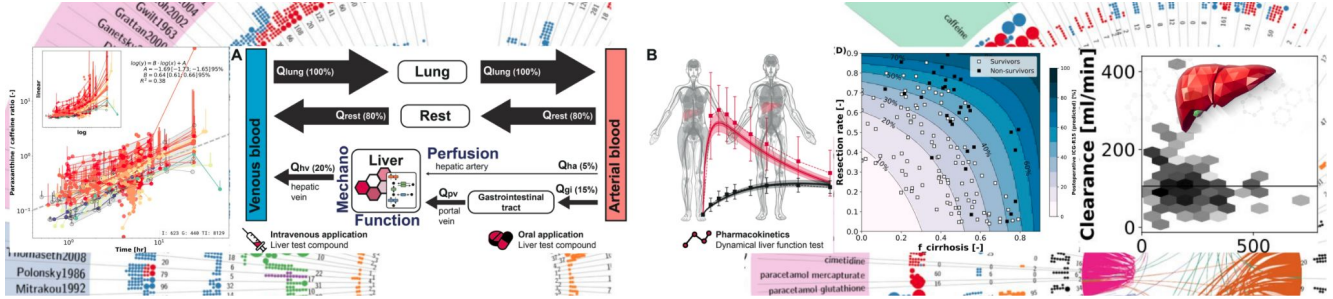

Pharmacokinetics Modeling Course

Pharmacodynamics

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https://livermetabolism.com

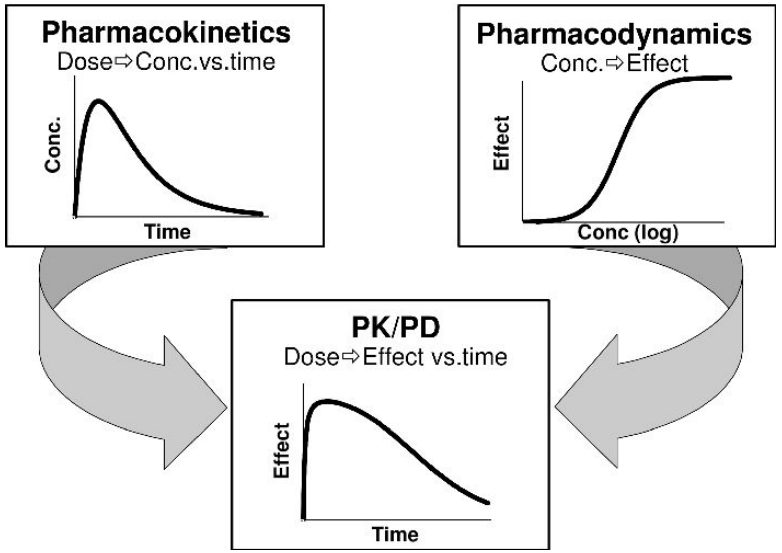
🎯 Teaching Goals

By the end of this section, you should be able to:

1. **Define pharmacodynamics** and understand its role in drug action.
2. **Describe the relationship** between drug concentration and effect.
3. Understand **receptor theory**, including affinity, efficacy, and potency.
4. Introduce **dose-response relationships**, including Emax and EC50.
5. Understand **types of PD models** (e.g., direct effect models, indirect response models, sigmoidal Emax models).
6. Explore **variability in pharmacodynamic response** (e.g., tolerance, sensitization).
7. Learn how **PD models** are used to **predict therapeutic and toxic effects**.
8. Understand the **integration of PK and PD models** to simulate time-course of drug effects.
9. Introduce examples of **PD modeling in drug development and clinical practice**.

Pharmacokinetics (PK) & pharmacodynamics (PD)

- **Pharmacokinetics** is **what the body does to the drug**
  - study of the time course of drug absorption, distribution, metabolism, and excretion
  - **drug disposition**
- **Pharmacodynamics** is **what the drug does to the body**
  - **desired** (and adverse) **effects**



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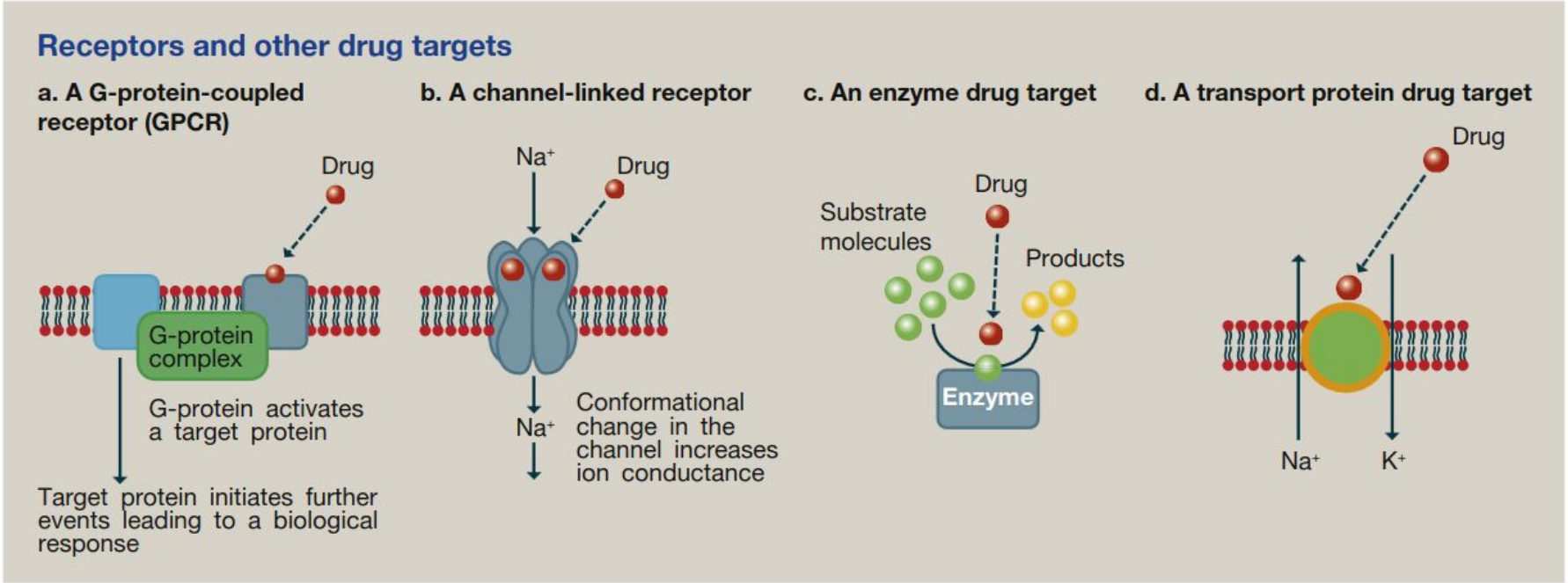
Drug targets

