

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Introductory Chapter: Linkages between Pharmacokinetics and Adverse Effects of Drugs

Ntambwe Malangu

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/intechopen.76511>

1. Introduction

This chapter aims to elaborate on the linkages between pharmacokinetics and the advent of adverse effects of drugs. It is well known that pharmacokinetics is about the journey of the drug in the body, from its absorption, through its distribution and metabolism, to its elimination from the body. During this journey, after its absorption and distribution, the drug reaches its specific sites where it interacts with its receptors, usually proteins and enzymes, and produces its biological effects; this is known as “pharmacodynamics.” The biological effects lead to clinical effects that are observed in patients; this is known as “therapeutics or pharmacotherapeutics.” In the following sections, the actions of the body on a drug and the actions of the drug on the body are reviewed in each stage to explain how adverse effects occur. In doing so, the mechanisms and risk factors of adverse effects will be addressed. The next section deals with the absorption, followed by the distribution and excretion of drugs as they relate to the occurrence of adverse effects. A final section will deal with risk factors before some concluding remarks are presented.

2. Rates of absorption influence on the occurrence of adverse effects

For the majority of drugs that are administered by other routes than intravenous injection, they need to overcome several hurdles before they reach the systemic circulation. These include the layers of the outer skin of the body or veins in case of subcutaneous and intramuscular routes or the walls of the digestive system. For drugs administered orally, the active substances must first be released from the dosage form, namely tablets, capsules, and other forms. There will be a reduction of therapeutic effects if there is little absorption, or destruction of the drug by

digestive system enzymes, or if the active substance was not released from its dosage form [1, 2]. Sometimes the absorption may be impaired by the presence of foods or other drugs or substances that react with the active substance and make it not absorbable. On the contrary, the presence of physical lesions in the digestive tract, or substances that increases the liposolubility of the active substance may actually increase its absorption [3].

Several factors affect the journey of the drug that result in increased or decreased absorption or volume of distribution as well as the metabolism thereof. The physicochemical characteristics of the drug itself, the pharmaceutical dosage form it is in and its intrinsic quality, the state of the first layers of skin or membranes through which the drug is to be absorbed through, the composition of the environment such as the presence or absence of foods or other chemicals in the digestive system as well as the type of foods or the other chemicals, the type and number of carriers subunits of enzymes or proteins complex available at the site of absorption, all influence the absorption rates [4].

For medicines administered orally, whether tablets, capsules, solution, suspension, syrup, or elixir, it should be noted that the gastrointestinal tract is a harsh environment. With its low pH, acid-labile drugs such as benzylpenicillin (penicillin G) and methicillin, they become inactivated as a result of the catalysis that takes place due to beta-lactamase enzymes [4–6]. Similarly, the presence of proteases makes the oral route unsuitable for many proteins and peptides such as insulin and oxytocin [1–3]. When taken orally, the absorption of drugs occurs chiefly by passive diffusion of lipophilic molecules and by carrier-mediated transport for drugs that are structurally similar to endogenous compounds such as levodopa and 5-fluorouracil. With passive diffusion, the rate of absorption is proportional to the concentration or the amount of drug to be absorbed and the fraction or percentage absorbed in a given interval remains constant.

With carrier-mediated mechanisms, be it active transport or facilitated diffusion, there is a limited capacity and the transporter can be saturated, hence limiting the amount of drug reaching the systemic circulation. In this instance, increasing the dose will result in local adverse effects [6]. Clinicians ought to understand the particularity of a particular drug before deciding to indiscriminately increase the dose when a subtherapeutic effect is observed. Indeed, this remark is true even for drugs absorbed by passive diffusion like aspirin (salicylic acid) as the percentage absorbed is independent of the continuous concentration but proportional to the initial drug concentration.

Nowadays, the proliferation of substandard and falsified drugs particularly in Africa makes it difficult to predict the beneficial effects of these drugs [7]. This is because the intrinsic pharmaceutical quality of these drugs is not optimal leading to several consequences with regard to the absorption and elicited effects of these drugs. Several examples have been encountered in clinical practice; for instance, cotrimoxazole tablets badly compressed have been taken by patients just to be excreted intact in their feces! This example means that no dissolution took place, so little or nothing of the drug was absorbed, consequently, the therapeutic effects expected from the drug could not be elicited rather than the placebo effect.

As depicted in **Figure 1**, largely unionized substances such as, aspirin when in acidic environment, it is absorbed from the stomach but most of the absorption occurs in the small intestine where the large surface area compensates for the less favorable degree of ionization. On the contrary, weak bases, which are highly ionized in gastric acid, cannot be absorbed until they have left the stomach, so delayed gastric emptying (when foods is in the stomach) can delay the effect of such drugs [6, 8].

On the other hand, it is often recommended that drugs should be taken at meal times. This is to aid adherence to treatment and in some circumstances, to reduce gastric irritation (a local adverse effect), as, for example, with aspirin, which may cause gastric bleeding. It is noted here that the effect of food is not always predictable, although, generally, food delays gastric emptying and increases the secretion of gastric acid while reducing the overall gastric pH. Hence, the presence of foods may reduce the absorption of drugs such as ketoconazole that are more soluble in acid; yet on the contrary, the absorption of griseofulvin, an antifungal drug, as well as that of saquinavir, an antiretroviral drug, is increased when taken with a “fatty” meal [6, 9, 10].

As depicted in **Figure 2**, several transportation mechanisms have been envisaged from the site of absorption. It should be noted that the preponderance of each transport mechanism is different for each individual patient due to their genetic and constitutional makeup.

