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An applied pharmacokinetic approach to adjusted drug dosing: Part II – pathophysiological states

S Mahomed

Department of Anaesthesia, School of Clinical Medicine, Faculty of Health Sciences, Charlotte Maxeke Johannesburg Academic Hospital, University of the Witwatersrand, South Africa
Corresponding author, email: *dr.smahomed@gmail.com*

In addition to age, gender, and pregnancy, pathophysiological states such as extremes of body weight, organ dysfunction, and critical illness with sepsis are factors that affect the pharmacokinetics of drugs, thereby necessitating an adjustment of drug dosing.[1-5]

Keywords: applied pharmacokinetics, adjusted drug dosing, pathophysiological states

Pharmacokinetics at extremes of body weight

In the normal-weight individual, the total body weight (TBW) comprises 20% fat weight (FW) and 80% lean body weight (LBW) or fat-free mass (FFM).[1] Extremes of body weight may result in altered physiology that affects the pharmacokinetics of a drug (Table I).[1,2]

Underweight/malnutrition

In the underweight or malnourished individual, FW accounts for a decreased proportion of TBW, and the LBW tends towards TBW.[1] Catabolic states, such as starvation, have several consequences that affect protein binding, drug distribution, and clearance.[1] Adipose tissue is lost first, followed by muscle and lean tissues.[1] There is a reduction in the synthesis and function of proteins and hepatic enzymes. Total body water increases gradually, resulting in oedema secondary to reduced intravascular oncotic pressure because of reduced protein synthesis.[1] The effect of this is multifold: there is a higher volume of distribution (Vd) for water-soluble drugs and a lower Vd for fat-soluble drugs. As a result of the reduced protein binding, there is an increase in the fraction of free drugs available for hepatic metabolism.[1]

There is a decrease in hepatic enzyme synthesis and function, which affects drugs with a low hepatic extraction ratio. The increased free drug concentration may exceed the capacity for hepatic metabolism, resulting in higher plasma concentrations, a delayed offset, or prolonged terminal elimination.[1]

Overweight/obesity

Body fat composition varies with age, gender, and genetics.[7] With increased TBW in the obese, there is a greater increase in FW compared to LBW.[1] The rate of drug distribution and elimination is proportional to the LBW, which mainly consists of muscle and vessel-rich organs or tissues. Blood flow to adipose tissues accounts for up to 5% of cardiac output compared with 22% to lean tissues, with a further decrease to 2% in obesity.[6] With increased body weight, total body water also increases, although, at extremes of obesity, the proportion of total body water is reduced because most of the excess weight is FW.[1,6]

FW is comprised of areas of high lipid density (e.g. poorly vascularised adipose tissue) in which lipophilic drugs are more likely to distribute.[1,2,6] Therefore, lipophilic drugs have a high Vd at steady-state. This is significant in critical care where prolonged, repeated administration of drugs like morphine, propofol, and midazolam can result in a prolonged duration of action.[1] Once the infusion is stopped, the plasma or effect-site concentration decreases, and the drug redistributes into plasma and its effect sites from fatty tissues, prolonging the clinical effect and delaying terminal elimination.[1,6] This is more evident in the obese where FW is higher.[1]

Dosing scalars in extremes of body weight

Depending on the biochemical characteristics of a drug (e.g. lipid solubility, Vd), using TBW sometimes fails to account for changes in compartment size, leading to either under- or

Table I: Pharmacokinetic changes at extremes of body weight[1]

Physiological variable	Change in obesity	Change in malnutrition	Pharmacokinetic consequence
Total body water	↑	↑	↑ Vd for water-soluble drugs
Fat mass	↑	↓	↑ dose in the obese due to ↑ Vd
LBW	↑	↓	↑ clearance in obese patients
Plasma proteins	↑	↓	↑ plasma protein binding in obese patients
Cardiac output	↑	↓	↑ clearance in obese patients

overdosing of the drug.[1] Using derived indices such as ideal body weight (IBW), which approximates compartment size, or adjusted body weight (ABW), which incorporates a correction factor for drug distribution is preferable, particularly where drug concentration is critical.[1,2] Males and females exhibit a difference in the distribution and metabolism of adipose tissue, therefore some measures account for differences in sex.[1,2,6]

