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An applied pharmacokinetic approach to adjusted drug dosing: Part I – physiological 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*

A patient's age, weight, gender, and pathophysiological state are some factors that may necessitate the adjustment of drug dosing. In addition, pharmacokinetics and pharmacogenomics, drug-drug and food-drug interactions may further alter the pharmacokinetics and pharmacodynamics of a drug. In part I of this topic, the basic principles of pharmacokinetics and the physiological factors that affect drug dosing viz. extremes of age and pregnancy are discussed.

Keywords: applied pharmacokinetics, adjusted drug dosing, physiological states

Introduction

The goal of any pharmacotherapeutic intervention is to achieve the desired clinical effect by reaching and maintaining an adequate effect-site concentration, using the minimum effective dose of a drug for a predictable amount of time.[1]

Dosing is prescribed according to the amount of drug per unit of time.[1] It must include the drug name, unit dose volume, route and frequency of administration, and length of treatment, e.g. cephazolin 1 g intravenously every 8 hours for 72 hours. Drugs may be prescribed as either a loading or a maintenance dose, with the main difference being that the loading dose is dependent on the volume of distribution (Vd), while maintenance doses are dependent on plasma clearance.[2,3] A loading dose is usually prescribed when a drug needs to reach a steady-state rapidly and it rarely needs to be modified.[3] In comparison, maintenance doses are used to maintain the steady-state plasma concentration and are dependent on patient physiological characteristics, and may therefore require dose adjustment.[3]

Drug dosage should be prescribed after careful consideration of both the patient and drug characteristics, and whether the need exists for adjustment from what would normally be prescribed. To appreciate the nuances of appropriate drug dosing, one needs a solid grasp of the fundamental principles of pharmacokinetics, as well as knowledge of individual drug pharmacology and patient pathologies.[4]

Basic principles of pharmacokinetics

Pharmacokinetics describe the factors that influence how a drug moves through the body from administration to elimination, and the resultant tissue drug concentrations over time.[5,6] The pharmacokinetic principles of absorption, distribution, metabolism, and excretion (ADME) apply.[7]

Drug absorption and bioavailability

Drug absorption influences the speed and concentration at which the drug reaches its effect site. It also includes liberation, which is the process where the drug is released to its active form.[5]

Bioavailability refers to the fraction of the administered drug that reaches the systemic circulation.[5] Drugs that are administered intravenously are 100% bioavailable, whereas drugs administered via other routes are subject to intra- and extrahepatic metabolism and excretion before reaching the systemic circulation.[2,5]

The area under the curve (AUC) method uses the plasma concentration over a given time to calculate the bioavailability of drugs with different distribution characteristics.[5] The integral of the curve is used to express the bioavailability of the substance in comparison to the 100% bioavailability of an intravenously administered substance.[5]

Distribution

Distribution refers to how the unmetabolised drug disperses between the intravascular (blood/plasma) and extravascular (intracellular and extracellular) compartments of the body and is dependent on the biochemical properties of the drug, as well as the physiology of the patient.[2,4,5,8]

Drugs have variable distribution patterns in different types of tissue based on their molecular structure and their binding abilities.[2,5] Drug distribution is influenced by various factors including tissue perfusion, tissue binding, lipid solubility, and plasma protein binding.[8] The goal is to reach an effective drug concentration at its designated compartmental destination, which is largely dependent on the Vd of the drug.[2]

Volume of distribution (Vd)

The Vd is the ratio of the total amount of the drug in the body to the drug concentration in the plasma at a given time.[2] It is useful in estimating the dose required to achieve a given plasma concentration.[6] Variations in Vd mainly affect the plasma concentration of the drug, which can directly impact the efficacy/toxicity of the drug.[2,8]

The following equation represents Vd:[2]

$$\text{Vd (L)} = \frac{\textbf{A(t)}\ \text{(mg) (Amount of drug in the body at time = t)}}{\textbf{C(t)}\ \text{(mg/L) (Plasma concentration of the drug at time = t)}}$$

Based on the above equation, a drug with a high Vd requires a higher dose to achieve the desired plasma concentration, as it tends to leave the plasma and enter the extravascular compartments of the body. The opposite is true for drugs with a low Vd.

Biochemical properties

The biochemical properties of a drug affect its distribution in the body.[2,5] These properties include the fat or water solubility (lipophilicity vs. hydrophilicity), polarity, and acidity or alkalinity of a drug.[2,5] Lipophilic drugs are more likely to have a higher Vd as they pass through lipid bilayers and distribute to areas with high lipid density, such as adipose. Hydrophilic molecules have a lower Vd as they are more likely to remain in the intravascular space.

