Physiologically-based pharmacokinetic modeling for predicting drug-drug interactions

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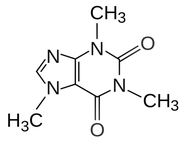
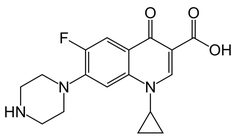
Abstract

Dynamics of interactions between the drugs caffeine and ciprofloxacin are predicted using physiologically-based pharmacokinetic (PBPK) modeling. *Pharmacokinetic* means the model determines where the drugs are distributed in the body over time. *Physiologically-based* means the anatomy and physiology of the human body is reflected in the structure and functioning of the model. Multiple drugs can interact to increase or decrease their beneficial and/or undesired effects. This is important because some common substances, such as caffeine in coffee and soft drinks, are actually drugs that affect the body. By implementing the model as a computer program, it is relatively straightforward to perform "experiments" that would be too costly, time-consuming, or even unethical, if done on humans.

Drugs included in the model



Caffeine is a common psychoactive stimulant found in coffee, tea, soft drinks, and energy drinks. Ciprofloxacin slows the rate at which the body eliminates caffeine.[1]



Ciprofloxacin is an antimicrobial used to treat bacterial infections by inhibiting DNA and protein synthesis.[2] It is also used by the military to protect against anthrax, a biological weapon.

References

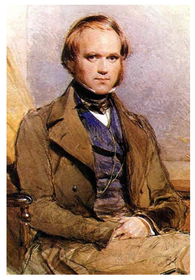
[1] Healy DP, Polk RE, Kanawati L, Rock DT, Mooney ML. Interaction between oral ciprofloxacin and caffeine in normal volunteers. *Antimicrob Agents Chemother*. 1989 Apr;33(4):474-8.
[2] LeBel M. Ciprofloxacin: chemistry, mechanism of action, resistance, antimicrobial spectrum, pharmacokinetics, clinical trials, and adverse reactions. *Pharmacotherapy*. 1988;8(1):3-33.
[3] Ginsberg G, Hattis D, Russ A, Sonawane B. Physiologically based pharmacokinetic (PBPK) modeling of caffeine and theophylline in neonates and adults: implications for assessing children's risks from environmental agents. *J Toxicol Environ Health A*. 2004 Feb 27;67(4):297-329.
[4] Lüpfert C, Reichel A. Development and application of physiologically based pharmacokinetic-modeling tools to support drug discovery. *Chem Biodivers*. 2005 Nov;2(11):1462-86.
[5] Fuhr U, Wolff T, Harder S, Schymanski P, Staib AH. Quinolone inhibition of cytochrome P-450-dependent caffeine metabolism in human liver microsomes. *Drug Metab Dispos*. 1990 Nov-Dec;18(6):1005-10.
Image sources: • Caffeine molecule: http://en.wikipedia.org/wiki/Caffeine • Ciprofloxacin molecule: http://en.wikipedia.org/wiki/Ciprofloxacin • Darwin, Charles portrait: http://en.wikipedia.org/wiki/Charles_Darwin • Earth globe: http://en.wikipedia.org/wiki/Globe • Earth from space: http://www.nasa.gov/multimedia/imagegallery/image_feature_1925.html • PBPK block diagram: http://www.flickr.com/photos/justhman/4130774457/ • World map: http://en.wikipedia.org/wiki/World_map

What is a model?

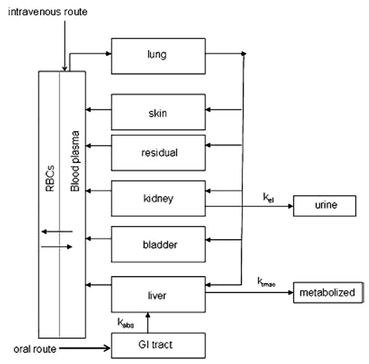
- A *model* is a representation of something.
- A model is designed for a purpose.
- The model abstracts details that are not important for its purpose.
- The model retains, exaggerates, or adds details that are important for its purpose.
- There are usually many different ways to model something.

- A map and a globe are models of the Earth.
- The map adds colors to show different countries.
- The globe exaggerates height to emphasize mountains.
- Neither is the same size as the Earth.
- A map is easy to carry and can be scaled for different purposes.
- A globe can illustrate seasons, day and night, and great circle routes.

