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Pharmacokinetics in Paramedic Practice

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Abstract:	Pharmacokinetics is the study of how drugs are absorbed, distributed, metabolised, and excreted by the body, and is often summarised as ‘what the body does to the drug.’ It focuses on the processes that influence a drug's journey through the body and its concentration over time. These processes—collectively known as ADME (absorption, distribution, metabolism, and excretion)—are shaped by factors such as the drug's formulation, route of administration, and individual patient characteristics. A robust understanding of pharmacokinetics equips paramedics to predict drug onset, duration of action, and potential accumulation, enabling accurate medication use and enhanced patient care in clinical practice.
Response to Reviewers:	Dear whom it may concern, Thank you for reviewing this article. Please find below how we have addressed your comments in the current revision Line 1 :We have removed the word ‘Pharmacology Series’ as we believe this will be in the title? Line 24-29: We would like to add this figure to further explain our point – please adapt as you see fit. Line 32: Oxford comma added as suggested Line 34-35: Yes, related to rate hence ‘given too rapidly’, which is linked to the administration – our argument is that another route of administration wouldn’t be able to be given at this rate, therefore fitting into ‘route’ - if you wish to remove this reference, please go ahead Line 41: We’ve added ‘Adapted from’ prior to the reference Table 1: IV – CONS – Reviewer stated that us stating that IV requires skill was

	subjective and a lay skill), we have changed ‘requires skill’ to ‘requires clinical training’ Table 1: IV- CONS – The word expensive has been changed to ‘less cost-effective than oral administration’ Line 42: Reviewer states that they are unsure that this table adds anything and is largely opinion based. We believe that as this is educational article, typically targeted at pre-registration paramedics, this table will highly benefit the student learning experience as an educational tool in their studies. It is important to note that the table is adapted from previous publications and therefore we believe this is not largely opinion based. However, you may remove it if you wish but from our experience in teaching students, we believe removing this table would reduce accessibility of the article. Line 49: Reviewers comment: the reader will know what the terms ‘intracellular and extracellular mean’. From our experience in teaching paramedic students, we believe these terms need to be reinforced as many students struggle with scientific terminology. However, you may remove these terms if you wish. Line 54: Reviewer stated that ‘small’ was vague and not all drugs that pass the plasma membrane are small. We agree and we acknowledge this, however this review is targeted as an introductory educational editorial for pre-registration paramedics, in which we aim to serve an overview. We have added the words ‘In general,’ prior to our statement to compensate for this, but please delete the word ‘small’ if you see fit. Line 124: Corrected as per reviewers comments. Line 157 onwards re: excretion Reviewer stated (in reference to aminoglycosides not being metabolised) ‘Isn’t this due to solubility (therefore route dependent) and/or degree of antibiotic resistance? I’m not sure this example is beneficial to the reader’. Please see line in the reference (Ramirez and Tolmasky, 2010) : ‘Aminoglycoside antibiotics are not metabolized, they are excreted as active compounds, and they show biphasic elimination with half-lives in the body of 2–3 h (as long as the renal function is normal) and 37–100 h (Veyssier and Bryskier, 2005, Wenk et al., 1979).’ We understand your point about solubility, however we believe this example is beneficial as an introduction to readers that not all drugs undergo metabolism. You may delete this example if you wish however we believe the example is illustrative of the point we are trying to make. Line 164: Reviewer said ‘not sure this is relevant - it’s the general process and not relevant pharmacokinetics’ referring to paragraph about excretion - we have now added extra information relating to the pharmacokinetics to address this. Line 176 onwards : Reviewer said ‘Half-life ? It’s relevance to absorption and distribution - ie why its measured as plasma half-life, for example why a lipid soluble drug would have such a long half-life’ – we have now added more information to action this point Line 185-Line 193 – Added a closing paragraph discussing the importance of pharmacokinetics in paramedicine. If you have any questions about these revisions, please don't hesitate to get in touch Kind regards, Anya Snary
Additional Information:	
Question	**Response**
Please enter the word count of your manuscript **excluding references and tables**	2278

Pharmacokinetics in Paramedic Practice: Pharmacology Series

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Abstract

Pharmacokinetics is the study of how drugs are absorbed, distributed, metabolised, and excreted by the body, and is often summarised as ‘what the body does to the drug.’ It focuses on the processes that influence a drug's journey through the body and its concentration over time. These processes—collectively known as ADME (absorption, distribution, metabolism, and excretion)—are shaped by factors such as the drug's formulation, route of administration, and individual patient characteristics. A robust understanding of pharmacokinetics equips paramedics to predict drug onset, duration of action, and potential accumulation, enabling accurate medication use and enhanced patient care in clinical practice.