- Drugs interact with components within the body to produce a response
  - proteins (receptors, enzymes)
  - DNA, genes



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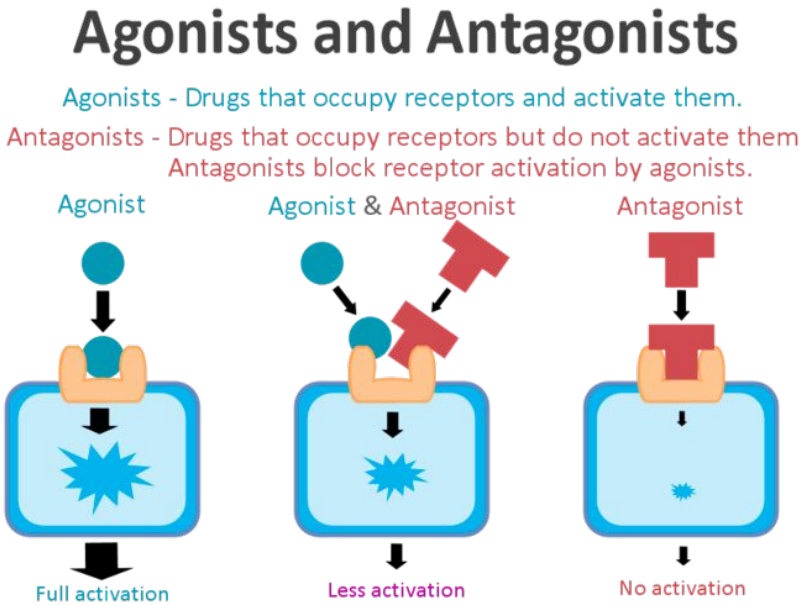
Agonists & Antagonists

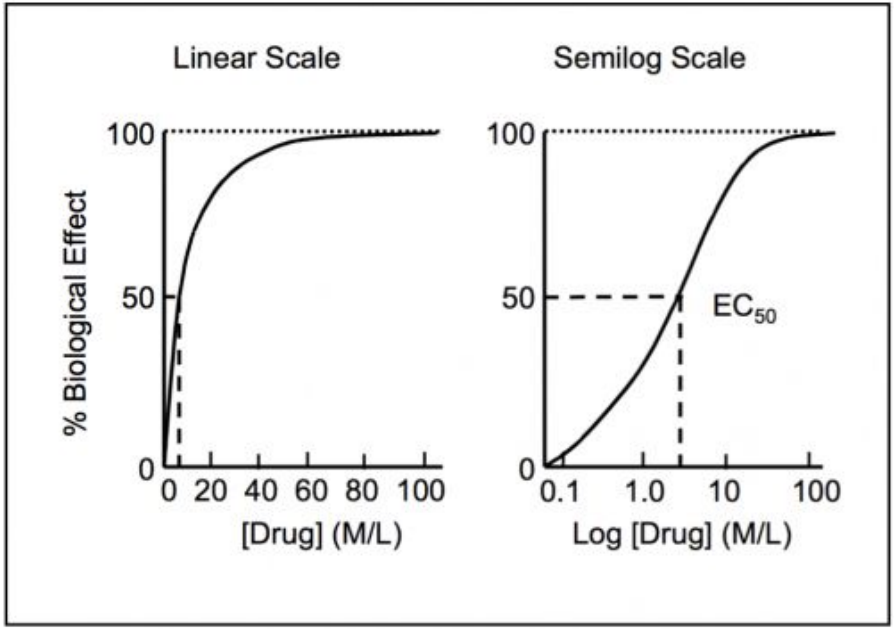
- **agonists:** increase functional response (e.g. receptor); facilitators
- **antagonists**: diminish functional response; inhibitors; blockers
  - **full agonists** or **full antagonists**: produce the maximum possible effect
  - **partial agonists** or **partial antagonists**: compounds that fail to achieve the greatest effect, even at very high concentrations
- **inducers:** increase synthesis (amount)
- **activators:** increase activity
- **inhibitors:** decreasing activity



https://psychonautwiki.org/wiki/Antagonist

Dose-response curve

- relationship between drug dose and biological response
- normally plotted on a logarithmic dose scale, appearing as a sigmoid curve
- **E_{max}**: maximal response
- **EC_{50}**: drug concentration for 50% Emax response
- Dose-response curve can be influenced by:
  - patient specific factors (e.g. age, disease)
  - presence of other drugs that compete for binding at the same receptor (e.g. receptor antagonists)



From time-response to dose response

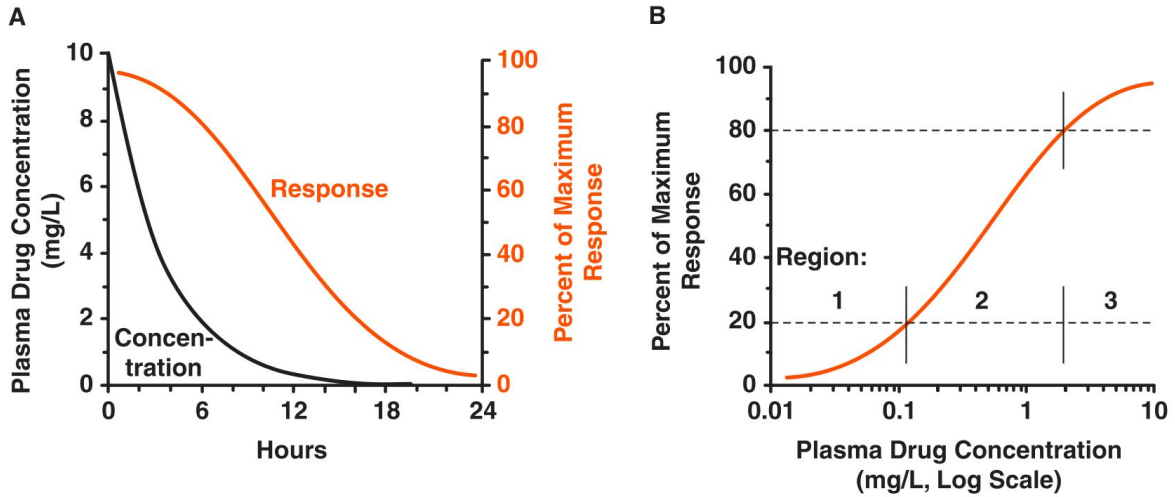


FIGURE 9-6 The decline in the intensity of pharmacologic effect with time (*colored line,* **A**) after a single large intravenous bolus dose of a drug displaying monoexponential decline (*black line,* graph **A**) depends on the region of the concentration–response curve (**B**). Initially, in Region 3, the response remains almost maximal despite a 75% fall in concentration. Thereafter, as long as the concentration is within Region 2, intensity of response declines approximately linearly with time. Only when concentration falls into Region 1 does decline in response parallel that of drug in plasma. The concentration–response relationship is defined by: $E = E_{max} \cdot C^{\gamma}/(C_{50}^{\gamma} + C^{\gamma})$ with $E_{max} = 100\%$, $C_{50} = 0.5$ µg/L, and $\gamma = 1$.

