PHARMACOKINETICS: HOW DOES THE BODY HANDLE DRUGS?

Olavi Pelkonen
Department of Pharmacology and Toxicology, University of Oulu, Finland

Jorma Ahokas
School of Medical Sciences, RMIT-University, Bundoora, Victoria, Australia

Keywords: Absorption, distribution, metabolism, excretion

Contents

Summary

Pharmacokinetics describes the absorption of drugs into the body and their distribution into various tissues and their eventual elimination. The elimination of drugs is a combination of metabolism and excretion. In this chapter we describe the processes involved during the transit of drugs through the body. The lipophilicity of a drug is very important to enhance its absorption into the body and distribution to the target sites, however eventually the drug needs to be eliminated. A lipophilic drug is poorly eliminated and a change in the chemical characteristics is often essential to facilitate the elimination. There is an extensive range of drug metabolizing enzymes that catalyze changes to the chemical structure of drugs. The metabolism of drugs result in two distinct outcomes: increased excretions and usually a pharmacologically inactive product.

Drug metabolism is important and changes in this process have profound effects on drug effects. It is well known that drug metabolism can be inhibited but it can also be induced, where its activity is enhanced. Both of these changes have caused numerous clinically recognized problems.

Pharmacokinetics describes the drug concentration versus time relationships mathematically. The basic pharmacokinetic parameters, clearance, volume of distribution and half-life as well as the common pharmacokinetic models are discussed below.

1. Introduction

Drugs or pharmaceuticals are used for the beneficial effects they have on the processes in the body which are important in treating diseases or alleviating symptoms. For them to exert these effects they have to reach the appropriate target sites in the body wherever these target sites are located. On the other hand, effects should not last forever, but just have the desired duration; consequently drugs should be eliminated from the body. All those processes that determine the movement and transformations of drugs in the body from entering to excretion are called pharmacokinetics. In essence, pharmacokinetics gives an answer to the question of how the body handles drugs (or foreign chemicals or xenobiotics in general)

2. Movement of Drugs in the Body

2.1. Mass Transport

In principle, the access of a drug to its site of action is dependent on two broad processes: movement and distribution of a drug via blood circulation, the so-called mass transport, and movement of a drug across biological membranes. Mass transport is not affected, at least not to a large extent, by specific properties of a drug. Thus when a drug is in the blood, it is transported by the circulation to places where circumstances allow it to be moved through cell membranes. Such locations are for example tissue capillary beds, hepatic sinuses and renal glomeruli. In general the capillary endothelium is not a barrier for the movement of drugs into extra cellular fluid, because endothelium is fenestrated. Only large molecules such as proteins do not move through fenestrated endothelium. In some tissues, brains, placenta, testes etc, the endothelium is practically without any fenestrae and in this situation drugs have to cross the real biomembrane. Somewhat incorrectly, the term barrier is used in this connection, but one has to remember that lipid-soluble drugs penetrate these "barriers" relatively quickly and efficiently.

The lymphatic system is a special case of drug mass transport, but it has a relatively restricted role in drug movements.

2.2. Passage through Biological Membranes

To reach the site of action, the drug has to cross biological membranes. In principle, there are four ways of crossing membranes: filtration (through the small pores in the membranes), passive diffusion, facilitated diffusion and active transport. Filtration seems practical only to very small molecules. In a majority of cases, drugs cross the membrane passively along a concentration gradient and molecular and physico-chemical factors become determining factors (lipid solubility, ionization, molecular size etc). Ionization of a drug is important especially when there is a pH gradient across the membrane such as in the stomach, small intestine, and kidney tubular fluid.

It has become increasingly apparent during the recent years that many drugs make use of transport proteins to get across biological membranes. The assortment of transporters is dependent on the specific tissue. For example, in the hepatocyte there are a different set of transporters in the apical and basolateral (canalicular) cell membranes, where apical transporters take their substrates into hepatocytes and basolateral transporters catalyze the outward flux of drugs and their metabolites into bile. Although this is a somewhat simplified concept, it suggests an unidirectional flux of drug and their metabolites in the tissue. The most studied transporter is probably P-glycoprotein (P-gp), which belongs to a large family of protein molecules known as ABC cassette transporters. In the enterocyte this transporter serves as an efflux pump, which actually prevents ligands from being absorbed. In the bile canalicular membrane it serves as a transporter for various drug metabolites for them to be excreted into bile.

3. Absorption of Drugs

Drugs taken by all routes, other than by direct injection, need to be absorbed. After absorption the drug gets into the blood and can then be circulated to its target(s). The only situation where absorption into the general circulation is neither necessary nor desirable is when we want to treat a condition involving the surface epithelial layer of

tissues. Even in these situations the drug needs to be absorbed into the surface layers of the tissue in question.