Dose adjustment according to LBW correlates well with drug clearance, and using a measure of LBW is better in obesity as it assumes either a distribution to lean tissues only (IBW) or to some of the additional fatty mass (ABW) to account for drug lipid solubility.[1,2] The predicted normal weight (PNWT) considers height, weight, and sex and corrects for the additional adipose tissue.[1]

Overall, TBW is used for drugs with a wide therapeutic window (e.g. succinylcholine) where absolute plasma concentration is less important but simultaneously at risk of overdosing hydrophilic drugs and underdosing hydrophobic drugs.[1,2] The LBW is best suited to the dosing of hydrophilic drugs, and ABW is used for drugs with a narrow therapeutic window where the effects of lipid distribution may significantly affect toxicity (e.g. gentamicin).[1-3] Table II is a summary of the various dosing scalars and their clinical application, and Table III presents the recommended dosing scalars for commonly used drugs in anaesthesia.

Patients who are at the extremes of weight need to be considered holistically when assessing their pathophysiological status along with the pharmacokinetic implications thereof. This includes associated comorbidities and potentially severe physiological or metabolic derangements with organ dysfunction.

Adjusted drug dosing in hepatic dysfunction and failure

Absorption and bioavailability

Patients with liver disease may present with alterations in drug absorption and bioavailability.[9,10] The decreased secretion of bile may result in malabsorption. Oral drug bioavailability may be increased in patients with portal venous hypertension as portosystemic shunts lead to a decrease in first pass metabolism.[9,11]

Distribution

Cirrhotic liver disease may result in the reduced protein binding of certain drugs due to the reduced hepatic synthesis and quality of plasma proteins viz. albumin and alpha-1-acid glycoprotein.[9] Moreover, the accumulation of endogenous compounds, such as bilirubin, may further inhibit the plasma protein binding of certain drugs with competition for binding sites.[9] Additionally, patients with ascites will have a higher Vd of water-solubility, necessitating larger loading doses.[10,12]

Biotransformation and elimination

Not all liver diseases have the same pharmacokinetic consequences affecting the hepatic biotransformation and

Table II: Formulae for weight-based calculations[1]

Term	Derivation	Explanation	Use	Caution
TBW (kg)	LBW + FW	As measured, includes both fat and lean weight	Dosing of many drugs most appropriate in the non-obese (where TBW tends to LBW) Succinylcholine, total intravenous anaesthesia (TIVA) maintenance (accounts for larger compartment size)	May lead to overdose if used in the obese population TIVA boluses by TBW may exaggerate haemodynamic effects
LBW (kg)	1.1 × TBW - 0.0128 × body mass index (BMI) × TBW (male) 1.07 × TBW - 0.0148 × BMI × TBW (female)	LBW comprised of non-adipose tissues	Useful for polar drugs with a small Vd, such as neuromuscular blocking agents, topical calcineurin inhibitors (bolus induction, avoids overdosing and instability)	Several formulae for calculation, and may be complex Error-prone, particularly at extremes of weight, depending on the formula used Not possible to measure directly in clinical practice
IBW (kg)	22 × height^2 (m)	The weight of an individual based on height and assuming a normal BMI of 22 kg/m^2	Recommended for calculation of local anaesthetic maximum doses	Assumes 15% body fat, which is not "normal" across all age ranges
ABW (kg)	LBW + C × (TBW - LBW) (where C is a drug-specific correction based on the solubility of the drug)	Assumes drug distribution to lean tissues and a proportion of the FW depending on the physiochemical properties of the drug	Dosing of drugs with a narrow therapeutic index (e.g. gentamicin)	Requires calculation using a correction factor specific to every drug Uses LBW (which may be error-prone, depending on the formula used)
PNWT (kg)	1.57 × weight - 0.0183 × BMI × WT - 10.5 (male) 1.75 × weight - 0.0242 × BMI × WT - 12.6 (female)	Consists of lean and fatty weight, corrected for the non-obese individual, an extension of IBW	Developed to overcome limitations of scaling to LBW or TBW	Specifically derived for drug dosing (rather than the classification of obesity) Not validated or in widespread clinical use currently

Table III: Dosing scalars for drugs commonly used in anaesthesia[1-3,8]