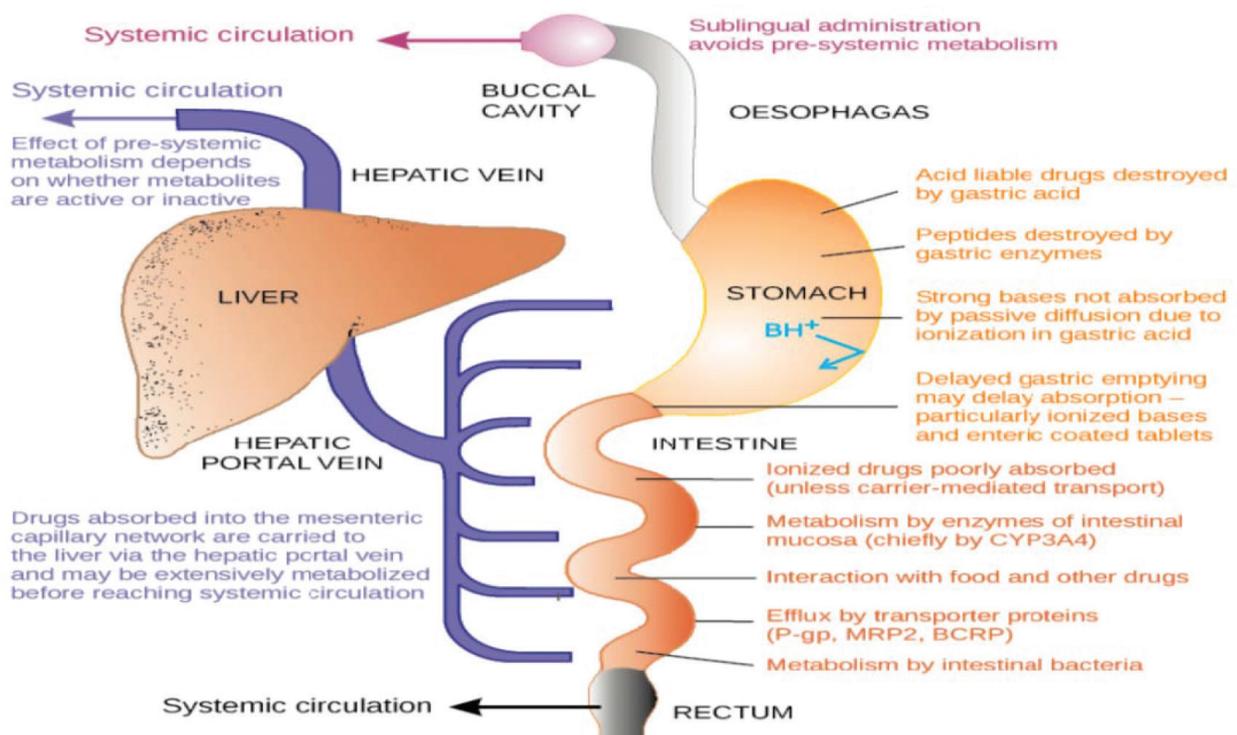


Figure 1. Absorption throughout the gastrointestinal tract. Source: [6].

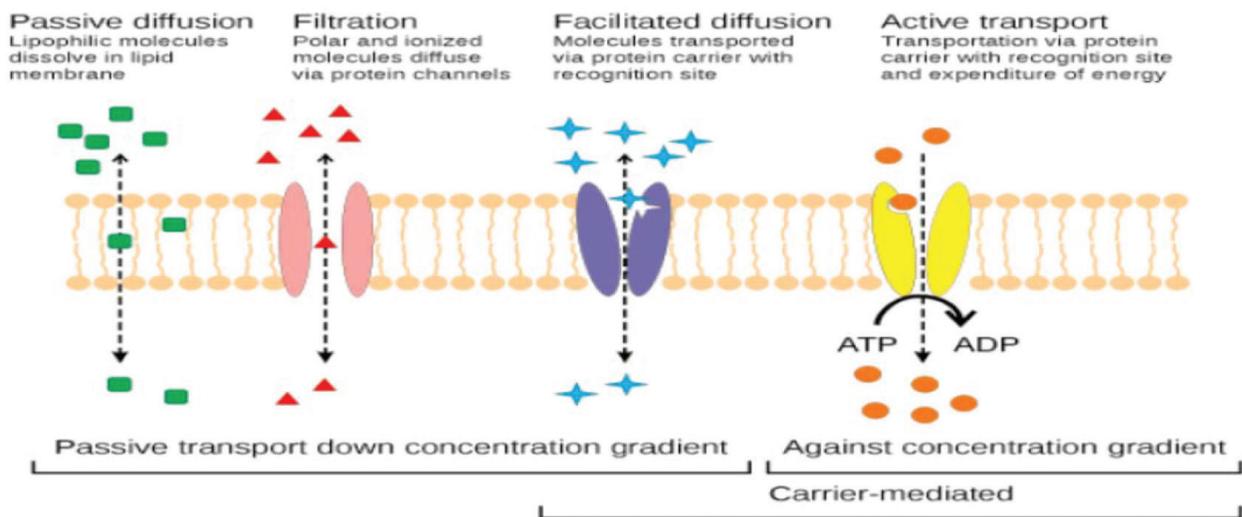


Figure 2. Transport mechanisms of drugs. Source: [6].

3. Systemic concentration and occurrence of adverse effects

The key concept in explaining the effects of drugs is “plasma concentration” or the amount of drug that reaches the systematic circulation; it reflects the amount of drug that will be available to act and produce effects at the site of action. Classically, it has been established that what is known as the effect of a drug is actually a combination of the action of a drug or drug action; its effect or drug effect and the body’s response or drug response. This may be illustrated as follows: For example, for a penicillin antibiotic, the “action” consists of inhibiting bacterial protein synthesis, the “effect” corresponds to the killing rate or growth inhibition rate of bacteria, and the clinical “response” would be the cure of the body from the infection and its manifestations [6, 11, 12].

In order to achieve its effect, a drug must first be released from its pharmaceutical form from the site of administration; be absorbed and distributed through the body to reach its site of action where it will interact with its specific receptors and/or some other nonspecific receptors. Through its journey, the body acts on it by metabolizing it in order, primarily, to wear off and eliminate it. The result of metabolism may sometimes achieve the goal of inactivating or destroying the structure of the drug; or sometimes it may lead to the production of active metabolites that actually will interact with receptors and produce the expected therapeutic effects of the particular drug [11, 13, 14].

For drugs subject to the first-pass effect are drugs that are metabolized before they reach the systemic circulation; generally, this pre-systemic metabolism reduces their bioavailability except when and if the resulting metabolites are pharmacologically active. In the case of nitroglycerin, which is almost totally first metabolized, its di- and mononitrate metabolites produced have very much reduced activity, and hence this drug is considered to be inactive when taken orally [15].

