Pharmacokinetic-Pharmacodynamic Modeling of Xenobiotics: Fate and Effect in Aquatic Animals

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1 Introduction

Twenty-first century has so far witnessed an evolution in every sphere of human existence, science, and technology not lagging behind. However, there is a drastic increase in the outbreak of diseases which need proper treatment using appropriate medicines. The aquatic animals have unfortunately become more prone to the diseases and infectious agents due to the pollution. Therefore, it is very important to understand the working mechanisms of available medicines and treatments.

Pharmacokinetics is the branch of medicine which describes the role of absorption of medicine by the body, its distribution throughout the body, and elimination of this medicine from the body of the organisms. On the other hand, how much drug should be given, what is the efficiency of the drug, and for how long does the selected drug remain in the tissue or targeted site are defined as pharmacodynamics (Hoberman et al. 1996). In simple words, the route of the drug throughout the body is termed as pharmacokinetics, while the efficiency of that drug and its impact on the body is termed as pharmacodynamics. The recent research conducted worldwide in the field of drugs has made it of extreme importance to understand the interrelationship and interdependence of pharmacokinetics and pharmacodynamics of drugs. The accurate understanding of pharmacokinetic-pharmacodynamic relationship of drugs will help to predict the efficiency and efficacy of the drugs.

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M. A. Rather et al. (eds.), *Xenobiotics in Aquatic Animals*,
https://doi.org/10.1007/978-981-99-1214-8_12

Fish being the aquatic animals are cold-blooded in nature which makes them highly susceptible to infections and various diseases. Various pathogens have been reported in fish as bacterial, viral, fungal, protozoans, etc. (Hanief et al. 2021; Rather et al. 2018). All these pathogens have to be treated with different drugs; however, the overall working of the drugs remains somewhat similar. Certain substances termed as xenobiotics have also been reported from aquatic animals. Xenobiotics can be defined as those chemical substances which are present in the body of an organism beyond the normal level. The abnormal levels of these chemicals disrupt the normal metabolic activities and itself become toxic. With respect to the aquatic animals, these xenobiotics have been found to disrupt the normal metabolic activities as development of reproductive organs, gamete formations, hormonal and endocrine disruption, and viability of eggs (Tyrpenou et al. 2003; Pokhrel et al. 2018). The main reason for so much xenobiotic accumulation in aquatic animals can be directly pointed toward the increasing effects of pollution, agricultural runoff, disposal of harmful heavy metals and chemical from various industries, and untreated sewage or partially treated sewage disposed from sewage treatment plants.

2 Pharmacokinetics of Drugs in Aquatic Animals

The drug after administration follows a route of travelling before reaching to its targeted area or site. The steps are as follows:

2.1 Absorption of Drugs

Absorption of drugs can be defined as the movement of drug from the site of administration into the bloodstream. The entry of drug in bloodstream facilitates its flow throughout the body and ultimately will reach to its targeted site. Majority of the administered drugs follow the route of passive transportation. Passive transportation of drugs is also known as the "downhill movement" of the drugs. The flow of administered drugs occurs via cell membranes of the cells. This method works on the principle of concentration gradient.

The major advantages of passive transportation of drugs are that it doesn't require any energy as the flow is across cell membranes. There is no use of any carriers and furthermore no threat of any competitive inhibition.

However, some drugs get absorbed in the bloodstream through active transportation. The term active transportation means that the involvement of certain mediators is required. Hence, this method involves the use of energy also (Tyrpenou et al. 2003). In active transportation, the flow of drugs can be against the concentration gradient as it involves the use of solutes (carriers). The active transportation of drugs can take place through two ways:

2.1.1 Transportation of Drugs

Primary active transportation of drugs: The energy required for drug transportation is derived from the ATP present in the cells.

Secondary active transportation of drugs: The energy required for drug transportation is derived from energy stored as ion gradients as Na^+ and K^+ which are generated during primary active transportation.

2.1.2 Factors Affecting Absorption of Drugs

The absorption of drugs into the body of aquatic animals particularly fish is dependent on various factors as molecular weight of the drug, solubility of lipids, polarity of the drugs within the bloodstream, the reaction of the targeted tissue when the drug comes in contact with it, and the time period within which it shows the required effect.

2.1.3 Route of Drug Administration in Fish

Administration of drugs in fish is usually done through oral cavity (drug administered in pelleted form or mixed with feed), muscle injection (intramuscular), or intravenously (Samuelsen 2006). Intramuscular drug or Intra- venous drug administration is more efficient and result oriented compared to the oral administration. However, intramuscular administration of drugs is not much convenient in aquatic animals.