Drug	Recommended dosing scaler	Notes
Opioids		
Morphine	LBW	Highly lipophilic with a relatively large Vd. The increased sensitivity to opioids risks apnoea when dosed according to TBW. Caution in obstructive sleep apnoea. Cautious titration is recommended due to the variability of clinical effects.
Fentanyl & sufentanil	LBW	Rapid initial offset because of redistribution, with increased clearance in the obese. Caution of increased sensitivity to opioids. Cautious titration is recommended due to the variability of clinical effects.
Remifentanil	LBW	Significantly greater plasma concentrations when dosed by TBW rather than LBW, risking bradycardia. Cautious titration is recommended due to the variability of clinical effects.
Alfentanil	ABW	No data available. Manufacturer suggests LBW.
Anaesthetic induction agents		
Propofol	Initial bolus: LBW Infusion: TBW	Highly lipophilic with rapid redistribution. Initial bolus dosing by TBW may result in haemodynamic instability, but dosing by LBW risks awareness. Practically, dose boluses by LBW, and infusions by TBW.
Thiopental	Initial bolus: LBW Infusion: TBW	Dosed based on the same principles as propofol with risks of awareness after a bolus dose.
Etomidate	LBW	No data available; recommendation based on pharmacokinetic similarities to propofol.
Neuromuscular blockers and reversal agents		
Succinylcholine	TBW	Increase in pseudocholinesterase activity in the obese, resulting in relatively increased metabolism of succinylcholine. Dosing by TBW is appropriate without any associated adverse effects.
Atracurium & rocuronium	LBW	Polar, charged molecules with a small Vd; dose by calculated LBW. Dosing according to TBW results in a prolonged duration of action with no improvement in onset time for rocuronium.
Reversal agents		
Sugammadex	TBW/ABW	Few studies of sugammadex in the obese. Recommend titration to effect. The manufacturer recommends dosing by TBW.
Neostigmine & glycopyrrolate	TBW/ABW	Recommend titration to effect.
Local anaesthetics		
Lidocaine Bupivacaine	LBW IBW	Overall maximal dose calculated using standard limits based on LBW. The absolute maximum dose depends on the route of administration.
Prilocaine Ropivacaine	LBW IBW	

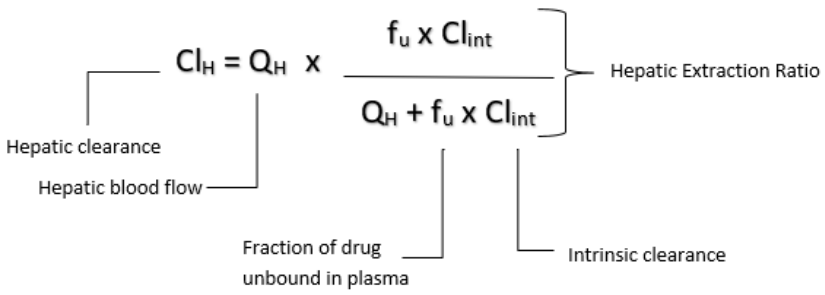

Figure 1: Determinants of hepatic clearance

clearance of drugs (i.e. the impairment of drug disposition has a strict correlation with the type and severity of liver disease).[9] Notably, the hepatic drug clearance in patients with liver cirrhosis is markedly decreased, whereas the metabolic function of the liver is usually maintained in patients with chronic hepatitis without cirrhosis, or with primary or secondary cancer.[9,11] Severe liver dysfunction is generally considered as albumin < 30 g/L, international normalised ratio > 1.2, and Child-Pugh class C.[11]

Importantly, there is no linear correlation between the hepatic metabolising capacity and biomarkers of liver function.[9,11]

Hepatic clearance is determined by hepatic blood flow and hepatic extraction ratio, which in turn is determined by the free drug in plasma and the intrinsic clearance (Figure 1).[13,14]

Intrinsic clearance is the ability of the liver to metabolise the drug without the restrictions of hepatic blood flow or protein binding. It is solely dependent on the activity of sinusoidal and canalicular transporters and hepatocyte metabolic enzymes.[9]

