Absorption, Distribution, Metabolism and Elimination: Part I

Joseph Graziano, Ph.D.

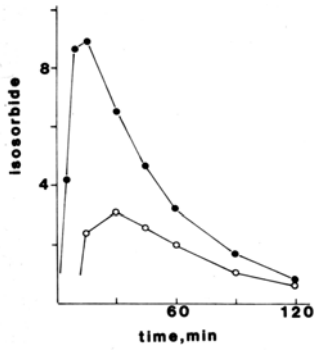
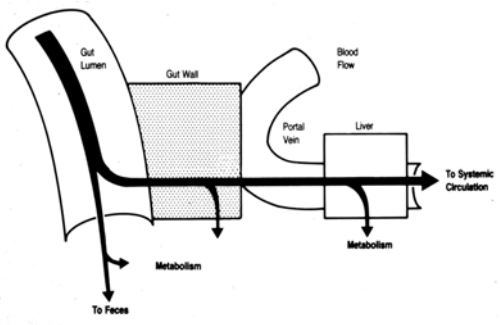


Fig. 6–11. Isosorbide concentrations in plasma fol
lowing a 5-mg sublingual (●) or oral (○) dose. (Data
from Assinder, D.F., Chasseaud, L.F., and Taylor, T.[110]



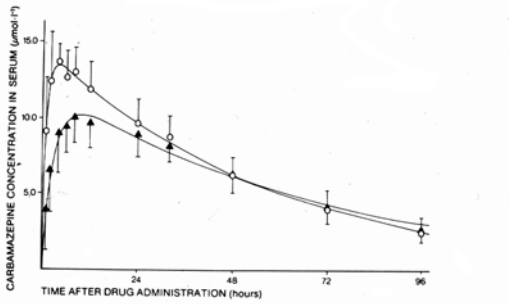


Fig. 8–2. Carbamazepine concentrations in serum after single 200-mg oral doses in 2 different tablet products. (Data from Anttila, M., et al.[6])

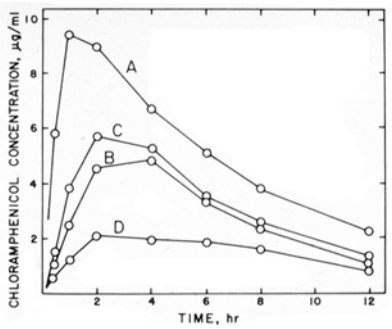


Fig. 8–10. Chloramphenicol concentrations in plasma after a single 500-mg oral dose of 4 different commercial products (Data from Glazko, A.J., et al.[40])

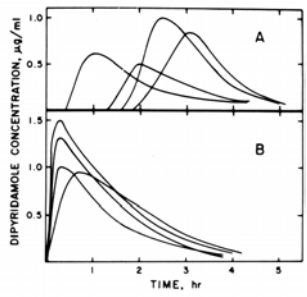


Fig. 5–5. Dipyridamole concentrations in serum of individual subjects after a 25-mg oral dose as intact tablets (A) or crushed tablets (B). When the tablets are chewed before swallowing, the peak concentration tends to be higher and the peak time tends to be earlier. (Data from Mellinger, T.J., and Bohorfoush, J.G.[22])

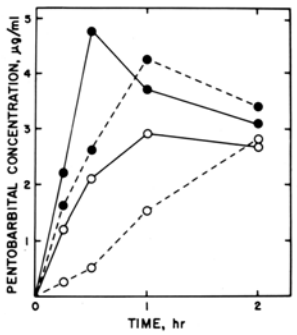


Fig. 5–1. Pentobarbital concentrations in plasma after a single 200-mg dose in various oral dosage forms. ●— aqueous solution, ●– – – aqueous suspension, ○— tablet (sodium salt), ○– – – tablet (acid). (Data from Sjögren, J., Sölvell, L., and Karlsson, I.[5])

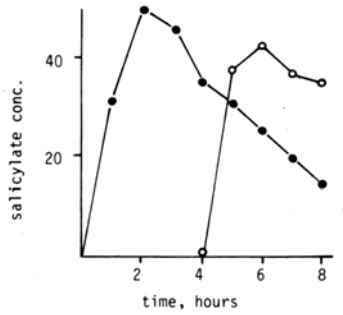


Fig. 5–7. Salicylate concentrations in plasma (μg/ml) after a 650-mg dose of aspirin in conventional tablets (●) or enteric-coated tablets (○). (Data from Day, R.D., et al.[34])

Major Routes of Drug Administration

Route of Administration	Absorption Pattern
Intramuscular:	Prompt from aqueous solutions, but slow and sustained from repository forms
Intravenous:	Immediate effects, since absorption is circumvented

Table 6–1. *Peak Cephradine Concentrations (μg/ml) in Plasma after Intramuscular Injections* at Different Sites to Male and Female Subjects†*