Drugs are administered by using a wide variety of routes and methods of administration. The most important routes and corresponding drug preparations are listed in Table 1.

Route	Absorbing membrane	Drug form
Mouth	Mucous membranes of gastro-intestinal tract	mixtures, tablets capsules etc.
Sublingual	Mucous membrane	lozenges, tablets
Rectal	Mucous membrane	suppositories
Colonic	Mucous membrane	enemas
Urethral	Mucous membrane	bougies
Vaginal	Mucous membrane	pessaries
Nasal	Mucous membrane	drops
Inhalation	Mucous membrane of respiratory tract	aerosols
Conjunctival	Mucous membranes of conjunctiva (for systemic absorption) epithelium of cornea (for local effect on eye)	drops, lamellae
Epidermis	Keratinized epithelium	ointments etc.
Parenteral injections		
Subcutaneous	Vascular and lymphatic endothelium	solutions and suspensions
Intramuscular		
Intravenous	None	solutions
Intra-arterial		
Intrathecal		

Table 1. Routes of administration of drugs.

3.1. Oral Administrations

Oral administration is the most common route of drug administration. When drugs are taken orally they can enter the circulation from all parts of the gastro-intestinal tract. One important feature of absorption of drugs from the alimentary tract to the circulation is dissolution. It is generally accepted that substances must dissolve before they can be absorbed by common mechanisms such as diffusion or active transport. Many drugs can undergo aqueous dissolution and lipids undergo emulsification by bile acids. The relative solubility of the drug in aqueous and lipid phases is important.

The pharmaceutical form of the drug preparation is very important in determining dissolution. Suspensions of drug preparations may lead to quicker dissolution of the active compound than if the drug is in solid preparation such as tablet form. Dissolution

can be improved by many methods e.g. by producing microcrystalline products, using buffered preparations, dispersants and co-solutes.

There are many underlying chemical and physiological factors affecting the absorption of chemicals from the GI (alimentary) tract into the circulation. These include molecular weight and degree of ionization. The most important physiological factors include local pH and gastrointestinal motility. pH affects the degree of ionization of the drug and consequently its absorption through membranes. Gastrointestinal motility is a very important physiological factor affecting the absorption of selected drugs. Increased motility may enhance absorption of drugs that are normally broken down by the mucosal membranes. On the other hand, decreased motility gives time for the dissolution of poorly soluble molecules.

There are also many compounds within the gastrointestinal tract that may interfere with drug absorption. Most commonly cited examples include divalent ions such as ferrous iron and calcium which complex with drugs such as tetracyclines to form chelates that are not absorbed.

Enzymatic and chemical degradation of drugs is also a very important factor interfering particularly with the oral administration of drugs. For example polypeptides such as insulin are ineffective when administered orally because they are denatured within the gastrointestinal tract. The degradation of orally administered drugs may occur within the gut, but a significant number of drugs absorbed from gastric or intestinal mucosa may be broken down by the liver before reaching systemic circulation The breakdown of drugs in the gastrointestinal mucosa and the liver is by metabolism which will be discussed separately.

3.2. Parenteral Route of Entry

3.2.1 Percutaneous

Absorption through the skin is important especially with respect to chemicals with occupational health implications, but dermal absorption is also used for drugs - usually for local therapeutic effect. Corticosteroids used topically on the skin may cause unwanted problems because they are absorbed into the systemic circulation. Absorption of drugs through the skin varies from one part of the body to another. This is due to differences in the thickness of the skin, the underlying blood circulation and the moisture content of the surface layers of the skin. Lipophilicity of the drug is the most important factor for absorption through healthy skin, but damaged skin, epidermis, can permit the passage of charged molecules.

Therapeutically it may be desirable to increase the permeability of the skin e.g. by hydrating the top layer (corneum). This can be achieved by soaking the skin in a warm salt solution with a pH different form the range (3.5-5) which is normal for keratin. Another way of increasing permeation through the skin is by occlusive dressings. For example plastic over the skin or hydrophobic ointments cause local sweating. Plastic covers over nappies tend to cause nappy rash and highly hydrated skin. In this

circumstance it is good to limit the use of steroids, as the steroids will pass easily through hydrated skin causing systemic toxicity.

Solvents with good aqueous and lipid solubility increase absorption through the skin, e.g.: dimethyl sulfoxide. This property of some solvents can be taken advantage of to enhance the absorption of drugs, but it can also contribute to the adverse effects of industrial and agricultural chemicals. Sometimes it is desirable to_ prevent transdermal absorption. Barrier creams can be used for this purpose as they protect skin against penetration by water and solvents and sensitizing chemicals. These creams are mainly silicones.

3.2.2 Nose and Eyes

The nose and eyes are easily accessible epithelial areas with good penetration by drugs. In both cases there is good local circulation and in the case of the nasal passages a large surface area that facilitates absorption of drugs and other chemicals to allow systemic effects.