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Potency & Efficacy

- **potency**: The potency of a drug is the amount of a drug required to produce a biological effect (normally expressed as the ED50, the dose required to produce 50% of Emax)
  - binding affinity for the target
  - x-Axis
- **efficacy**: Emax, i.e., maximum effect of the drug. Efficacy of a drug is a measure of its capacity to produce a biological effect.
  - clinical effect of the protein
  - y-Axis
- **desensitization** to drugs is a common phenomenon; when it occurs rapidly it is known as **tachyphylaxis**, and when it occurs more slowly it is known as **tolerance**.

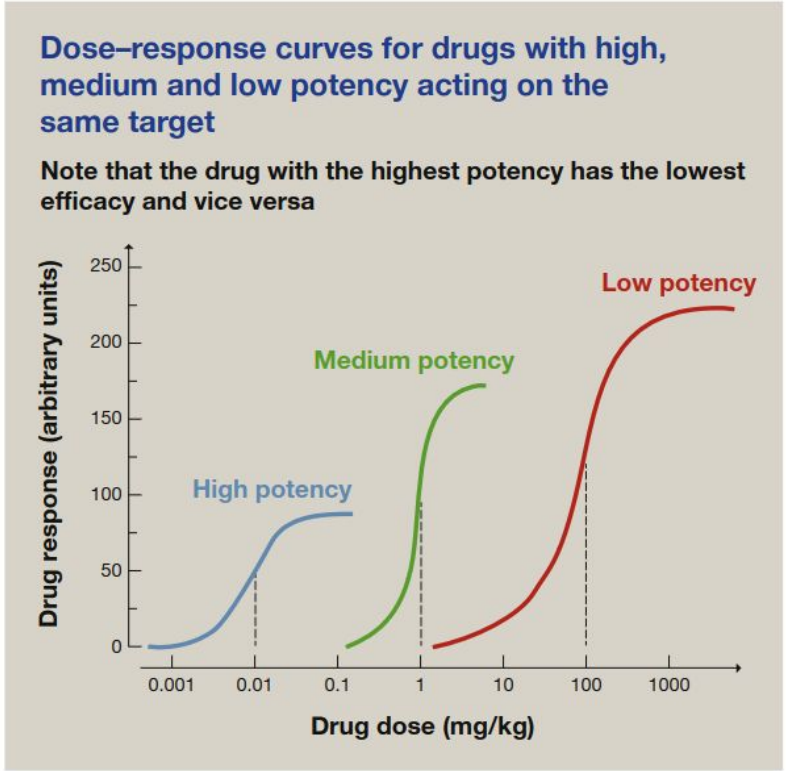

Figure 3

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Desensitization

- **desensitization** to drugs is a common phenomenon;
- **tachyphylaxis:** when it occurs rapidly
- **tolerance:** when it occurs more slowly it is known as.
    - a larger dose is required to produce an equal pharmacological outcome (4). In Tolerance, increasing the dose is enough to maintain pharmacological effectiveness. However, in tachyphylaxis, an increase in dose may or may not have an effect on therapeutic results.

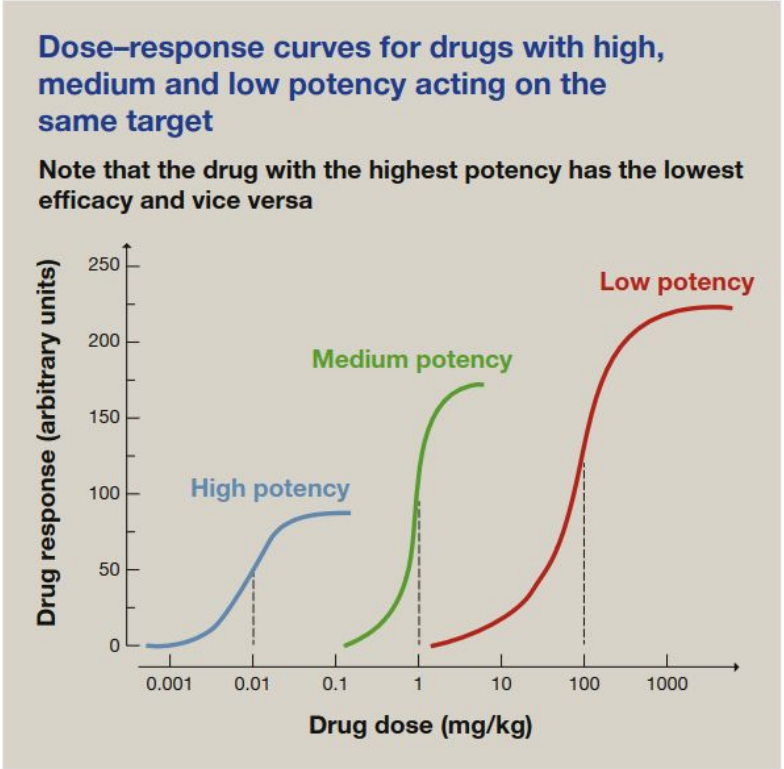

Figure 3

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Dose-dependency drug response

- An equation for describing the response is

$$E = \frac{E_{\max} \cdot C^{\gamma}}{C_{50}^{\gamma} + C^{\gamma}}$$

  - **E_{max}**: maximum response
  - **C_{50}**: concentration to achieve 50% effect
  - **γ**: steepness factor (for drugs normally 1-3)

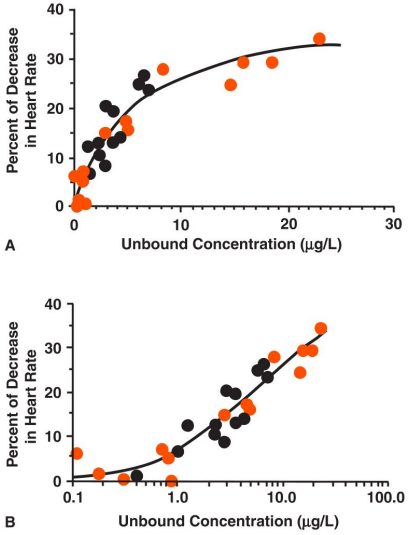

FIGURE 3-6 A. Response, measured by the percent decrease in exercise-induced tachycardia, to propranolol increases with an increase in the unbound concentration of the drug in plasma. **B.** The same data as in (**A**), except that now concentration is plotted on a logarithmic scale. The data points represent measurements after single and multiple (daily) oral doses of two 80-mg tablets of propranolol (*black circle*) or a 160-mg modified-release capsule (*color*) in an individual subject. The solid line is the fit of Equation 3-2 to the data. The response appears to follow the E_{max} model with a γ of 1, an E_{max} of 40%, and a C_{50} of 5.3 μg/L. (Redrawn from Lalonde RL, Straka RJ, Pieper JA, et al. Propranolol pharmacodynamic modeling using unbound and total concentrations in healthy volunteers. *J Pharmacokinet Pharmacodyn* 1987;15:569–582.)