When a drug successfully crosses the physical and biochemical barriers described above, it will reach the systemic circulation and its plasma concentration will continue to rise as for as it will be absorbed. If, the increase is beyond a certain threshold, toxic effects or adverse effects will be clinically observed. This is well established now that there is an optimum range of concentrations over which a drug has beneficial or expected useful effects, with no clinical toxicity, this is known as the “therapeutic range,” sometimes referred to as the “therapeutic window” [6]. Moreover, it has been established also that there is a threshold concentration below which the drug is deemed ineffective, or not producing expected therapeutics effects, and a higher threshold above which adverse or unwanted toxic effects become apparent as shown in **Figure 3**.

The plasma concentration fluctuates based on the rates of absorption, the influence of the first-pass effect, and based on whether the drug is following a one compartment model of distribution or a multiple compartment model. For drugs using the multiple compartment model, which are drugs that accumulate in other compartments other than the systemic circulation, namely the liver, skeletal muscles, bones, adipose tissues; their absorption, distribution, and metabolism may be complex. For instance, thiopental, once absorbed, its liver concentrations rapidly equilibrate with those in plasma while the concentrations in skeletal muscle rise initially and then equilibrate later and their concentrations in adipose tissue will rise for at least the first 3.5 h following the bolus injection of thiopental; its duration of action will be short due to uptake of the drug into skeletal muscle and fat [16–18].

In order to understand the influence of multiple compartments, it is important to remember that typically the body is made of 11 chemical elements, namely carbon, calcium, chlorine, hydrogen, nitrogen, magnesium, oxygen, phosphorus, potassium, sodium, and sulfur; and 5 molecules such as water which comprises 60–62%; proteins 16–18%; fat 10–15%; minerals 6–7%; up to 1% of carbohydrates [19, 20] (**Figure 4**).

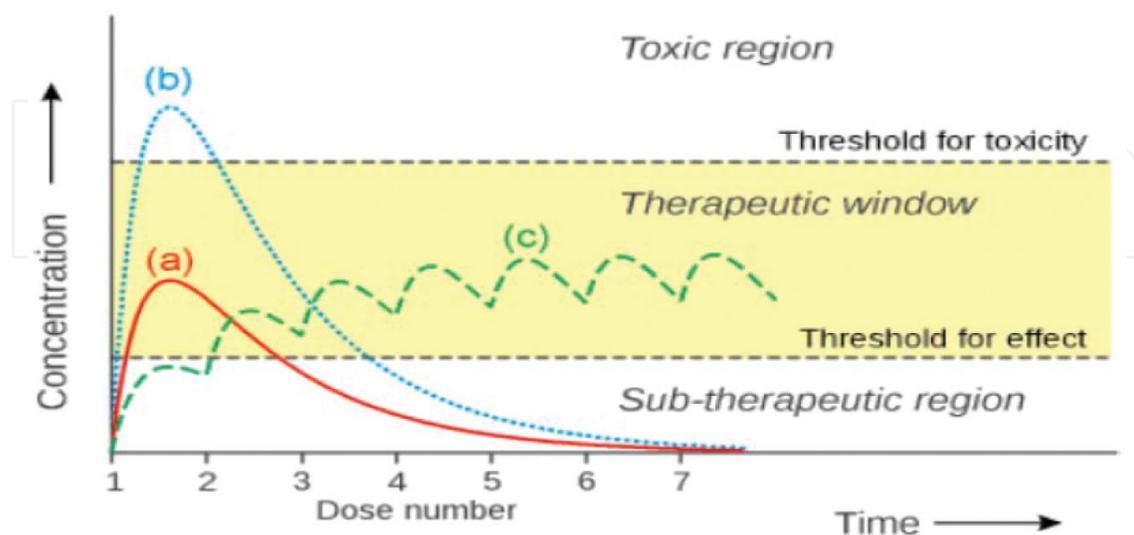


Figure 3. Drug levels in relation to elicited effects. Source: [6].

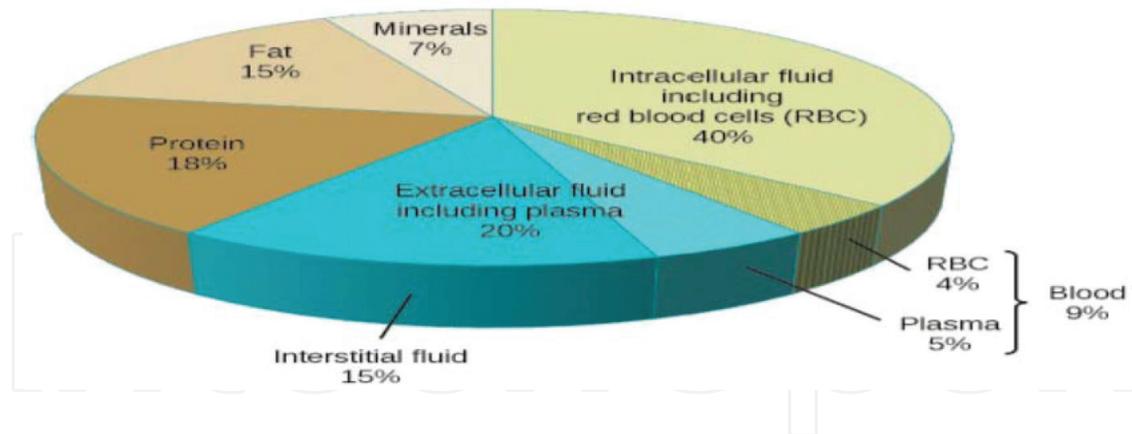


Figure 4. Body composition. Source: Fomon et al. [19]; Chumlea et al. [20].

It should be noted that there are variations in the concentration of the elements and molecules making up the body. These variations are rhythmic, cyclic, and dependent on the age, sex, and health status of the individuals. It is known that, in each disease state, and in case of multi-morbidity, the composition of these elements and molecules vary in relation to the lifestyle of an individual, namely his/her water and food intake, smoking and alcohol consumption, exercise and sleeping patterns in terms of quantity, quality, and variety or diversity [21–24]. This situation largely explains why a same dose of a drug may not always produce similar effects (beneficial or adverse) on a group of individuals even if they have same body-weights, are of same ethnicity or sex. This observation explains why standard doses cannot be prescribed indiscriminately to each individual patient; hence the new concept of individualized treatment regimen.