In patients with cirrhosis with increased disease severity, there is a proportional decrease in the concentrations of drug-binding proteins (especially albumin), as well as in the content and activity of phase I hepatic microsomal enzymes.[12] Notably, however, cirrhosis results in a variable and non-uniform

reduction in hepatic enzyme metabolic potential.[9,11] There is a greater decrease in the liver content of the phase I oxidising cytochrome (CYP) P450 enzymes with a resultant decrease in the clearance of drugs metabolised by CYP3A4/3A5, such as midazolam, in comparison to phase II conjugation reactions, such as glucuronidation.[9-12]

Data suggest that if the drug is a high clearance drug (liver blood flow dependent), a 50% reduction in dose is recommended, although there seems to be little difference in the metabolic clearances of both highly and poorly extracted drugs in cirrhotic patients.[11,12]

Elimination

Drugs with < 20% hepatic elimination and those that are mainly renally excreted are less likely to be affected by liver disease.[9] Drugs and metabolites that rely on biliary excretion will be retained and may require dose adjustment. Drugs that undergo enterohepatic recirculation may have decreased half-lives due to the failure of recirculation.[9,10]

Pharmacodynamic changes

Patients with decompensated liver failure may have altered tissue sensitivity to drugs.[3,9,11,12] For many drugs, both the drug and the metabolite(s) contribute to the overall therapeutic response of the patient to the drug. Therefore, the effect on the concentration of the active drug and the metabolite in the body should be known. A decrease in hepatic metabolism can result in a change in the potency of a drug; depending on whether the drug or its metabolite is more potent.[11] If a drug is more potent than its metabolite, the overall pharmacological activity will increase as the drug concentration will be higher. If the metabolite is more potent than the drug, the pharmacological effect of the drug will be decreased as less of the active metabolite is formed. Hepatic disease may result in complex pharmacological outcomes as the disease process itself has the potential to affect both the pharmacokinetics and pharmacodynamics of a drug.[3]

Extreme caution is recommended when using drugs with a narrow therapeutic index in patients with liver disease and when administering any drug to patients with severe liver dysfunction (Child-Pugh class C).[12] Drugs with a wide therapeutic range will be less affected by moderate hepatic dysfunction.[11]

There is an increased sensitivity to central nervous system depressants. The recommendations are to either avoid or reduce the dose of barbiturates, benzodiazepines, and opioids. Short-acting drugs that are reversible are preferable.[11]

In comparison to impaired renal function, the dose adjustment for impaired liver function, such as in patients with liver cirrhosis, is more complex because there is no single marker that can be used to adjust the dose.[11] The information on individual drug dose adjustment in patients with liver cirrhosis should ideally be found on the drug label or in published clinical studies.

Adjusted drug dosing in renal impairment and failure

Kidney disease can result in pharmacokinetic derangements of both the renal- and non-renal drug clearance, Vd, and bioavailability of drugs.[15] Renal impairment may lead to drug accumulation and potential toxicity by modifying the effects of many medications. Many of these alterations can and should be predicted and subsequently alleviated by adjusting drug doses, particularly in patients with chronic kidney disease (CKD).[15,16]

CKD (Table IV) is a pathology of gradual loss of kidney function occurring over a period of months to years and is characterised by the presence of both glomerular filtration rate (GFR) < 60 ml/min and albumin > 30 mg/g of creatinine, together with structural or functional abnormalities of the kidney for longer than three months. End-stage renal disease is defined as a GFR < 15 ml/min.[17] Therefore, the pharmacokinetic impact of the renal dysfunction should first be quantified according to the patient's actual GFR.[3,16]

Table IV: Stages of CKD

CKD stage	GFR (ml/min)	Renal insufficiency
1	120–90	Nil
2	89–60	Mild
3a	59–45	Intermediate
3b	44–30	Moderate
4	29–15	Severe
5	14–0	End stage; needs renal replacement therapy

The Cockroft-Gault formula (1973)

Historically, the Cockcroft-Gault equation was used as a measure of creatinine clearance; however, the use of this biomarker may lead to an underestimation of renal impairment, specifically among the elderly.[16,17] Furthermore, the Cockcroft-Gault equation relies on TBW and so overestimates the GFR in patients with obesity.[16,18]

GFR = {[(140–age) × weight] / (72 × creatinine)} × 0.85 [if female]

