

DOSE- AND TIME- DEPENDENT PHARMACOKINETICS

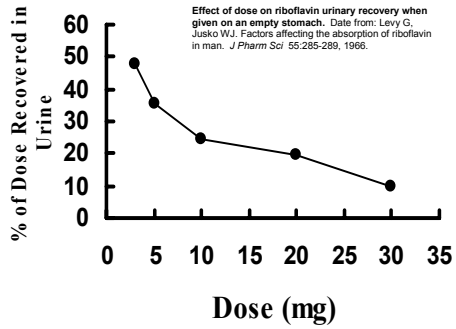
CAUSES OF DOSE- OR TIME-DEPENDENT KINETICS

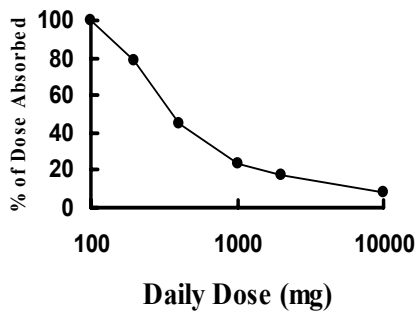
<u>PROCESS</u>	<u>EXAMPLE</u>	<u>PARAMETER</u>
Saturable gut wall transport	riboflavin	F
Saturable gut wall metabolism	salicylamide	F
Poor solubility	griseofulvin	F
Saturable plasma protein binding	disopyramide	f_{up}
Active tubular secretion	penicillin G	CL_R
Active tubular reabsorption	ascorbic acid	CL_R
Alterations in urine pH	salicylic acid	CL_R
Alterations in urine flow	theophylline	CL_R
Nephrotoxicity	gentamicin	CL_R

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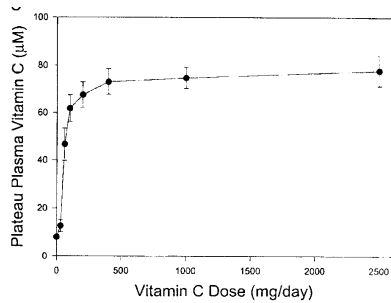
<u>PROCESS</u>	<u>EXAMPLE</u>	<u>PARAMETER</u>
Capacity-limited metabolism	phenytoin	CL_H
Autoinduction	carbamazepine	CL_H
Co-substrate depletion	acetaminophen	CL_H
Product (metabolite) inhibition	phenylbutazone	CL_H

I. ABSORPTION





Effect of dose on ascorbic acid absorption. Data from Blanchard J et al. *Am J Clin Nutr* 66:1165-1171, 1997



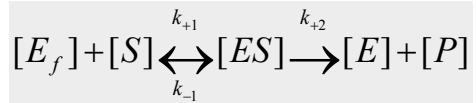
Steady-state Vitamin C plasma concentration as a function of dose in 13 female subjects receiving doses from 30 to 2,500 mg. From: Levine M, et al. A new recommended dietary allowance of vitamin C for healthy young women. *Proc Natl Acad Sci USA* 98:9842-9846, 2001.

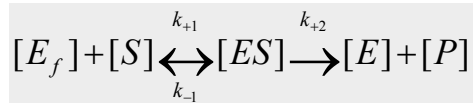
II. ELIMINATION

A. CAPACITY-LIMITED ELIMINATION

1. MATHEMATICAL ANALYSIS

These processes can be described via the *Michaelis-Menten* relationship:





$$[E_T] = [E_f] + [ES]$$

$$\frac{d[ES]}{dt} = k_{+1}[E_f][S] - k_{-1}[ES] - k_{+2}[ES]$$

$$\frac{d[ES]}{dt} = k_{+1}[E_f][S] - k_{-1}[ES] - k_{+2}[ES]$$

at steady state $\frac{d[ES]}{dt} = 0$

$$k_{+1}[E_f][S] = k_{-1}[ES] + k_{+2}[ES]$$

$$k_{+1}[E_f][S] = (k_{-1} + k_{+2})[ES]$$

$$\frac{[E_f][S]}{[ES]} = \frac{k_{-1} + k_{+2}}{k_{+1}}$$

k_{-1} is a dissociation process, whereas k_{+2} requires the breaking of bonds; thus, $k_{-1} \gg k_{+2}$

$$\frac{[E_f][S]}{[ES]} = \frac{k_{-1}}{k_{+1}} = K_m$$

$$K_m = \frac{[E_f][S]}{[ES]}$$

Remember that $[E_f] = [E_T] - [ES]$

$$K_m = \frac{[E_T - ES][S]}{[ES]}$$

$$K_m[ES] = [E_T][S] - [ES][S]$$

$$K_m[ES] + [ES][S] = [E_T][S]$$

$$[ES](K_m + S) = [E_T][S]$$

$$[ES] = \frac{[E_T][S]}{(K_m + S)}$$

$$[ES] = \frac{[E_T][S]}{(K_m + S)}$$

The rate of formation of the product is given as:

$$k_{+2}[ES] = v \quad \text{or} \quad [ES] = \frac{v}{k_{+2}}$$

By implication, the maximum rate is given as

$$V_{\max} = [E_T]k_{+2} \quad \text{or} \quad [E_T] = \frac{V_{\max}}{k_{+2}}$$

$$\frac{v}{k_{+2}} = \frac{\left(\frac{V_{\max}}{k_{+2}}\right)[S]}{K_m + [S]}$$

$$v = \frac{V_{\max}[S]}{K_m + [S]}$$

$$\frac{dC}{dt} = \frac{V_{\max}[C]}{K_m + [C]}$$

For most drugs, $K_m \gg C$. Hence

$$\frac{dC}{dt} = \frac{V_{\max}[C]}{K_m}$$

$$-\frac{dC}{dt} = \frac{V_{\max} [C]}{K_m}$$

Since V_{\max} and K_m are constant for a given drug in a given individual, this ratio will be constant. Elimination will proceed in a first-order fashion.

$$\frac{V_{\max}}{K_m} = \lambda \quad \text{where} \quad -\frac{dC}{dt} = \lambda C$$

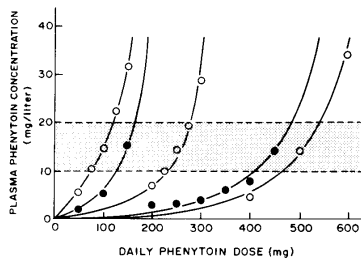
Drugs for which $K_m \ll C$:

ethanol
salicylate
phenytoin

Numerous drugs after first-pass

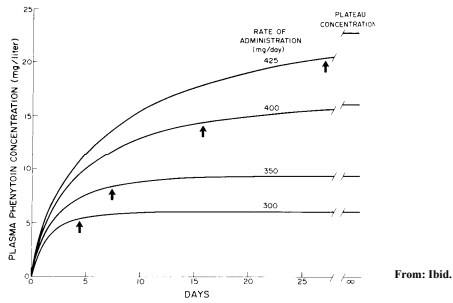
2. Clinical Consequences

a. Relationship btwn dose and C_p

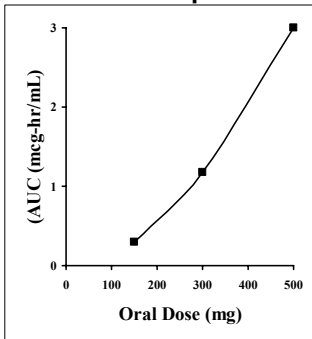


Reproduced from: Tazer TN, Winter ME. Phenytoin. In: Evans WE, Schentag JJ, Jusko WJ, *Applied Pharmacokinetics - Principles for Therapeutic Drug Monitoring*, 3rd edition, 1992, p. 25-12

b. Relationship btwn dose and time to steady-state

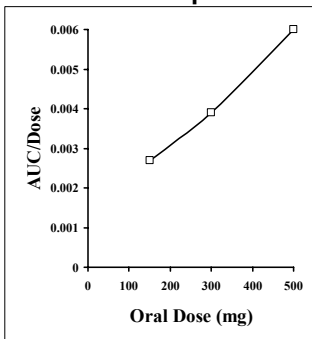


c. Relationship btwn dose and AUC₀



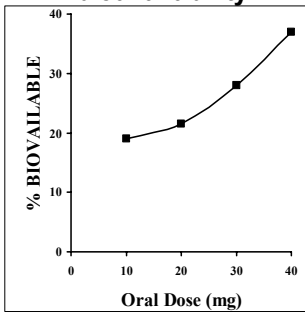
Plasma AUC of lorcinide in a subject as a function of dose. Data from: Janchen E et al. *Clin Pharmacol Ther* 26:187, 1979.

c. Relationship btwn dose and AUC₀



Plasma AUC/Dose of lorcinide in a subject as a function of dose. Data from: Janchen E et al. *Clin Pharmacol Ther* 26:187, 1979.

d. Relationship btwn dose and bioavailability



Bioavailability of nicardipine after oral administration. Data from: Wagner JG et al. *Biopharm Drug Dispos* 8:133-148, 1987.

e. Relationship btwn Cp and time

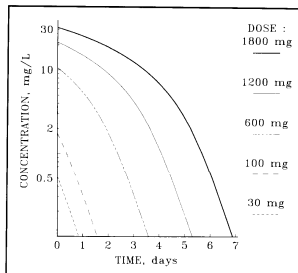


Figure 1. Simulated concentration versus time profiles for the one-compartmental model with parameter values of $V_{max} = 433$ mg/day, $K_m = 3.62$ mg/liter, and $V = 57$ liters. The indicated bolus doses of drug were assigned at $t = 0$. Adapted from Ref. 8.