The need for individualized regimen can be more understood when one considers the “half-life” concept. Half-life is a very useful parameter in pharmacokinetics; it is defined as the time it takes for the concentration of a drug to halve from its initial peak concentration in plasma or urine. It is important to note that even drugs from the same class have different half-lives because they have different volumes of distribution and/or systemic clearance. This is so because the apparent volume of distribution depends, as said earlier, upon the nature of the drug and the makeup of individuals. For instance, lipophilic drugs tend to have large apparent volumes of distribution and to be widely distributed in someone who is obese, due to the availability of more adipose tissue. Hence, the lipophilic drugs will have a longer elimination half-life in obese people; their longer stay may mean also longer lingering affects both beneficial and unwanted [23, 25, 26].

When drugs accumulating in other compartments continue to be taken, there will be a saturation of the receptors or even storage spaces in these compartments, resulting in much more concentrations in the interstitial liquids, and overwhelming of related receptors, thus the advent of adverse and side effects not typical of drug class. Such side effects may and should become a subject of pharmacovigilance investigation. It should be said here that atypical or new side effects may occur even with normal doses in certain individuals because of their uniqueness with regard to the receptors, enzymes, or proteins, they may have in abundance or absence thereof as a matter of their genetic makeup or as a result of a subclinical or clinical

disease state as well as their lifestyle as already explained. In case of overdose, drug metabolism is altered because enzymes responsible for metabolism become saturated; this leaves the excess drug free to force its way to nonspecific receptors by overcoming both inhibition or competition; consequently, it produces nontypical adverse effects while its clearance is decreased and its half-life is prolonged [27–30].

4. Elimination or excretion of drugs and adverse effects

Once a drug is metabolized and reduced to hydrosoluble entities, it is ready to be excreted through the kidneys and eliminated in the urine. However, some changes may impact negatively to this process. An important pharmacokinetic change in the elderly, for instance, is the decrease in renal drug elimination due to the fact that as someone ages, his/her renal mass as well as glomerular filtration and tubular secretion capacities decrease. It should be noted that after age 40, there is a decrease in the number of functional glomeruli, and the renal blood flow is estimated to decline by approximately 1% yearly. The clinical effect of decreased renal clearance includes prolonged drug half-life, increased serum drug level to toxic level which obviously leads to increased potential for adverse drug reactions [6, 31].

5. Pharmacokinetics related risk factors of adverse effects

At the core, genetic factors play a major role because of the genetic polymorphism or difference in drug responses between individuals. The drug response is genetically determined by the type, quality, and quantity of genes, proteins, enzymes that one has. A well-known example suffices here, the case of the enzyme, N-acetyltransferase which differs between individuals such that the population may be divided into slow and fast acetylators. People who are slow acetylators may experience more adverse effects unless doses of drugs requiring acetylation for metabolism are reduced. Other inherited variations in pharmacokinetics include deficiency of one or more hepatic cytochrome-P450 isozymes or plasma cholinesterase enzymes. The metabolic conversion of drugs into metabolites is established as a source of several idiosyncratic drug reactions [32–38].

As stated above, lifestyle factors such as diet and exercise affect bodyweight which is used as the basis for determining the dose administered. In case of chronic diseases, an increase or a drop of 10–20% in bodyweight should normally be noted and followed by a dose adjustment. Tuberculosis treatment is an example whereby patients normally increase their bodyweights sometimes up to 30% of their initial weights within 2–4 months. Clearly based on the treatment algorithms as defined by WHO, the doses or number of tablets for these patients should increase following the increase in their bodyweights; however, often this is not usually done [39, 40]. Moreover, diet, smoking, and alcohol may affect enzyme activity and lead to unexpected drug interactions. Cigarette smoking affects drug therapy by pharmacokinetic. The polycyclic aromatic hydrocarbons in tobacco smoke are believed to be responsible for the induction of cytochrome P450 (CYP) 1A1 and CYP1A2 which are responsible for the metabolism

of a number of drugs. Drugs for which induced metabolism because of cigarette smoking may have clinical consequence include theophylline, caffeine, tacrine, imipramine, haloperidol, pentazocine, propranolol, flecainide, and estradiol. Cigarette smoking results in faster clearance of heparin, possibly related to smoking-related activation of thrombolysis that results in enhanced heparin binding to antithrombin factor III [41, 42]. Moreover, cutaneous vasoconstriction by nicotine may slow the rate of insulin absorption after subcutaneous administration. Hence, the impact of cigarette smoking needs to be considered in planning and assessing responses to drug therapy; this why clinicians should regularly enquire of smoking and drinking habits of their patients [43, 44].

With regard to sex, differences between male and female will include differences in weight and weight distribution as well as hormonal differences particularly in relation to the menstrual cycle and its absence in prepubescent girls and postmenopausal women [45]. Moreover, physiological differences relating to body composition, gastric motility, liver metabolism, renal function, and glomerular filtration rates all affect differently the disposition of drugs with regard to gender. Simply put, drug absorption, distribution, metabolism, and elimination are not actually similar in men and women. Drug absorption in the lung may differ according to gender [46]. It has been demonstrated that there is a significant less deposition of an aerosolized drug in women than men which has been ascribed to differences in breathing patterns. Gastrointestinal transit time is longer in women (mean 91.7 h) than in men (44.8 h), as is gastric emptying time. This situation causes delays in the absorption of certain drugs. It has been shown for instance that following oral doses of levofloxacin and losartan, the areas under the curve (AUC) of these drugs were significantly greater in females than males. Moreover, relatively fast absorption of oral salicylates and that of ferrous sulfate has been shown in females and prepubertal girls than in boys. After intravenous infusion, the systemic clearance of verapamil was shown to be greater in women than in men. In case of propofol, women are said to be less sensitive to the effects of propofol and recover from anesthesia more quickly than men. This observation was demonstrated in a study that showed that the AUC values for the metabolites, 4-hydroxypropofol and propofol glucuronide, were significantly higher in women than in men and that this effect was 3.6 times higher in Hispanic females than in Caucasian females. On the contrary, protein binding is reportedly higher in males than females, for chlordiazepoxide and warfarin. Hepatic enzyme CYP3A4 is more active in females than males; drugs metabolized by this enzyme are thus affected more efficiently in females than males [47–50].

