Pharmacokinetics

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2016.

Definition

Two aspects of pharmacology:

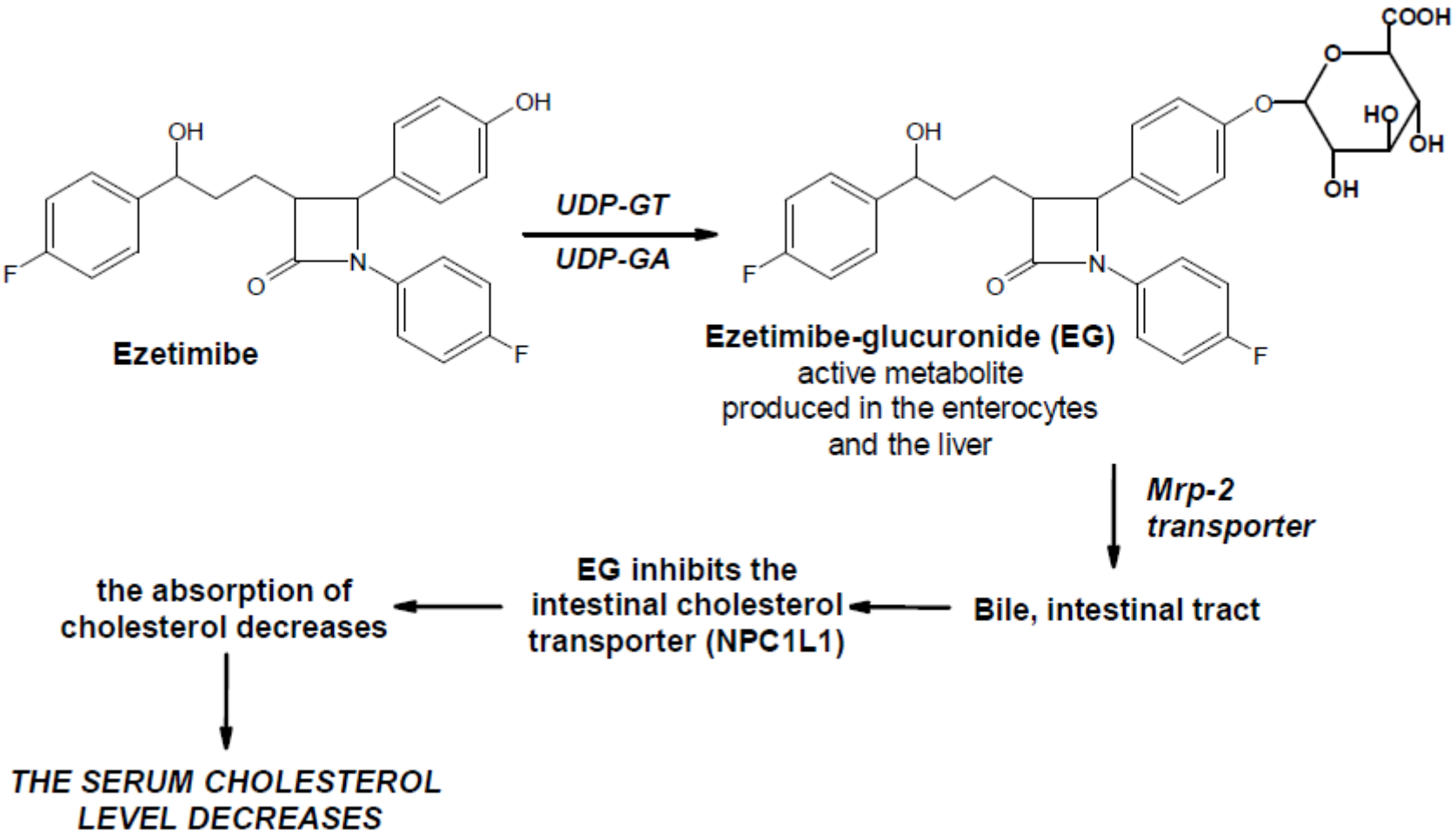
1. **PHARMACODYNAMICS: study of the effect of the *drug* on the *body***
2. **PHARMACOKINETICS: study of the effect of the *body* on the *drug***

The body ABSORBS, DISTRIBUTES, and ELIMINATES drugs.

Pharmacokinetics is the study of the

FATE, or
DISPOSITION, or
MOVEMENT

of drugs in the body.


OH
OH
F
O
N
F
Ezetimibe
UDP-GT
UDP-GA
COOH
O
HO
OH
OH
O
OH
F
O
N
F
Ezetimibe-glucuronide (EG)
active metabolite
produced in the enterocytes
and the liver
Mrp-2
transporter
Bile, intestinal tract
EG inhibits the
intestinal cholesterol
transporter (NPC1L1)
the absorption of
cholesterol decreases
THE SERUM CHOLESTEROL
LEVEL DECREASES

THE FATE OF DRUGS IN THE BODY – 3 phases:

1. ABSORPTION
2. DISTRIBUTION
3. ELIMINATION
    a. Chemically: BIOTRANSFORMATION
    b. Physically: EXCRETION

Drugs are transported across membranes in the course of their absorption, distribution and excretion.

MEMBRANE TRANSPORT MECHANISMS

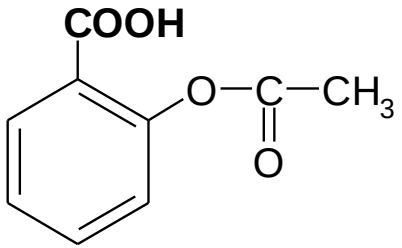
DIFFUSION		SPECIALIZED TRANSPORT	
via aqueous channels (AQP)	***across the lipid matrix***	***carrier-mediated transport***	***vesicular transport***
For small hydrophilic uncharged molecules e.g., glycerol, urea, arsenite: $As(OH)_3$ <u>unimportant for most drugs</u>	IMPORTANT for most drugs for ***absorption and distribution***	IMPORTANT for several drugs for ***GI absorption and cellular uptake,*** and for many drugs and most drug metabolites (acidic conjugates) for ***excretion via biliary and renal tubular secretion***	For proteins (rec-med. endocytosis e.g., LDL, transferrin) <u>unimportant for most drugs</u> ***Exceptions***: - IF-***Vit B12:*** rec-med. EC - ***Folate:*** rec-med. EC* - ***AGs***: adsorptive EC - ***Deferoxamine:*** fluid-phase EC

Diffusion across the lipide matrix

DETERMINANTS OF DIFFUSION

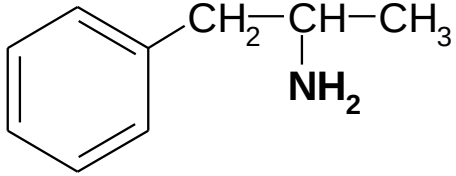
- area
- concentration gradient
- lipid solubility

