illness (Roberts and Lipman, 2009).

The increased volume of distribution of hydrophilic drugs (including ceftriaxone as used in this case) in critical illness may reduce the efficacy of antibiotics with concentration-dependent mechanisms through failure to achieve the minimal inhibitory concentration. This limitation may be overcome by increasing the loading dose of these medications. On the other hand, the impact of an increased total body water on hydrophilic drugs with time-dependent mechanisms is not necessarily deleterious. As volume of distribution is proportional to clearance and inversely proportional to half-life (t1/2β), an increased volume of distribution may increase the amount of time an antibiotic is above the minimum inhibitory concentration, resulting in an equivalent or even improved efficacy (Gonçalves-Pereira and Póvoa, 2011).

Drug interactions

Because polypharmacy is common in the intensive care unit, drug–drug interactions affecting metabolism are particularly important (Boucher et al, 2006; Kopp et al, 2006). Medications commonly administered in the intensive care unit such as benzodiazepines, fentanyl, azoles, certain anticonvulsants and macrolides are metabolized through the CYP450 3A4 system (Spriet et al, 2009). Drugs may act as either inhibitors or inducers of that particular enzyme, thereby influencing the rate of metabolism of other drugs metabolized through the same

Case Report

A 54-year-old man was brought into the emergency department by his wife when she noticed that he 'looked blue'. He had a 2-week history of cough, intermittent fever as well as worsening shortness of breath. On physical examination he had a blood pressure of 80/40 mmHg with a heart rate of 110 bpm. He was cyanotic and dyspnoeic with an oxygen saturation (SaO_2) of 80% and a respiratory rate of 35 breaths/minute. Initial arterial blood gas analysis revealed a pH of 7.10, PaO_2 45 mmHg, $PaCO_2$ 70 mmHg, bicarbonate 16 mmol/litre, lactate 14 mmol/litre. His body mass index was 38 kg/m^2. A chest radiograph demonstrated a right lower lobe infiltrate. A presumptive diagnosis of community-acquired pneumonia was made and erythromycin and ceftriaxone were administered after blood cultures were obtained. The SaO_2 failed to improve with supplemental oxygen and the patient was placed on positive pressure mechanical ventilation. Infusions of fentanyl, propofol and midazolam were initiated to provide sedation and analgesia. Despite 6 litres of initial fluid resuscitation, the patient remained hypotensive. He was admitted to the intensive care unit for further management. Laboratory blood chemistry determined that the plasma albumin concentration was reduced at 18 g/dl and the estimated creatinine clearance was elevated at 150 ml/min/1.73m^2. He was started on subcutaneous low molecular weight heparin for venous thromboembolism prophylaxis. A nasogastric tube was inserted and enteral nutrition was initiated.

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isoform (Spriet et al, 2009). Knowledge of these interactions is important as toxicity has been demonstrated in critically ill patients treated with multiple medications (Skrobik et al, 2013).

Plasma protein binding

In response to inflammation, the acute phase response alters the production of a variety of proteins (Bauer et al, 2013). These changes may have important pharmacokinetic and pharmacodynamic consequences. Albumin and α1-acid glycoprotein are the two most relevant with well-known roles in drug binding (Boucher et al, 2006; Smith et al, 2012). As it is the unbound fraction of a protein-bound drug that is available to distribute and bind to receptors, changes in the serum concentrations of albumin (reduced) or α1-acid glycoprotein (increased) have an inversely proportional relationship to the level of active drug available to exert physiological effects. Furthermore, as unbound drug is able to distribute more freely, the volume of distribution of protein-bound drugs increases as the unbound fraction increases (Boucher et al, 2006; Smith et al, 2012).