3.3. Inhalation

Various drugs including gases, and vapors such as anesthetics are administered by inhalation. They can enter all parts of the respiratory system. Aerosols and solid particles enter the respiratory "tree" depending on particle size. A particle size of 1 µm can get all the way into the respiratory system (into the alveoli). Gases are absorbed very readily if they get into the lungs. Drugs, numerous toxicants inhaled into the lungs are readily absorbed whether they are gasses, vapors of volatile liquids, liquid aerosols or particles.

The epithelial cells lining the alveoli are very thin and the capillaries are in close contact with these so the distance for a chemical to diffuse is very short. Since the whole cardiac output flows through the lungs this results in fast uptake and subsequent rapid distribution.

As with gastrointestinal absorption a number of factors affect absorption via the lungs. The drug or chemical related factors include:

- Dissolution in the blood described by the blood-to-gas phase partition coefficient
- Water solubility
- Aerosol / particle solubility in lung fluids
- Aerosol / particle size and deposition

The rate and the depth of respiration are very important in determining absorption of airborne drugs and contaminants. Obviously the pulmonary blood flow is important, but in the case of the lungs it is hardly a limiting factor.

The degree of ionization and lipid solubility of chemicals are very important for oral and percutaneous exposures, however, since diffusion through cell membranes is not rate limiting in pulmonary absorption of gases, these factors are less important here.

3.4. Bioavailability

When a drug is administered, the entire dose is not delivered to the site of action. The bioavailability of a drug or compound is defined as 'the physiologically or biologically available fraction of a drug or a chemical'. Bioavailability signifies the extent of absorption of a drug or a chemical from its dosage form into the systemic circulation. For this reason, by definition, drugs administered intravenously (IV) are said to have a bioavailability of 100%.

Bioavailability (F) of a drug can be defined as the fraction of the dose that reaches the systemic circulation in an unchanged (and usually active) form at a particular time (x).

The area under the time versus plasma concentration curve is reflective of the amount of drug that has been absorbed into the circulation. Assuming that the same dose is administered, bioavailability can be calculated in the following way:

$$F = \frac{AUC_{0 \to x(oral)}}{AUC_{0 \to x(IV)}} \qquad (1)$$

AUC is the area under the plasma concentration versus time curve from time 0 to time x after intravenous (iv) dosage or another chosen route e.g. oral. A relative bioavailability can also be determined by comparing the AUC for oral administration of two different oral preparations. This is useful in the comparison of different formulations.

Many factors cause variations in bioavailability. A number of these factors are related to the drug preparation and dosage form. The chemical form of the drug and its particle size and solubility are highly important. Readily soluble drugs are absorbed quickly. The type or quantity of excipient or vehicle added can also impact on bioavailability.

Bioavailability plays an important role in the toxicity of various compounds/drugs. For example phenytoin (anticonvulsant) toxicity was observed in the 1960's. Patients treated with this antiepileptic had a sudden and unexpected incidence of side effects (e.g. gum hyperplasia) that was normally associated with excessive doses. The manufacturer had changed the capsule formulation, increasing bioavailability 2-3 fold and this was either not known or taken into consideration in the clinical use of the new product. In the 1970's a number of pharmaceutical companies proceeded to improve their formulation of digoxin achieving improved bioavailability. This resulted in cardiac arrhythmias due to unexpected overdosing.

Tetracyclines (antibiotic) can chelate calcium and Fe^{2+} (divalent ions). These chelates are large molecules that cannot be absorbed. If tetracyclines are taken with milk or iron preparations, their bioavailability is reduced greatly.

3.4.1. Physiological Factors

Physiological factors affecting bioavailability include first pass hepatic metabolism and entero-hepatic shunting or circulation. Metabolism by the gastrointestinal epithelium and liver during the first passage of the drug through them can affect bioavailability greatly. Drug loss due to this mechanism is commonly known as first pass metabolism of the drug. In some cases where there is high first pass metabolism it is virtually impossible to administer the drug orally such as the case with lignocaine.

Other very important physiological factors impacting on absorption of drugs (and bioavailability) involves the drug transporter P-glycoprotein (P-gp). Individual variability may exist with respect to P-gp and drug metabolizing enzymes. The additional complication with respect to these two factors is that the expression of metabolizing enzymes and P-gp can be modified by drugs.

3.4.2. Other Properties

Tablets are mostly packing material and compaction pressure of tablets is important.
The stomach has a much smaller surface area than the small intestine. Consequently most absorption will take place in the small intestine, even though the other factors may be working against it.