Conflict of interest statement

CW is a member of the editorial board of the Journal of Paramedic Practice. However, they were not involved in the review or decision-making process for this manuscript. The authors declare no other conflicts of interest.

Pharmacokinetics in Paramedic Practice.

Abstract

Pharmacokinetics is the study of how drugs are absorbed, distributed, metabolised, and excreted by the body, and is often summarised as 'what the body does to the drug.' It focuses on the processes that influence a drug's journey through the body and its concentration over time. These processes—collectively known as ADME (absorption, distribution, metabolism, and excretion)—are shaped by factors such as the drug's formulation, route of administration, and individual patient characteristics. A robust understanding of pharmacokinetics equips paramedics to predict drug onset, duration of action, and potential accumulation, enabling accurate medication use and enhanced patient care in clinical practice.

Key Words

Pharmacology; pharmacokinetics; drug absorption; drug distribution; drug metabolism; drug excretion

Routes of administration and absorption

A medicine's therapeutic effect on the body is described in pharmacodynamics—the study of how drugs act to produce their effects (Patel, 2021). However, for pharmacodynamics to take place, the drug must first enter the body and reach its site of action. This process depends on pharmacokinetics, which explores how the body

absorbs, distributes, metabolises, and excretes the drug, ultimately determining its concentration and availability at the target site (Fig 1).

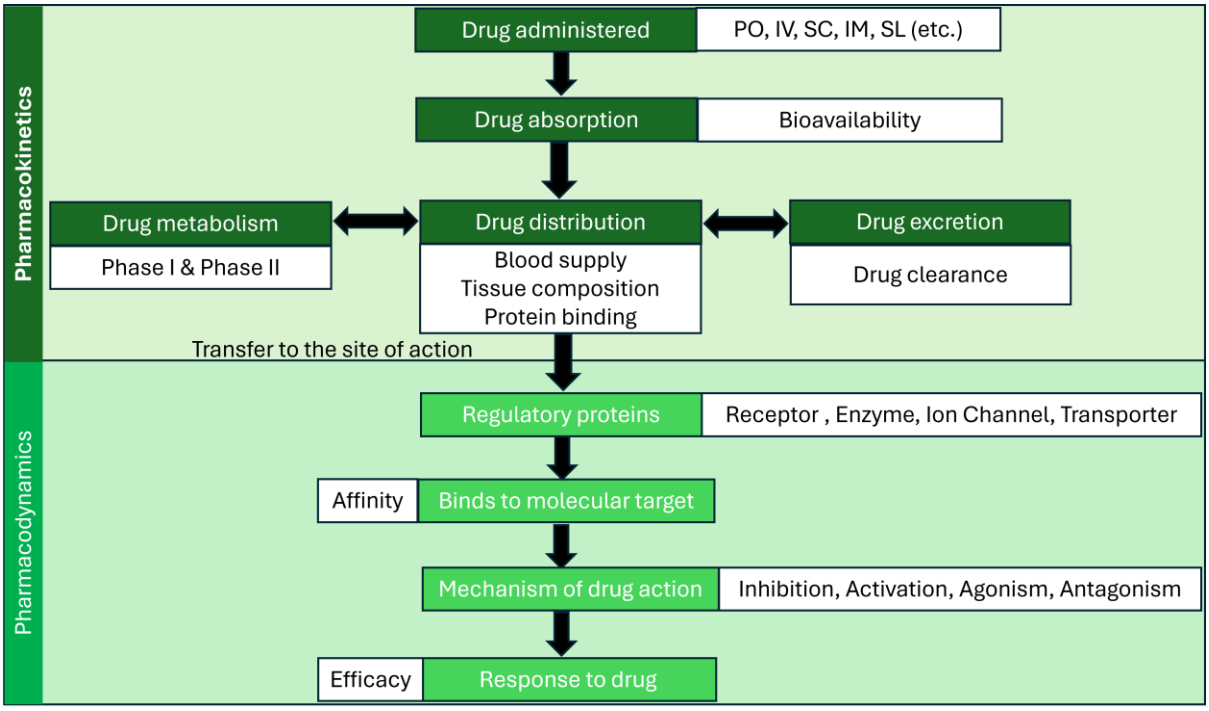

FIGURE 1: Schematic representation of relationship between pharmacokinetics and pharmacodynamics (adapted from Currie, 2018a). Drugs administered through several routes – PO (Per os- Oral), IV – Intravenously, SC – Subcutaneous, IM – Intramuscular, SL – Sublingual, more information can be found in Table 1.