Although the relevance of changes in protein binding has been questioned (Sellers, 1979; Rolan, 1994), several studies, including a systematic review, have demonstrated clinically relevant findings in specific settings where changes in the unbound fraction alter drug exposure through changes in clearance (Benet and Hoener, 2002) (*Table 1*). Exposure of a receptor to a drug (loosely defined as the integral of the concentration *vs* time curve, or the area under the curve (AUC)) is necessary for the drug to exhibit its physiological effect and is dependent on both dose and clearance of a drug. The effect of the unbound fraction of a drug on AUC is determined by the specific drug's extraction ratio. For drugs with high extraction ratios, AUC is influenced by unbound fraction and dosing adjustments may be necessary (Benet and Hoener, 2002). Proof of this principle can be found in studies examining the effect of alterations in α1-acid glycoprotein level on lidocaine effect. Lidocaine is highly protein bound to α1-acid glycoprotein and demonstrates a high extraction ratio. As a result of increased levels of α1-acid glycoprotein in inflammatory states, this drug has been reproducibly shown to have a lower unbound fraction and require higher doses in several critically ill populations to maintain its antiarrhythmic effect (Edwards et al, 1982; Holley et al, 1984). Although the list of drugs where protein binding may be clinically significant is small, many of these drugs are commonly used in the intensive care unit (Benet and Hoener, 2002).

Table 1. Drugs where altered protein binding may have clinically significant implications

Drug	Protein binding (%)	Clearance (ml/min/kg)
Diltiazem	78	6.2
Erythromycin	84	8.0
Fentanyl	84	12.3
Haloperidol	92	11.8
Lidocaine	70	9.2
Methylprednisolone	78	6.2
Midazolam	98	6.6
Milronone	70	5.2
Propofol	98	27
Sufentanil	93	12
Verapamil	90	15

Adapted from Benet and Hoener (2002)

Alterations in renal clearance

While adjusting drug dosing in response to decreased renal function is a well-accepted practice in intensive care, a previously unrecognized group of intensive care unit patients exhibit heightened glomerular filtration secondary to increased cardiac output and renal blood flow, and represent a unique population requiring careful consideration of drug dosing (Joynt et al, 2001; Conil et al, 2007; Shimamoto et al, 2013; Udy et al, 2013b). While originally identified in the acute surgical and trauma populations, individuals with sepsis and systemic inflammation seem to be at risk as well (Fuster-Lluch et al, 2008). A prospective cohort study by Udy et al (2014) demonstrated the presence of augmented renal clearance in nearly two thirds of their intensive care unit population admitted with a normal serum creatinine level.

Moreover, this population seems to be under recognized when the glomerular filtration rate is calculated using widely used formulae such as the Chronic Kidney Disease Epidemiology Collaboration estimated glomerular filtration rate (Udy et al, 2013a). The pharmacokinetic consequences of this hyperfiltration are poorly understood. It is possible that unaltered dosing in patients with augmented creatinine clearance may lead to therapeutic failure and is a strong argument for measurement of therapeutic levels to ensure appropriate pharmacodynamic effect when possible. Studies which examine whether increased dosages of drugs in this population improves outcomes are needed.

Gastric pH

Administration of gastric antisecretory medications such as H_2 receptor antagonists (H_2RAs) and proton pump inhibitors have become commonplace in many intensive care units for the prevention of stress ulceration (Boucher et al, 2006). As most medications are weak acids or bases, increasing the pH of the stomach has the potential consequence of changing a drug's net charge and, ultimately, its subsequent absorption (Lahner et al, 2009).

Continued on p. 91

Continued from p. 90

Lahner et al (2009) conducted a systematic review of randomized trials investigating the absorption of a variety of medications with the co-administration of an antisecretory medication. The authors concluded that gastric acid plays a significant role in the absorption of many orally delivered medications including some azole antifungal agents and cardiovascular drugs.