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Steepness factor

$$E = \frac{E_{max} \cdot C^{\gamma}}{C_{50}^{\gamma} + C^{\gamma}}$$

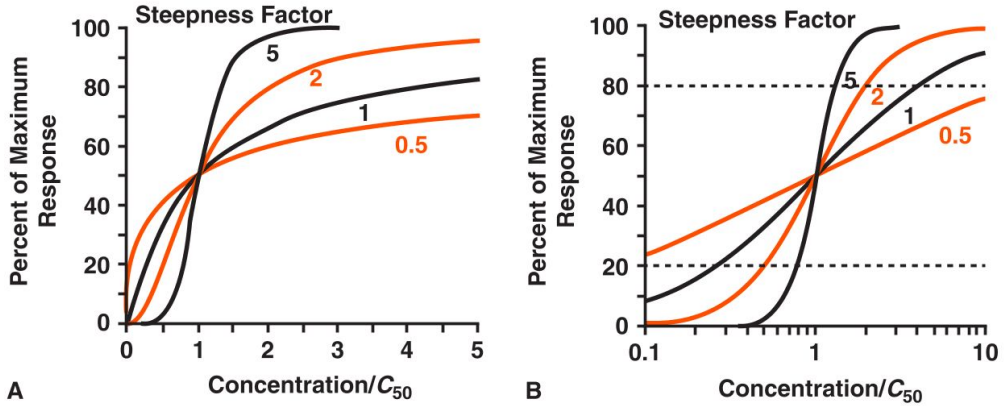

FIGURE 3-5 Linear (**A**) and semilogarithmic (**B**) concentration–response plots, predicted according to Equation 3-2, for three hypothetical drugs that have the same C_{50}, the concentration at which the response is one-half the maximum value, but different values of the steepness factor, γ. At low concentrations, the effect increases almost linearly with concentration (**A**), when $\gamma = 1$, approaching a maximal value at high concentrations. The greater the value of γ, the steeper is the change in response around the C_{50} value. Between 20% and 80% of maximal effect, the response appears to be proportional to the logarithm of the concentration (**B**) for all values of γ. Concentrations are expressed relative to C_{50}.

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Beneficial and adverse effects

- The **therapeutic index** is the ratio between the dose of a drug that causes adverse effects and the dose that achieves therapeutic benefits
- **selectivity** of the drug, that is, a greater therapeutic response relative to its adverse responses.

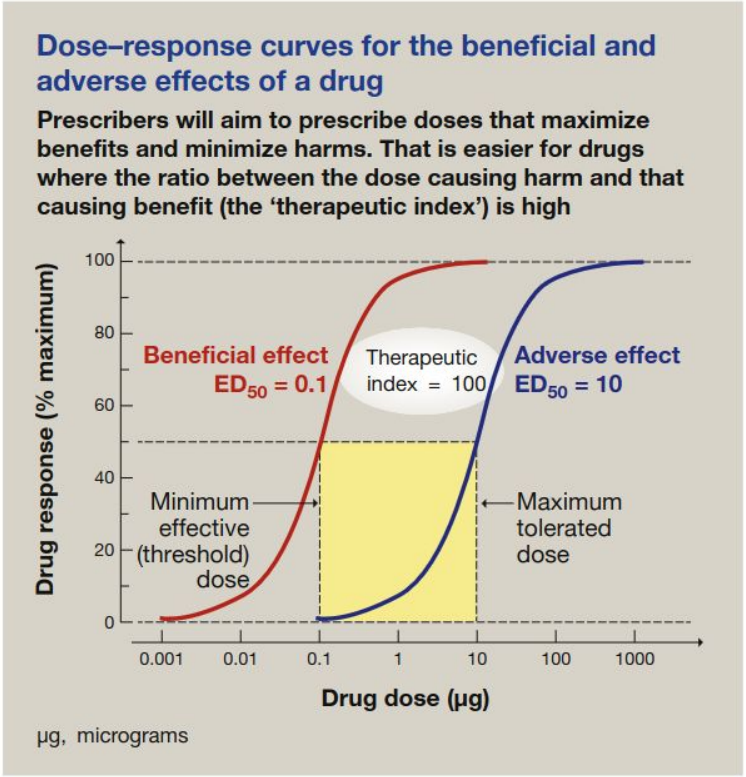

Figure 4

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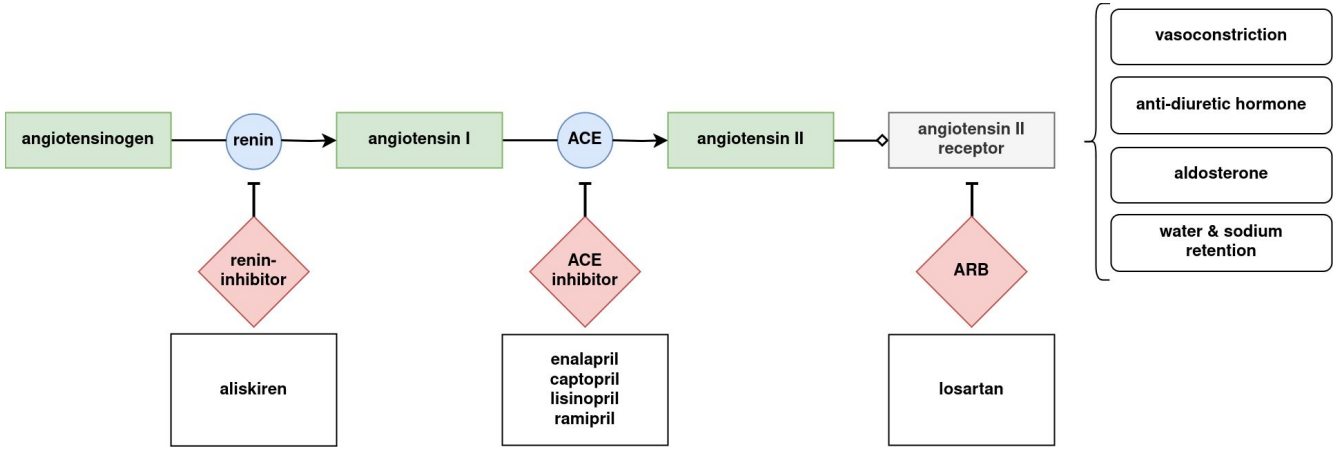
Example: ACE inhibitor ramipril/ramiprilat



Ruggenenti, P., Cravedi, P., & Remuzzi, G. (2010). **The RAAS in the pathogenesis and treatment of diabetic nephropathy.** *Nature Reviews Nephrology*, *6*(6), 319-330.

