Concepts in Pharmacokinetics and Pharmacodynamics

Lecture 1

J Tyler Smith

May 14, 2024

Outline

Why do we do this?

Pharmacokinetics (PK) and pharmacodynamics (PD) refer to two complementary halves of a strategy to assess what happens when a dose of drug is given to an individual. Put together, they can be used to create a quantitative strategy for optimizing a dosing strategy with respect to both magnitude of drug given and timing of administration to both achieve a therapeutic response and minimize toxic effects.

Pharmacokinetics and Pharmacodynamics

Pharmacokinetics refers to the quantitative assessment of the concentration of a drug in the body after its administration. *Pharmacodynamics* refers to the action of a concentration of drug that results in some biological response, often therapeutic or toxic.

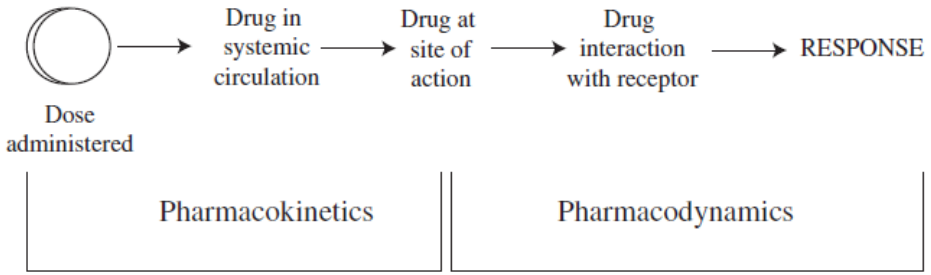

Figure: Rosenbaum, Figure 1.1

Pharmacokinetics

Pharmacokinetics is specifically concerned with the time course of concentration profiles of a drug within body compartments. In practice with models of pharmacokinetics, we look most frequently at the plasma concentration, as it's the most readily measurable site and plasma is the central fluid of receipt and distribution of drugs. Plasma concentration is often a good proxy measure for concentration at a site of action, absent more complex kinetics. We'll denote this concentration as C_p, and the function relating it to dose and time as f_{PK}.

$$C_p = f_{PK}(dose, time)$$

Principles of ADME

Given a drug, there are essentially four things that can happen to it in a body that need can be accounted for in f_{PK}:

- Absorption
- Distribution
- Metabolism
- Excretion

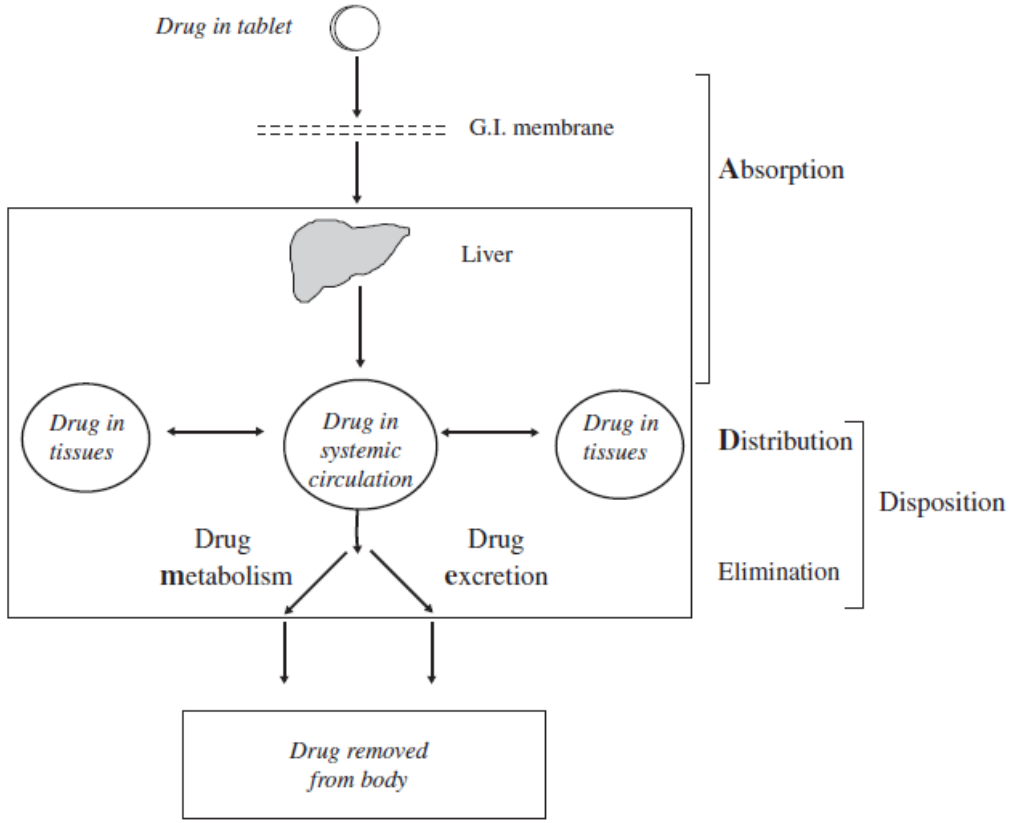

Figure: Rosenbaum, Figure 1.8

Absorption

Absorption is the process by which an agent enters systemic circulation or migrates to the site of activity. It applies most obviously to orally administered agents, being digested and passing through gut tissue, but more generally applies to anything not administered intravenously.

Distribution

Distribution is the process by which an agent concentrates itself through the rest of the body and binds to tissues.

In blood, albumin is a particularly prolific protein, and accounts for most binding in most agents, resulting in terms like fu_b and fu_p (fraction unbound in blood and plasma, resp). When circulating through other tissues in the body, this results in the apparent volume of distribution, V_D.

Distribution obeys the law of mass action; assuming there's endogenous protein P and drug D that bind to form a complex PD, we have the following:

$$[\mathrm{P}] + [\mathrm{D}] \underset{k_2}{\overset{k_1}{\rightleftharpoons}} [\mathrm{PD}]$$

Metabolism

Metabolism is the process by which an agent encounters any of a number of enzymes and becomes a metabolite. This is most commonly a result of the cytochrome P450 superfamily of enzymes, abbreviated CYP. For many drugs, metabolic enzymes are in sufficient excess such that metabolism is linear with respect to the concentration of drug.

In some cases, metabolism is a sufficient endpoint for a pharmacokinetic analysis; in others, we may also be concerned with the metabolites as well.

In some cases, an administered agent may be what's called a *prodrug*, where the administered version is pharmacologically inactive, but a metabolite is pharmacologically active.

Excretion

Excretion is the process by which an agent and its metabolites are removed from the body. The two largest routes are through the liver (via bile ducts) and kidney (via nephrons). More complex physiologically based pharmacokinetic models (PBPKs) deal with these organs in special ways.

Refresher on DE representation

$$[\mathrm{P}] + [\mathrm{D}] \underset{k_2}{\overset{k_1}{\rightleftharpoons}} [\mathrm{PD}]$$

Given this chemical equation for a simple binding reaction, a reminder on how to represent this in terms of differential equations. Suppose each of these species is well-mixed in a single compartment. The governing differential equations for the concentrations at time t are:

$$\begin{aligned}
\frac{d[P](t)}{dt} &= k_2[PD](t) - k_1[P](t)[D](t) \\
\frac{d[D](t)}{dt} &= k_2[PD](t) - k_1[P](t)[D](t) \\
\frac{d[PD](t)}{dt} &= k_1[P](t)[D](t) - k_2[PD](t)
\end{aligned}$$

Refresher on Equilibrium and Association/Dissociation Constants

If the system is at equilibrium, all rates of change are zero. This yields:

$$k_1[P][D] = k_2[PD]$$

So the concentration ratios at equilibrium able to be expressed in terms of the dissociation and association constants (resp. K_d and K_a, which are reciprocals):

$$K_d = \frac{k_2}{k_1} = \frac{[P][D]}{[PD]} \quad \text{or} \quad K_a = \frac{k_1}{k_2} = \frac{[PD]}{[P][D]}$$

If we want an unbound fraction of drug, we want $\frac{[P][D]}{[PD]+[P][D]}$. Divide through by $[P][D]$ and obtain $\frac{1}{1+K_a}$ as an expression for the unbound fraction (at equilibrium) in terms of the reaction rates.

Pharmacodynamics

Pharmacodynamics is concerned with the magnitude of a drug response. Specifically, it seeks to find a relation between the concentration of a drug at its site of action and the onset, intensity, and duration of the response.