MDRD equation

The MDRD (Modification of Diet in Renal Disease) formula is now routinely reported on and indexes the GFR based on a normalised body surface area (i.e. ml/min/1.73 m^2). Conversion of MDRD-estimated GFR to non-normalised body surface area overestimates the GFR in patients with obesity.[16,18]

186 × (creatinine / 88.4) × (age) × 0.742 [if female, but × 1.210 if black]

CKD-EPI equation

A newer formula, CKD-EPI (named after the Chronic Kidney Disease Epidemiology Collaborative), has been adapted for research purposes.[19]

GFR = 141 × min (S/κ, 1) × max (S/κ, 1) × 0.993 × 1.018 [if female, but × 1.159 if black]

Abbreviations/units: S = serum creatinine in mg/dL, κ = 0.7 for females and 0.9 for males, α = -0.329 for females and -0.411 for males, min = the minimum of S/κ or 1, and max = maximum of S/κ or 1.

Understanding the concentration-time profile of a drug

The concentration-time profile approximates the clinical effect of most drugs, and drug exposure relates to the maximum plasma concentration (C_{max}) and/or the area under the concentration-time curve (AUC).[15] In general, high drug exposures increase the risk of adverse drug reactions, and low drug exposures are subtherapeutic.

In kidney disease, failure to appropriately adjust dosing may result in sub- or supratherapeutic dosing.[16,17] Subtherapeutic dosing may lead to treatment failure or drug resistance, while supratherapeutic exposure to drugs and their metabolites may result in systemic toxicity.[16,17] Increased renal clearance leads to lower drug concentrations and decreased clearance results in greater drug effects.

When the changes in pharmacokinetics due to kidney disease and other conditions are understood, the dosing regimen can be adjusted so that the concentration-time profile is optimised for the individual.[3,15] To avoid harm, the dose of renally cleared drugs should be decreased equivalent to the calculated reduction of drug clearance. The adjustments can be made in the following ways:[20]

- Constant interval: dose reduction method.
- Constant dose: interval extension method.
- By administering a loading dose at the start of the treatment.
- By monitoring the concentrations of drugs that have a narrow therapeutic index.

Changes in either the Vd or clearance have differing effects on the concentration-time profile.[15] Although a doubling in the Vd and a halving of clearance have the same effect on the elimination half-life, their concentration-time profiles are different. When clearance is halved, the AUC is doubled. When the Vd is doubled, the C_{max} is reduced, but there is no change to AUC despite the change in the concentration-time profile. In patients with altered kinetics, continuous dosing will lead to drug accumulation if the regimen is not adjusted.[15-17] Onset of toxicity will occur earlier from a decrease in clearance. Increasing the dosing interval will prevent drug accumulation, although where Vd is doubled, the C_{max} and average concentration will be lower than in an individual with normal kinetics, and the dosing regimen might be subtherapeutic.[15]

Table V: Recommendations for drug dosing in patients with hepatic and renal insufficiency[6,9-11]

Drug	Problem	Suggested action
Alfentanil	CL decreased by 50% t1/2β is prolonged Reduced protein binding	Reduce dose in patients with severe liver disease
Codeine	Metabolised to morphine CYP2D6, ceiling effect	Serum levels unpredictable Do not use for analgesia
Fentanyl	Pharmacokinetics of a single intravenous dose remain unaltered	A normal single dose can be used Prolonged recovery time after termination of continuous infusion
Hydrocodone	Metabolised to hydromorphone	As above
Hydromorphone	Reduced hepatic glucuronidation leads to an increase in oral bioavailability, decreased CL & prolonged t1/2β	Dose reduction Safe in renal impairment
Meperidine	Increased bioavailability of CNS active metabolite in renal and hepatic impairment with prolonged t1/2β	Avoid in patients with hepatic/renal impairment
Methadone	Prolongation of t1/2β & increase of Vd in patients with severe hepatic dysfunction Chronic alcohol abuse may increase methadone metabolism	A normal dose can be used in mild to moderate liver diseases Accumulation may occur in severe liver dysfunction
Morphine	Reduced hepatic glucuronidation leads to an increase in oral bioavailability, decreased CL & prolonged t1/2β in oral dose	Use with care in patients with severe liver cirrhosis Reduce the oral dose Metabolites increase toxicity in patients with renal failure
Oxycodone	Multiple metabolite levels are unpredictable	Reduce dose and frequency in renal impairment
Remifentanil	Pharmacokinetics unaltered	A normal dose can be used
Sufentanil	Pharmacokinetics altered & reduced protein binding with alkalosis associated with an increased Vd & t1/2β	A normal dose can be used Use with care when plasma pH is elevated
Tramadol	Reduced metabolism t1/2β of tramadol & O-desmethyltramadol approximately doubled	Prefer alternative analgesic; reduce dose frequency in patients with liver and renal impairment