Enhancing Our Understanding of Enalapril's Pharmacokinetics: A Physiologically Based Modeling Approach. Master Thesis Shubhankar Palwankar (supervisor: **Matthias König**) May 2024

- **RAAS system**: Renin-angiotensin-aldosterone system;
  Blood pressure regulation, homeostasis and electrolyte balance.
- **Abnormal function** leads to hypertension and a range of other cardiovascular disorders
- **Intervention**:
  - **renin inhibitors** directly block the activity of renin, preventing the initial production of angiotensin I;
  - **ACE inhibitors**, which block the conversion of angiotensin I to angiotensin II, thereby reducing blood pressure;
  - **angiotensin II receptor blockers (ARBs)** block the action of angiotensin II on its receptors

Example: ACE inhibitor ramipril/ramiprilat

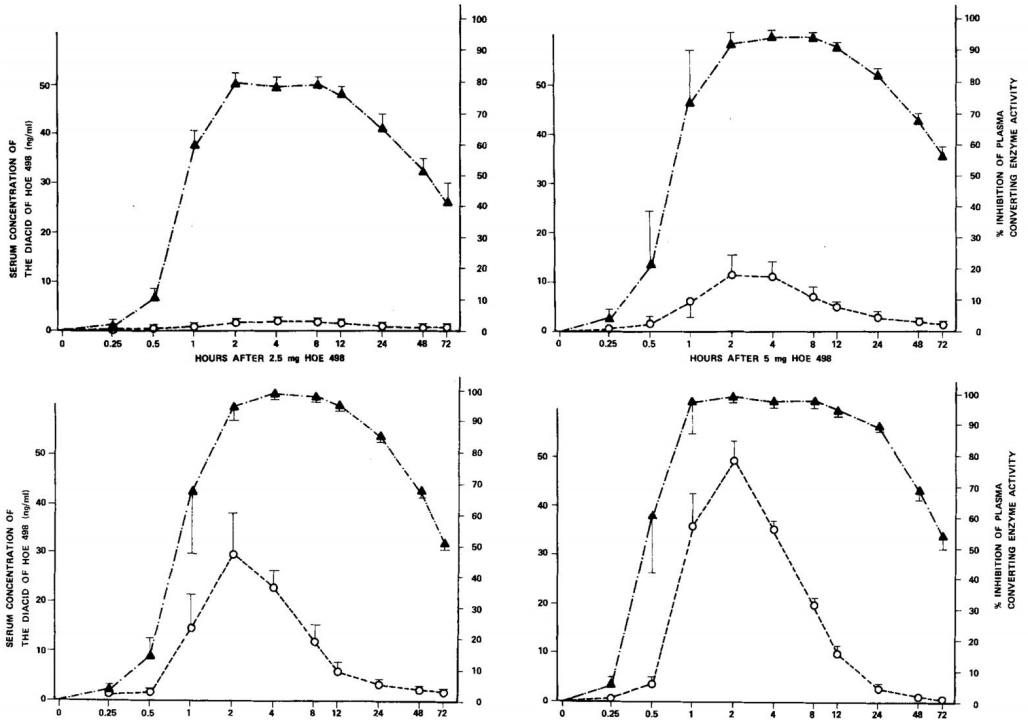


Fig. 8. Time course of the serum levels of the HOE 498 diacid (○) and the inhibition of plasma converting enzyme activity (▲) after administration of a single dose of HOE 498. *Upper left panel*: 2.5 mg HOE 498; *upper right panel*: 5 mg; *lower left panel*: 10 mg; *lower right panel*: 20 mg

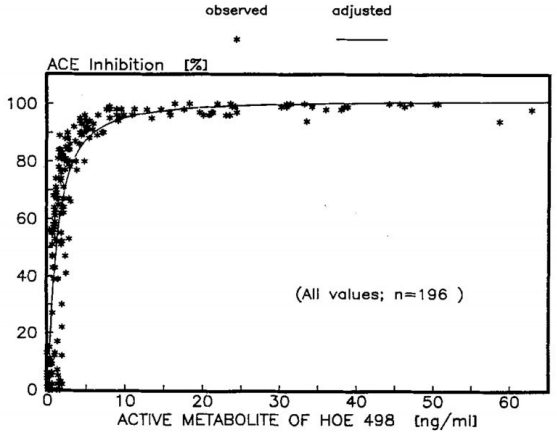


Fig. 9. Correlation between plasma diacid levels and inhibition of plasma converting enzyme activity. According to the Hill equation $r = 0.837$, $n = 196$, $P < 0.001$

TABLE 2. *Inhibition of ACE activity: mean values and standard deviations* (n = *11*)

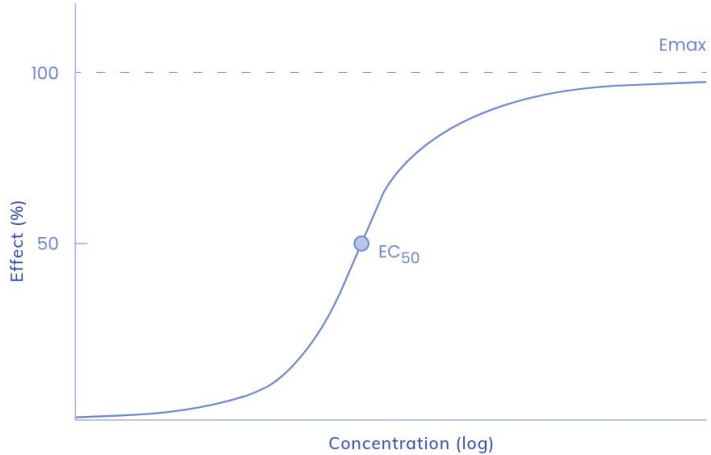
Variable	Day 1	Day 14
I_{max} [%]	99.5 ± 1.0	99.2 ± 1.2
$t_{max.I}$ [h]	4.2 ± 2.3	3.6 ± 2.7
$I_{24\ h}$ [%]	85.3 ± 7.7	82.8 ± 9.2
$IC_{50\%}$ [ng/ml] (pooled data)	1.39 ± 0.87	
Slope factor (pooled data)	3.6 ± 3.3	

