Basic concepts in pharmacology, drug action and pharmacokinetics

Part 4: The pharmacokinetic processes of metabolism and elimination

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This is the fourth and final instalment in a series of articles on the basics of pharmacology, drug action and pharmacokinetics, in which interactive explanations are used to illustrate the last two of the four basic pharmacokinetic processes, namely metabolism and elimination (i.e. the ‘M’ and ‘E’ of the “ADME” processes). This series uses excerpts and diagrams with permission from the 2nd edition of Pharmacology in Clinical Practice: Application Made Easy for Nurses and Allied Health Professionals, and is compiled and expanded upon by the author.

Introduction

In Part 2, we introduced the kinetic processes of metabolism and elimination, as part of our discussion on the fundamentals of pharmacokinetics and the “ADME” processes. Part 2 and 3 also contained a more detailed explanation of the first two of the four fundamental pharmacokinetic processes, namely absorption and distribution.

Now, in Part 4 (the final instalment in the current series), we will focus on the termination of drug action, with specific reference to the interplay between the last two of the four kinetic processes, metabolism and elimination. An example from the clinical practice setting will also be used to illustrate the four processes in a more applied and integrated manner.

Before we consider the last two processes in more detail, it should be mentioned, that some authors prefer to use the term “excretion” for the “E” of the “ADME” processes and therefore effectively substituting “elimination”, since the latter could also be interpreted as including the process of metabolism. However, whether one prefers to use “elimination”, or chooses to use “excretion”, the process will remain linked to the termination of drug action, together with metabolism (also referred to as biotransformation).

Can you still remember the three most important ways in which drug action may be terminated in the human body?

The termination of drug action

As was previously mentioned in Part 2, the action of absorbed drugs may be ended (or terminated) in a number of ways:1-4

Drug action may be terminated through biotransformation: The microsomal enzymes of the liver and the non-microsomal enzymes of other tissues may detoxify and inactivate circulating drugs. This is also referred to as metabolism (i.e. the ‘M’ of “ADME”)

Drugs may be excreted by the kidneys, lungs and liver (biliary excretion) and in body secretions: Nasal secretions, saliva and sweat may contain the secreted molecules of certain drugs. Drugs with a volatile nature are excreted in part by the lungs. Certain drugs may also be excreted in the breast milk. As mentioned in the introduction to this article, one could use either “elimination” or “excretion” to represent the “E” of “ADME”.

Drug action may be decreased or terminated by miscellaneous mechanisms: Other mechanisms for the termination of drug action include redistribution (i.e. drugs with large volumes of distribution may be redistributed to other tissue areas), the development of tolerance towards the effects of a certain drug, or drug antagonism (the actions of certain drugs may be terminated through the use of their corresponding antagonists).

We will now consider metabolism and elimination (or excretion) in more detail.

Drug metabolism

As was previously discussed in Part 2, elimination is the process whereby drug action is terminated via biotransformation or excretion. The elimination processes of certain drugs may become saturated (i.e. reaching their maximum capacity). These drugs will accumulate in the bloodstream, should their rates of absorption exceed their rates of elimination, and may reach toxic plasma levels. Drugs such as these are said to follow zero-order elimination kinetics. However, most drugs follow first-order elimination kinetics.1-4

Metabolism may be seen as the third of the four kinetic processes. Except for the first-pass effect, drugs are metabolised after having been absorbed and distributed.
When discussing metabolism, the term “biotransformation” is used when referring to the metabolism of substances, such as drugs, that are foreign to the body.

The liver is the primary organ responsible for drug metabolism (or biotransformation) in the body. However, other tissues may also participate in the metabolism of drugs. These include the lungs, kidneys, skin, adrenal cortex, brain and intestines. Drug molecules need to enter the liver cells to access the liver and intestines. Drug molecules need to be nonpolar and rather lipid soluble to be transformed by the liver and intestines. This requires their molecules to be nonpolar and rather lipid soluble (refer back to Part 3).1-4

Almost all endogenous substances that require biotransformation are water soluble. The steroid hormones are an important exception. These hormones, together with drug molecules that mostly exhibit lipid solubility, undergo liver biotransformation since they are capable of entering liver cells. Drugs that have chemical structures similar to the water-soluble endogenous substances are biotransformed by nonmicrosomal enzymes, or they may be excreted in their unchanged (original) form. These latter enzymes are the plasma esterases, such as cholinesterase or the mitochondrial enzymes, e.g. monoamine oxidase (MAO).1-4

Liver metabolism entails the biotransformation of drug molecules into more polar, water-soluble metabolic products (metabolites). The kidneys can then excrete these metabolites since tubular reabsorption will no longer take place.

Generally drugs are metabolised in two phases:1-4

Phase I: The reactions that take place during phase I metabolism are aimed at unmasking or inserting functional groups that produce more polar and water-soluble metabolites, which are less active. Oxidation is the most common phase I reaction. Reduction and hydrolysis are other phase I reactions. Figure 1 illustrates the possible outcomes of phase I liver biotransformation.