If E is an expression for the magnitude of the response to a concentration C, we want:

$$E = f_{PD}(C)$$

Connecting PK and PD

Recalling that the pharmacokinetic relationship seeks to describe the dose and time of dose to concentration, and the pharmacodynamic relationship seeks to describe the concentration at the site of action to the effect of interest, we have the following complete expression for the dose-response relationship:

$$E = f_{PD}\left(f_{PK}(dose, time)\right)$$

Note that this simplification sometimes assumes plasma concentration as a proxy for concentration at the site of activity.

Drug responses

The most typical drug action is through some interaction with a receptor (often a protein).

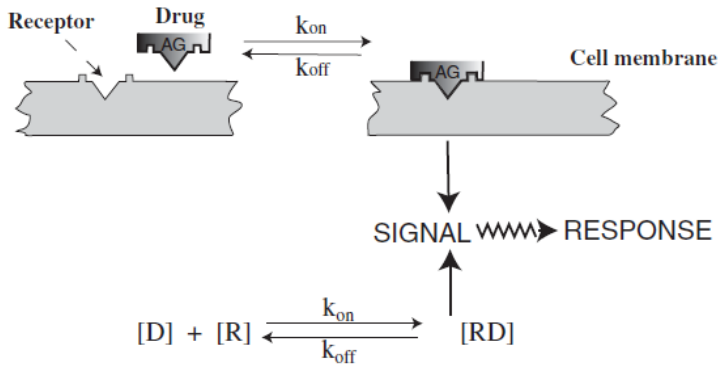

Figure: Rosenbaum, Figure 1.2

Most of the time this is reversible, though in some cases (such as aspirin with cyclooxygenase) the binding is strong enough to persist beyond the lifespan of the receptor.

In many cases, drugs either mimic or antagonize activity of endogenous ligands.

Post-receptor Events

Drugs often act by bringing about some kind of change in the intracellular environment (though some drugs, like antacids, are an exception). This can happen through any of the following:

- Interaction with an ion channel
- Transduction via a G-protein receptor (and through subsequent messengers)
- Stimulation of protein kinases (e.g. tyrosine kinase)
- Direct penetration through the lipophilic membrane or transport through via uptake transporters

Agonists and Antagonists

A drug that is similar enough to the endogenous receptor ligand to activate a receptor is called an *agonist*, and generally mimics the effect of the ligand.
A drug that competes for the receptor site but does not activate it - and instead "blocks" it from an endogenous ligand - is called an *antagonist*.

Concentration Response

At low concentrations, there is typically a linear response between concentration and effect. At higher concentrations, saturation occurs, and response diminishes, until eventually a maximal response is approached as free receptors are no longer available.