For a drug to do anything, we need to get it into the body in one form or another, preferably as close to the target site of action as possible. Luckily, we have many routes of administration such as oral, inhalation, intravenous, subcutaneous, transdermal, and intramuscular (Verma et al, 2010). The routes of administration of drugs are key in their role of therapeutic action – for instance, penicillin will not be adequately absorbed if taken with meals, and intravenous (IV) furosemide can cause deafness if given too rapidly (Shepherd & Shepherd, 2020). The most common administration method is oral medication, estimated to be responsible for 90% of pharmaceutical formulations (Alqahtani et al, 2021). However, there are different

advantages and disadvantages to the routes of administration related to pharmacokinetics (Table 1).

Table 1. Characteristics of Common Routes of Drug Administration in Relation to Pharmacokinetics (Adapted from Brunton et al. 2018)		
Routes of Administration	**Advantages**	**Disadvantages**
Oral (PO)	• Convenient and non-invasive. • Suitable for most patients. • Cost-effective.	• Lowered bioavailability due to first-pass metabolism. • Slow onset of action. • Affected by food and GI conditions.
Intravenous (IV)	• 100% bioavailability. • Rapid onset of action. • Precise control of drug levels.	• Invasive and requires clinical training. • Risk of infection or vascular complications. • Less cost-effective than oral administration
Subcutaneous (SC)	• Allows slow and sustained drug release. • Suitable for self-administration.	• Limited to small volumes. • Slower onset compared to IV or IM. • May cause local irritation.
Intramuscular (IM)	• Faster absorption than SC. • Suitable for depot formulations for sustained release.	• Can be painful. • Risk of tissue or nerve damage. • Absorption depends on blood flow to muscle.
Inhalation	• Rapid absorption due to large surface area and blood supply in the lungs. • Localised effects for respiratory conditions.	• Requires proper technique. • May cause irritation to respiratory tract. • Limited to certain drugs.
Sublingual (SL)	• Bypasses first-pass metabolism. • Rapid absorption and onset of action.	• Limited to lipid-soluble and small drugs. • Requires patient compliance to hold medication under tongue.
Buccal	• Avoids first-pass metabolism. • Provides sustained release for systemic effects.	• Limited absorption for some drugs. • Can cause discomfort or irritation.

Transdermal	• Bypasses first-pass metabolism. • Provides prolonged drug release.	• Limited to lipid-soluble drugs. • Delayed onset of action. • Risk of local skin irritation.
Rectal	• Partially bypasses first-pass metabolism. • Useful when oral administration is not possible.	• Absorption can be erratic. • May be uncomfortable for the patient. • Limited drug options.
Intranasal	• Bypasses first-pass metabolism. • Rapid absorption through nasal mucosa.	• Limited drug formulations. • May cause irritation to nasal passages. • Requires correct technique.
Topical	• Provides localised effects with minimal systemic absorption.	• Limited to specific conditions. • Ineffective for systemic effects. • Potential for skin irritation.

Drug absorption factors: Plasma membrane

The first stage of pharmacokinetics is absorption. Drug absorption is the process by which a drug moves from the site of administration into the systemic circulation. One of the key barriers of drug absorption is crossing the plasma membrane. The plasma membrane is a phospholipid bilayer surrounding cells that plays a key role in separating the extracellular (outside a cell) and intracellular (inside a cell) environments and regulates the passage of substances into and out of the cell. Plasma membranes are semi-permeable and have transport proteins, receptors, and channels which assist the transport from the extracellular to intracellular space (Childstone & Hardman, 2017).

In general, drugs that are small, un-ionised and lipid soluble can easily pass through the plasma membrane through a process of passive diffusion. This is where drugs

pass from the extracellular space to the intracellular space from a high-low concentration gradient, without any involvement from the plasma membrane. Sometimes, through a process called facilitated diffusion, carrier proteins combine with drugs to facilitate the movement across the plasma membrane. Additionally, drugs can be transported against the concentration gradient through active transport, a process in which transporter proteins use energy to facilitate movement (Bertram-Ralph & Amare, 2023).