With regard to age, in children, their low gastric acid secretion can result in increased serum concentrations of weak bases and acid-labile medications, such as penicillin, and decreased serum concentrations of weak acid medications, such as phenobarbital, due to increased ionization. Additionally, gastric emptying time and intestinal transit time are delayed in premature infants; this increases drug contact time with the GI mucosa, hereby increasing drug absorption. In neonates, infants, and young children, there is increased risk of ADRs because of their incapacity to metabolize most drugs due to lack of appropriate enzymes and related functions. For instance, in neonates of less than 2 months old, because of their immature renal tubular function, it is recommended to avoid digoxin, aminoglycosides, ACE inhibitors, and NSAIDs [11, 51–53].

In the elderly, it is well known that the incidence of diseases increases with aging. A major consideration is the presence of comorbid conditions present in aging people that affect plasma concentrations of drugs through changes in the extent of absorption, in the rates of metabolism and/or excretion, and changes in tissue localization, for example, increased tissue binding leading to reduced plasma concentrations. In case of warfarin, age was found to have a significant effect on dosing; older patients require much lower doses than the young adults. Furthermore, it is well established that higher gastric pH, delayed gastric emptying, and decreased intestinal motility and blood flow are observed in elderly individuals. Consequently, even normal doses for health adults may become overdosage in the elderly patients who may experience more and severe adverse effects. Other factors that affect distribution of drugs in the body are changes in body fat and water and changes in protein binding. In the elderly, lean body mass can decrease by as much as 12–19% through the loss of skeletal muscle. Thus, blood levels of drugs primarily distributed in muscle such as digoxin will increase and become a risk for overdose when normal or standard dose are used. Moreover, due to a decrease in water concentration in older people, hydrosoluble drugs would reach higher concentrations because there is less water to dilute them while liposoluble drugs would accumulate more because there is relatively more fat tissue to store them. Furthermore, the kidney and liver functions perform less optimally; hence drugs are not readily metabolized and excreted into the urine to be eliminated. This leads to many drugs staying much longer than they do in a younger person's body, the net result would be the prolongation of pharmacodynamic effects and occurrence of side effects [2, 54–63].

With regard to disease states, there are pharmacodynamic differences in patients with liver disease. Effects have been observed with β -blockers and drugs that depress the CNS. In case of β -blockers, it is documented that there is a reduction in β -adrenoceptor density in mono-nuclear cells which results in a decrease in effect; this has been observed with propranolol. Similarly, patients with liver cirrhosis had been found to be particularly sensitive to opioids and anxiolytics. In case of kidney disease, a drug that is 100% metabolized may also be affected to some extent particularly its excretion if its metabolites accumulate in plasma, leading to an exaggerated response if the metabolites contribute to the pharmacological effect; or, atypical toxicity that is not seen when the metabolites are excreted normally. Additionally, renal impairment is likely to lead to varying degrees of water loading and this may lead to the changes in the concentrations of the drug in the fluid compartments of the body, including plasma. Children with cystic fibrosis present with greater renal clearance of drugs such as aminoglycosides when compared with children without the disease; this observation suggests that higher doses by weight and more frequent dosing intervals are required in these children [64–72].

With regard to drug-drug interactions, it should be said that patients commonly use two or more drugs concurrently; some prescribed by their health care providers, others bought by themselves or received from family and friends. Because patients are often unaware of the multiple drug interactions, they suffer from adverse drug reactions resulting from alterations of the pharmacokinetics parameters due to interacting substances; often with the end result being a decreased therapeutic efficacy, or an increased toxicity or occurrence of adverse effects. The binding of drugs to macromolecules such as receptors on plasma proteins is governed

by the law of mass action which states that “the rate at which a chemical reaction proceeds is proportional to the active masses (usually molar concentrations) of the reacting substances.” Taken from chemistry point of view, this concept means that for the reaction to occur, collision between the reacting molecules must take place. It follows that the rate of reaction will be proportional to the number of collisions; while the number of collisions will be proportional to the molar concentrations of the reacting molecules. Hence, drugs-foods and drugs-drugs interactions will affect the rates of a drug disposition based on the quantities available of the doses taken and the synchronicity which implies the presence of both substances at the same time for them to interact directly or indirectly through competition or inhibition of relevant receptors. The above observations imply that the degree of drug interaction depends on the relative concentrations of each drug; hence, the dose and the time of administration are critical elements in the onset of adverse effects resulting from drug-drug interactions. These interactions may produce changes in absorption rate, competition for binding sites on plasma proteins, oral bioavailability, extent and volume of distribution in organs and tissues, and hepatic and renal clearance as well as the extent of elimination from the body. Indeed besides other medicines, drugs of abuse, herbal medicines, and foodstuffs have been reported to affect the pharmacokinetics of specific drugs [73–78].

The above observations suggest the need for caution when prescribing more than one drug as well as the need to counsel patients about the dangers of taking nonprescribed drugs, drugs for entertainment including alcoholic drinks without seeking proper advice from health care professionals [79–84].

6. Concluding remarks

Adverse effects as unwanted outcomes of drugs effects occur generally when the upper threshold of therapeutic dosage range is reached. However, several factors may lower this threshold or bring about the trespassing of the therapeutic level. Risks factors include intrinsic properties of the drugs and the pharmaceutical dosage forms issues and interactions that affect their pharmacokinetics as well as the sociodemographic, health status, and lifestyle factors superimposed on the genetic makeup of a person. Clinicians ought to understand the pharmacokinetics of a drug before deciding to adjust dosages particularly upwardly as a precautionary measure to preempt dose-related adverse effects. Equally, they should not refrain from doing so when the situation warrants it; such as when the bodyweights of patients have significantly increased or when pharmacokinetic changes dictate so.