The degree of ionization



Acetylsalicylic acid

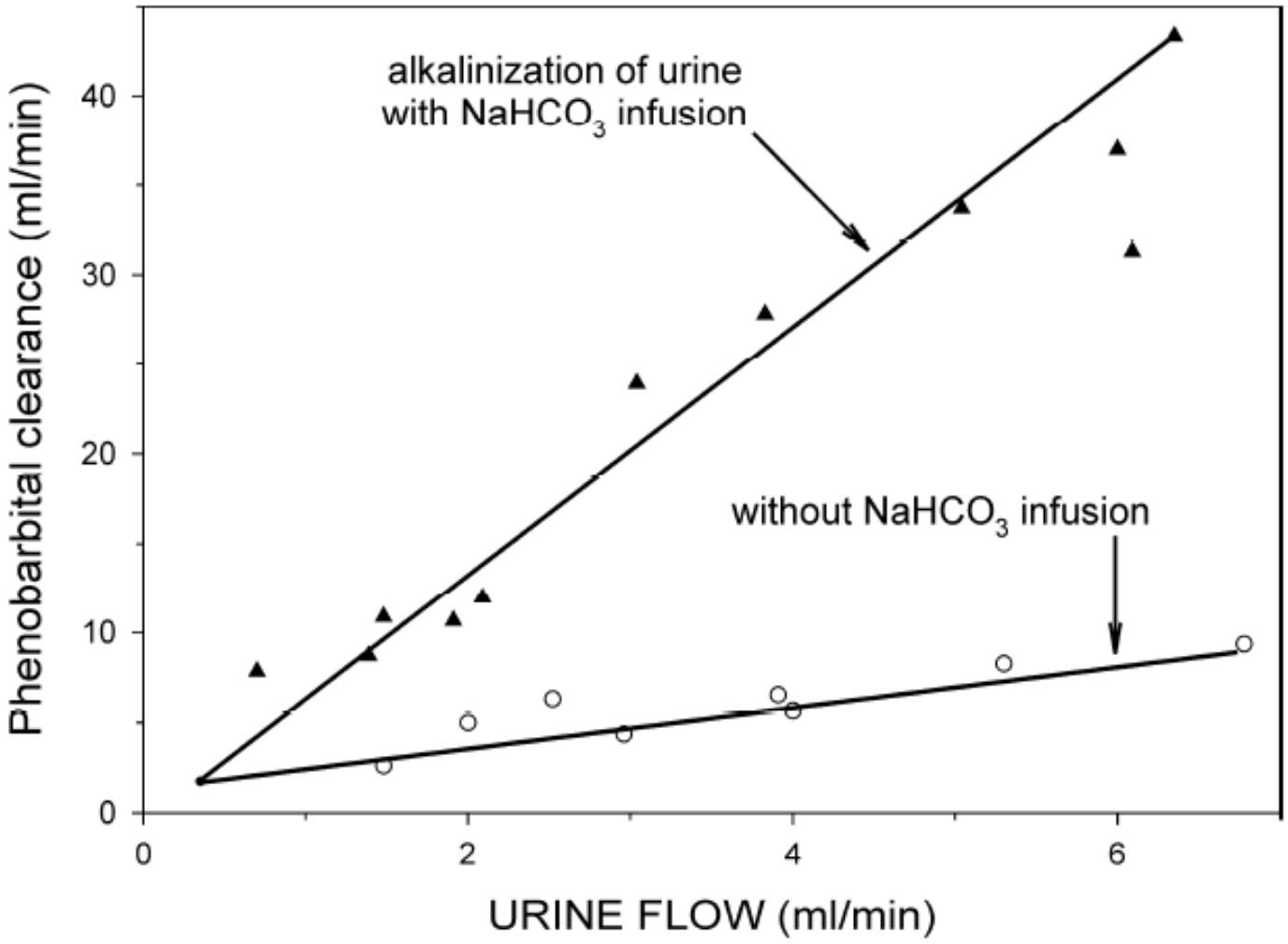
pKa ~ 3,5

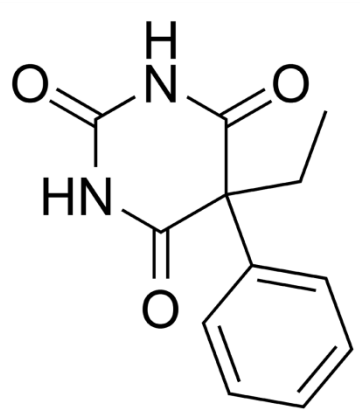


Amphetamine

pKa ~ 10

pH vs. pKa


alkalinization of urine
with NaHCO3 infusion
without NaHCO3 infusion
Phenobarbital clearance (ml/min)
URINE FLOW (ml/min)
0
10
20
30
40
0
2
4
6


H
N
O
O
HN
O

pKa ~ 7,3

Absorption through the skin

Mechanism: diffusion

The concentration gradient is the driving force:

Example: **hexachlorophene in baby powder**

Accidentally **6 %** instead of 1 %

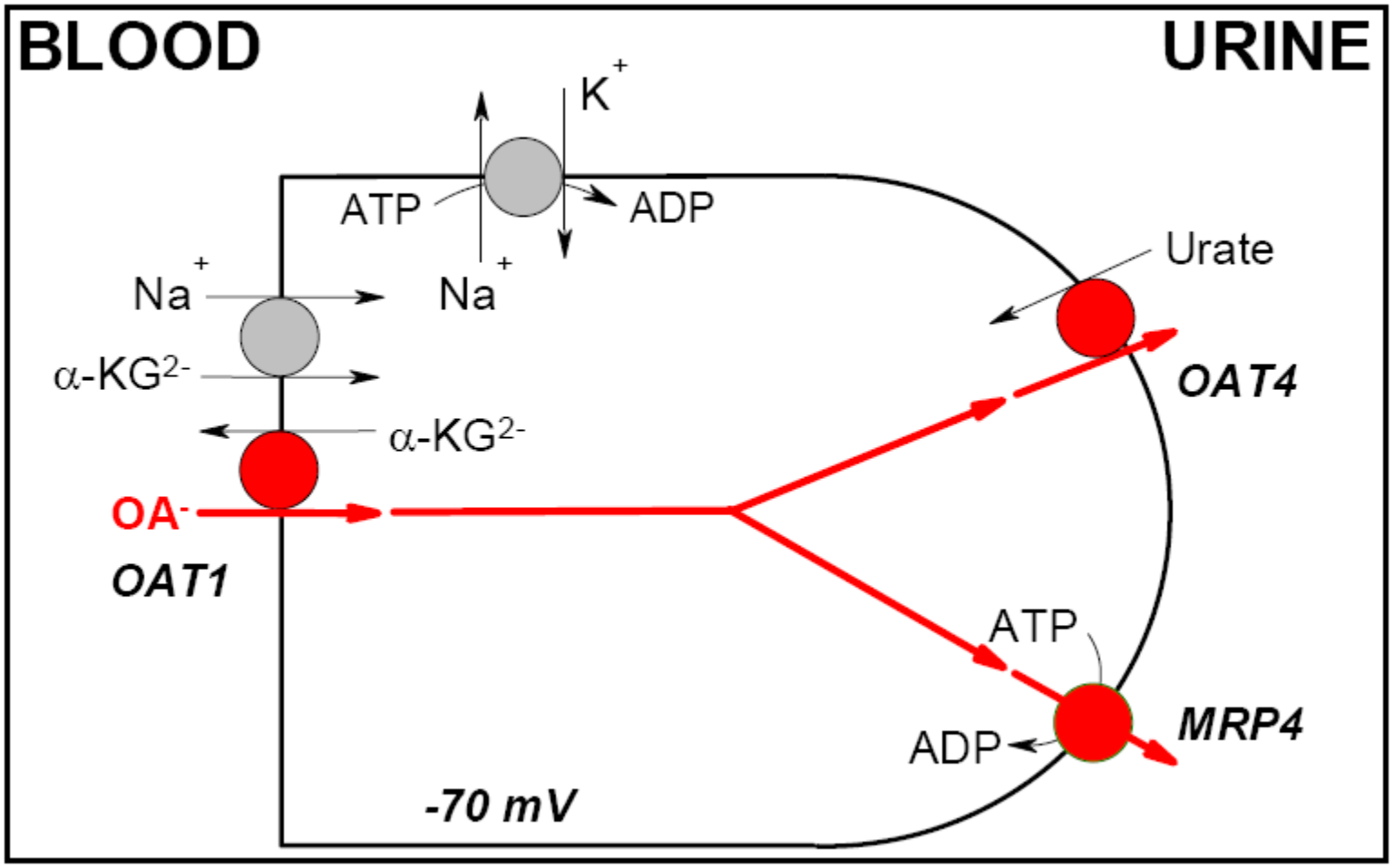
↓

encephalopathia, ulceration of the skin

↓

36 children had died

Urinary excretion of organic anions



Urinary excretion of organic cations

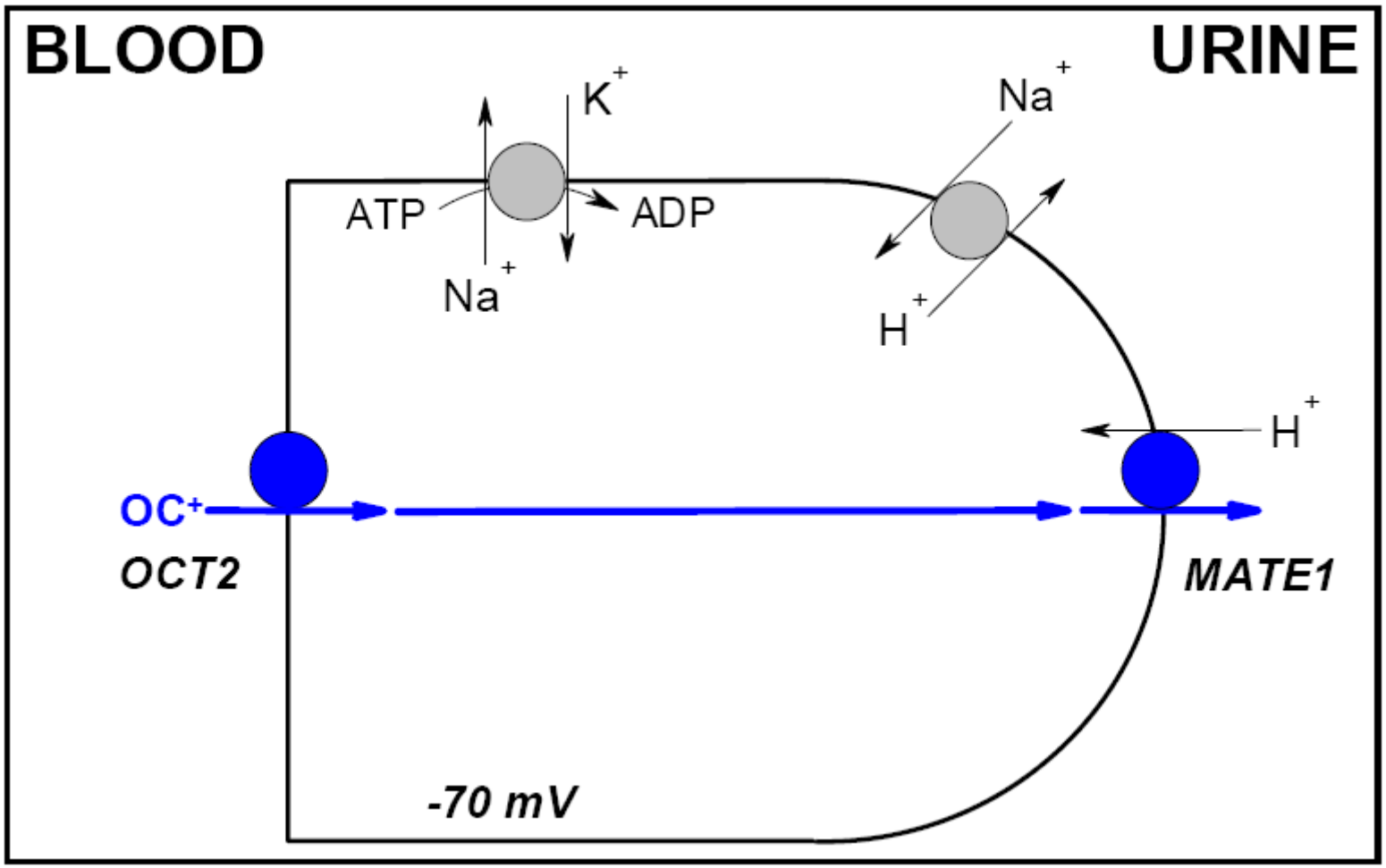


TABLE: Mdr1a (Pgp)-knockout mice exhibit much higher brain/plasma concentration ratios for Pgp substrate drugs than the wild type (WT) mice. The WT mice pump these drugs out from their brain capillary endothelial cells back into the blood, counteracting their entry to the brain. Thus, Pgp represent a biochemical mechanism for the blood-brain barrier (BBB).

Drug	BRAIN : PLASMA ratio	
	Mdr1a (+/+)	Mdr1a (-/-)
Cyclosporin A (Immunosuppressant)	0.28	3.3
Digoxin (Cardiotonic)	0.06	1.7
Ivermectin (Anthelminthic)	0.09	2.5
Loperamide (Antidiarrheal)	0.31	2.1
Quinidine (Antiarrhythmic)	0.09	0.77
Vinblastine (Antineoplastic)	1.67	18.7

Pgp substrates do not have CNS effects. Examples:

- **Fexofenadine** — *Antihistamine with no sedative effect*
- **Diphenoxylate, loperamide** — *Opioids for slowing intestinal motility, but not for pain relief!*
- **Vinblastine, adriamycin** — *Antitumor drugs, but not for brain tumors!*

A. ABSORPTION FROM THE GI TRACT

I. MECHANISMS:

1. **Diffusion**: for most drugs

2. **Carrier-mediated transport** – for several drugs:

Secondary active transport:

- *Amino acid transporter* (Na^+-coupled): **L-DOPA**, α-methyldopa, gabapentin
- *Purine nucleoside transporter* (Na^+-coupled): ribavirin
- *Phosphate transporter* (Na^+-coupled): foscarnet

Tertiary active transport:

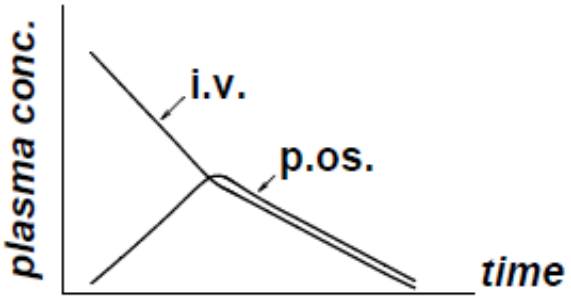
- *Monocarboxylate transporter* – **MCT** (H^+-cpl.): salicylate, valproate, pravastatin
- *Peptide transporter* – **PEPT** (H^+-coupled, *see Figure*):
  - β-lactam antibiotics, e.g. ceftibuten
  - **ACE** inhibitors, e.g. captopril, lisinopril
- *Divalent metal transporter* – **DMT** (H^+-coupled): Fe^{++} (Cd^{++})
- *Organic anion-transp. polyp.* - **OATP** (OA-GSH exch.): fexofenadine, digoxine