Gastric absorption

Delayed gastric emptying

Delayed gastric emptying is common in the intensive care unit, with an incidence reported to be as high as 60% of intensive care unit admissions (MacLaren et al, 2001; Nguyen et al, 2007). At-risk populations include those with burns, traumatic brain injury, multiple trauma patients and patients with sepsis (Nguyen et al, 2007). The aetiology of delayed gastric emptying remains unclear, but abdominal surgery, mechanical ventilation, electrolyte abnormalities, opioid requirements, splanchnic hypoperfusion, hyperglycaemia and sedative use are all risk factors (McArthur et al, 1995; Heyland et al, 1996; Nguyen et al, 2007). For drugs that are administered orally, delayed gastric emptying will prolong the time (T_{max}) to achieve the peak concentration (C_{max}). When oral paracetamol was administered to a group of intensive care unit patients and healthy controls by nasogastric tube, the AUC, C_{max} and T_{max} of paracetamol were all significantly lower in the critically ill population than the control group (Tarling et al, 1997). Because of the uncertainty of effective gastric absorption of drugs, particularly in the initial phase of a critical illness, it is suggested that, where possible, drugs should be administered intravenously.

Interactions with enteral feeds

The administration of enteral feeds themselves may affect the bioavailability of oral agents through alterations in the rate of absorption, adherence to absorptive surfaces, alterations in motility, or through physical or chemical reactions with the administered agent (Maka and Murphy, 2000; Papadopoulos and Smithburger, 2010). Ciprofloxacin is a commonly used agent in the intensive care unit with good oral bioavailability (Mimoz et al, 1998). Because this has been known to interact with several mineral supplements commonly found in enteral feeds, there have been several studies conducted in both healthy volunteers and intensive care unit patients evaluating the absorption of ciprofloxacin in the presence of enteral nutrition (Yuk et al, 1989; Cohn et al, 1996; de Marie et al, 1998; Mimoz et al, 1998). Most of these studies demonstrated a reduction of up to 56% in the bioavailability of oral ciprofloxacin when co-administered with enteral feeds.

In addition to fluoroquinolones, several other drugs have been reported to interact with enteral feeds, including warfarin, phenytoin, tetracyclines and fluconazole (Leyden, 1985; Au Yeung and Ensom, 2000; Boucher et al, 2006). Although clinical outcomes have not been the focus of most studies, some authors have correlated the interaction between drugs and enteral feeds to therapeutic failures (Au Yeung and Ensom, 2000). For drugs that are critical for therapeutic success, e.g. antibiotics, careful consideration should be given to use of intravenous formulations, at least in the initial phases of treatment, to ensure 100% bioavailability.

Enteral absorption

Inflammation-induced proteomic changes within the brush border of the gut may be responsible for clinically significant changes in the enteral absorption of drugs. Several members of the superfamily of adenosine triphosphate binding cassette (ABC) transporters are expressed within enterocytes and may play an important role in the pharmacokinetics of several enterally administered drugs. P-glycoprotein, the best studied member of this family, acts as an efflux pump which transports many drugs into the intestinal lumen after absorption, substantially influencing the bioavailability of many enterally administered drugs (Zhou, 2008; Papadopoulos and Smithburger, 2010). Changes in the expression or function of these transporters can therefore be reasonably hypothesized to influence the pharmacokinetics of the drugs they transport.

Several studies have been conducted examining alterations in these proteins in the setting of inflammation. A systematic review from non-human models concluded that decreased expression and functionality of P-glycoprotein in the setting of proinflammatory cytokines was a reproducible finding (Fernandez et al, 2004). Furthermore, several drugs commonly administered in the intensive care unit are also known inhibitors of P-glycoprotein, raising the possibility of drug interactions for co-administered enteral agents (Kharasch et al, 2003). Although limited, some data exist demonstrating increased therapeutic effects of oral morphine, a P-glycoprotein substrate, when it is co-administered with a P-glycoprotein inhibitor (Kharasch et al, 2003) to intensive care unit patients. Careful consideration of intravenous alternatives and use of therapeutic monitoring is suggested.