Author details

Ntambwe Malangu

Address all correspondence to: gustavmalangu@gmail.com

School of Public Health, Sefako Makgatho Health Sciences University, South Africa

References

- [1] Alomar MJ. Factors affecting the development of adverse drug reactions. *Saudi Pharmaceutical Journal*. 2014;**22**(2):83-94
- [2] Anderson BJ, Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. *Annual Review of Pharmacology and Toxicology*. 2008;**48**:303-332
- [3] Yang Z. The roles of membrane transporters on the oral drug absorption. *Journal of Molecular Pharmaceutics and Organic Process Research*. 2013;**1**:e102
- [4] Shugarts S, Benet LZ. The role of transporters in the pharmacokinetics of orally administered drugs. *Pharmaceutical Research*. 2009;**26**:2039-2054
- [5] Derendorf H, Hochhaus G, editors. *Handbook of Pharmacokinetic/Pharmacodynamic Correlation*. Boca Raton, FL: CRC Press; 1995
- [6] Curry SH, Whelpton R. *Introduction to Drug Disposition and Pharmacokinetics*. 1st ed. UK: John Wiley & Sons, Ltd; 2017
- [7] Malangu N. Risks associated with international trading of medicines by non-licensed entities and non-professionals. In: Macek A, editor. *International Trade-on the Brink of Change*. InTech; 2017. ISBN-978-953-51-2912-7
- [8] Wasan KM, Brocks DR, Lee SD, Sachs-Barrable K, Thronton SJ. Impact of lipoproteins on the biological activity and disposition of hydrophobic drugs: Implications for drug discovery. *Nature Reviews. Drug Discovery*. 2008;**7**:84-99
- [9] Müller F, Fromm MF. Transporter-mediated drug-drug interactions. *Pharmacogenomics*. 2011;**12**:1017-1037
- [10] Johnson TN, Thomson M. Intestinal metabolism and transport of drugs in children: The effects of age and disease. *Journal of Pediatric Gastroenterology and Nutrition*. 2008;**47**:3-10
- [11] De-gregori S, Ranzani GN, Borghesi A, Regazzi M, Stronati M. Drug transporters and renal drug disposition in the newborn. *The Journal of Maternal-Fetal & Neonatal Medicine*. 2009;**22**:31-37
- [12] Beer J, Wagner CC, Zeitlinger M. Protein binding of antimicrobials: Methods for quantification and for investigation of its impact on bacterial killing. *The AAPS Journal*. 2009;**11**(1):1
- [13] Amdur MO, Doull J, Klaassen CD, editors. *Casarett and Doull's Toxicology: The Basic Science of Poisons*. Elmsford, NY: Pergamon Press; 1991
- [14] Starner CI, Gray SL, Guay DR, et al. Geriatrics. In: DiPiro JT, Talbert RL, Yee GC, et al., editors. *Pharmacotherapy: A Pathophysiologic Approach*. 7th ed. New York, NY: McGraw-Hill; 2008. pp. 57-66
- [15] Kitteringham NR, Park BK, Pirmohamed M. The role of active metabolites in drug toxicity. *Drug Safety*. 1994;**11**:114-144

- [16] Barre J, Houin G, Rosenbaum J, Zini R, Dhumeaux D, Tillement JP. Decreased alpha 1-acid glycoprotein in liver cirrhosis: Consequences for drug protein binding. *British Journal of Clinical Pharmacology*. 1984;**18**:652-653
- [17] Anderson SG, Livingston M, Couchman L, Smith DJ, Connolly M, Miller J, et al. Sex differences in plasma clozapine and norclozapine concentrations in clinical practice and in relation to body mass index and plasma glucose concentrations: A retrospective survey. *Annals of General Psychiatry*. 2015;**14**(1):39
- [18] Routledge PA, Stargel WW, Kitchell BB. Sex-related differences in the plasma protein binding of lignocaine and diazepam. *British Journal of Clinical Pharmacology*. 1991;**11**:245-250
- [19] Fomon SJ, Haschke F, Ziegler EE, Nelson SE. Body composition of reference children from birth to age 10 years. *The American Journal of Clinical Nutrition*. 1982;**35**:1169-1175
- [20] Chumlea WC, Guo SS, Zeller CM, Reo NV, Siervogel RM. Total body water data for white adults 18 to 64 years of age: The Fels longitudinal study. *Kidney International*. 1999;**56**:244-252
- [21] Aguilar-Roblero R. Chronostasis: The timing of physiological systems. In: *Mechanisms of Circadian Systems in Animals and Their Clinical Relevance*. Springer International Publishing; 2015. pp. 221-236
- [22] Backman JT, Filppula AM, Niemi M, Neuvonen PJ. Role of cytochrome P450 2C8 in drug metabolism and interactions. *Pharmacological Reviews*. 2016;**68**(1):168-241
- [23] Bern M, Sand KMK, Nilsen J, Sandlie I, Andersen JT. The role of albumin receptors in regulation of albumin homeostasis: Implications for drug delivery. *Journal of Controlled Release*. 2015;**211**:144-162
- [24] Kuebler WM. Tides of blood: Cyclic changes in lung blood volume during a single breath. *American Journal of Respiratory Cell and Molecular Biology*. 2017;**57**(4):386-387
- [25] Jahn A, Bodreau C, Farthing K, Elbarbry F. Assessing Propylene Glycol Toxicity in Alcohol Withdrawal Patients Receiving Intravenous Benzodiazepines: A One-Compartment Pharmacokinetic Model. *European Journal of Drug Metabolism and Pharmacokinetics* 2018:1-8
- [26] Shao J, Kraft JC, Li B, Yu J, Freeling J, Koehn J, Ho RJ. Nanodrug formulations to enhance HIV drug exposure in lymphoid tissues and cells: Clinical significance and potential impact on treatment and eradication of HIV/AIDS. *Nanomedicine*. 2016;**11**(5):545-564
- [27] Dartois V. The path of anti-tuberculosis drugs: From blood to lesions to mycobacterial cells. *Nature Reviews Microbiology*. 2014;**12**(3):159-167
- [28] Zhitomirsky B, Assaraf YG. Lysosomal accumulation of anticancer drugs triggers lysosomal exocytosis. *Oncotarget*. 2017;**8**(28):45117-45132

