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PHARMACOKINETICS: DRUG EXCRETION

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Abstract: This chapter discusses the last stage of pharmacokinetics: *elimination (clearance) of the drug*. In general, it is important to emphasize the role of the study of pharmacokinetics here: it is the study of what the body does with the drug. At this point, we believe that you already understand the processes of Absorption, Distribution and Biotransformation seen in previous chapters. We can now discuss the main drug clearance processes, mainly via the urinary and biliary routes.

INTRODUCTION

Drug clearance is the subject of pharmacokinetics, in which the waste products of drug metabolism are eliminated from the body (Goodman et al., 2012). The elimination of a drug is a crucial process in pharmacokinetics, referring to its irreversible removal from the body through metabolism and excretion. Metabolism, which encompasses the processes of anabolism and catabolism, involves the enzymatic conversion of substances within the body, while excretion deals with the exit of drugs or their metabolites from the body. Thus, the main routes of excretion are the kidneys, the hepatobiliary system and the lungs, with the renal route being the most predominant. Thus, most drugs are excreted in the urine, either unchanged or as polar metabolites. In addition, lipophilic substances, which are not eliminated efficiently by the kidneys, undergo metabolism in the liver by the cytochrome P450 system, becoming more polar and facilitating renal excretion (Di Giulio et al, 2018).

Urinary elimination, predominantly for polar drugs or their metabolites, stands out as the main route of excretion. In contrast, biliary elimination is important for lipophilic substances, which are excreted in the bile and can be reabsorbed in the intestine (Goodman et al., 2012). For polar or gaseous agents, such as general anesthetics, pulmonary elimination is particularly relevant. In addition, small amounts of some drugs are excreted in breast milk or sweat, with elimination through milk being especially important due to the potential effects on the infant. Renal clearance, which quantifies the elimination of drugs by the kidneys, varies widely between different drugs and involves processes of glomerular filtration, active tubular secretion and passive reabsorption (Rang et al., 2020).

The choice to work on the subject of drug elimination and excretion is justified by its importance in clinical practice and in the development of new therapies. Understanding these processes is essential to optimize the efficacy and safety of drug treatments, especially in patients with impaired renal or hepatic function, and to avoid toxicity caused by the accumulation of drugs in the body. The overall aim of this chapter is to provide a detailed understanding of the mechanisms of drug elimination and excretion, highlighting the importance of drug clearance processes via the urinary and biliary routes. By exploring these pathways and the factors that influence drug elimination, we aim to provide a solid basis for the practical application of these concepts in the optimization of pharmacological therapy, contributing to a more effective and safer medical practice.

LITERATURE REVIEW

DEPURATION

After the various reactions already discussed in previous chapters, such as redox reactions, conjugation and hydrolysis, the drugs undergo an increase in aqueous affinity, becoming more hydrophilic substances, which facilitates their excretion.

In this way, it is possible to understand the mechanisms associated with their elimination, which preferably occurs through renal and biliary excretion. On the other hand, it is worth noting that many drugs ingested orally

are not completely absorbed in the gastrointestinal tract and, consequently, this unabsorbed residue is eliminated through fecal excretion (Whalen et al., 2016).

RENAL EXCRETION

Renal elimination is the most important mechanism for eliminating drugs and their metabolites. Considering this aspect, it is notorious that patients with renal dysfunction may have difficulties excreting these substances, making them more susceptible to the risk of accumulating in the body and presenting greater adverse effects (Golan et al., 2014).

Given this route of clearance and understanding that the chemical constitution of the final product of urine is mostly composed of water, it is clear that the easiest way to eliminate any drug in this route is for it to have polar characteristics. This physicochemical characteristic can be obtained, for example, from phase I and phase II reactions in the liver (Whalen et al., 2016).