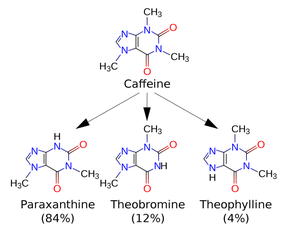
Physiologically-based pharmacokinetic (PBPK) modeling[3]



Example human (Charles Darwin)



Example PBPK model



Example metabolic pathways (caffeine metabolism)

- The block diagram (middle) is an example of how a human (left) can be modeled.
- Organs important for the drugs under study appear as *compartments* (blocks) connected by blood flow (arrows).
- Features not important for the drugs under study are omitted or combined into *other* (e.g., there is no brain).
- The model is described using mathematics (differential equations[4]).

Drugs enter or leave the body:

- Drugs can enter through various portals including intravenous or oral routes.
- Drugs circulate through the body via blood flow, or accumulate in tissue.
- Drugs are eliminated by the kidney (urine), the liver (metabolism), or the lungs.
- Metabolism breaks down drugs using enzymes (see example at right).

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Results

- A PBPK model was implemented for caffeine and ciprofloxacin using the *Mathematica* program.
- Figures 1 and 2 show the concentrations of the drugs in each of the compartments of the model. The different characteristics of each compartment result in different drug concentrations.

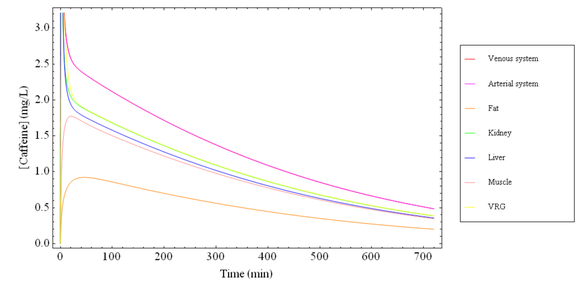

Figure 1: Concentration of caffeine in the model compartments. Initial caffeine dose: 100 mg.

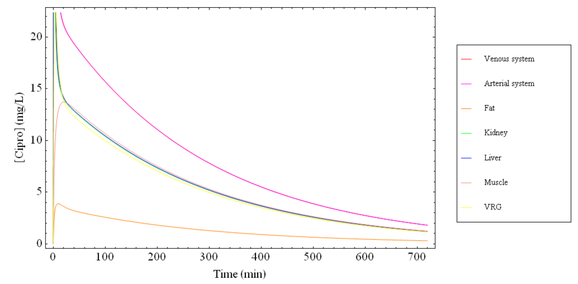

Figure 2: Concentration of ciprofloxacin in the model compartments. Initial ciprofloxacin dose: 750 mg.

- Ciprofloxacin inhibits the CYP1A2 enzyme.
- A model parameter K_I is the dissociation constant of the enzyme-inhibitor complex. A paper by Fuhr et al. provides a value for K_I for ciprofloxacin and CYP1A2: 0.18 mM.[5]
- A paper by Healy et al. gives the results of an experiment where patients were given both caffeine and ciprofloxicin.[1]
- Figure 3 shows that when both drugs are present (blue, green), the level of caffeine is higher than for caffeine alone (black) because ciprofloxacin inhibits CYP1A2 from metabolizing caffeine.
- When Fuhr's value for K_I is used in the model (blue), the value for $t_{1/2}$ for caffeine, the time for the caffeine concentration to reach half the original dose, does not match Healy's experimental results.
- The PBPK model predicts a value of 7.5 μM for K_I based on Healy's experiment (green).

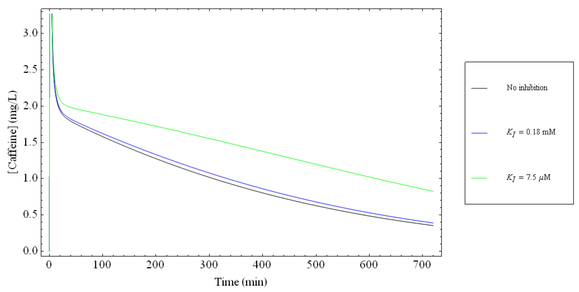

Figure 3: Concentration of caffeine in the liver under different inhibition scenarios. Initial caffeine dose: 100 mg. Initial ciprofloxacin dose: 750 mg.