2.2 Distribution of Drugs

When the drug enters to the targeted site from the bloodstream, it is termed as the distribution of the drug. The transfer of drug from blood to the targeted tissue continues till an equilibrium is achieved. The distribution of drugs depends on several factors as the ionization of the solute molecules, lipid solubility of the drugs, and the binding efficiency of the drugs with the targeted tissues.

2.3 Metabolism of Drugs

The metabolism of drugs can be defined as the biotransformation of drugs from nonpolar lipid-soluble compounds to polar lipid-soluble compounds. The aim of biotransformation of drugs is to prevent the reabsorption of drugs by excretory

system so to prevent excretion of the drug with metabolic wastes (Craig and Andes 1996). The biotransformation of drugs also helps to protect the body from accumulation of toxic wastes or xenobiotics.

The biotransformation of drugs is a complex phenomenon. It takes place in several gradual steps, each step aiming in converting the simpler metabolite. The biotransformation of drugs is broadly categorized in two phases, which are as follows:

Phase I: In Phase I, administered drug is subjected to various reactions as oxidation, reduction, hydrolysis, etc. During this phase, the reactions help in activating the drug. Oxidation is the most important reaction in Phase I as it involves using Cytochrome 450 monooxygenase (CYP), NADPH, and oxygen	**Phase II**: In Phase II, glucuronidation of activated drugs from Phase I takes place which helps in generating a conjugated product of the administered drug

The factors which play an important role in the biotransformation of drugs are the exposure to the pollutants and chemicals, the age of the aquatic animals, the habitat, the strength of the immune system, etc. In the overall process of pharmacokinetics, biotransformation plays a key role as it determines the ultimate use of the administered drug.

2.4 Excretion of the Drug

The excretion of the drug helps in eliminating the left-out drug from the body. The excretion of drug holds an important place as it helps in preventing the buildup of toxic substances. The major organs associated with excretion involve the liver and kidney.

The excretion which takes place under the influence of the liver is termed as "hepatic excretion." Liver accomplishes the process of excretion by throwing away the unwanted substances along with bile juices. Hepatic excretion is easily facilitated when the metabolic wastes are in the conjugated form with glucuronic acid.

Renal excretion takes place in kidneys. It is easier to excrete the hydrophilic and lipophilic compounds from the body of the aquatic organisms. The excretion in the kidney takes place in the following steps:

2.4.1 Filtration Mechanism (Steps)

Glomerulus filtration: In glomerulus filtration, the excretion of all the hydrophilic and lipophilic substances takes place. The filtration takes place in the glomerulus part of kidneys. All the drugs which do not have any protein component in them

are easily filtered in glomerulus filtration, but drugs with protein presence are not filtered here.

Tubular reabsorption: The excretion of the lipid-insoluble drugs takes place in tubular reabsorption.

Tubular secretion: In this part of excretion, the dissociation of the remaining drug takes place from the bloodstream. The dissociation breaks down the complex drug components into simpler forms which facilitate excretion.

3 Pharmacodynamics of Drugs in Aquatic Animals

The role which a drug plays in the body of an organism or in other words what does a drug do in the body is explained by pharmacodynamics. Pharmacodynamics provides a deeper understanding of what will be the efficiency of the administered drug. The mechanism of pharmacodynamics is well explained by *Clarke* in his *receptor occupation theory* in *1937*.

According to this theory, every drug has a certain number of receptors which are occupied by it during its course of action. The intensity of the effect of the drug is directly proportional to the number of receptors it occupies. The more the receptor, the more the action. Whenever the drug binds itself to a specific receptor, the binding brings in certain structural changes in the framework of the receptor (Maiti et al. 2019). Those drugs which can positively change the structure of the receptor are said to have agonistic effect on the receptor, while those drugs which fail to bring the requisite changes in the receptor are said to have antagonistic effect. After binding itself to the receptor, the pronounced action begins to come into play. This is called as the *action-effect sequence*.

Furthermore, the intensity of the effect also is determined by the concentration of the drug administered. The more the concentration, the more will be the affect and vice versa. This is called as the "*dose-response relationship*." Dose-response relationship plays an important role in determining the fate of pharmacodynamics of the drug or any xenobiotic.

3.1 Drug Dosage

The amount of drug required to generate a specific impact is called as its dosage. The specific concentration of a selected drug can provide the desired results. Therefore, it is very important to determine the exact amount of concentration that should be administered which is known as the dosage of the drug.

Drug dosage can be of the following types:

Standard dose: The concentration of the dug which is almost similar for all the population of the specific organisms.

Regulated dose: The concentration of the drug is measured or determined by frequent administrations in the specific set of targeted species in order to obtain a standard value.

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