3. **Receptor-mediated endocytosis**: vitamin B_{12} – intrinsic factor complex

ORAL BIOAVAILABILITY

1. Definition: the *fraction* (F) of orally administered dose that reaches the systemic circulation

2. Detemination of *F*:



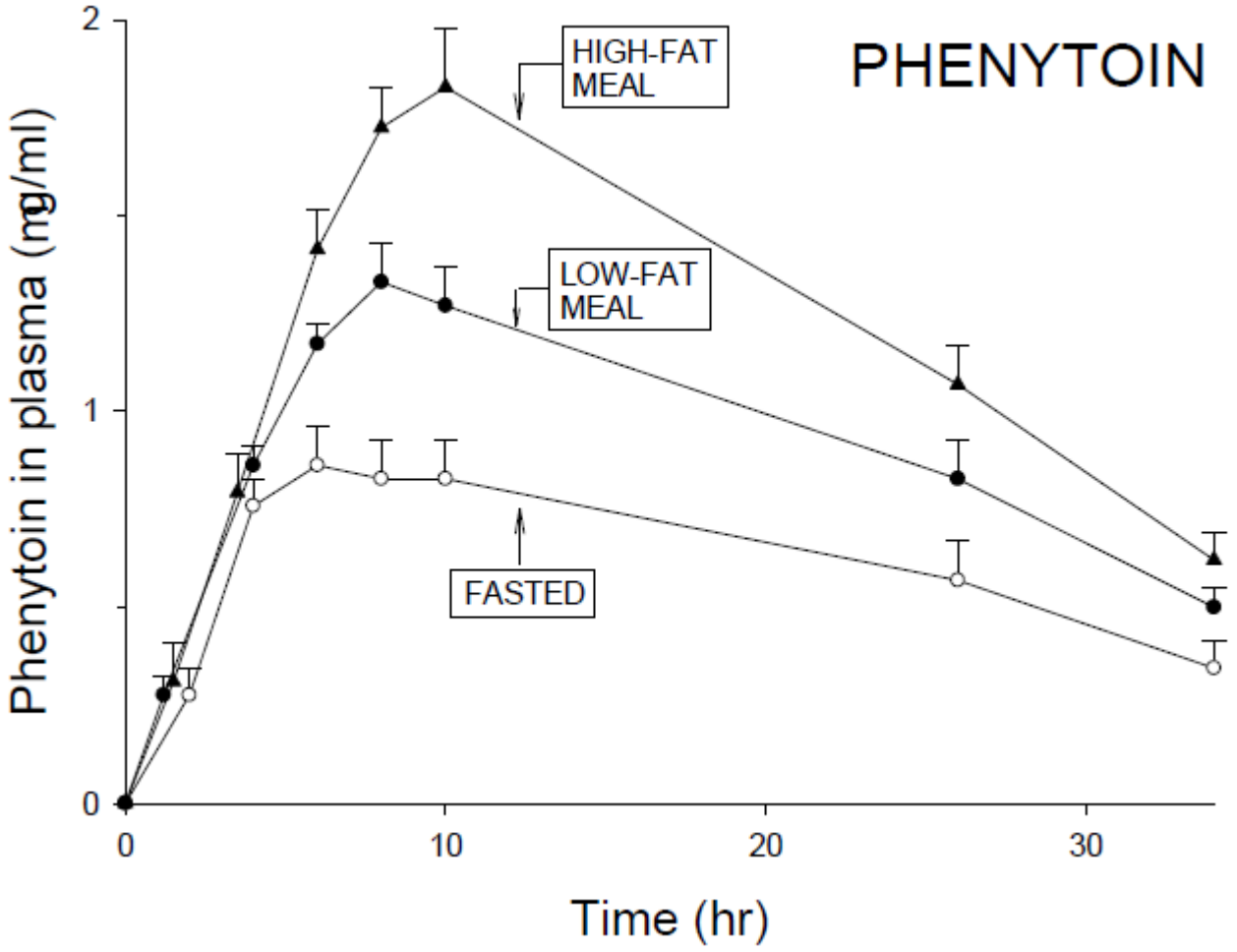
$$F = AUC_{p.o.} : AUC_{i.v.}$$

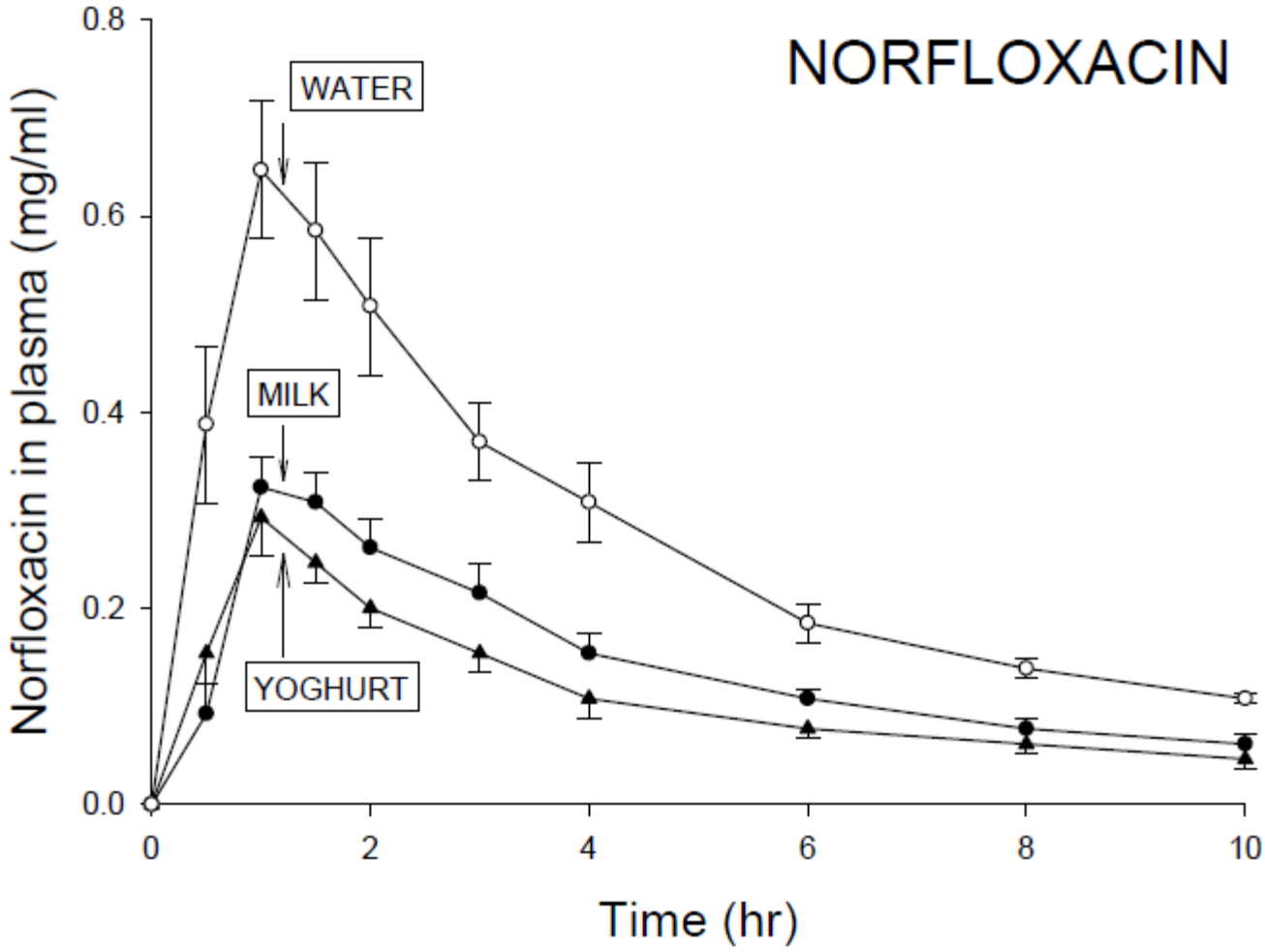
Presystemic elimination of the drug (= first pass elimination)