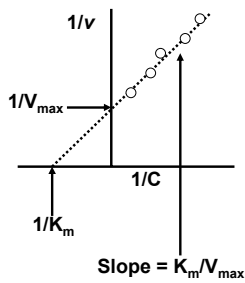
3. Determination of Michaelis-Menten Parameters

a. Lineweaver-Burke Expression

$$v = \frac{V_{max} \times C}{K_m + C}$$

$$\frac{1}{v} = \frac{K_m + C}{V_{max} \times C}$$

$$\frac{1}{v} = \frac{K_m}{V_{max} \times C} + \frac{1}{V_{max}}$$



b. In Vivo Determination

$$v = \frac{V_{max} \times C_{ss}}{K_m + C_{ss}}$$

If K_0 = input rate

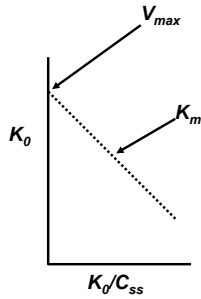
$$K_0 = \frac{V_{max} \times C_{ss}}{K_m + C_{ss}}$$

$$K_0(K_m + C_{ss}) = V_{max} \times C_{ss}$$

$$K_0 K_m + K_0 C_{ss} = V_{max} \times C_{ss}$$

$$K_0 C_{ss} = (V_{max} \times C_{ss}) - K_0 K_m$$

$$K_0 = V_{max} - K_m \left(\frac{K_0}{C_{ss}} \right)$$



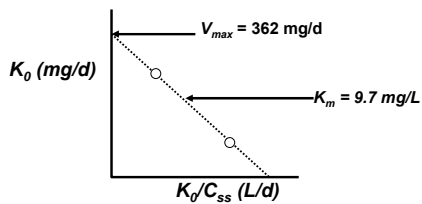
JB is an 18 yo male receiving phenytoin for prophylaxis of post-traumatic head injury seizures. The following steady state concentrations were obtained at the indicated doses:

Dose (mg/d)	Css (mg/L)
100	3.7
300	47

From this data, determine this patient's K_m and V_{max} for phenytoin.

JB is an 18 yo male receiving phenytoin for prophylaxis of post-traumatic head injury seizures. The following steady state concentrations were obtained at the indicated doses:

Dose (mg/d)	Css (mg/L)	Dose Rate/Css (L/d)
100	3.7	27
300	47	6.4



What C_{ss} would be expected if a dose of 200 mg/d were given to this patient?

$$K_0 = \frac{V_{max} \times C_{ss}}{K_m + C_{ss}}$$

$$200 \text{ mg/d} = \frac{(362 \text{ mg/d})C_{ss}}{(9.7 \text{ mg/L}) + C_{ss}}$$

$$C_{ss} = 12 \text{ mg/L}$$

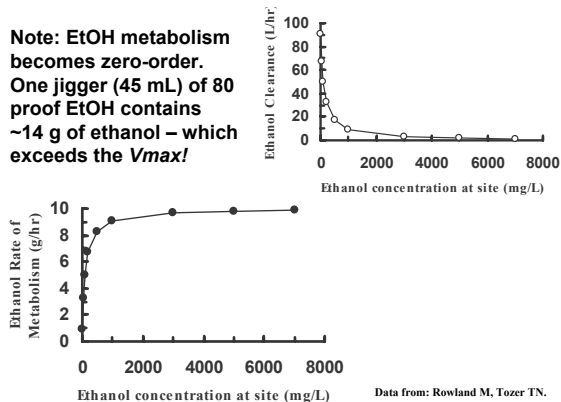
4. Application to Alcohol



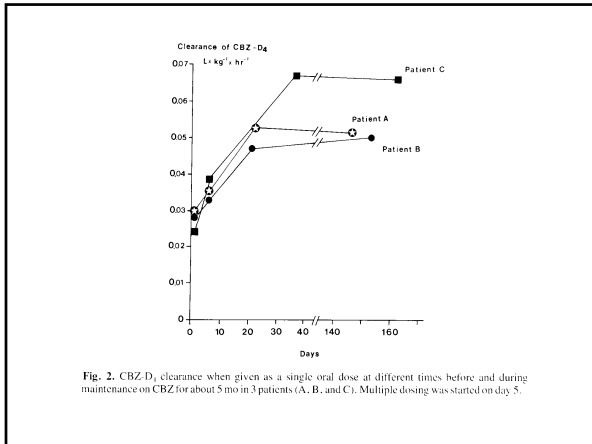
Avg $V_{max} = 10 \text{ g/hr}$
 $K_m = 100 \text{ mg/L}$