Drug absorption factors: Bioavailability

Bioavailability is ‘the amount of the administered dose of a drug reaching the bloodstream in the form of the active ingredient which is then available to the body to produce a therapeutic effect’ (Stielow et al, 2023).

Bioavailability is typically referenced against intravenous (IV) administration, as IV delivers the entire drug dose directly into the bloodstream, resulting in 100% bioavailability. Although one of the most common forms of pharmaceuticals, oral medication has the lowest bioavailability, and this is due to ‘first-pass metabolism’.

Drug absorption factors: First-pass metabolism

First-pass metabolism describes the metabolism of a drug before it has reached systematic circulation, thereby reducing the therapeutic effect of the drug itself. This is common in oral medication, as drugs are broken down in the stomach which is then absorbed through the GI tract walls which then passes into the liver.

The liver and GI tract contain metabolising enzymes that reduce drug concentration in the bloodstream, thereby limiting the amount of drug that can get to its site of action (Stanley, 2024). It is possible to bypass first-pass metabolism by using differing routes of administration such as intranasal, sublingual, buccal and rectal routes (Table 1). The use of buccal midazolam is very common in treating epileptic seizures and the intranasal use of naloxone is used in opioid overdoses (Yoshinaga et al, 2021 and Lapidot et al, 2022).

Distribution

The second stage of pharmacokinetics is distribution. Distribution refers to how a drug moves across different compartments of the body, ideally to the target site of action. Once a drug is absorbed into the bloodstream, it is carried to various parts of the body, such as interstitial fluid, fat tissue, bone, and muscle. Distribution is commonly expressed as the 'volume of distribution,' calculated by dividing the drug dose by its concentration in blood plasma (Bertram-Ralph & Amare, 2023). This measure provides an indication of the drug's dispersion: a high volume of distribution suggests significant movement of the drug out of the bloodstream, while a low volume indicates it remains primarily within the plasma.

Distribution factors: Blood supply & tissue composition

Blood supply is vital in distribution - organs with higher blood flow, such as the heart, brain, and liver, receive more of the drug due to their abundant blood supply and areas of the body that are rich in adipose tissue will receive less due to their lack of blood

supply. In addition to this, adipose tissue may store lipophilic drugs which can also affect distribution (Lucas, Galettis and Schneider, 2018).

Distribution factors: Protein binding

Protein binding in plasma proteins is a key factor which affects distribution. Albumin is the main plasma protein responsible for binding many drugs in the bloodstream. However, the extent of protein binding varies between drugs; some bind extensively, while others have minimal binding. This has consequences, as only the unbound (free) drug can cross plasma membranes, distribute into tissues, and thereby produce a pharmacological effect. A lower degree of albumin binding increases the free drug concentration, which can enhance therapeutic effects but also raise the risk of toxicity. Liver or kidney disease can lower albumin levels, resulting in a condition known as hypoalbuminemia. This reduction in albumin increases the free drug fraction in circulation, which may enhance therapeutic effects but also heightens the risk of adverse effects, potentially leading to severe toxicity and, in extreme cases, mortality. (Alves et al, 2018 and Bihari, Bannard-Smith and Bellomo, 2020). Hypoalbuminemia and hepatic impairment are often a caution for drugs like phenytoin, which are highly albumin-bound, as reduced protein binding increases the risk of drug accumulation and toxicity.

Metabolism

Metabolism is described as ‘the biotransformation of substances which enables its elimination’ (Correia, 2018). The liver is by far the most important drug metabolising organ; however the kidney, gut mucosa, lung and skin may also contribute. The goal

of metabolism is to modify the drug to increase its excretion, by making it more hydrophilic so it is easier to excrete from the body in a form called metabolites. To increase excretion, the biotransformation is controlled by groups of enzymes which can be split into two main types of chemical reactions: Phase 1 and Phase 2 (Hughes, 2014).