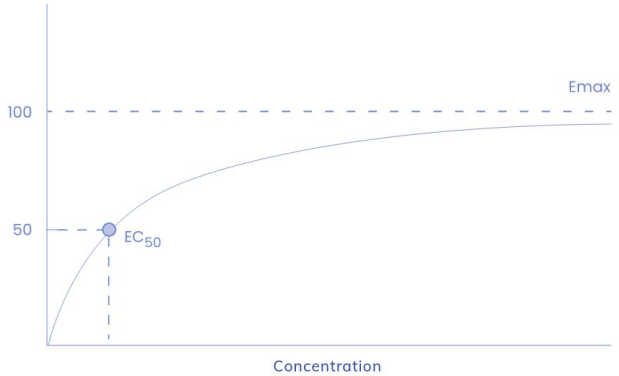
Heintz B, Verho M, Brockmeier D, Lückel G, Maigatter S, Sieberth HG, Rangoonwala B, Bender N. **Multiple-dose pharmacokinetics of ramipril in patients with chronic congestive heart failure.** J Cardiovasc Pharmacol. 1993;22 Suppl 9:S36-42.

Bussien JP, Nussberger J, Porchet M, Waeber B, Brunner HR, Perisic M, Tansey MJ, Bomm M, Hajdu P. **The effect of the converting enzyme inhibitor HOE 498 on the renin angiotensin system of normal volunteers.** Naunyn Schmiedebergs Arch Pharmacol. 1985 Mar;329(1):63-9. doi: 10.1007/BF00695194.

🏃 Exercise: Pharmacodynamic 🏃

https://www.icp.org.nz/pharmacodynamics





Dapagliflozin: SGLT2 inhibitor

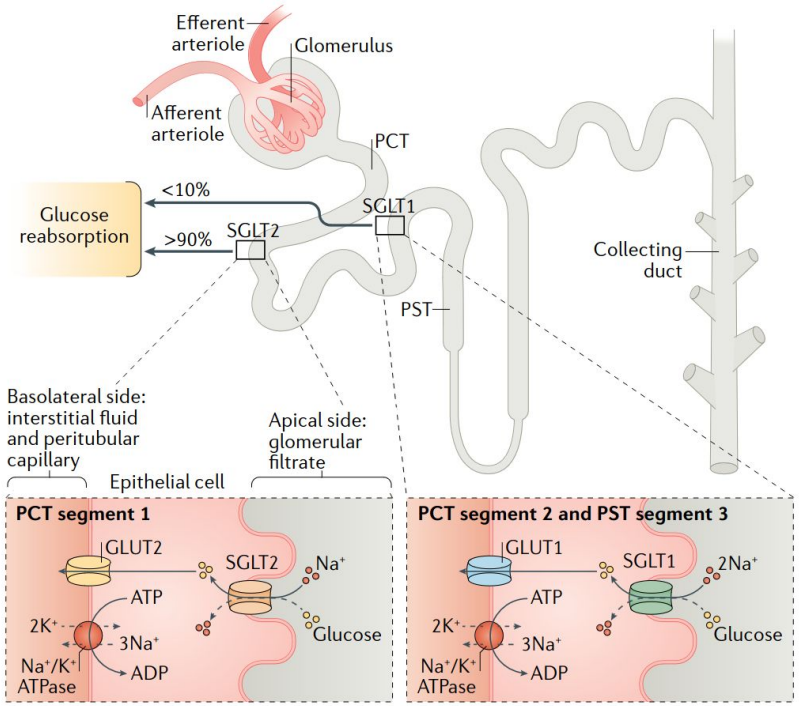


Fig. 1 | **Glucose reabsorption in the kidney.** Most (>90%) of the glucose is reabsorbed from the glomerular filtrate into the epithelial cells via sodium–glucose cotransporter 2 (SGLT2) in segment 1 of the proximal convoluted tubule (PCT); the remainder of the glucose (<10%) is reabsorbed via SGLT1 in PCT segment 2 and proximal straight tubule (PST) segment 3. The glucose then passes into the interstitial fluid via the glucose transporter 2 (GLUT2) in segment 1 or via GLUT1 in segments 2 and 3.

SGLT2 Inhibitors: class of medications that lower blood glucose levels by blocking the reabsorption of glucose in the kidneys, promoting its excretion in urine.

Dapagliflozin: A specific SGLT2 inhibitor used to treat type 2 diabetes, helping to control blood sugar levels, reduce cardiovascular risk, and support weight loss.

Benefits and Usage: Effective in improving glycemic control, dapagliflozin also offers protective benefits for heart and kidney health, often used in combination with other diabetes medications.

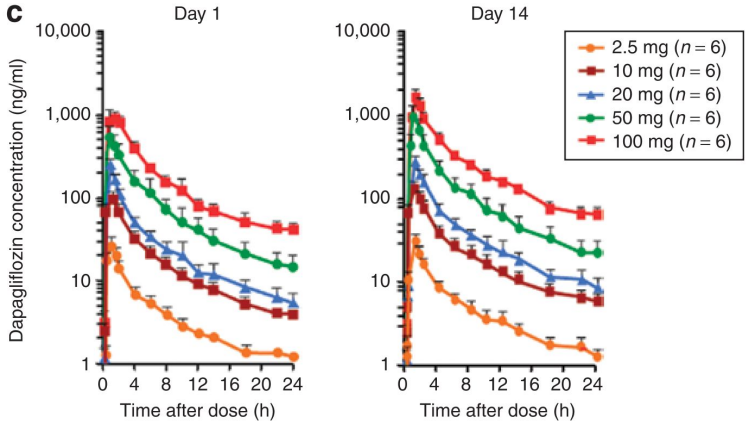


Figure 4 Multiple-ascending-dose study. Dose-normalized (**a**) C_{max} and (**b**) AUC for dapagliflozin at day 14; midlines of boxes are median values, boundaries are ~95% confidence limits for the median. (**c**) Mean (SD) plasma

Dapagliflozin: SGLT2 inhibitor

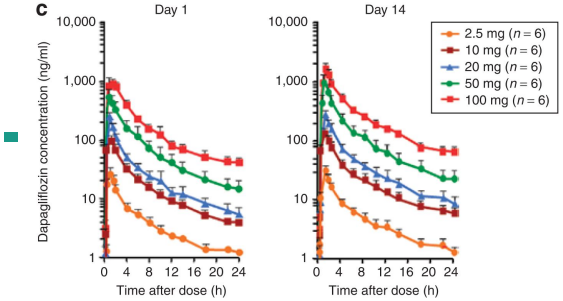


Figure 4 Multiple-ascending-dose study. Dose-normalized (**a**) C_{max} and (**b**) AUC for dapagliflozin at day 14; midlines of boxes are median values, boundaries are ~95% confidence limits for the median. (**c**) Mean (SD) plasma concentration–time profiles for dapagliflozin on days 1 and 14.