Depending on its charge at physiological pH, a drug may bind macromolecules inside or outside the plasma.[5] Compared to neutral or basic molecules, acidic molecules have a higher affinity for albumin molecules at lower lipophilicity and are more likely to bind albumin and remain in the plasma, leading to a lower Vd.[2] Basic (alkaline) molecules have strong interactions with negatively charged phospholipid head groups located on phospholipid membranes; however, the overall lipophilicity of the drug will determine the extent of binding. In general, basic molecules will leave the systemic circulation leading to a higher Vd compared to acidic molecules.[2]

Plasma protein binding

Depending on its affinity for plasma proteins, a drug exists in equilibrium between a protein-bound or free form within each compartment of the body.[9] The greater the affinity, the greater the proportion of binding. If the protein binding is reversible, then a chemical equilibrium will exist between the bound and unbound states, such that protein + drug ⇌ protein-drug complex.[5,9] As the unbound fraction of the drug is metabolised and cleared, the bound fraction will then be released to maintain equilibrium. It is only the unbound fraction that exerts a pharmacological effect and that can undergo metabolism and elimination.[5] The bound fraction of the drug may act as a reservoir from which the drug is slowly released, thus influencing the drug's biological half-life.[5,9]

Acidic and neutral drugs primarily bind to albumin, which is alkalotic. Once albumin becomes saturated, these drugs then bind to lipoprotein. Basic drugs will bind to the acidic alpha-1-acid glycoprotein.[9] If plasma protein levels are low, the unbound fraction of the drug will be greater than expected and may potentiate the effects of the drug. The concentration of the drug in the body, the amount and quality of plasma proteins and their binding sites, and competition from other drugs that bind to plasma proteins all determine the unbound fraction of the drug.[2,5,9]

Hepatic clearance and metabolism

Hepatic metabolism is the major elimination pathway for most drugs.[10] The clearance of a drug in the liver is determined by hepatic blood flow and the hepatic extraction ratio (ER) of the drug.[10] Hepatic extraction is dependent on liver blood flow, the intrinsic clearance of the unbound drug, and the fraction of unbound drug in the blood [6,10] The ER refers to the proportion of hepatocyte uptake of the drug from the hepatic arterial circulation, subsequently making it available for metabolism.[6] Intrinsic hepatic clearance refers to the activity of enzymes and transporters involved in the elimination of drugs by metabolism and biliary excretion.[10] For high ER drugs (e.g. propofol and fentanyl), hepatic elimination is limited only by hepatic blood flow.[6] Conversely, hepatic clearance of low ER drugs (e.g. phenytoin and ceftriaxone) is limited by the intrinsic metabolic capacity of hepatocytes and the unbound fraction of the drug in plasma, and it remains relatively independent of hepatic blood flow. Drugs can be classified as having a high (> 0.7), intermediate (0.3–0.7), or low (< 0.3) ER, which is a function of the efficiency of the liver in removing the substance from circulation.[10]

The metabolism of drugs can occur in various reactions, categorised as phase I (modification), phase II (conjugation), and in some instances, phase III (additional modification and excretion).[11,12] Phase I modifications are made either by removing hydrogen or adding oxygen to more polar molecules. In some instances, this process changes an inactive prodrug into a metabolically active drug.[11,12] In phase II reactions, a drug molecule couples with another molecule in a conjugation reaction. Conjugation usually renders the compound pharmacologically inert and water-soluble, allowing the compound to be easily excreted.[11,12] A critical factor in the efficient metabolism of drugs is the enzymatic catalysis of phase I and II processes, which are heavily dependent on the concentrations of the various liver enzymes.[11]

Metabolism affects the plasma concentration of some drugs, and the reverse is also true. Certain drugs have an inhibitory effect on enzymes, increasing the patient's sensitivity to other medications metabolised through the action of those enzymes.[11] In contrast, enzyme induction may occur consequent to the repeated use of the same chemical. The body becomes tolerant of the drug and compensates by increasing the production of enzymes necessary for the drug's metabolism. This necessitates increasing doses to produce the same effect. Furthermore,

drugs that share elements of their metabolic pathways can also "compete" for the same binding sites on enzymes, decreasing their metabolism's efficiency.[11] Therefore, dose adjustments for drug-drug interactions should be taken into consideration.