CL – clearance, CNS – central nervous system, t1/2β – terminal elimination half-life, Vd – volume of distribution

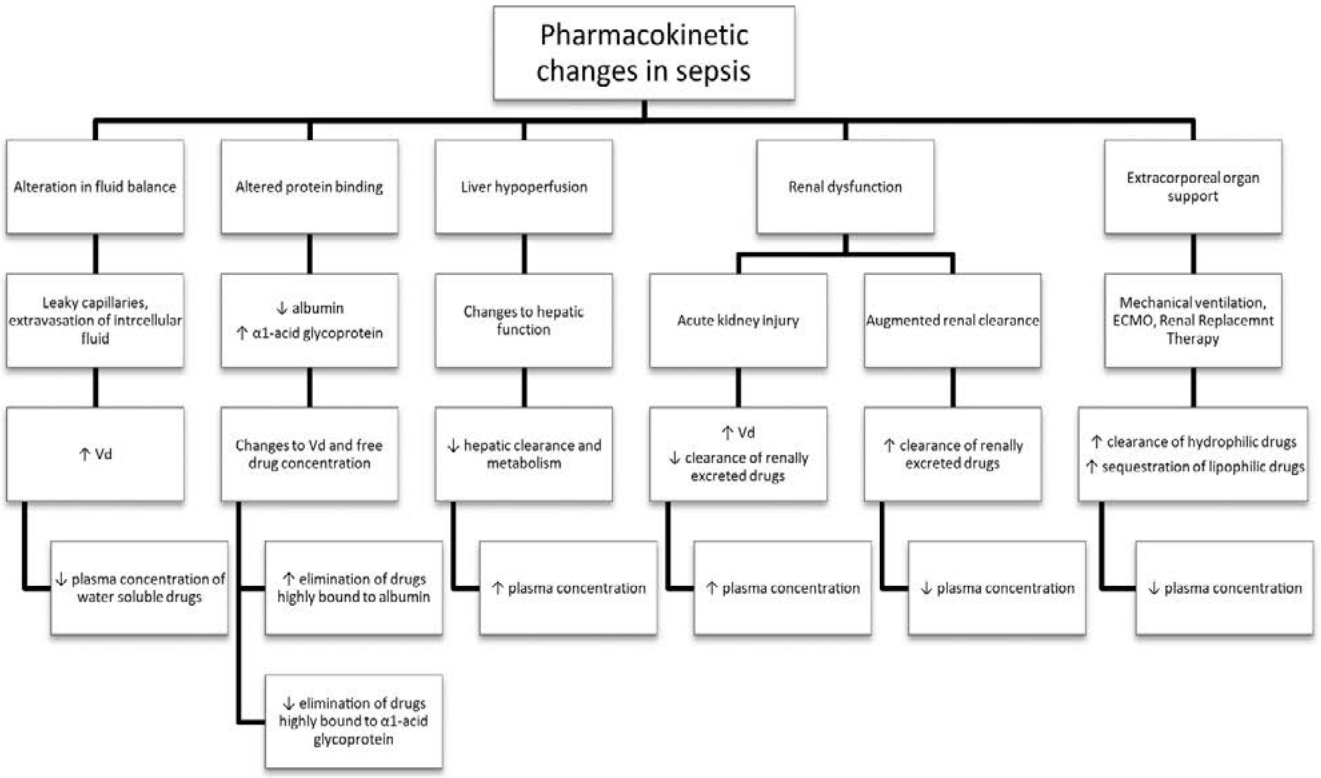

Figure 2: Pharmacokinetic changes in sepsis

Often, dose adjustments are crudely made in terms of halving the dose or doubling the dosing interval. Despite this, minor changes in dose or the concentration of drugs with a narrow therapeutic index may result in significant adverse effects.[15] Therefore, drug dosing should be optimised on a case-by-case basis using rational dose design grounded in an understanding of basic pharmacokinetic concepts along with therapeutic drug monitoring, particularly for drugs that have a narrow therapeutic index. This should be guided by knowledge of individual drug pharmacology and advice from the drug manufacturer, usually included in the package insert (Table V).