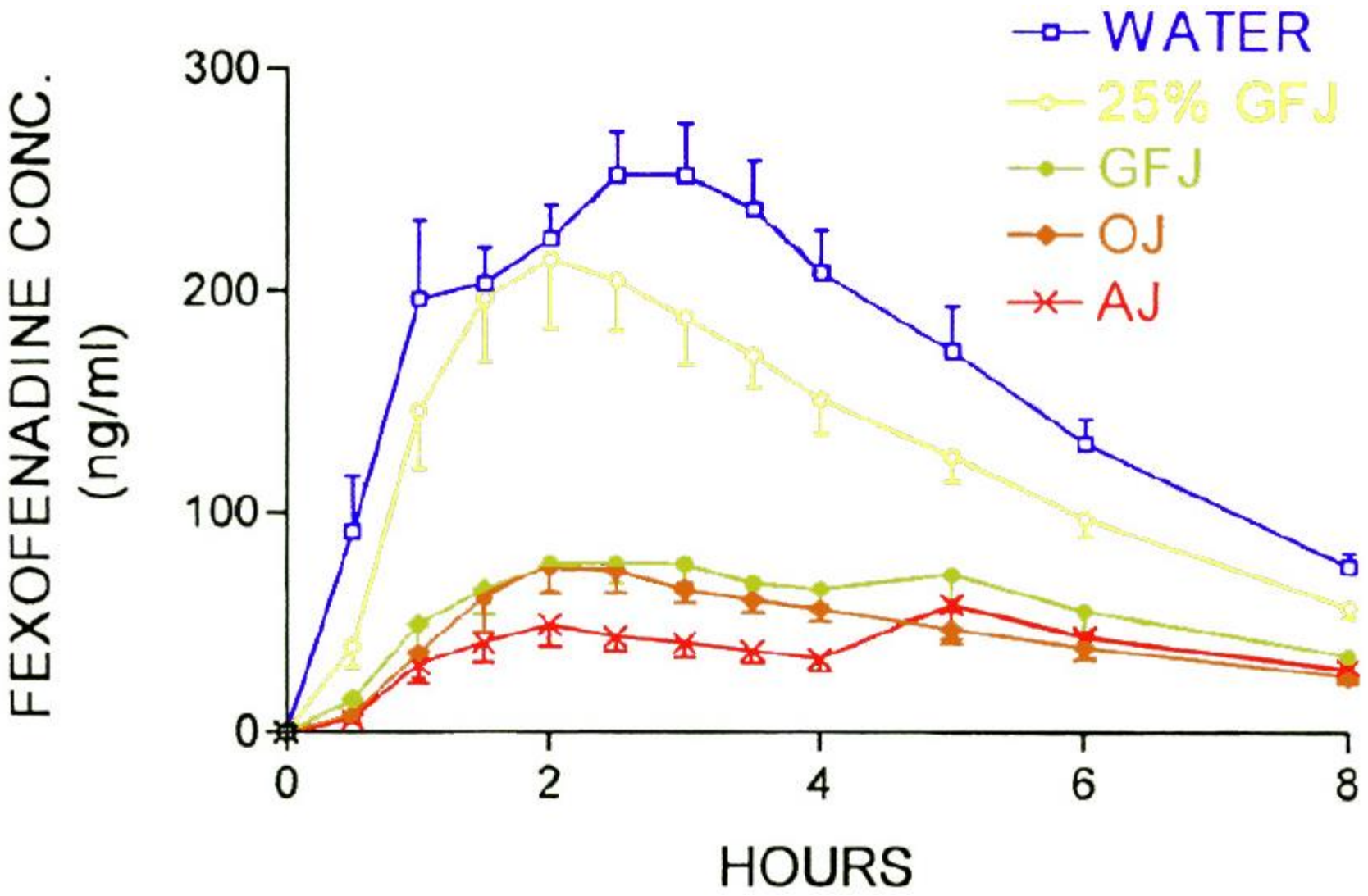
- *In the intestinal mucosa* (intestinal presystemic elimination)
  - by biotransformation: - CYP3A4: cyclosporine (F=0.3), midazolam (F=0.4)
    - MAO: tyramine (MAO-A inhib. → cheese react.)
    - SULT: terbutaline (F=0.1), isoprenaline
    - UGT: morphine (F=0.2), labetalol
  - by export into the lumen by Pgp (or by mrp2): Digoxin (F=0.6), verapamyl (F=0.2), cyclosporine (F=0.3), paclitaxel (F=0.07), vinca alkaloids (F<0.02)

- *In the liver* (hepatic presystemic elimination) *by uptake and biotransformation:*
  - lidocaine: by N-deethylation (F= 0.3)
  - verapamyl: by N-demethylation (F = 0.2; *i.v.: 5 mg, p.o.: 40-80 mg!!!)*
  - propranolol: by aromatic hydroxylation (F=0.3)

- *In both the intestinal mucosa and the liver, e.g.:*
  - morphine: by glucuronidation (F=0.2)


PHENYTOIN
HIGH-FAT MEAL
LOW-FAT MEAL
FASTED
Phenytoin in plasma (mg/ml)
Time (hr)
0
1
2
0
10
20
30


NORFLOXACIN
WATER
MILK
YOGHURT
Norfloxacin in plasma (mg/ml)
0.0
0.2
0.4
0.6
0.8
0
2
4
6
8
10
Time (hr)


WATER
25% GFJ
GFJ
OJ
AJ
FEXOFENADINE CONC.
(ng/ml)
300
200
100
0
0
2
4
6
8
HOURS

2. Biological factors:

a. Blood flow:

- INITIALLY, distribution of drugs is dictated by the blood flow: drugs distribute first to tissues with large blood flow (lung: 14, kidneys: 4, heart: 1, brain: 1, liver: 1 ml/min/g). For example, all *i.v. general anesthetics* rapidly distribute to the brain and therefore cause anesthesia within 1 min.
- LATER, the distribution may be altered by „tissue affinity" – **redistribution** occurs.
  - All i.v. general anesthetics redistribute to other tissues, causing decline of the anesthetic concentration in the brain and recovery of the patient from anesthesia in ~10 minutes.
  - Thiopental (a highly lipid soluble i.v. gen. anesthetic) redistributes to the muscle and fat, forming depots there. Therefore repeated doses of thiopental would cause longer and longer anesthesia. Thus thiopental, unlike other anesthetics, should not be injected repeatedly and is not suitable for total i.v. anesthesia.
  - Chloroquine (a cationic amphiphilic antimalarial drug) gradually redistributes to the liver due to pH-entrapment within the lysosomes (pH ~5) of hepatocytes.
  - Lead redistributes from the soft tissues into the bone due to incorporation into Ca-apatite.

CONSEQEUENCES OF STRONG PLASMA PROTEIN BINDING

a. General rules:

Rule 1:

Plasma proteins represent silent binding site (depot) for drugs:

- ***the BOUND drug is inactive,***
- ***the FREE, UNBOUND drug can leave the blood and act and can be acted upon.***

As long as a drug is bound to plasma protein, it

- ***cannot act (as it can not reach the site of action)***
- ***cannot be eliminated (as it can not reach enzymes and transporters, and can not be filtered at the glomeruli).***

b. Specific consequences of strong PPB:

1. Delayed the onset of effect

Extensive PPB delays and restricts distribution of the drug to the target, therefore it delays the onset of effect, or (in extreme case) may even prevent the systemic effect.