Injection site	Males	Females
Gluteus maximus	11.1	4.3
Deltoid	11.7	10.2
Vastus lateralis	9.8	9.4

*Injected doses = 475 mg.
†Data from Vukovich, R.A. et al.[14]

Major Routes of Drug Administration

Route of Administration	Absorption Pattern
Oral Ingestion:	Variable; depends on many factors
Subcutaneous:	Prompt from aqueous solutions, but slow and sustained from repository forms

Other Routes of Administration

- Transdermal patch
- Inhalation
- Intra-arterial
- Intrathecal
- Topical: ocular, dermal, intranasal, intravaginal routes all lead to some systemic absorption

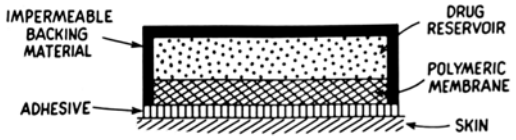


FIGURE 16 Diagram of a membrane-moderated transdermal drug delivery system. (Reproduced by permission from *J. Controlled Release* 4: 237–251, 1987.)

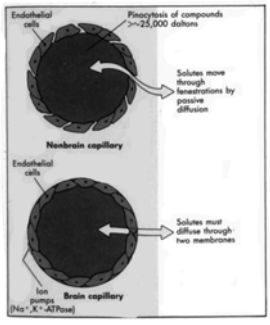


FIGURE 5-5 Structural differences between nonbrain and brain capillaries. In brain capillaries, lack of openings between endothelial cells in capillary wall requires drugs and other solutes to pass through two membranes to move from blood to tissue or the reverse. Ion pumps are mainly on the outer membrane of the brain endothelial cells and maintain a concentration difference between the two fluid regions.

Table 4–3. *Comparison of Barbiturate Absorption in Rat Colon and Partition Coefficient (Chloroform/Water) of Undissociated Drug**

Barbiturate	Partition coefficient	% Absorbed
Barbital	0.7	12
Aprobarbital	4.9	17
Phenobarbital	4.8	20
Allylbarbituric acid	10.5	23
Butethal	11.7	24
Cyclobarbital	13.9	24
Pentobarbital	28.0	30
Secobarbital	50.7	40
Hexethal	>100	44

*Data from Schanker, L.S.[5]

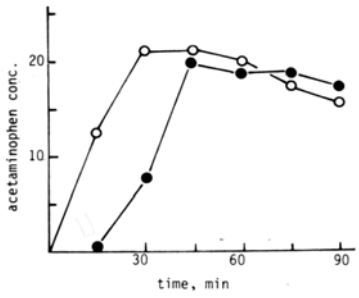


Fig. 3–5. Mean acetaminophen concentrations in plasma (μg/ml) after a single oral dose to ambulatory (○) and supine (●) subjects. The supine position results in delayed gastric emptying and absorption of acetaminophen. (Data from Nimmo, W.S., and Prescott, L.F.[24])

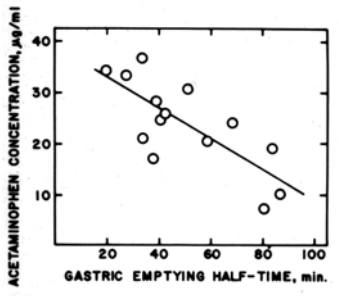


Fig. 3–4. Relationship between peak concentration of acetaminophen in plasma and gastric emptying half-time after a single oral dose. Rapid gastric emptying results in high peak levels. (Data from Heading, R.C., et al.[22])

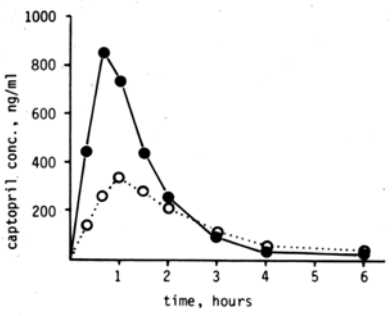


Fig. 14–3. Captopril concentrations in blood after a single 100-mg oral dose to fasted (●) and fed (○) healthy subjects. (Data from Singhvi, S.M., et al.[37])

TABLE 1 Effect of Food on Absorption of Some Drugs

Reduced	Delayed	Unaffected	Increased
Ampicillin	Acetaminophen	Bendroflume-thiazide	Carbamazepine
Aspirin	Aspirin	Bevantolol	Chlorothiazide
Atenolol	Cephalosporins (most)	Chlorpropamide	Diazepam
Captopril	Sulfonamides	Enoxacin	Dicoumarol
Ethanol	Diclofenac	Ethambutol	Diftalone
Hydrochloro-thiazide	Digoxin	Hydralazine	Griseofulvin
Penicillins (most)	Furosemide	Oxazepam	Labetalol
Tetracyclines (most)	Indoprofen	Oxprenolol	Metoprolol
Iron	Tolmesoxide	Phenazone	Propranolol
Levodopa	Valproate	Pivampicillin	Nitrofurantoin
Penicillamine		Propoxyphene	
Sotalol		Tolbutamide	
Warfarin		Tranexamic acid	