Pharmacokinetic implications in critically ill patients with sepsis

Critically ill patients pose a challenge to optimal drug dosing due to a plethora of haemodynamic, metabolic, and biochemical derangements (Figure 2).[5] These derangements can affect various pharmacokinetic processes, including drug absorption, distribution, metabolism, and elimination to differing degrees.

Absorption and bioavailability

In shock, blood flow is preferentially shunted to vital organs, including the brain and heart, whereas flow to other organs, including the gastrointestinal tract or subcutaneous tissue, may be reduced.[5] As a result, drug absorption may be altered in a haemodynamically compromised patient (with hypotension and shock) when administered via the gastrointestinal tract or subcutaneously. Intravenously administered drugs are recommended during the acute phase of sepsis or septic shock to avoid these concerns.[5]

Distribution

Several factors may influence the Vd in a critically ill patient.[5] Aggressive fluid resuscitation in response to hypotension and/or third spacing leads to an increase in the Vd, which in turn decreases plasma drug concentrations with standard dosing.[4,5] Hypoalbuminaemia is common in critically ill patients and may lead to an increase in both the Vd and elimination of unbound acidic antimicrobials. In addition, there may be increased expression of alpha-1-acid glycoprotein, an acute-phase reactant that binds to basic drugs, thereby decreasing their free drug concentrations.[4,5]

Metabolism and elimination

In sepsis or septic shock, hypoperfusion may lead to "shock liver" and significant hepatic dysfunction.[5] This may lead to alterations in hepatic enzyme activity and hepatic blood flow, which influence drug metabolism and clearance respectively.[4,5] The use of inotropes and vasodilators will increase portal and hepatic blood flow, while vasopressors induce the opposite effect by alpha-adrenergic-mediated vasoconstriction and consequent reduction of blood flow.[5]

Acute kidney injury (AKI) is common in critically ill patients. Renal clearance of hydrophilic drugs decreases with a decline in the GFR, potentially requiring dose adjustment depending on the degree of renal impairment. However, the need for increased loading doses in the setting of increased Vd should also be considered.[4,5] Furthermore, in some patients interventions like aggressive fluid resuscitation and the use of vasopressors can lead to an early increase in cardiac output and enhanced

renal blood flow, resulting in augmented renal clearance (ARC) defined as a GFR of ≥ 130 ml/min.[5] Patients with ARC may require dose modifications to avoid suboptimal antimicrobial exposure.

In patients undergoing renal replacement therapy, the drug clearance across a haemodiafilter membrane depends on the molecular weight and protein binding of the drug.[21] The larger the molecular weight, the less the filtration. Because blood proteins are too large to be cleared by the membrane, they will remain in the blood together with highly protein-bound drugs. The effluent (dialysate + ultrafiltrate) rate determines the drug clearance during dialysis. The faster the affluent rate, the greater the drug removal.[21]

The physiological alterations that affect drug pharmacokinetics pose a significant challenge in the management of critically ill patients. Standard dosing strategies are unlikely to consistently achieve therapeutic targets, which can lead to an increased risk of both clinical failure and the development of antimicrobial resistance.[4] The adjustment of dosing strategies with the use of loading doses or continuous infusions may be beneficial. Where possible, using an individualised dosing approach with therapeutic drug monitoring would be advantageous, considering the significant interpatient variability, especially in antimicrobial concentrations.[4,5] Pharmacotherapy targeted at therapeutic goals and therapeutic drug monitoring is currently the best option for the safe care of the critically ill.[4]

Conclusion

While this article by no means serves as a comprehensive formulary for adjustments in drug dosing, the author hopes that it stimulates thought on the physiological and pathophysiological processes that influence how drugs should be dosed and prescribed. Thorough background knowledge of individual drug pharmacology and disease processes is imperative and cannot be overemphasised.

ORCID

S Mahomed https://orcid.org/0009-0002-6298-0879

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