- [29] Srinivas N, Maffuid K, Kashuba AD. Clinical pharmacokinetics and pharmacodynamics of drugs in the central nervous system. *Clinical Pharmacokinetics*. 2018;1-16
- [30] Jusko WJ. Clarification of contraceptive drug pharmacokinetics in obesity. *Contraception*. 2017;**95**(1):10-16
- [31] Ritter J, Lionel L, Timothy M, Albert F. *A Textbook of Clinical Pharmacology and Therapeutics*. CRC Press; 2008
- [32] Daly AK. Using genome-wide association studies to identify genes important in serious adverse drug reactions. *Annual Review of Pharmacology and Toxicology*. 2012;**52**:21-35
- [33] Pirmohamed M, Park BK. Genetic susceptibility to adverse drug reactions. *Trends in Pharmacological Sciences*. 2001;**22**(6):298-305
- [34] Falzon D, Holger JS, Elizabeth H, Licé GA, Christian L, Ernesto J, Karin W. World Health Organization treatment guidelines for drug-resistant tuberculosis, 2016 update. *European Respiratory Journal*. 2017;**49**(3):1602308
- [35] U.S. Department of Health and Human Services. Health Consequences of Smoking: A Report of the Surgeon General [Internet]. Atlanta, GA: U.S.: Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2004 [cited 2011 Oct 20]. Available from: <http://www.surgeongeneral.gov/library/Smokingconsequences/>
- [36] van Hasselt JC, Iyengar R. Systems pharmacology-based identification of pharmacogenomic determinants of adverse drug reactions using human iPSC-derived cell lines. *Current Opinion in Systems Biology*. 2017;**4**:9-15
- [37] Chung WH, Chang WC, Lee YS, Wu YY, Yang CH, Ho HC, et al. Genetic variants associated with phenytoin-related severe cutaneous adverse reactions. *JAMA*. 2014;**312**(5):525-534
- [38] Crews KR, Gaedigk A, Dunnenberger HM, Leeder JS, Klein TE, Caudle KE, et al. Clinical Pharmacogenetics implementation consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. *Clinical Pharmacology & Therapeutics*. 2014;**95**(4):376-382
- [39] World Health Organization. WHO Treatment Guidelines for Drug-Resistant Tuberculosis 2016 Update. World Health Organization; 2016
- [40] Zumla A, Chakaya J, Centis R, D'Ambrosio L, Mwaba P, Bates M, et al. Tuberculosis treatment and management—An update on treatment regimens, trials, new drugs, and adjunct therapies. *The Lancet Respiratory Medicine*. 2015;**3**(3):220-234
- [41] Verbeeck RK, Günther G, Kibuule D, Hunter C, Rennie TW. Optimizing treatment outcome of first-line anti-tuberculosis drugs: The role of therapeutic drug monitoring. *European Journal of Clinical Pharmacology*. 2016;**72**(8):905-916

- [42] S Z, Benowitz NL. Drug interactions with tobacco smoking-An update. *Clinical Pharmacokinetics*. 1999;**36**(6):425-438
- [43] Himmelmann A, Jendle J, Mellen A. The impact of smoking on inhaled insulin. *Diabetes Care*. 2003;**26**:677-682
- [44] Taghavi T, Helen GS, Benowitz NL, Tyndale RF. Effect of UGT2B10, UGT2B17, FMO3, and OCT2 genetic variation on nicotine and cotinine pharmacokinetics and smoking in African Americans. *Pharmacogenetics and Genomics*. 2017;**27**(4):143-154
- [45] Mitchell SC, Smith RL, Waring RH. The menstrual cycle and drug metabolism. *Current Drug Metabolism*. 2009;**10**(5):499-507
- [46] Ofotokun I, Pomeroy C. Sex differences in adverse reactions to antiretroviral drugs. *Topics in HIV Medicine*. 2003;**11**(2):55-59
- [47] Ensom M. Gender-based differences and menstrual cycle-related changes in specific diseases: Implications for pharmacotherapy. *Pharmacotherapy*. 2000;**20**(5):523-539
- [48] Rodenburg EM, Stricker BH, Visser LE. Sex differences in cardiovascular drug-induced adverse reactions causing hospital admissions. *British Journal of Clinical Pharmacology*. 2012;**74**(6):1045-1052
- [49] El-Eraky H, Thomas SHL. Effects of sex on the pharmacokinetic and pharmacodynamic properties of quinidine. *British Journal of Clinical Pharmacology*. 2003;**56**:198-204
- [50] Ferrari M, Bolla E, Bortolaso P, Callegari C, Poloni N, Lecchini S, et al. Association between CYP1A2 polymorphisms and clozapine-induced adverse reactions in patients with schizophrenia. *Psychiatry Research*. 2012;**200**(2):1014-1017
- [51] Franconi F, Campesi I. Pharmacogenomics, pharmacokinetics and pharmacodynamics: Interaction with biological differences between men and women. *British Journal of Pharmacology*. 2014;**171**(3):580-594
- [52] Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology—drug disposition, action, and therapy in infants and children. *The New England Journal of Medicine*. 2003;**349**:1157-1167
- [53] Clavenna A, Bonati M. Adverse drug reactions in childhood: A review of prospective studies and safety alerts. *Archives of Disease in Childhood*. 2008;**94**:724-728
- [54] Anderson GD, Lynn AM. AM. Optimizing pediatric dosing: A developmental pharmacologic approach. *Pharmacotherapy*. 2009;**29**(6):680-690
- [55] Brown R, Dimond AR, Hulisz D, Saunders LA, Bobula JA. Pharmacoepidemiology of potential alcohol-prescription drug interactions among primary care patients with alcohol-use disorders. *Journal of the American Pharmaceutical Association*. 2007;**47**(2):135-139
- [56] Coleman JJ, Ferner RE, McDowell SE. Systematic review and meta-analysis of ethnic differences in risks of adverse reactions to drugs used in cardiovascular medicine. *BMJ*. 2006;**332**:1177-1181