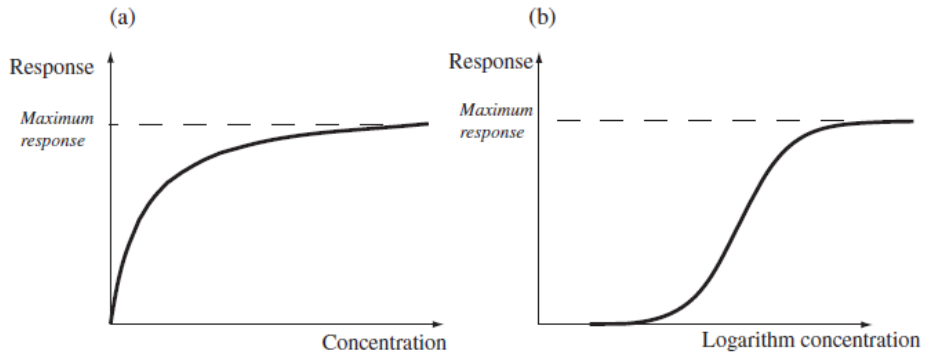

Figure: Rosenbaum, Figure 1.4

Therapeutic Range

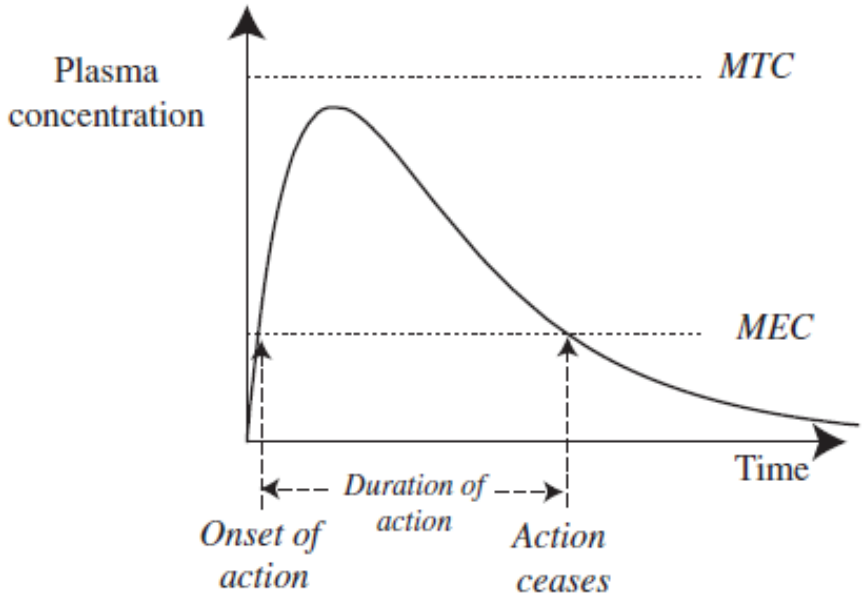

Figure: Rosenbaum, Figure 1.10

In practice, there is typically some level of (plasma) concentration that is the *Minimally Effective Concentration* (MEC) at which we see a therapeutic response, and a *Maximal Tolerated Concentration* (MTC), after which toxicity responses become clinically relevant.

Toxicity Profiles

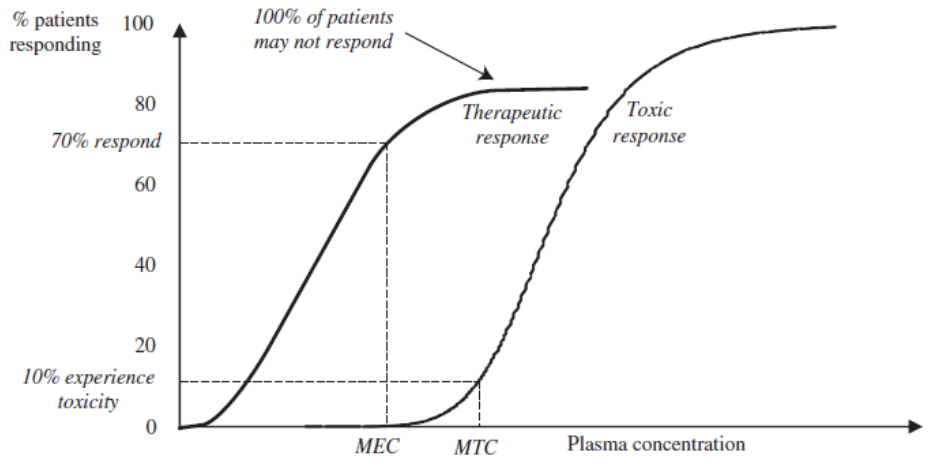

Figure: Rosenbaum, Figure 1.11

A plot from a population study comparing the therapeutic response against the toxicity response can be used in early trials to assess optimal dosing. Here, we see the dose at which 70% of patients respond is below the dose at which any of the sample experiences toxicity.

Limitations of the Therapeutic Range

- Sensitive to selection of study participants. May not generalize to a larger population, where some persons may experience toxicity before the MEC (e.g. liver/renal failure).
- The response in the prev figure is binary, not graded.
- Only applies to plasma concentrations in equilibrium wiht drug concentrations at site of action. More complex PK dynamics require more complex analyses.

Therapeutic Ratio

Analogy: the LD_{50} (usually in animal studies) is the dose per weight at which 50% of animals experience a lethal response to a drug (LD - Lethal Dose). Similarly, we have the TD_{50} and the ED_{50} for the toxic dose and therapeutic/effective dose, respectively - though these are more common in clinical trials. This gives us the Theraputic Index:

$$TI = \frac{TD_{50}}{ED_50}$$

Recap

- *Pharmacokinetics* refers to the concentration profile of drug in tissues after administration. *Pharmacodynamics* refers to the quantitative action of the drug at the site of activity as a function of the local concentration.
- The goal in many studies is to find a pair of approximating functions relating dose to concentration, and concentration to response.
- The therapeutic index relates the concentration at which 50% of patients respond to the drug to the concentration at which 50% of patients experience a toxic effect.