Phase 1 (Functionalisation)

Phase one reactions, also known as 'functionalisation' reactions, are primarily carried out by Cytochrome P450 (CYP450) enzymes. These reactions involve chemical modifications, such as oxidation, hydrolysis, or reduction, to increase the drug's water solubility. The CYP450 enzyme family is responsible for metabolising over 75% of drugs. Additionally, some drugs can induce CYP450 enzymes, enhancing their activity, while others inhibit them, reducing their activity—both of which have important clinical implications (Zhao et al., 2021). For example, grapefruit juice contains 6',7'-dihydroxybergamottin, a compound that inhibits CYP3A4, an enzyme responsible for metabolising approximately 50% of drugs. Inhibition of CYP3A4 can lead to increased plasma concentrations of these drugs, such as the pro-drug lovastatin, which has been associated with a higher risk of adverse effects (Fuhr et al, 2023).

Box 1 – Prodrugs
Prodrugs are medications administered in an inactive or less active form that must undergo metabolism to exert a therapeutic effect. Prodrugs are typically activated during Phase 1 metabolism, where enzymes modify the drug to produce its active form. A common example is codeine, which is metabolised by the enzyme CYP2D6 into morphine in the body, enabling its analgesic effects (Thorn, Klein, and Altman, 2009).

Phase 2 (Conjugation)

Phase two reactions are often referred to as conjugation which involves adding molecules that are already present in the body (endogenous) to convert drugs into less active or inactive forms. The processes are called acetylation, sulphation, and glucuronidation with the aim to produce polar and water-soluble metabolites. Inactive metabolites are the altered forms of a drug that don't exert the same pharmacological effects as the original drug. Some metabolites however are toxic by-products. For example, paracetamol is metabolised by CYP2E1 and CYP1A2 enzymes which leads to the production of N-acetyl-p-benzoquinone imine (NAPQI), a toxic by-product responsible for acute liver damage (Freo et al, 2021).

Excretion

Excretion is the process of removing drugs and their metabolites from the body, primarily through urine but also via the lungs, bile, faeces, sweat, and breast milk (Currie, 2018b). It is a key component of pharmacokinetics, determining how a drug is eliminated and influencing its half-life, duration of action, and dosing frequency.

The kidneys serve as the primary route of excretion for many drugs, particularly hydrophilic compounds. Renal excretion involves three key processes: glomerular filtration, tubular reabsorption, and tubular secretion. Glomerular filtration allows small molecules to pass from the blood into the renal tubules for excretion. However, drugs extensively bound to plasma proteins are not readily filtered due to their high molecular weight and charge. Tubular secretion is the active transport of molecules, including drugs, from the peritubular capillaries into the proximal tubule via specialised

transporters. When multiple drugs rely on the same transporters, competition may occur, reducing excretion and leading to increased plasma concentrations. Tubular reabsorption determines whether a drug remains in the urine for excretion or is reabsorbed back into the bloodstream. Hydrophilic drugs, such as Gentamicin, are excreted unchanged in the urine, whereas lipophilic drugs, such as Diazepam, undergo hepatic metabolism to increase their water solubility and reduce tubular reabsorption before excretion (Ramirez and Tolmasky, 2010; Khalid et al., 2021). Renal function is important for drug clearance, which is defined as the volume of plasma cleared of a drug per unit time (box 2). Reduced renal clearance, as seen in kidney disease, can lead to drug accumulation and toxicity, necessitating dose adjustments (Lea-Henry et al., 2018).

Some drugs undergo biliary excretion, where they are conjugated in the liver and excreted into bile. These conjugates may be metabolised in the intestine, regenerating the parent drug, which can then be reabsorbed into circulation. This process, known as enterohepatic circulation, can prolong a drug's half-life and sustain its effects, as seen with morphine (Gao, 2014).

Conclusion

Understanding pharmacokinetics is necessary for comprehending how drugs move through the body, influencing their onset, duration, and intensity of action. Insight into the principles of drug absorption, distribution, metabolism, and elimination, can help optimise drug administration to ensure safe and effective treatment. Given the increasing scope of pharmacological interventions in emergency and urgent care, a

sound understanding of pharmacokinetics can enable paramedics to make informed decisions, anticipate drug effects, and refine their clinical practice.