Elimination and clearance

The kidneys are primarily responsible for the completion of the drug elimination process, which begins in the liver.[12] As lipophilic drugs readily cross the cell membrane of the kidney tubules and are reabsorbed into the blood, they first need to be metabolised in the liver before excretion of the drug becomes possible.[12] Polar drugs, or their metabolites, undergo glomerular filtration and typically do not undergo reabsorption before being excreted in the urine.[12] Urinary pH has a significant impact on drug ionisation and subsequent excretion (i.e. increased excretion occurs with weak acidic drugs in basic urine and weak basic drugs in acidic urine).[7]

Ionised drugs with a molecular weight > 300 g/mol are actively secreted by the liver into bile, which reaches the digestive tract and is either eliminated in faeces or reabsorbed as part of the enterohepatic cycle.[12] Excretion may also take place in the lungs, breast milk, sweat, saliva, and tears.[12]

Pharmacokinetic differences at the extremes of age

Body composition

Age and gender determine the patient's body composition (Table I).[7,13] At birth, the total body water (TBW) is at its highest, with term and preterm neonates having a TBW of 75% and 80%, respectively.[7] With increasing age, there is a progressive reduction in TBW and lean body mass, resulting in a relative increase in body fat.[13] The intracellular water remains relatively stable after the first month of life to adulthood.[7]

Table I: Average TBW composition according to age[7,13]

Age	Average TBW (as a % of weight)
Neonate	75–85
Toddler	70
Child	65
Adult male	60
Adult female	55
Geriatrics	50–55

Volume of distribution (Vd)

Hydrophilic versus lipophilic drugs: paediatrics

Younger children require higher doses of water-soluble drugs per kilogram weight because they have a higher percentage of TBW.[7] Lipophilic drugs have a relatively larger Vd in infants when compared to older children, due to a higher fat percentage (22.4% at 12 months *vs*. 13% at 15 years).[7]

Hydrophilic versus lipophilic drugs: geriatrics

With age-related changes in body composition, water-soluble drugs tend to have a lower Vd resulting in higher serum levels in older people.[13] Lipid-soluble drugs (notably diazepam, thiopentone, and lignocaine) have an increasing Vd with age, with the subsequent effect of a half-life prolongation.[13] Notably, the reduction in Vd for water-soluble drugs tends to be balanced by a reduction in renal clearance with little net effect on elimination half-life.[13]

Plasma protein binding: paediatrics

In newborns, total plasma protein concentrations are 86% of adult values.[7] The influence of plasma protein binding becomes significant in drugs that have a high degree of protein binding (> 95%) and is likely to be most pronounced in newborns and infants.[7] Table II shows a comparison of plasma protein composition binding in paediatric populations compared with adult reference values.[7]

Table II: Difference in plasma protein composition within the paediatric population

Parameter	Neonate	Infant	Child
Total protein	↓	↓	↔
Plasma albumin	↓	↔	↔
Plasma globulin	↓	↓	↔
alpha-1-acid glycoprotein	↓	N/A	↔
Free fatty acids	↑	↔	↔
Unconjugated bilirubin	↑	↔	↔

Plasma protein binding: geriatrics

In the older population, no substantial age-related changes in the concentrations of both these proteins have been observed. However, it should be considered that the geriatric population is at risk for malnutrition as well as recurrent illness. Albumin is commonly reduced in malnutrition or acute illness, whereas alpha-1-acid glycoprotein is increased.[13]

Metabolism

Paediatrics

The microsomal protein content within the liver increases with age from an estimated 26 mg/g in newborns, rising to a maximum of 40 mg/g in a 30-year-old adult. [7] Therefore, drugs that are highly metabolised are usually administered at a lower mg/kg^{-1} dose in newborns compared with preschool children.[7]

Infants and preschool children have a larger ratio of liver to total body mass, resulting in increased hepatic clearance of drugs as liver blood flow is increased compared with adults.[7,14] This can increase the first pass effect, but the overall metabolism is still subject to the level of enzyme activity.

Interestingly, there are differences in enzyme expression and activity that may result in the altered metabolism of drugs or the production of metabolites in paediatric populations that are not observed in adults Therefore, the ontogeny of specific metabolic pathways needs to be understood before extrapolating adult data onto paediatric populations.[14,15]

Geriatrics

There is an association of a reduction in liver mass and blood flow with increasing age, which will mainly affect first pass metabolism and the clearance of drugs with a high ER that are metabolised by phase I pathways in the liver.[13,16] The activity of drug-metabolising enzymes is usually preserved, and enzyme inhibition and conjugation pathways remain similar in young subjects.[13,16]

