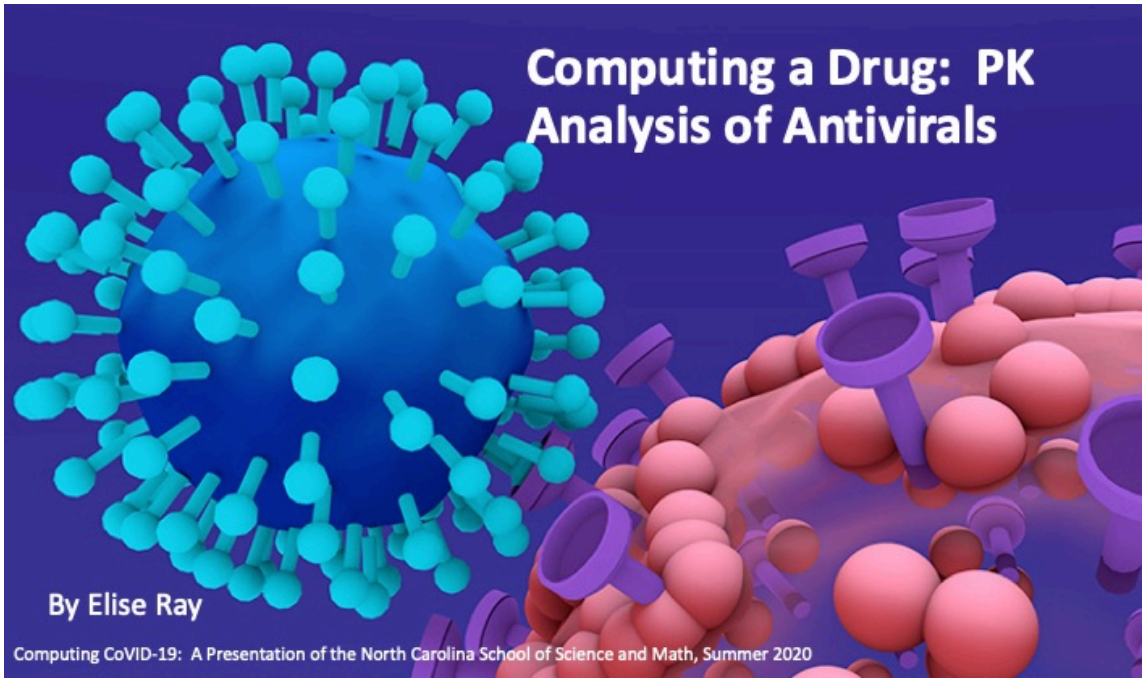

Computing CoVID-19: Summer 2020

Computing the Drug:

PK Analysis of Antivirals

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Introduction

Pharmacokinetics (PK) is the study of what the body does to a drug and is focused largely on the body's role with xenobiotics rather than the intended purpose of the drug; it is often characterized by a variety of parameters regarding ADME(T): absorption, distribution, metabolism, elimination/excretion, toxicity. When considering the body's role with drugs, it is important to examine multiple factors, including drug solubility, bioavailability (the amount of drug that is available/in circulation), etc. In order for a drug to be administered most efficiently, numerous absorption parameters are evaluated in order to determine the best route of administration.

1.1 Absorption

In order for a drug to have a therapeutic effect on an individual, it is essential for that drug to first enter the body. This process can be conducted using numerous methods, including a topical application, intravenous administration, intramuscular administration, etc.

When examining the antivirals in this lab, oral administration will be closely examined, therefore allowing us to use Lipinski's Rules. Lipinski, a physical organic chemist at Pfizer, developed a series of parameters that serve to evaluate how well a drug will be absorbed through oral methods; these parameters include:

- Molecular weight less than 500 grams/mole
- Number of hydrogen donors less than 5
- Number of hydrogen acceptors less than 10
- Computed logP value (partition coefficient*) less than 5

* The partition coefficient measures the ability of a drug to cross through a cell membrane.

1.2 Distribution

Once the drug is absorbed into the body, the drug's chemical structure and properties play a crucial role in determining the drug's movement throughout the system; based on the tissue type at hand, drugs can enter different organs and reside in different tissues, which greatly aids in the therapeutic effect of many xenobiotics. When evaluating the distribution of a drug, it is important to keep in mind the volume of distribution, which measures the volume of distribution per kilogram of body weight (i.e. overall concentration of the drug in the bloodstream).