Table 2. Key definitions in pharmacokinetics	
Term	**Definition**
Pharmacokinetics	The study of how the body absorbs, distributes, metabolises, and excretes drugs.
Absorption	The process by which a drug moves from the site of administration into the systemic circulation.
Bioavailability	The proportion of an administered drug that reaches the bloodstream in an active form, influencing its therapeutic effect.
First-pass metabolism	The metabolism of a drug before it reaches systemic circulation, reducing its therapeutic concentration.
Distribution	The process by which a drug is transported to different parts of the body, including tissues and organs.
Volume of Distribution	A measure of how extensively a drug is distributed in body tissues relative to the plasma concentration.
Protein Binding	The binding of drugs to plasma proteins (e.g., albumin), affecting their availability to cross membranes and exert effects.
Metabolism	The biotransformation of drugs, primarily in the liver, to make them easier to excrete.
Phase 1 Reactions	Functionalisation reactions (e.g., oxidation, reduction) performed by enzymes like CYP450 to increase drug solubility.
Phase 2 Reactions	Conjugation reactions that add endogenous molecules to drugs, forming polar metabolites for easier excretion.
Inactive Metabolites	Altered drug forms that no longer have pharmacological effects.
Pro-drugs	Drugs that become active only after being metabolised (e.g., codeine converting to morphine).
Excretion	The removal of drugs and their metabolites from the body, primarily through urine but also via bile, faeces, lungs, or sweat.

Passive Diffusion	Movement of drugs across the plasma membrane along a concentration gradient without energy expenditure.
Active Transport	Energy-dependent movement of drugs across the plasma membrane against a concentration gradient.
Plasma Membrane	A phospholipid bilayer that regulates the passage of substances, including drugs, into and out of cells.
Transporter Proteins	Proteins that assist in the movement of drugs across the plasma membrane.

CPD Questions

- How can knowledge of pharmacokinetics influence your choice of drug and route of administration in an emergency situation? Provide an example from your clinical practice.
- What factors should you consider when administering medications to patients with compromised liver or kidney function, and how might these affect drug metabolism and excretion?
- How does an understanding of bioavailability and first-pass metabolism help you anticipate the onset and duration of action for commonly used medications in prehospital care?

Key Points

- Pharmacokinetics encompasses four key processes—absorption, distribution, metabolism, and excretion (ADME)—which collectively determine a drug's concentration and therapeutic availability in the body.

- Bioavailability, influenced by the route of administration and first-pass metabolism, is important to understanding a drug's effectiveness, with intravenous routes providing 100% bioavailability.
- Understanding factors such as protein binding and tissue distribution helps to predict drug action, therapeutic effects, and potential toxicity in patients.

Box 2. Elimination Kinetics and Drug Stability

Half-Life

The half-life of a drug is the time it takes for its concentration in the bloodstream to reduce by half. This determines how long a drug's effects last and guides dosing schedules. For repeated doses, the half-life helps maintain stable drug levels in the blood. In simple terms, it indicates how quickly the body clears half of the drug.

Drug Clearance

Drug clearance measures how efficiently the body removes a drug, expressed as the volume of blood cleared per unit of time. High clearance means faster elimination, while low clearance indicates slower removal. Together, half-life and clearance help tailor dosing for safe and effective treatment.

Steady State

A drug reaches steady state—where drug input equals elimination—after about four to five half-lives. This is crucial for maintaining effective drug levels without causing harm. Drugs with short half-lives reach steady state quickly, while those with long half-lives take longer. For urgent effects, a loading dose can achieve therapeutic levels faster while the body stabilises over several half-lives.

References

Alqahtani, M.S., Kazi, M., Alsenaidy, M.A. and Ahmad, M.Z., 2021. Advances in oral drug delivery. *Frontiers in pharmacology*, *12*, p.618411.

Alves, F.C., Sun, J., Qureshi, A.R., Dai, L., Snaedal, S., Barany, P., Heimbürger, O., Lindholm, B. and Stenvinkel, P., 2018. The higher mortality associated with low serum albumin is dependent on systemic inflammation in end-stage kidney disease. *PloS one*, *13*(1), p.e0190410.

Bertram-Ralph, E. and Amare, M., 2023. Factors affecting drug absorption and distribution. *Anaesthesia & Intensive Care Medicine*, *24*(4), pp.221-227.

Bihari, S., Bannard-Smith, J. and Bellomo, R., 2020. Albumin as a drug: its biological effects beyond volume expansion. *Critical Care and Resuscitation*, *22*(3), pp.257-265.

Brunton LL, Hilal-Dandan R, Knollmann BC. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 13th ed. New York, NY: McGraw-Hill Education; 2018.

Chillistone, S. and Hardman, J.G., 2017. Factors affecting drug absorption and distribution. *Anaesthesia & Intensive Care Medicine*, *18*(7), pp.335-339.