Elimination

Paediatrics

The elimination of drugs and their metabolites occurs predominantly via the kidneys. In term neonates, the glomerular filtration rate (GFR) is 2–4 ml/min/1.73 m^2, and it doubles by day seven, reaching adult values after the first year of life.[17,18] Newborns have a lower renal excretion of the unchanged drug due to renal immaturity, while infants and older children have a higher rate of renal clearance for some drugs due to a relatively larger kidney-to-body size.[18] The elimination of drugs can also be influenced by the origination and development of renal tubular transport mechanisms.[19]

Creatinine clearance is often used to estimate GFR in children; a reduction in drug dose is advised if creatinine clearance is less than the normal GFR.[19] Infant urinary pH is lower than adult values, which may increase the reabsorption of weak acidic drugs.[7]

Geriatrics

There is an age-associated reduction in renal function that may significantly affect not only renally excreted drugs but also drugs undergoing extensive metabolism in the liver.[13] In addition, polypharmacy is common in the elderly and can lead to an increase in side effects, drug interactions, adverse drug reactions, and non-adherence.[20] Together with alterations in other pharmacokinetic parameters, elderly patients are more susceptible to the side effects of drugs, viz. sedation, nephrotoxicity, hepatotoxicity, cardiotoxicity, confusion, dizziness, hypotension, and hypoglycaemia. There should therefore be an increased awareness about common drug interactions and whether prescribed drugs are inducers or inhibitors of the cytochrome (CYP) P450 enzymes.[20]

Pharmacokinetic changes in pregnancy

Body composition

During pregnancy, there is approximately a 42% increase in plasma volume, with parallel increases in TBW and all body fluid compartments.[21]

Volume of distribution (Vd)

This expanded extracellular volume and TBW increases the Vd for hydrophilic drugs.[6] Additionally, the increase in maternal body fat increases the Vd for lipophilic drugs, leading to overall lower plasma concentrations.[6]

There is an increase in uterine perfusion, and small molecular weight and lipophilic drugs readily cross the placenta. Additional compartments in the form of the foetus, placenta, and amniotic fluid can lead to increased drug accumulation and an apparent increase in Vd of certain drugs.[6]

Plasma protein binding

In pregnancy, there is a decreased plasma protein concentration of both albumin and alpha-1-acid glycoprotein, which can be clinically significant for certain drugs.[6] Where possible, it is safest to monitor free drug concentrations and adjust drug dosing to maintain the unbound drug concentration within its therapeutic range. A dose titration strategy aiming at maintaining therapeutic plasma concentrations can lead to increased free drug concentrations and increase the likelihood of drug-related toxicity.[6]

Metabolism

While the liver accounts for the metabolism of a vast majority of drugs, other organs including the intestine and placenta can also contribute to the clearance of certain drugs.[6] Metabolic enzyme activity in pregnancy is highly variable with maternal genotype, in addition to variations associated with ethnicity, gender, age, and certain disease states that are unrelated to pregnancy. Oxidative phase I reactions, which are predominantly carried out by the CYP450 enzymes, are significantly affected in pregnancy.[6] The activities of CYP3A4 (50–100%), CYP2A6 (54%), CYP2D6 (50%), and CYP2C9 (20%) are all increased.[6] In contrast, other CYP isoforms, like CYP1A2 and CYP2C19, demonstrate a gradual decrease in activity with advancing gestation. However, the effects of drug therapy remain uncertain.[6]

The activity of phase II enzymes, including uridine 5'-diphosphate glucuronosyltransferases (UGTs), is also altered during pregnancy with a 200% increase in UGT1A4 activity during the first and second trimesters, and a 300% increase during the third trimester.[6] This change leads to lower concentrations of UGT1A4 substrates such as lamotrigine, leading to subtherapeutic outcomes in the absence of appropriate dose titration.[6]

Elimination

In pregnancy, there is increased renal clearance of drugs that are solely excreted by glomerular filtration, as the GFR is 50% higher in the first trimester and continues to increase until the last week of pregnancy.[22] Despite a uniform increase in GFR during pregnancy, differences in renal tubular transport (secretion or reabsorption) can result in differing effects of various renally cleared drugs (e.g. lithium, digoxin, and atenolol), thereby limiting generalisation about the effect of pregnancy on renally eliminated drugs.[22]

Conclusion

Several physiological factors need to be considered when dosing a drug. Changes in pharmacokinetics may be non-linear in many cases. Therapeutic drug monitoring should be instituted where feasible, particularly in drugs with a narrow therapeutic index.