2. Delayed elimination

Extensive PPB restricts distribution of the drug to the organs of drug elimination (biotransformation and excretion) and thus delays the elimination of the drug.

Tissue accumulation
(examples)

ADIPOSE TISSUE

Accumulates and stores highly lipid soluble drugs/chemicals:

- ***Amiodarone, probucol, ergocalciferol (Vit D_2), terbinafine, fulvestrant***
- ***Halogenated hydrocarbons, halogenated ethers*:**
  e.g.: halothane, (methoxyflurane)
  DDT (dichloro-diphenyl-trichloroethane)
- ***Drugs esterified with long-chain fatty acids (depot drugs, prodrugs!)*:**
  e.g.: pipothiazine ***palmitate***
  testosterone *cypionate* (cypionate = cyclopentano-propionate)

BONE:

Contains *calcium-apatite*: $Ca_{10}[(PO_4)_6(OH)_2]$,

- **to which some drugs** (with affinity to calcium) **may bind** (by adsorption):
  tetracyclines **(deposition into growing bone) → discoloration of teeth**
- **into which some ions may be incorporated:**
  - **In place of calcium ions:**
    - **Pb^{2+} → stored in bone** (increasingly mobilized during pregnancy → fetus!!!)

Drugs may be eliminated by biotransformation and/or excretion:

ELIMINATION MECHANISMS	
Chemical mechanism: **BIOTRANSFORMATION**	*Physical mechanism:* **EXCRETION**

CONTRIBUTION OF EXCRETION AND BIOTRANSFORMATION TO ELIMINATION OF DRUGS – Examples		
DRUGS ELIMINATED BY BIOTRANSFORMATION, i.e. fully biotransformed, and excreted only as metabolites	**DRUGS ELIMINATED BY EXCRETION, i.e. NOT biotransformed and excreted as parent drugs (in unchanged form)**	**DRUGS ELIMINATED BY BOTH BIOTRANSFORMATION AND EXCRETION, i.e. excreted both as parent drugs and as metabolites**
Tricyclic antidepressants form several metabolites Phenothiazines form several metabolites Chloramphenicol forms one main metabolite, the glucuronic acid conjugate	Benzylpenicillin Aminoglycosides Metformin Tubocurarine Amantadine	Salicylates Paracetamol (Acetaminophen) Phenobarbital

The sites of biotransformation:

- Predominantly, the **liver** (where enzymes are typically most abundant)
  The liver contributes to both the presystemic (or first-pass) and the systemic elimination of many drugs, partly by biotransformation.
- Often **other tissues,** as well. For example:
  - in the intestinal mucosa cells (e.g. by CYP3A4, SULT) – The enterocytes also contribute to both the presystemic and the systemic elimination of many drugs, partly by biotransformation.
  - in the renal tubular cells (e.g. glycine conjugation of salicylic acid, the metabolite of aspirin)
- **The colon, by bacteria** – e.g. azo and C=C bond reduction, hydrolytic reactions

1. TYPICALLY: ACTIVE DRUG → INACTIVE METABOLITE

• warfarin	→	7-hydroxy-warfarin	CYP2C9
• phenytoin	→	4-hydroxy-phenytoin	CYP2C9
• theophylline	→	1- or 3-methylxanthine	CYP2A1
• morphine	→	morphine-3-glucuronide	UDP-GT
• acetaminophen	→	acetaminophen-glucuronide	UDP-GT
• isoniazide	→	acetyl-isoniazide	NAT2

2. EXCEPTIONALLY: ACTIVE METABOLITE IS FORMED

a. Inactive parent compound (PRODRUG) → active metabolite

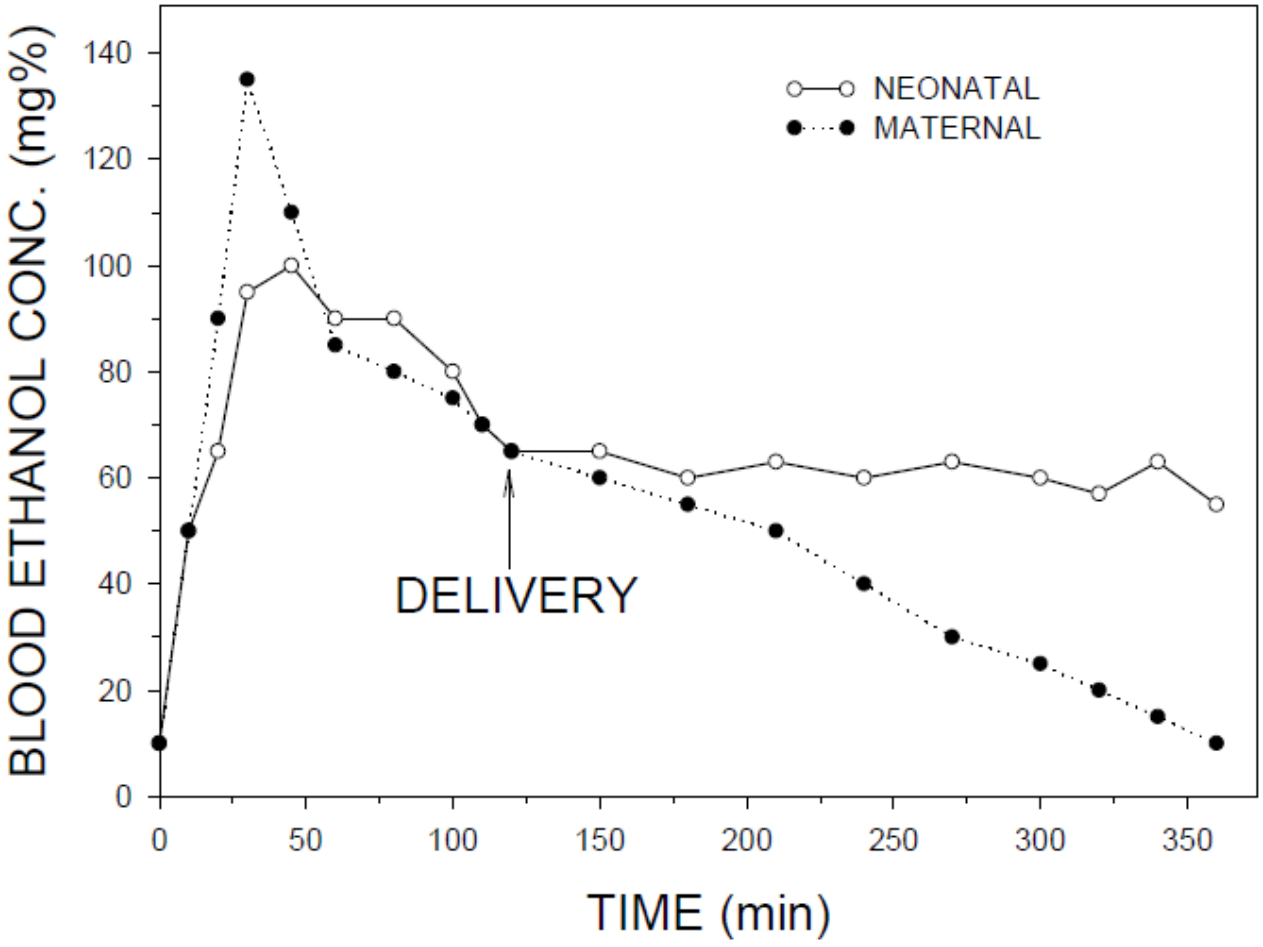
• cyclophosphamide	→	phosphoramide mustard	CYP2B6
• tamoxifen	→	4-hydroxy-tamoxifen	CYP2D6
• parathion	→	paraoxon	CYP3A4
• terfenadine	→	alcohol → acid	CYP3A4
• chloral hydrate	→	trichloroethanol	ADH (rev.), AR
• sulfasalazine	→	5-aminosalicylic acid	Azo-reductase
• oxcarbazepine	→	10-hydroxy-carbazepine	AK-reductase
• lovastatin (lactone)	→	lovastatin (free acid)	Paraoxonase
• enalapril (ester)	→	enalaprilate (free acid)	Esterase
• fenofibrate (ester)	→	fenofibric acid (free acid)	Esterase
• ezetimibe	→	ezetimibe-glucuronide	UDP-GT
• minoxidyl	→	minoxidyl-sulfate	SULT
• ethacrynic acid (EA)	→	EA-cysteine	GST→GGT, DP