1.3 Metabolism and Excretion/Elimination

Once a drug enters the bloodstream, metabolism will typically occur in the liver, once the drug reaches that tissue; through first-pass metabolism, the drug will be metabolized into metabolites, small molecules created from breaking down the drug. For prodrugs, it is essential that metabolism occurs, as the metabolites themselves have a therapeutic benefit, not the original drug. In order for this important process to occur, various enzymes are needed, many of which are a part of the Cytochrome P450 (CYP450) enzyme family.

1.4 Toxicity

As all drugs are foreign entities to the body, they are by definition poisonous or toxic. All drugs have a number of properties that aren't ideal for the body, and many may even cause adverse effects. However, when these drugs are prescribed, it is due to the extent of the positive effects that outweigh the negative effects of the drug. As toxicity is evaluated in pharmacokinetics, there are two common terms that need to be well understood:

- Effective Dose (ED50): The dosage at which fifty percent of a group of test animals show improvement from a drug.
- Lethal Dose(LD50): The dosage at which fifty percent of a group of test animals die or show adverse effects.

1.5 Antivirals

The antiviral class of drugs describes a type of medication that reduces the capacity for viruses to replicate, therefore preventing widespread illness from afflicting a patient's body. Antivirals as a whole have been responsible for greatly increasing the quality of life for many people; not only have antivirals allowed for societies to progress in terms of development, but they have

also assisted in preventing deaths in third world countries that still struggle to treat illnesses like the flu or measles. Within this lab, nine antivirals will be analyzed:

- Chloroquine
- Hydroxychloroquine
- Colchicine
- Remdesivir
- Darunivir
- Favipiravir
- Oseltamivir
- EID0-2801 (an experimental drug currently in clinical trials for CoVID-19)
- Galidesivir

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Student Activity

2.1 Part 1 – Lipinski Rule Of Five Analysis

In order to establish that a drug is suitable for oral consumption, it is important that the Lipinski Rule of Five parameters are measured; luckily, StarDrop provides a very simplistic method to examine the Lipinski Rule of Five.

Once the nine antivirals are uploaded into StarDrop, select the Lipinski Rule of Five parameters (listed under the category "Scoring"). Feel free to examine additional scoring profiles, such as "Intravenous CNS Scoring Profile." Once the results have been calculated (i.e. once you have pressed the arrow), analyze the number that is given for each antiviral. The higher the number (answers range from 0 to 1), the more parameters that are met.

2.1.1 Questions

1. What is the Lipinski Rule of Five value for each of the nine antivirals?
2. What is the Intravenous CNS Scoring profile value for each of the nine antivirals?
3. Which method is best for the nine antivirals (in general)? Oral introduction, or an intravenous (CNS) introduction?

2.2 Part 2 – PK Analysis

When beginning to evaluate the pharmacokinetics based analysis of the nine antiviral drugs, it is important to keep in mind the factors that impact the absorption, distribution, metabolism, excretion/elimination, and the toxicity of the drugs. Keeping these ADME(T) properties in mind, some of the following models should be used in StarDrop (refer to the following website for additional information on these models: http://www.asteris-app.com/technical-info/adme-properties.htm)

- logD
- logS
- logS@7.4
- BBB log ([brain]:[blood])
- hERG plC50
- 2C9 pKi
- HIA Category
- BBB Category
- P-gp Category
- 2D6 Affinity Category
- PPB90 Category

In order to analyze the nine antivirals based upon these categories, go to StarDrop and select the desired parameters; once the parameters are selected, run the calculations using the arrow!

Once you have completed the runs, answer the questions on the Canvas lab quiz "Day 7 Lab 1: Computing the Antivirals".

References

[1] Gotwals, R. R. (2009). Intro to ADME(T).

[2] StarDrop ADME Properties. (2020). Retrieved from http://www.asteris-app.com/technical-info/adme-properties.htm

[3] Doogue, M. P., Polasek, T. M. (2013, February). The ABCD of clinical pharmacokinetics. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4110820/