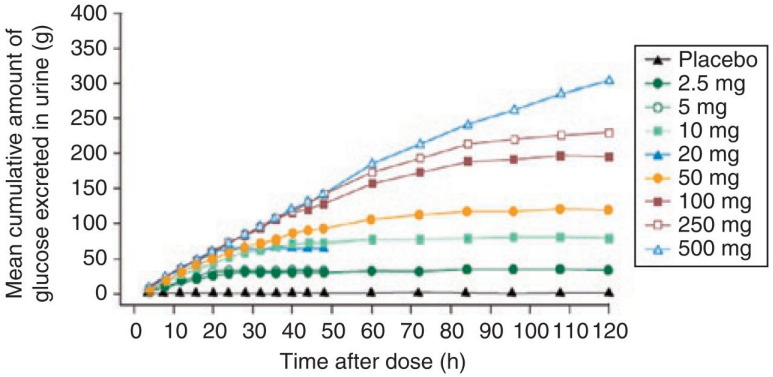


Figure 5 Single-ascending-dose study. Total mean cumulative amount of urinary glucose after a single dose of dapagliflozin. The mean cumulative amount of glucose excreted in the urine was dose-dependent. Data are shown for up to 120 h after a single dose.

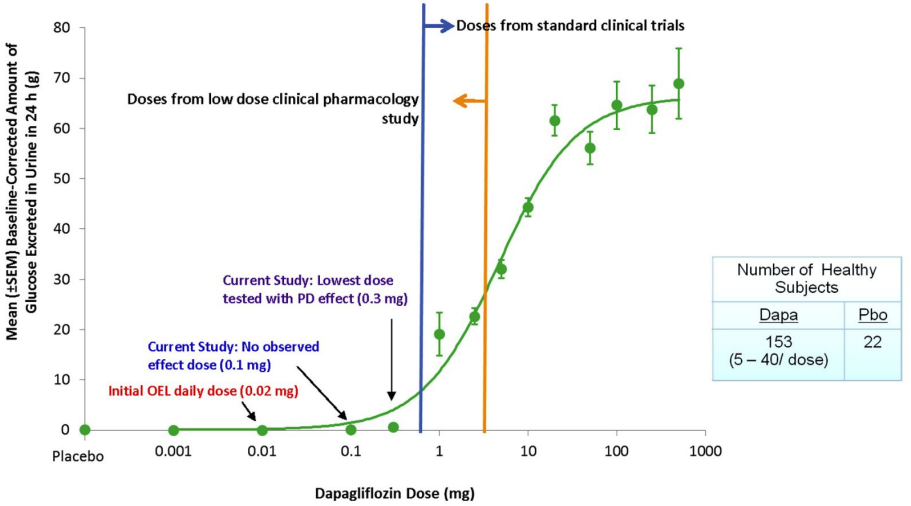


Fig. 1. Dose response of urine glucose excretion after single oral dose of dapagliflozin. Emax (90% CI) for 24 h glucose in healthy subjects: 66 g (60, 73 g).

Gould JC, Kasichayanula S, Shepperly DC, Boulton DW. **Use of low-dose clinical pharmacodynamic and pharmacokinetic data to establish an occupational exposure limit for dapagliflozin, a potent inhibitor of the renal sodium glucose co-transporter 2.** Regul Toxicol Pharmacol. 2013 Oct;67(1):89-97. doi: 10.1016/j.yrtph.2013.07.002. Epub 2013 Jul 11. PMID: 23851069.

Komoroski B, Vachharajani N, Boulton D, Kornhauser D, Geraldes M, Li L, Pfister M. **Dapagliflozin, a novel SGLT2 inhibitor, induces dose-dependent glucosuria in healthy subjects.** Clin Pharmacol Ther. 2009 May;85(5):520-6. doi: 10.1038/clpt.2008.251. Epub 2009 Jan 7.

Time-dependency of response (time delays)

- drug response often lags behind its plasma concentration
- causes
  - delayed distribution to the site of action
  - underlying dynamics of affected system
- **pharmacokinetic rate-limited response** (instantaneous response)
- **pharmacodynamic rate-limited response** (pharmacodynamics slower then pharmacokinetics)

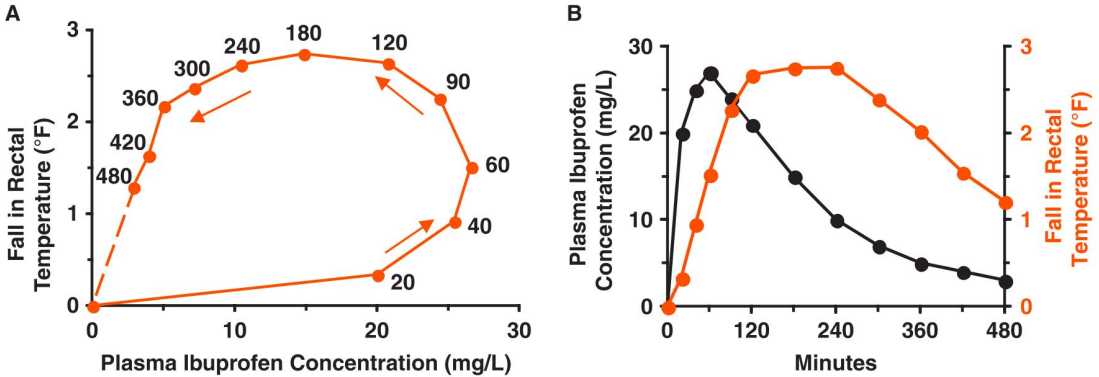


FIGURE 9-3 The fall in rectal temperature (observation minus baseline in degrees Fahrenheit, 1.8°F = 1.0°C) in 36 febrile children from 6 months through 11 years of age after a 6-mg/kg oral dose of ibuprofen. **A.** Relationship between the fall in temperature and plasma ibuprofen concentration. Note the large degree of hysteresis present. The time of sampling (minutes) is indicated next to each point. **B.** Plasma ibuprofen concentration (*black line*) and fall in temperature (*colored line*) as a function of time after dosing. (Redrawn from Kelley MT, Walson PD, Edge JH, et al. Pharmacokinetics and pharmacodynamics of ibuprofen isomers and acetaminophen in febrile children. *Clin Pharmacol Ther* 1992;52:181–189.)