b. Active parent compound → active metabolite

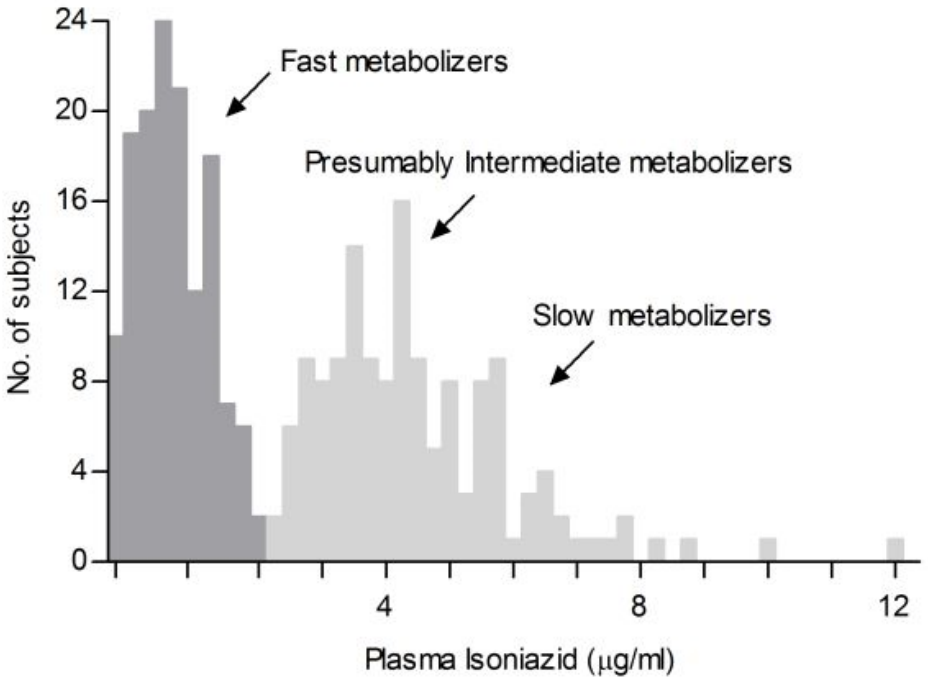
• phenylbutazone	→	γ-OH-phenylbutazone	CYP2D6, 2C9
• carisoprodol	→	meprobamate	CYP2C19
• risperidone	→	9-OH-risperidone (paliperidone)	CYP2D6
• imipramine	→	desmethyl-imipramine	CYP2D6
• codeine	→	morphine	CYP2D6
• diazepam	→	nordiazepam → oxazepam	CYP → CYP
• morphine	→	morphine 6-glucuronide	UDP-GT

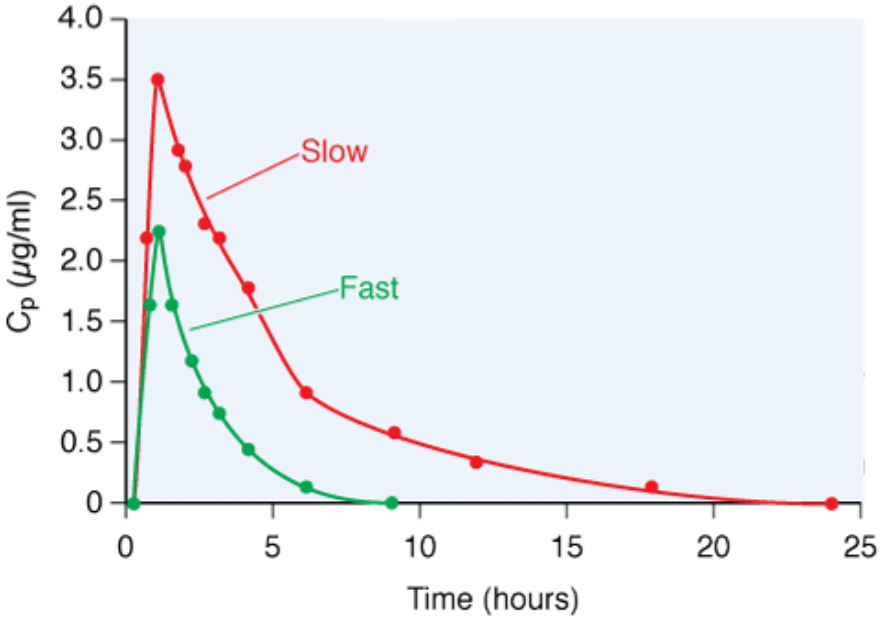
c. „Non-toxic" parent compound → toxic metabolite

• acetaminophen	→	N-acetyl-p-benzoquinoneimine	CYP2E1
• halothane	→	trifluoroacetyl chloride	CYP2E1
• cyclophosphamide	→	acrolein	CYP3A4, 2B6
• methanol	→	formic acid	ADH → ALDH
• ethylene glycol	→	glycolic-, glyoxylic- oxalic acid	ADH → ALDH
• doxorubicin	→	doxorubicinol	AK-reductase