- [57] Bruce R, Altice FL, Fried GH. Pharmacokinetic drug interactions between drugs of abuse and antiretroviral medications: Implications and management for clinical practice. *Expert Review of Clinical Pharmacology*. 2008;**1**(1):115-127
- [58] Routledge P, O'mahony MS, Woodhouse KW. Adverse drug reactions in elderly patients. *BJCP*. 2003;**57**(2):121-126
- [59] Prybys KM, Melville KA, Hanna JR, Gee PA. Polypharmacy in the elderly: Clinical challenges in emergency practice: Part I: Overview, etiology, and drug interactions. *Emergency Medicine Reports*. 2002;**23**(11):145-151
- [60] Klotz U. Pharmacokinetics and drug metabolism in the elderly. *Drug Metabolism Reviews*. 2009;**41**(2):67-76
- [61] Steinman MA, Seth Landefeld C, Rosenthal GE, Berthenthal D, Sen S, Kaboli J. Polypharmacy and prescribing quality in older people. *Journal of the American Geriatrics Society*. 2006;**54**(10):1516-1523
- [62] Ahmed N, Mandel R, Fain MJ. Frailty: An emerging geriatric syndrome. *The American Journal of Medicine*. 2007;**120**(9):748-753
- [63] Hilmer SN, McLachlan AJ, Le Couteur DG. Clinical pharmacology in the geriatric patient. *Fundamental & Clinical Pharmacology*. 2007;**21**(3):217-230
- [64] Hutchison LC, O'Brien CE. Changes in pharmacokinetics and pharmacodynamics in the elderly patient. *Journal of Pharmacy Practice*. 2007;**20**(1):4-12
- [65] Cannon KT, Choi MM, Zuniga MA. Potentially inappropriate medication use in elderly patients receiving home health care: A retrospective data analysis. *The American Journal of Geriatric Pharmacotherapy*. 2006;**4**(2):134-143
- [66] Hajjar ER, Cafiero AC, Hanlon JT. Polypharmacy in elderly patients. *The American Journal of Geriatric Pharmacotherapy*. 2007;**5**:345-351
- [67] Petrone K, Katz P. Approaches to appropriate drug prescribing for the older adult. *Primary Care; Clinics in Office Practice*. 2005;**32**:755-775
- [68] American Geriatrics Society Clinical Practice Committee. The use of oral anticoagulants (warfarin) in older people. *Journal of the American Geriatrics Society*. 2002;**50**:1439
- [69] Branch RA, James J, Read AE. A study of factors influencing drug disposition in chronic liver disease, using the model drug (+)-propranolol. *British Journal of Clinical Pharmacology*. 1976;**3**:243-249
- [70] Dreisbach AW, Lertora JJ. The effect of chronic renal failure on hepatic drug metabolism and drug disposition. *Seminars in Dialysis*. 2003;**16**:45-50
- [71] Frye RF, Zgheib NK, Matzke GR, Chaves-Gnecco D, Rabinovitz M, Shaikh OS, Branch RA. Liver disease selectively modulates cytochrome P450-mediated metabolism. *Clinical Pharmacology and Therapeutics*. 2006;**80**:235-245

- [72] Hasselstrom J, Eriksson S, Persson A, Rane A, Svensson JO, Sawe J. The metabolism and bioavailability of morphine in patients with severe liver cirrhosis. *British Journal of Clinical Pharmacology*. 1990;**29**:289-297
- [73] Ogasawara K, Terada T, Katsura T, Hatano E, Ikai I, Yamaoka Y, Inui K. Hepatitis C virus related cirrhosis is a major determinant of the expression levels of hepatic drug transporters. *Drug Metabolism and Pharmacokinetics*. 2010;**25**:190-199
- [74] Sun H, Frassetto L, Benet LZ. Effects of renal failure on drug transport and metabolism. *Pharmacology & Therapeutics*. 2006;**109**(1-2):1-11
- [75] Venitz R. Effect of chronic renal failure on the disposition of highly hepatically metabolized drugs. *International Journal of Clinical Pharmacology and Therapeutics*. 2000;**38**(5):245-253
- [76] Yurdaguel Z, Christina C, Antje A, Eckhart GH, Harald D. Risk factors associated with adverse drug reactions following hospital admission: A prospective analysis of 907 patients in two German university hospitals. *Drug Safety*. 2008;**31**(9):789-798
- [77] Macdonald JB, Macdonald B, Golitz LE, LoRusso P, Sekulic A. Cutaneous adverse effects of targeted therapies: Part I: Inhibitors of the cellular membrane. *Journal of the American Academy of Dermatology*. 2015;**72**(2):203-218
- [78] Pack A, Davis AR, Kritzer J, Yoon A, Camus A. Antiepileptic drugs: Are women aware of interactions with oral contraceptives and potential teratogenicity. *Epilepsy & Behavior*. 2009;**14**(4):640-644
- [79] Obreli-Neto PR, Nobili A, de Oliveira Baldoni A, Guidoni CM, de Lyra Júnior DP, Pilger D. Adverse drug reactions caused by drug–drug interactions in elderly outpatients: A prospective cohort study. *European Journal of Clinical Pharmacology*. 2012;**68**:1667-1676
- [80] Pringle K, Ahern FM, Heller DA, Gold CH, Brown TV. Potential for alcohol and prescription drug interactions in older people. *Journal of the American Geriatrics Society*. 2005;**53**(11):1930-1936
- [81] Schmiedl S, Rottenkolber M, Hasford J, Rottenkolber D, Farker K, Drewelow B, Thürmann P, et al. Self-medication with over-the-counter and prescribed drugs causing adverse-drug-reaction-related hospital admissions: Results of a prospective, long-term multi-Centre study. *Drug Safety*. 2014;**37**(4):225-235
- [82] Brooks KM, George JM, Pau AK, Rupert A, Mehaffy C, De P, et al. Cytokine-mediated systemic adverse drug reactions in a drug–drug interaction study of Dolutegravir with once-weekly isoniazid and Rifapentine. *Clinical Infectious Diseases*. 2018
- [83] Moore N, Pollack C, Butkerait P. Adverse drug reactions and drug–drug interactions with over-the-counter NSAIDs. *Therapeutics and Clinical Risk Management*. 2015;**11**:1061-1065
- [84] Aronson JK, editor. *Meyler's Side Effects of Drugs: The International Encyclopedia of Adverse Drug Reactions and Interactions*. Elsevier; 2015