Phase II: This phase is characterised by conjugation reactions. During these reactions an endogenous conjugate (a substrate such as glucuronic acid) is joined to the polar group that was added during phase I. The resultant metabolic products (conjugated products) are wholly inactive and highly ionised. The kidneys can therefore readily excrete these metabolic products. Acetylation may be an exception to the rule, since acetylated metabolites may actually be less water soluble than their parent drugs (e.g. the sulphonamides), necessitating adequate hydration to prevent the possibility of crystalluria (i.e. when crystals are excreted in the urine).

The rate of liver metabolism or hepatic clearance of a drug is determined by hepatic blood flow and the extraction ratio of the drug. The extraction ratio is expressed as a fraction (from 0 to 1) and gives an indication of how much of the drug will be removed on a single pass through the liver (0 indicates that none of the drug is removed and 1 implies that the drug is completely removed). The extraction ratio multiplied by hepatic blood flow equals what may be termed the “hepatic clearance” of the drug. Lignocaine is an example of a drug with a very high extraction ratio. Therefore, it cannot be administered orally because the first-pass effect will eliminate virtually the entire amount of drug from the bloodstream.1-4

Another example is glyceryl trinitrate, which must be administered via the buccal or sublingual route. The bioavailability of these drugs is extremely poor. Drugs that exhibit a very low extraction ratio, including warfarin and phenytoin, are biotransformed at a much slower rate since the liver has a smaller capacity for the biotransformation of these drugs, compared to its capacity for biotransforming those with higher extraction ratios. Very little of the drug is removed on a single pass through the liver.1-4

Certain drugs may act as inducers and others as inhibitors of liver microsomal enzymes, especially the cytochrome P450 enzymes, implying that they can increase or decrease the rate at which substances, such as other drugs, are biotransformed (and, therefore, extruded) by the liver. Some interactions between such enzyme inducers or inhibitors and other drugs are of real clinical significance. Table I lists some important examples of such enzyme inducers and inhibitors.1-4

Note that enzyme induction will lead to increased levels of the relevant drug metabolite(s), which may be active or inactivated, while enzyme inhibition will cause an accumulation of the relevant parent drug or compound, a pharmacologically active substance or a pro-drug.

Excretion of drug molecules and their metabolites

The kidneys are not the only excretory organs in the body. Organs such as the lungs and exocrine glands may also participate in the excretion of drugs. Excretion is the last of the four kinetic processes.

Drugs may be excreted in a variety of ways: via the lungs, the gastrointestinal tract, the kidneys and in body secretions.
Basic Pharmacology

From the scenario an event as commonplace as taking two paracetamol-containing headache tablets could be used to illustrate the interplay and interrelationship among the four pharmacokinetic processes.

Four questions follow the scenario:

**How did the molecules of paracetamol reach their site of action in Mr. A-Z's body?**

Follow the diagram in Figure 2. The tablets are taken via the oral route (i.e. swallowed, with some water). Upon entering the stomach, and coming into contact with its gastric juices, the tablets enter the “pharmaceutical phase” (1). During this phase the active ingredient, paracetamol, needs to be liberated (“set free”) from its dosage form (the two tablets). This entails the disintegration of the tablets and the subsequent dissolving of the drug. Free drug molecules will then be available for absorption to take place from the gastrointestinal tract. This implies that the pharmacokinetic phase (2) has subsequently been reached. The drug molecules are now distributed throughout the body. Paracetamol is widely distributed, and even crosses the placenta and appears in breast milk.1-4

**How did the paracetamol-containing tablets alleviate Mr. A-Z’s pounding headache?**

Paracetamol is thought to act as an inhibitor of the COX-3 isoform of the cyclooxygenase (COX) enzyme. Paracetamol is capable of alleviating mild to moderate pain. It is also effective as an antipyretic agent (for the management of fever). However, it is not effective as an anti-inflammatory agent owing to its lack of activity on the COX-2 isozyme. Therefore, to answer this specific question, one needs to understand paracetamol’s mechanism of action and resultant effects, which form part of its pharmacodynamic profile [this represents the pharmacodynamic phase, or (3) on the diagram].1-4

**What happened to the paracetamol molecules once the headache subsided?**

Paracetamol is ultimately metabolised by the liver, which results in hepatic metabolites. These metabolites, together with a very small percentage of the unchanged drug, are excreted by the kidneys. Therefore, the termination of drug action is dependent upon both hepatic and renal clearance.1-4

**Why should patients not exceed the maximum recommended dosage of four grams of paracetamol in any given 24-hour period?**

One of paracetamol’s minor metabolites, commonly referred to as NAPQI, is highly reactive and could become fatally toxic when it accumulates in the body. At recommended therapeutic dosage ranges NAPQI will be conjugated with glutathione in the liver. However, when