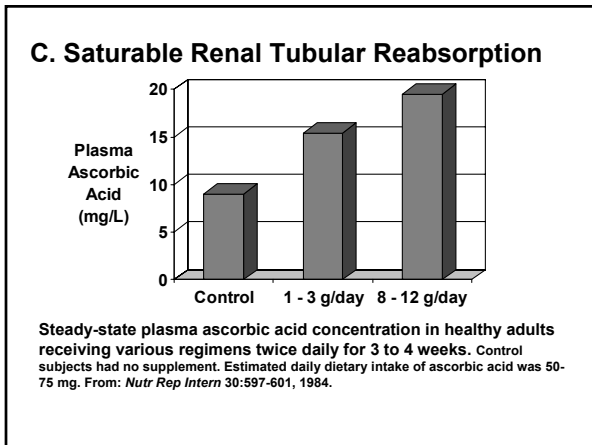
Detectable pharmacologic effect: 250 mg/L
 Lethal concentrations >7000 mg/L

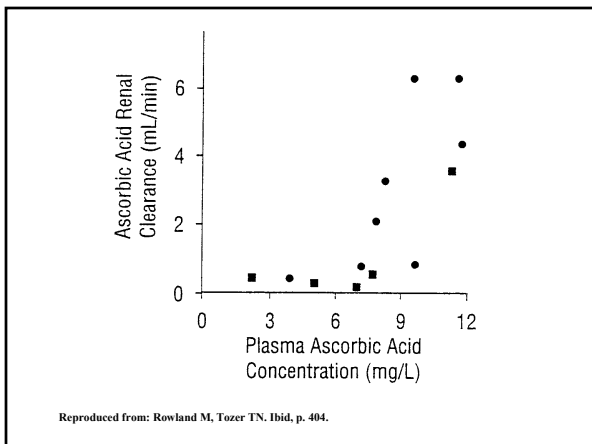
Note: EtOH metabolism becomes zero-order.
 One jigger (45 mL) of 80 proof EtOH contains ~14 g of ethanol – which exceeds the V_{max} !



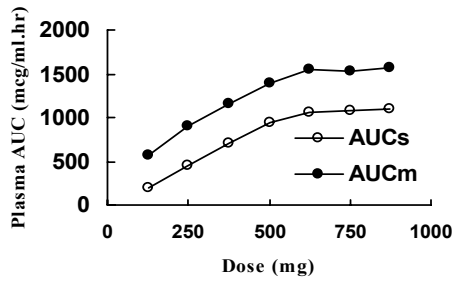
Data from: Rowland M, Tozer TN. Ibid, p. 406.



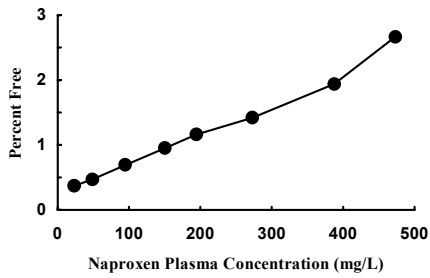




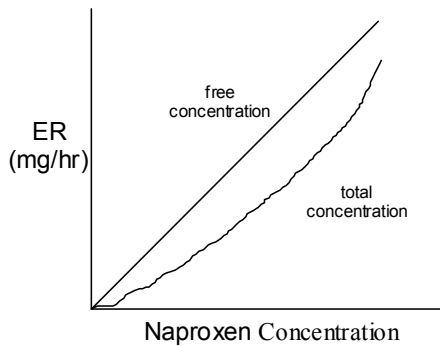
III. SATURABLE PROTEIN BINDING

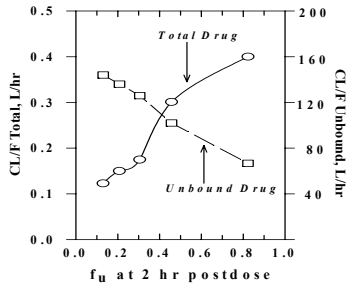


Dose vs AUC for naproxen after single (AUCs) and multiple (AUCm) doses. From: *Clin Pharmacol Ther* 15:261-266, 1974.



In vitro binding of naproxen as a function of C_p .





Relationship between oral clearance and fraction unbound of oxaprozin. From: *J Clin Pharmacol* 36:985-997, 1996.