Thus, after a series of metabolic reactions, the free drug enters the **glomerular filtrate**, passes through Bowman's capsule, followed by **active tubular secretion** of the drug in the proximal **tubule**. It then travels through the loop of Henle, reaches the distal tubule and two things can happen (Goodman et al., 2012):

- The first is the **reabsorption** of non-ionized (more fat-soluble) drugs that have been concentrated inside the lumen, in higher concentrations than the perivascular space (Rang et al., 2020);
- Second, is the sequence of ionizable species (more water-soluble) from the distal tubule to the collecting tubule, which are stored together with urine in the bladder, until fine ejection (Rang et al., 2020).

Figure 1 (Servier Medical Art) shows a representation of the filtration process until it reaches the collecting tube.

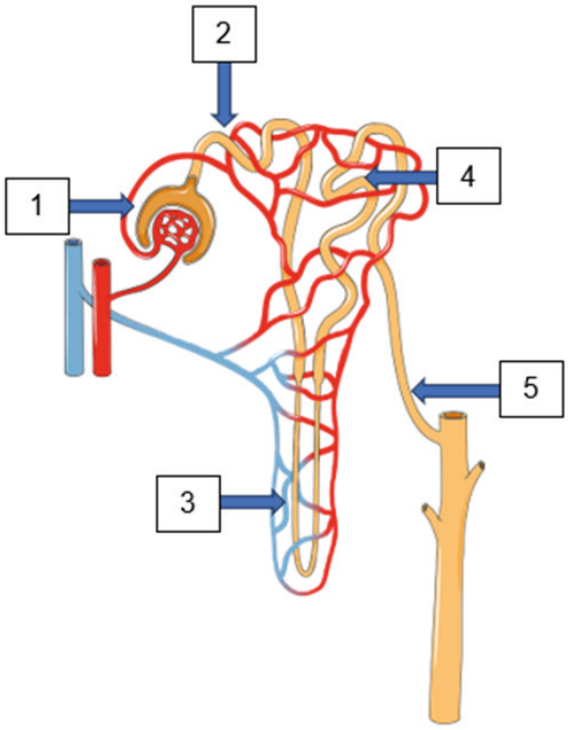

Figure 1 - Elimination of drugs by the kidneys.

Source: Servier Medical Art

The drugs reach the kidneys via the renal arteries, which divide to form the glomerular capillary plexus. The free drug diffuses through the capillary clefts into Bowman's space as part of the glomerular filtrate. Drugs that have not been transferred to the glomerular filtrate leave the glomeruli (1) via the efferent arterioles, secretion occurring primarily in the proximal tubules (2). As the drug moves through the loop of Henle (3) towards the distal convoluted tubule (4), its concentration increases and exceeds that of the perivascular space. Neutral drugs diffuse out of the lumen and return to the systemic circulation. It then travels through the collecting duct (5), passing through the ureter and into the bladder, to be eliminated later.

Renal elimination can be quantified by renal clearance (CL_{ren}). This is defined as the volume of plasma containing the concentration of the substance removed by the kidneys in a given time interval. This is quantified using the following equation (Guyton et al., 2021):

$$CL_{ren} = \frac{C_u \times V_u}{C_p}$$

Where C_u corresponds to the urinary concentration; V_u is the urinary flow velocity and C_p is the plasma concentration (Rang et al., 2020). With this in mind, it is important to note that CL_{ren} can vary greatly, from 1 mL/min to the theoretical maximum value given by renal flow, which is around 700 mL/min (Guyton et al., 2021).

In addition, knowledge of drug clearance mechanisms is of paramount importance in the clinical sphere. This is because in some cases of intoxication, some devices related to drug excretion are adopted by health professionals in order to reverse the intoxication. An example of this is the alkalinization of urine in order to eliminate phenobarbital, which was only possible due to knowledge of the physical-chemical aspects involved in these processes (Silva et al., 2021).

As already mentioned, the elimination of drugs by the kidneys in the urine involves the processes of *glomerular filtration*, *proximal tubular secretion* and *tubular reabsorption*. We will briefly discuss these stages below.