3.5. Therapeutic Delivery Systems (Prodrugs, Implants, etc.)

To avoid problems inherent in oral drug administration, such as inefficiency, variability, first pass effect, patient compliance, various pharmaceutical technological approaches have increasingly been adopted (Table2). For example, transdermal preparations or inhalational devices lead to more stable and predictable plasma concentrations than oral drug preparations.

The final goal of drug delivery systems is to deliver the drug at the right target at the right concentration and at the right time and leave the rest of the body untouched. Specifically prepared nanoparticles as carriers of drugs can target the drug to a specific tissue with an affinity to the nanoparticle in question. Devices which respond to a specific change in blood composition (e.g. increase in blood glucose level), with a consequent release of a drug (e.g. insulin) are now being developed.

Therapeutic delivery system	Example	Condition to be treated
Corneal lamelle	Pilocarpine	glaucoma
Intrauterine device	Progesterone	prevention of pregnancy
Transdermal patch	Scopolamine	motion sickness
	Nitroglycerine	angina pectoris
Osmotic pump	Insulin	diabetes
Liposomes	cancer drugs	cancer

Table 2. Examples of therapeutic delivery systems in use or in development.

-
-
-

TO ACCESS ALL THE **26 PAGES** OF THIS CHAPTER,
Visit: http://www.eolss.net/Eolss-sampleAllChapter.aspx

Bibliography

Fitchl B. (1999) Principles of Toxicokinetics. In: Marquardt, Schäfer, McCellan and Welsch. Eds. Toxicology. 1st ed. London: Academic Press : 43-82. ISBN: 0-12-473270-4. [An excellent and extensive treatment of pharmacokinetics].

Gibson GG and Skett P. (2001) Introduction to Drug Metabolism. 3rd ed. London, Nelson Thomas, 264 pp. [Comprehensive introductory coverage of pharmacokinetics, with emphasis on metabolism, in an easily accessible format].

Goodman Gilman A, Rall TW, Nies AS, Taylor P (eds.). (2005) The Pharmacological Basis of Therapeutics, 10th Edition. McMillan-Graw . [this standard pharmacology textbook contains a brief but informative introduction to pharmacokinetic processes].

Klaassen CD and Doull J (editors). (2001) Casarett and Doull's Toxicology: The basic science of poisons. 6th ed. New York: McGraw-Hill : 113-186. ISBN: 0071347216 [This standard toxicology textbook contains good basic articles on ADME: Parkinson A. Biotransformation of xenobiotics (an excellent chapter on drug metabolism) and Rozman KK, Klaassen CD. Absorption, distribution and excretion of toxicants (a good introduction to pharmaco/toxicokinetic processes)].

Oesch F and Arand M. Xenobiotic metabolism. In: Marquardt, Schäfer, McCellan and Welsch. Eds. (1999) Toxicology. 1st ed. London: Academic Press : 83-109. ISBN: 0-12-473270-4. [An extensive treatment of drug metabolism extended to metabolism of chemicals in general].

Rowland M and Tozer TN (2003): Clinical pharmacokinetics. Concepts and applications. 3rd ed. Williams & Wilkins . [An advanced textbook gives an excellent conceptual and practical basis for pharmacokinetics].

Biographical Sketches

Professor Olavi Pelkonen is a pharmacologist/toxicologist by training and has been working in the University of Oulu, Finland for more than 30 years. He received MD, PhD in Finland, did postdoctoral training in NIH in USA and has been a visiting professor in Spain, UK and Australia. Currently, he is a professor of pharmacology at University of Oulu, but is contributing to several EU research programs and serving as an expert in several EU-level functions. Furthermore, he has been a consultant to several big and SME pharmaceutical companies. Prof. Pelkonen is the author of over 350 publications, which cover especially drug and carcinogen metabolism, pharmaco/toxicokinetics and in vitro and in silico approaches in early drug development. Olavi Pelkonen is a Professor of Pharmacology and Head of the Department of Pharmacology and Toxicology University of Oulu

Professor Jorma Ahokas is a pharmacologist/toxicologist by training and he received PhD in Finland and did a postdoc as a Merck Sharp & Dohme Research Fellow in Clinical Pharmacology in the Department of Medicine, University of Queensland followed by an Australian National Health & Research Council funded research post. After lectureships in Department Pharmacology, University of Melbourne and RMIT, in 1991 he was appointed to a position of Foundation Professor in Toxicology at RMIT. It was the first full professorship in toxicology in Australia. Since 1998 he has been a Docent in toxicology at the University of Helsinki and since 1999 a visiting professor of toxicology at Toho

University, Japan. His research has related to problems of drug and carcinogen metabolism as well as food and environmental toxicology. His current research interests relate to adverse effects of complementary remedies and their interactions with prescription medicines. He has been a consultant in areas of drug toxicity and environmental toxicology to industry and government bodies. Jorma Ahokas is a Professor of Toxicology, School of Medical Sciences, RMIT-University