Subcutaneous absorption

Venous thromboembolism is a frequent complication among intensive care unit patients with estimates ranging from 10–80% of intensive care unit admissions (Rommers et al, 2006). Most intensive care unit patients therefore receive venous thromboembolism prophylaxis in the form of subcutaneously administered unfractionated or low molecular weight heparin (Geerts and Selby, 2003). Because shock states, peripheral oedema and vasopressor use may all interfere with cutaneous blood flow, subcutaneously administered drugs

may have reduced bioavailability in the intensive care unit population (Dörffler-Melly et al, 2002). Although some studies that have investigated the effects of subcutaneous oedema have come to contradictory conclusions, the finding that absorption of subcutaneously administered anticoagulants is reduced in critically ill populations appears reasonably robust (Haas et al, 2005; Rommers et al, 2006).

Jochberger et al (2005) demonstrated that 96% of their mixed medical/surgical intensive care unit population had subtherapeutic Anti-Xa activity following standard once-daily dosing of 3000 units of certoparin. This decreased only to 70% following twice-daily dosing. Vasopressor use was also a strong independent risk factor for subtherapeutic Anti-Xa levels in this population, possibly related to vasoconstriction in the subcutaneous tissues (Jochberger et al, 2005). Reduced Anti-Xa levels have been shown in 15 medical/surgical intensive care unit patients requiring vasopressors compared to other intensive care unit patients and non-critically ill controls (Dörffler-Melly et al, 2002). Suggesting that these findings may have clinical relevance is a prospective cohort study by Cook et al (2005), where 261 medical/surgical intensive care unit patients were followed from admission until discharge for the presence of venous thromboembolism with regular lower extremity ultrasound. They demonstrated a high incidence of venous thromboembolism within their population and found vasopressor use as an independent risk factor for its development.

Extracorporeal support

Various types of extracorporeal support are often required in the critically ill population. Intermittent haemodialysis, slow, low efficiency haemodialysis, continuous renal replacement therapy and extracorporeal membrane oxygenation are all used in the intensive care unit for a variety of indications. Because each of these methods requires the exchange of substances non-specifically between the blood and another fluid using a semi-permeable membrane, there are important pharmacokinetic considerations (Trotman et al, 2005; Dager and King, 2006; Choi et al, 2009). The properties of the membrane, the sieving coefficient of the drug (the fraction of the drug that passes across the membrane), the molecular weight of the drug as well as the type and volume of fluid used may be expected to alter volume of distribution and protein binding, as well as drug excretion (Dager and King, 2006; Teigen et al, 2006; Choi et al, 2009).

Although native non-renal and renal (depending on the level of renal impairment) mechanisms of drug elimination still need to be considered in the setting of renal replacement therapy, clearance across the membrane is likely the most important variable (Mehrotra et al, 2004). Altered elimination and increased volumes of distribution have been reported for several drugs for various types of extracorporeal support. Mulla and Pooboni (2005) described an increased volume of distribution for vancomycin as well as decreased clearance. This result has been replicated for other hydrophilic antibiotics as well, including beta-lactams, and aminoglycosides (Dager and King, 2006; Pea et al, 2007). The requirement of dosing adjustments can be determined by comparing the clearance of a drug through the membrane to the clearance of the same drug by healthy kidneys. For drugs where these values are markedly different, dosing adjustments may be required (Pea et al, 2007). Notably there is a large amount of variability in the pharmacokinetic changes observed during renal replacement, and this is thought to be secondary to residual organ function and the variability in dialysate flow rates (Pea et al, 2007). This variability has led to the development of nomograms designed to generate dosing guidelines for many antimicrobial agents (Choi et al, 2009).