Currie, G.M., 2018a. Pharmacology, part 1: introduction to pharmacology and pharmacodynamics. *Journal of Nuclear Medicine Technology*, *46*(2), pp.81-86.

Currie, G.M., 2018b. Pharmacology, part 2: introduction to pharmacokinetics. Journal of nuclear medicine technology, 46(3), pp.221-230.

Freo, U., Ruocco, C., Valerio, A., Scagnol, I. and Nisoli, E., 2021. Paracetamol: a review of guideline recommendations. *Journal of clinical medicine*, *10*(15), p.3420.

Fuhr, L.M., Marok, F.Z., Fuhr, U., Selzer, D. and Lehr, T., 2023. Physiologically based pharmacokinetic modeling of bergamottin and 6, 7-dihydroxybergamottin to describe CYP3A4 mediated grapefruit-drug interactions. *Clinical Pharmacology & Therapeutics*, *114*(2), pp.470-482

Gao, Y., Shao, J., Jiang, Z., Chen, J., Gu, S., Yu, S., Zheng, K. and Jia, L., 2014. Drug enterohepatic circulation and disposition: constituents of systems pharmacokinetics. *Drug discovery today*, *19*(3), pp.326-340.

Hughes, G., 2014. A simple introduction to pharmacokinetics: Part 1. Nurse Prescribing, 12(10), pp.497-503.

Khalid, S., Rasool, M.F., Imran, I., Majeed, A., Saeed, H., Rehman, A.U., Ashraf, W., Ahmad, T., Bin Jardan, Y.A. and Alqahtani, F., 2021. A physiologically based pharmacokinetic model for predicting diazepam pharmacokinetics after intravenous, oral, intranasal, and rectal applications. Pharmaceutics, 13(9), p.1480

Lapidot, T., Bouhajib, M., Faulknor, J., Khan, S., Krayz, G.T., Abrutzky, C. and Megiddo, D., 2022. A novel faster-acting, dry powder-based, naloxone intranasal formulation for opioid overdose. *Pharmaceutical Research*, *39*(5), pp.963-975.

Lea-Henry, T.N., Carland, J.E., Stocker, S.L., Sevastos, J. and Roberts, D.M., 2018. Clinical pharmacokinetics in kidney disease: fundamental principles. Clinical journal of the American society of nephrology, 13(7), pp.1085-1095.

Lucas, C.J., Galettis, P. and Schneider, J., 2018. The pharmacokinetics and the pharmacodynamics of cannabinoids. *British journal of clinical pharmacology*, *84*(11), pp.2477-2482.

Patel, D., 2021. Prescribing for paramedics: pharmacodynamics. Journal of Paramedic Practice, 13(3), pp.96-99.

Ramirez, M.S. and Tolmasky, M.E., 2010. Aminoglycoside modifying enzymes. *Drug resistance updates*, *13*(6), pp.151-171.

Robertson, D., 2017. Introduction to pharmacokinetics. *Nurse Prescribing*, *15*(3), pp.146-148.uStanley, L.A., 2024. Drug metabolism. In *Pharmacognosy* (pp. 597-624). Academic Press.

Stielow, M., Witczyńska, A., Kubryń, N., Fijałkowski, Ł., Nowaczyk, J. and Nowaczyk, A., 2023. The bioavailability of drugs—the current state of knowledge. *Molecules*, *28*(24), p.8038.

Thorn, C.F., Klein, T.E. and Altman, R.B., 2009. Codeine and morphine pathway. *Pharmacogenetics and genomics*, *19*(7), pp.556-558.

Verma, P., Thakur, A.S., Deshmukh, K., Jha, A.K. and Verma, S., 2010. Routes of drug administration. *International Journal of Pharmaceutical Studies and Research*, *1*(1), pp.54-59.

Yoshinaga, H., Benitez, A., Takeda, S., Fournier, M. and Kugler, A.R., 2021. A Phase 3 open-label study of the efficacy, safety and pharmacokinetics of buccally administered midazolam hydrochloride for the treatment of status epilepticus in pediatric Japanese subjects. *Epilepsy Research*, *174*, p.106651.

Zhao, M., Ma, J., Li, M., Zhang, Y., Jiang, B., Zhao, X., Huai, C., Shen, L., Zhang, N., He, L. and Qin, S., 2021. Cytochrome P450 enzymes and drug metabolism in humans. *International journal of molecular sciences*, *22*(23), p.12808.

Schematic diagram (Figure 1)