### Table I: Examples of drugs that induce or inhibit liver microsomal enzymes

<table>
<thead>
<tr>
<th>Inducers</th>
<th>Inhibitors</th>
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<tbody>
<tr>
<td>Barbiturates</td>
<td>Chloramphenicol</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Cimetidine</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Clarithromycin</td>
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<tr>
<td>Rifampicin</td>
<td>Erythromycin</td>
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<td></td>
<td>Flucloxacillol</td>
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<td></td>
<td>Fluonoxazole</td>
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<td></td>
<td>Fluoxetin</td>
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<tr>
<td></td>
<td>Isoniazid (INH)</td>
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<tr>
<td></td>
<td>Itraconazole</td>
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<tr>
<td></td>
<td>Ketoconazole</td>
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<tr>
<td></td>
<td>Ritonavir</td>
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<tr>
<td>Also note:</td>
<td>Also note:</td>
</tr>
<tr>
<td>Chronic alcohol</td>
<td>Grapefruit juice</td>
</tr>
<tr>
<td>Smoke</td>
<td></td>
</tr>
<tr>
<td>St John’s Wort</td>
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such as saliva, tears and sweat. An important kinetic feature of excretion is the fact that the concentration of a drug is higher in the organ(s) that excrete it than in the rest of the body. This explains why drug toxicity is usually detected in these organs first. Also refer to the notes on clearance in part 2.1-4

**Biliary excretion**

Drugs and their metabolites may be actively transported from the bloodstream to the bile. The liver acts as the excretory organ for highly polar substances (i.e. substances that are water soluble), with molecular masses in excess of 300 to 350 Da.1-4

**Renal excretion**

Whenever drugs are excreted in the urine, it is either in their original, unchanged, polar, water-soluble form (called the parent drug or compound), or in the form of their polar, water-soluble drug metabolites (produced during drug biotransformation). Renal excretion involves three important physiological processes, namely glomerular filtration, active tubular secretion and passive tubular reabsorption.1-4

**Applying the pharmacokinetic processes in the clinical practice setting**

Study the scenario in Table II, as well as the accompanying diagram in Figure 2.

### Table II: An illustration of the most fundamental questions that underlie pharmacodynamics and pharmacokinetics

Consider the following scenario:

A man, Mr A-Z, suffering from a pounding headache decides to take two headache tablets to alleviate the pain.

According to the label the tablets contain 500 mg of paracetamol each, with an added preservative, and are sugar free. The recommended dosage is one to two tablets every four to six hours while symptoms persist and patients are warned not to exceed four grams of paracetamol in a 24-hour period.

The man therefore took one gram of paracetamol for his headache, which subsided a while later following the tablets, a glass of water and some rest.

**Some obvious questions to consider are:**

- How did the molecules of paracetamol reach their site of action in Mr A-Z’s body?
- How did the paracetamol-containing tablets alleviate Mr A-Z’s pounding headache?
- What happened to theparacetamol molecules once the headache subsided?
- Why should patients not exceed the maximum recommended dosage of four grams of paracetamol in any given 24-hour period?
Two headache tablets, containing 500 mg of paracetamol each

**Pharmaceutical phase:**
- Disintegration of the tablets
- Dissolution (dissolving) of the drug

Drug available for absorption (pharmaceutical availability)

**Pharmacokinetic phase:**
- A: Absorption
- D: Distribution
- M: Metabolism
- E: Excretion/Elimination

Drug concentration in the target organ over time

**Pharmacodynamic phase:**
- Affinity
- Drug-receptor interaction and signal transduction
- Intrinsic activity
- Efficacy

**Pharmacological effect**

Paracetamol is readily absorbed from the gastrointestinal tract and is widely distributed with minimal plasma protein-binding. It crosses the placenta and appears in breast milk.

Paracetamol is metabolised in the liver and the biotransformation results in the formation of a toxic metabolite, NAPQI. The metabolites and a very small percentage of the unchanged drug are cleared through renal excretion.

Paracetamol relieves mild to moderate pain and fever through the inhibition of COX-3, an isoenzyme of the cyclooxygenase enzyme.

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Figure 2: The movement of drug molecules. Adapted from Venter DP, Brunton LL and Brenner GM²,³
glutathione stores become depleted during an overdose, this toxic metabolite accumulates which could result in liver cell necrosis.

Conclusion

This article concludes the series on basic concepts in pharmacology, drug action and pharmacokinetics. In this, the final instalment, we focused on the last two of the pharmacokinetic processes, namely metabolism and elimination. The two most important organs involved in the termination of drug action are the kidneys for renal excretion and the liver for hepatic biotransformation (and biliary excretion to a much lesser extent). The four ADME processes are interlinked and, although discussed as separate entities, cannot function independently of one another.

Answers

**Name the two most important ways in which drug action may be terminated in the human body.**

- Hepatic (liver) biotransformation
- Renal (kidney) excretion.

**Name four organs/glands that could potentially excrete drug molecules from the body.**

Any four of the following:
- Kidneys
- Tear glands
- Sweat glands
- Lactating breast tissue
- Salivary glands
- Liver, via biliary excretion.

**Name the three physiological processes that are involved in renal excretion.**

The three fundamental processes are:
- Glomerular filtration
- Active tubular secretion
- Passive tubular reabsorption.

References