A study by Isla et al (2008), which demonstrated differences in the volume of distribution and clearance of meropenem in patients receiving renal replacement therapy depending on the underlying aetiology of the renal failure (sepsis *vs* trauma), adds another dimension (i.e. type of disease process) to the complexity of dosing drugs when renal replacement therapy is undertaken. All these data suggest that extracorporeal support alters the pharmacokinetics of many drugs, and although guidelines exist for some agents, rational dosing with defined physiological endpoints in mind and/or therapeutic drug monitoring with defined therapeutic levels, where possible, may be the preferred approaches to minimize therapeutic failure or toxicity in the critically ill population.

Obesity

The effects of critical illness on drug handling are further complicated by the presence of obesity, and although some groups have attempted to develop guidelines for this population, their efforts have been hampered by data obtained from small studies conducted after a new medication has already been brought to market (Medico and Walsh, 2010). With the exception of unaltered absorption, obesity has been associated with several pharmacodynamic changes, and an understanding of these is important for rational drug dosing (Cheymol, 1993).

Using standard or weight-based dosing in morbidly obese patients has the potential to lead to therapeutic failure or drug toxicity respectively. The application of the large number of weight-based dosing calculations (e.g. ideal body weight, body mass index adjusted, gender adjusted) which exist may give very different results potentially resulting in dosing confusion (Shearer, 2013). Because lipophilicity is the chief determinant of a drug's volume of distribution, lipophilic drugs are usually associated with a higher volume of distribution in obese patients and are usually dosed based on total body weight. Although dosing of hydrophilic drugs

would therefore be expected to be relatively unaltered in obese patients or based on ideal body weight, some studies have demonstrated increased volume of distribution for hydrophilic drugs administered to obese patients. In theory this may be the result of the observation of a water content of adipose tissue of up to 30% as well as increased plasma volumes of obese patients when corrected for gender and weight (Medico and Walsh, 2010).

These studies suggest that drug dosing in obese patients would be generally higher, and although this is probably true for many antibiotics such as cephalosporins, penicillins and carbapenems, dosing for other drugs such as propofol and remifentanil is unchanged (Medico and Walsh, 2010). The variability of data in this patient population again underscores the need for careful attention to therapeutic effect, monitoring drug levels, as well as consultation with clinical pharmacists.

Conclusions

The management of the patient presented at the beginning of this article could potentially be improved following careful attention to some key pharmacokinetic principles. Because of the significant fluid resuscitation required in the patient's initial management, an increased loading dose of ceftriaxone could be considered given its expected increased volume of distribution. Similarly, this patient's body habitus suggests an elevated volume of distribution for hydrophobic drugs, making total body weight-based dosing of erythromycin a reasonable consideration. Furthermore, this patient required sedation with three drugs potentially influenced by his decreased serum albumin concentration, making careful attention to the therapeutic effects of these drugs warranted, as opposed to reliance on standard dosing. The venous thromboembolism prophylaxis in this patient could also be expected to be less efficacious compared to a non-critically ill patient. Although it remains unclear if increasing the dose of low molecular weight heparin improves outcomes, a higher index of suspicion for venous thromboembolism-related complications needs to be maintained in this patient. Finally, given this patient's elevated creatinine clearance, an increased maintenance dose rate could also be considered for all renally cleared medications.

While there are many theoretical alterations in the pharmacokinetic handling of drugs, rigorous investigations into the therapeutic consequences of these alterations are few. Studies of alterations in the pharmacokinetics of drugs administered to the critically ill have been hampered by methodological restraints, small numbers of patients, a diversity of patient populations with different physiological disturbances (e.g. cardiogenic shock *vs* septic shock), and lack of a correlation to potential adverse outcomes. Further studies in this area should be designed with these limitations in mind. **BJHM**

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KEY POINTS

- Large volume fluid resuscitation and body habitus have the potential to alter the volume of distribution for hydrophilic and hydrophobic drugs, potentially necessitating increases in initial dosing.
- As there are several alterations in gut physiology in the critically ill population, careful consideration of intravenous alternatives is required before selecting an enterally administered drug.
- Changes in renal function are common in the critically ill population and may have important pharmacokinetic consequences despite potentially creatinine values.

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