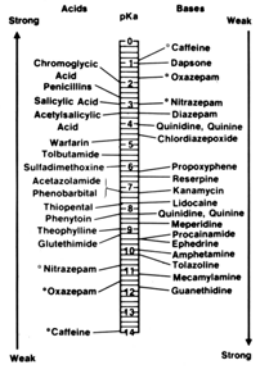


Fig. 4–1. The pKa values of certain acidic and basic drugs. Those drugs denoted with an asterisk* are amphoteric. (From Rowland, M., and Tozer, T.N.[36])

Table 5-1 pH of Selected Body Fluids

Fluids	pH
Gastric juice	1.0 to 3.0
Small intestine: duodenum	5.0 to 6.0
Small intestine: ileum	8
Large intestine	8
Plasma	7.4
Cerebrospinal fluid (CSF)	7.3
Urine	4.0 to 8.0

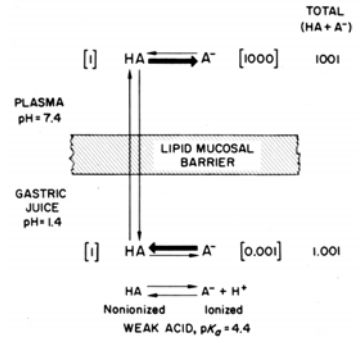
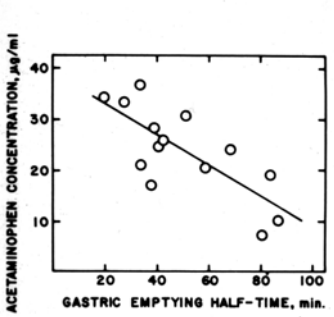


Figure 1-2. *Influence of pH on the distribution of a weak acid between plasma and gastric juice, separated by a lipid barrier.*

Table 4–2. *Comparison of Intestinal Absorption in the Rat at Several pH Values**

		% Absorbed at			
	pKa	pH 4	pH 5	pH 7	pH 8
Acids					
5-Nitrosalicylic	2.3	40	27	0	0
Salicylic	3.0	64	35	30	10
Acetylsalicylic	3.5	41	27	—	—
Benzoic	4.2	62	36	35	5
Bases					
Aniline	4.6	40	48	58	61
Amidopyrine	5.0	21	35	48	52
p-Toluidine	5.3	30	42	65	64
Quinine	8.4	9	11	41	54

*Data from Schanker, L.S., et al.[3]



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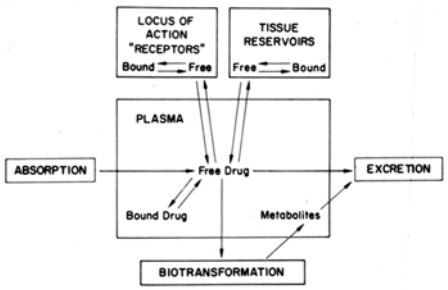
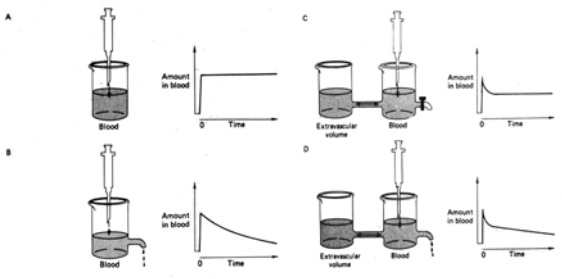


Figure 1–1. *Schematic representation of the interrelationship of the absorption, distribution, binding, biotransformation, and excretion of a drug and its concentration at its locus of action.*

Possible distribution and binding of metabolites are not depicted.



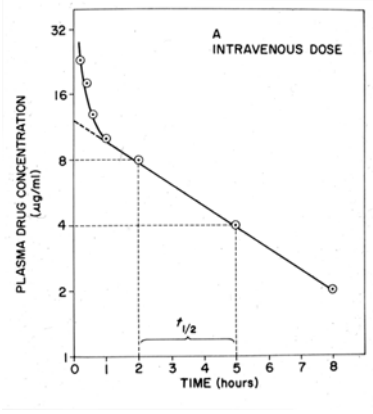


Table 12–1. *Half-Lives ($t_{1/2}$) and Apparent Volumes of Distribution (V) of Sulfamethoxypyridazine in Human Subjects of Different Ages**

Age groups	$t_{1/2}$ (hr)	V (L/kg)
Newborns	136	0.47
Infants	54	0.36
Children	51	0.20
Adults	63	0.22
Elderly subjects	98	0.26

*Data from Sereni, F., et al.[32]