GLOMERULAR FILTRATION

Drugs reach the kidneys from the renal arteries, which subdivide to form the glomerular capillary plexus. These, in turn, allow drug molecules with a molecular weight of less than 20,000 Da to diffuse into the glomerular filtrate. In addition, it is crucial to understand that this structure is practically impermeable to plasma albumin, i.e. considering drugs bound to this protein, only those in free form will be filtered under physiological conditions (Golan et al., 2014).

The next step is the diffusion of the above molecules into Bowman's space. The speed of the glomerular filtrate on average corresponds to 125 mL/min, although this can vary in pathophysiological situations. It is also important to note that liposolubility and pH do not influence the passage of drugs into the glomerular filtrate (Golan et al., 2014).

TUBULAR SECRETION

Tubular secretion represents the main route of elimination, whereby approximately 80% of the drug is directed through these tubules, interacting with a specific transporter mechanism. In this way, substances that have not been transported to the glomerular filtrate leave the system from the efferent arterioles, which subdivide to form a capillary plexus close to the lumen in the proximal tubule (Rang et al., 2020).

The two main mechanisms involved in this energy-intensive transport are: anion transport channels (responsible for transporting deprotonated species from weak acids) and cation transport channels (responsible for transporting deprotonated species from weak bases). Each of these systems can transport numerous different molecules, as there are no specificities. On the other hand, competition can occur between different chemical species for the transporters in each of the systems. An example that can be cited here is the use of **probenecid**, developed to potentiate **penicillin** by delaying its tubular secretion fraction. However, in some cases, this relationship can be harmful, resulting in the rapid excretion of a drug and, consequently, reducing its therapeutic effect (Rang et al., 2020).

EFFECTS OF DRUGS ON RENAL TUBULAR SECRETION

According to Rang (2020), it is important to address the effects of some drugs on renal tubular secretion, highlighting their mechanisms of action and clinical implications:

Acetazolamide

Acetazolamide is a diuretic that inhibits carbonic anhydrase, increasing the renal excretion of bicarbonate and sodium. Around 90% is eliminated by active tubular secretion and passive reabsorption in the renal tubules.

Dofetilide

Dofetilide, an antiarrhythmic, is excreted mainly through the urine, via active tubular secretion. Due to the risk of proarrhythmias, its use requires hospital monitoring, avoiding drugs that inhibit its tubular secretion.

Niacin

Niacin, used to treat dyslipidemia, can cause skin flushing, itching, nausea and abdominal pain. It also inhibits the tubular secretion of uric acid, increasing the risk of hyperuricemia and gout.

Probenecid

This uricosuric blocks the reabsorption of uric acid in the renal tubules and the tubular secretion of penicillins, increasing their serum levels. It requires dose adjustment in patients with impaired renal function.

Adefovir Dipivoxila

Excreted in the urine, this antiviral used in hepatitis B can cause nephrotoxicity, especially in patients with renal dysfunction. Concomitant use with tenofovir should be avoided due to competition for tubular secretion. These examples highlight the importance of understanding the processes of renal elimination of drugs and their clinical implications. This knowledge is essential for safe and effective drug therapy.

TUBULAR REABSORPTION

Throughout the filtration process as a whole, a large part of the filtrate is reabsorbed, generating on average only 1 mL of urine for every 100 mL of filtrate formed. Thus, if the tubule is freely permeable to neutral or apolar drug molecules, a large part of the filtered drug will be passively absorbed in favor of the resulting concentration gradient. Polar drugs, on the other hand, will concentrate as water is reabsorbed and they are eliminated (Goodman et al., 2012).

Furthermore, this is the region in which the process of acidification or alkalinization of the urine is important in affecting the degree of elimination of a drug. Thus, by reducing the pH of the urine formed, weak alkaline drugs are ionized, i.e. the balance of their structure shifts towards the ionized form, which results in greater polarity and consequently increases their concentration in the urine. The same also applies to raising the pH of urine to facilitate the clearance of acidic drugs by the same mechanism (Rang et al., 2020).