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Rate-limiting Pharmacodynamic

- Omeprazole, an inhibitor of the proton pump within the acid-secreting parietal cells of the stomach
- **Gastric acid production** promptly falls, but the **return to baseline is very slow**, over days
- omeprazole **covalently binds and inactivates its receptor**—in this case the proton pump—which takes time to be resynthesized

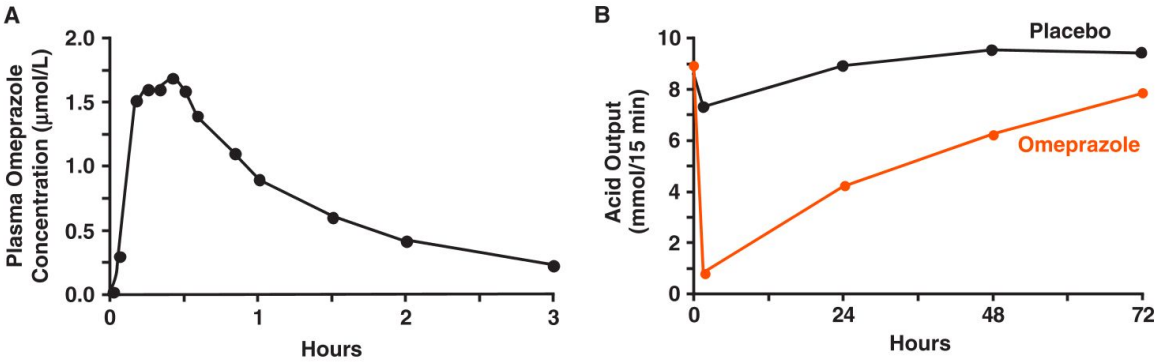

FIGURE 9-9 Despite being very rapidly metabolized within the body, such that little remains in plasma after 3 hours following a 40-mg oral dose of omeprazole (**A**), the inhibition of gastric acid secretion (*colored line*) continues for several days (**B**). Also shown is the response after a placebo dose (*black line*). The response (expressed as a decrease in acid output over 15 minutes following a 1-hour infusion of intravenous pentagastrin, which maximally induces gastric acid secretion) was assessed before administration of drug or placebo at 2 hours postadministration, and again at 1, 2, and 3 days. This slow restoration of gastric acid secretion after omeprazole administration is due to a combination of very slow dissociation of tightly bound omeprazole-derived compounds to the proton pump receptor within the parietal cells of the stomach, together with the covalent binding and inactivating by omeprazole of this receptor, requiring synthesis of new receptor, which takes time. (A composite figure taken from data provided in Lind T, Cederberg C, Ekenved G, et al. Effect of omeprazole-a gastric proton pump inhibitor on the pentagastrin simulated secretion in man. *Gut* 1983;24:270–276.)

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Accounting for delays via effect compartments

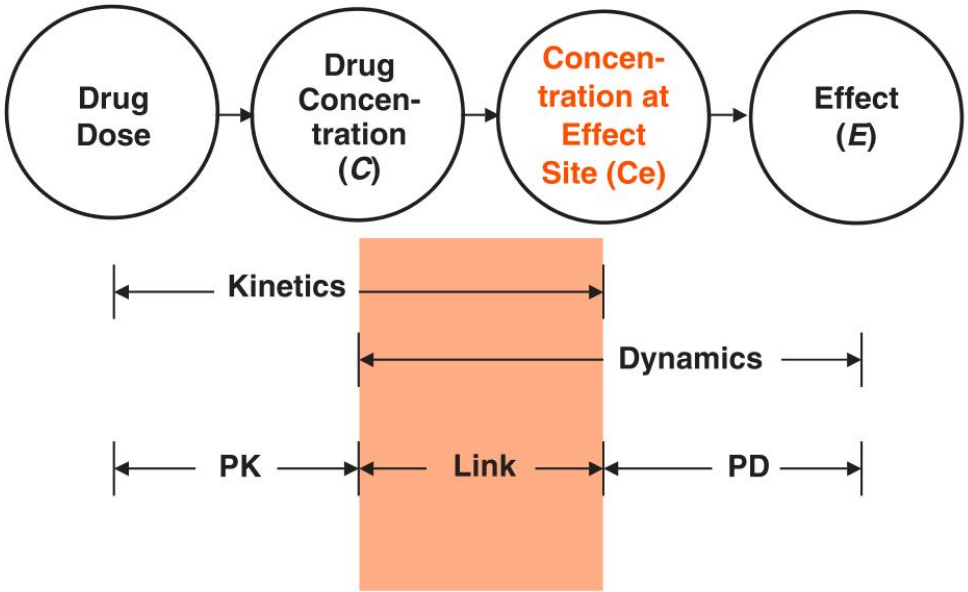

FIGURE 9-10 The concept of an effect compartment linking plasma concentration (PK) with response (PD) helps to accommodate the frequently observed delay in time between plasma concentration and response. The delay is due to the time needed to distribute into the site of action. By accommodating for and thus effectively removing this delay, it is possible to reveal the underlying direct relation between effect site concentration (Ce) and response.

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Drug response & placebo effect

- **placebo effect** is a deviation from the baseline value produced when the patient takes or receives what has all the appearances of drug treatment but lacks the active principle

$$\text{Measured response} = \text{Drug response} + \text{Placebo response} + \text{Baseline} \qquad \text{Eq. 3-1}$$

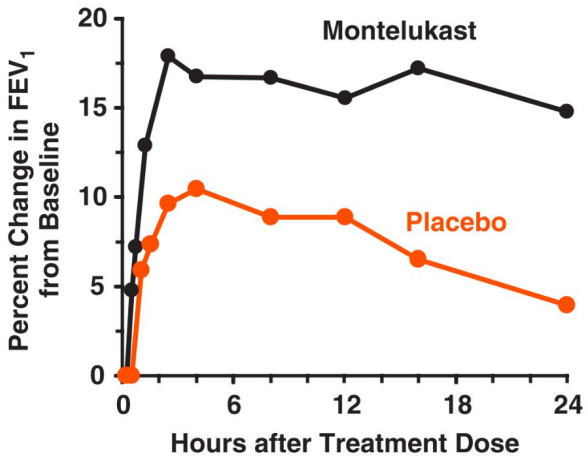

FIGURE 3-2 Figure showing changes in FEV_1, a measure of respiratory function, with time following administration of a single dose of a placebo (*color*) or montelukast (10 mg, *black*), a specific leukotriene receptor antagonist, in asthmatic patients. Notice both the appreciable difference in FEV_1 from baseline between the two treatments, which is sustained over the 24-hour period response and also the positive effect of montelukast seen as the difference in FEV_1 between the two treatments, which is sustained over the 24-hour period of study. (Redrawn from Dockendorf RJ, Baumgartner RA, Leff JA, et al. Comparison of the effects of intravenous and oral montelukast on airway function: a double blind, placebo controlled, three period, crossover study in asthmatic patients. *Thorax* 2000;55:260–265.)

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