ORCID

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

References

1. Maheshwari R, Sharma PA, Seth A, et al. Drug disposition considerations in pharmaceutical product. In: Tekade RK, editor. Dosage form design considerations. Elsevier; 2018. p. 337-69. https://doi.org/10.1016/B978-0-12-814423-7.00010-1.
2. Mansoor A, Mahabadi N. Volume of distribution [Internet]. Treasure Island: StatPearls Publishing; 2023. Available from: http://www.ncbi.nlm.nih.gov/books/NBK545280/. Accessed 26 September 2023.
3. Toutain PL, Bousquet-Mélou A. Volumes of distribution. J Vet Pharmacol Ther. 2004;27(6):441-53. https://doi.org/10.1111/j.1365-2885.2004.00602.x.
4. Powell JR, Cook J, Wang Y, Peck R, Weiner D. Drug dosing recommendations for all patients: a roadmap for change. Clin Pharmacol Ther. 2021;109(1):65-72. https://doi.org/10.1002/cpt.1923.
5. Grogan S, Preuss CV. Pharmacokinetics [Internet]. Treasure Island: StatPearls Publishing; 2023. Available from: http://www.ncbi.nlm.nih.gov/books/NBK557744/. Accessed 26 September 2023.
6. Feghali M, Venkataramanan R, Caritis S. Pharmacokinetics of drugs in pregnancy. Semin Perinatol. 2015;39(7):512-9. https://doi.org/10.1053/j.semperi.2015.08.003.
7. Batchelor HK, Marriott JF. Paediatric pharmacokinetics: key considerations. Br J Clin Pharmacol. 2015;79(3):395-404. https://doi.org/10.1111/bcp.12267.
8. Onetto AJ, Sharif S. Drug distribution [Internet]. Treasure Island: StatPearls Publishing; 2023. Available from: http://www.ncbi.nlm.nih.gov/books/NBK567736/. Accessed 26 September 2023.
9. Scheife RT. Protein binding: what does it mean? DICP. 1989;23(7-8 Suppl):S27-31. https://doi.org/10.1177/106002808902300706.
10. Verbeeck RK. Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction. Eur J Clin Pharmacol. 2008;64(12):1147-61. https://doi.org/10.1007/s00228-008-0553-z.
11. Susa ST, Hussain A, Preuss CV. Drug metabolism [Internet]. Treasure Island: StatPearls Publishing; 2023. Available from: http://www.ncbi.nlm.nih.gov/books/NBK442023/. Accessed 26 September 2023.
12. Garza AZ, Park SB, Kocz R. Drug elimination [Internet]. Treasure Island: StatPearls Publishing; 2023. Available from: http://www.ncbi.nlm.nih.gov/books/NBK547662/. Accessed 26 September 2023.
13. Mangoni AA, Jackson SHD. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. Br J Clin Pharmacol. 2003;57(1):6-14. https://doi.org/10.1046/j.1365-2125.2003.02007.x.
14. Hines RN. The ontogeny of drug metabolism enzymes and implications for adverse drug events. Pharmacol Ther. 2008;118(2):250-67. https://doi.org/10.1016/j.pharmthera.2008.02.005.
15. Anantharaju A, Feller A, Chedid A. Aging liver. A review. Gerontology. 2002;48(6):343-53. https://doi.org/10.1159/000065506.
16. Schmucker DL. Liver function and phase I drug metabolism in the elderly: a paradox. Drugs Aging. 2001;18(11):837-51. https://doi.org/10.2165/00002512-200118110-00005.
17. Anderson BJ, Holford NHG. Understanding dosing: children are small adults, neonates are immature children. Arch Dis Child. 2013;98(9):737-44. https://doi.org/10.1136/archdischild-2013-303720.
18. Chen N, Aleksa K, Woodland C, Rieder M, Koren G. Ontogeny of drug elimination by the human kidney. Pediatr Nephrol. 2006;21(2):160-8. https://doi.org/10.1007/s00467-005-2105-4.
19. Schwartz GJ. Does kL/PCr estimate GFR, or does GFR determine k? Pediatr Nephrol. 1992;6(6):512-5. https://doi.org/10.1007/BF00866487.
20. Cantlay A, Glyn T, Barton N. Polypharmacy in the elderly. InnovAiT. 2016;9(2):69-77. https://doi.org/10.1177/1755738015614038.
21. Qasqas SA, McPherson C, Frishman WH, Elkayam U. Cardiovascular pharmacotherapeutic considerations during pregnancy and lactation. Cardiol Rev. 2004;12(4):201-21. https://doi.org/10.1097/01.crd.0000102420.62200.e1.
22. Davison JM, Dunlop W. Renal hemodynamics and tubular function normal human pregnancy. Kidney Int. 1980;18(2):152-61. https://doi.org/10.1038/ki.1980.124.