On the other hand, lowering the pH for acidic drugs and raising the pH for alkaline drugs leads to a shift to the non-ionizable form, which facilitates the permeability of these species due to their lipophilic nature (Rang et al., 2020).

Drugs can modulate tubular reabsorption in various ways. Some substances can increase the reabsorption of certain solutes, while others can inhibit or block this process, resulting in increased excretion in the urine (GOLAN, et al., 2014).

The ability of drugs to affect tubular reabsorption has a direct impact on the renal excretion of these substances. Drugs that promote tubular reabsorption can increase the plasma concentration of the drug and prolong its half-life, while those that inhibit tubular reabsorption can accelerate the elimination of the drug through the urine (Golan et al., 2014).

EXCRETION BY OTHER ROUTES

Not all drugs are eliminated by the renal route, especially lipophilic drugs that do not undergo adequate metabolization. Examples include steroid hormones, digoxin and some chemotherapeutic agents, which are largely excreted via the bile (Rang et al., 2020).

In these cases, the drug or its metabolite is incorporated into the bile salts, which in turn are sent to the duodenum via the bile duct, passing through the entire length of the gastrointestinal tract. However, these chemical substances are often reabsorbed and taken to the liver again, where they are deconjugated once more, followed by a new conjugation and, once again, eliminated along with the bile salts. It is estimated that a small percentage of these drugs, when they reach the intestine, are eliminated in the feces, while the largest percentage of them return to the circulation (Golan, et al., 2014). Consequently, they are retained in the portal circulation and then in the systemic circulation until they are eliminated again. This means that their duration of action is much longer than that of hydrophilic drugs. An example of this is contraceptives, which are highly lipophilic and are metabolized at slow rates by the liver, resulting in their systemic circulation for a prolonged period of time (Rang et al., 2020).

In addition to these pathways, the lungs are also involved in the elimination of some drugs, such as inhaled anesthetics. In these cases, some factors are important in relation to the clearance of these drugs, such as: ventilation intensity; solubility in plasma and vapor tension (Lisboa, 2016). These processes are possible due to the difference in partial pressure, i.e. when the gas has high pressure in the plasma and lower in the alveolus, it will migrate from the capillary to the alveoli and thus be eliminated via the airway (Faria, et al., 2021).

Breast milk can also secrete some drugs, which justifies caution when prescribing medication to breastfeeding women. Other routes, to a lesser extent, may also be involved in drug clearance, such as sweat and tears (Whalen, et al., 2016).

Another way in which the human body eliminates some drugs is through dermal excretion. In this case, through sweat, the skin can become an outlet for the clearance of xenobiotics, albeit in small quantities (Goodman et al., 2012). However, considering the forensic aspect, this elimination has high reservations, given its importance related to toxicology (Federico et al., 2017).

FINAL CONSIDERATIONS

The aim of this chapter was to discuss drug excretion from a pharmacological point of view, highlighting the importance of the renal and biliary pathways, with an emphasis on renal excretion, which is predominant for most drugs. Knowledge of glomerular filtration, tubular secretion and reabsorption is essential for understanding how drugs are eliminated and avoiding toxicity in patients with renal or hepatic dysfunction. In this way, these precepts are of important value within medical therapy, since they play a crucial role in the pharmacokinetics and therapeutic efficacy of drugs.

Understanding the renal and biliary elimination pathways, as well as the influence of various factors such as urinary pH and tubular reabsorption, is essential to ensure the safety of drug treatment. It is important to consider the individuality of each patient, especially those with impaired renal or hepatic function, in order to avoid toxicity and maximize the therapeutic benefits of drugs. In short, the study of drug excretion is essential for more effective and safer clinical practice.

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