BLOOD ETHANOL CONC. (mg%)
140
120
100
80
60
40
20
0
0
50
100
150
200
250
300
350
TIME (min)
NEONATAL
MATERNAL
DELIVERY

Genetic differences – fast vs. slow acetylators

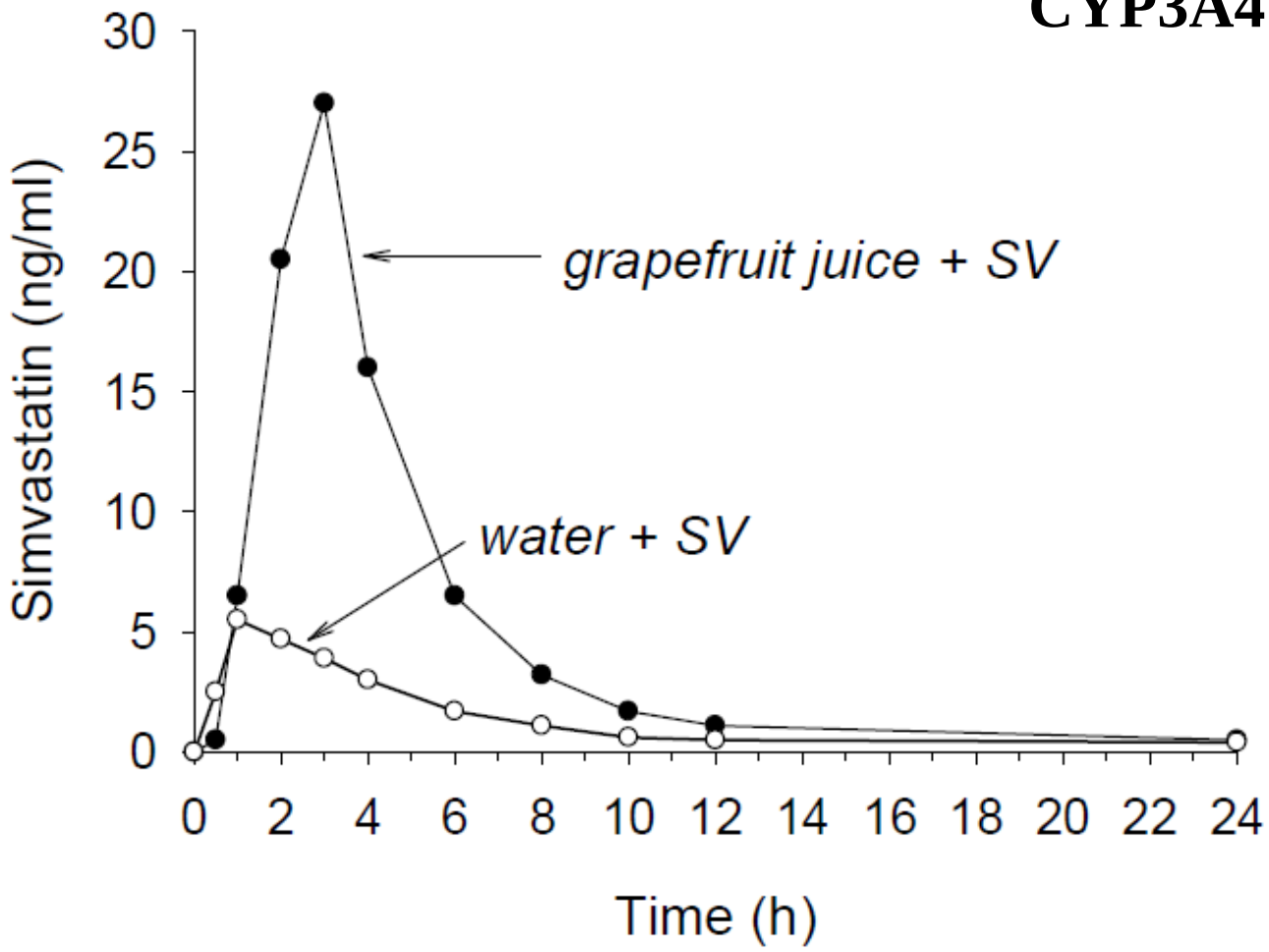




Source: Brunton LL, Chabner BA, Knollmann BC: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition:* www.accessmedicine.com

CYP inhibition

CYP3A4: naringenin, bergamottin



A. RENAL EXCRETION MECHANISMS

I. GLOMERULAR FILTRATION – is the mechanism for the elimination of:

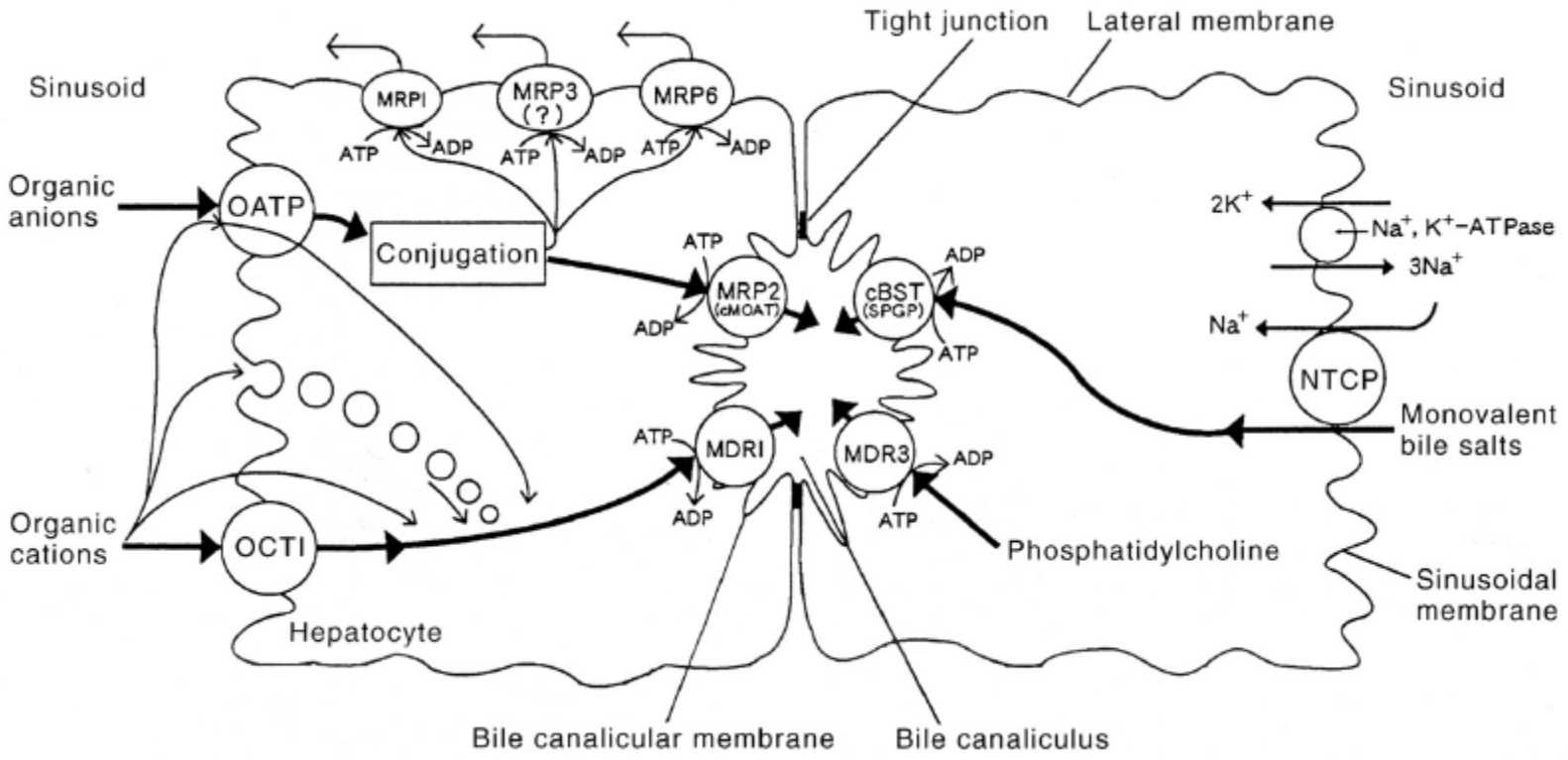
aminoglycosides, vancomycin, fluconazole, flucytosine, vigabatrin, gabapentin, topiramate, Li

GENERAL FEATURES:

- **Prerequisites for efficient filtration: 1. Water solubility 2. Low affinity to plasma proteins**
- **Rate determining factors: 1. Free drug concentration in plasma 2. Glomerular Filtration Rate**
- **Maximal renal clearance achievable: GFR (= $Cl_{KREATININE}$; only if PP-binding = 0, Reabs. = 0)**

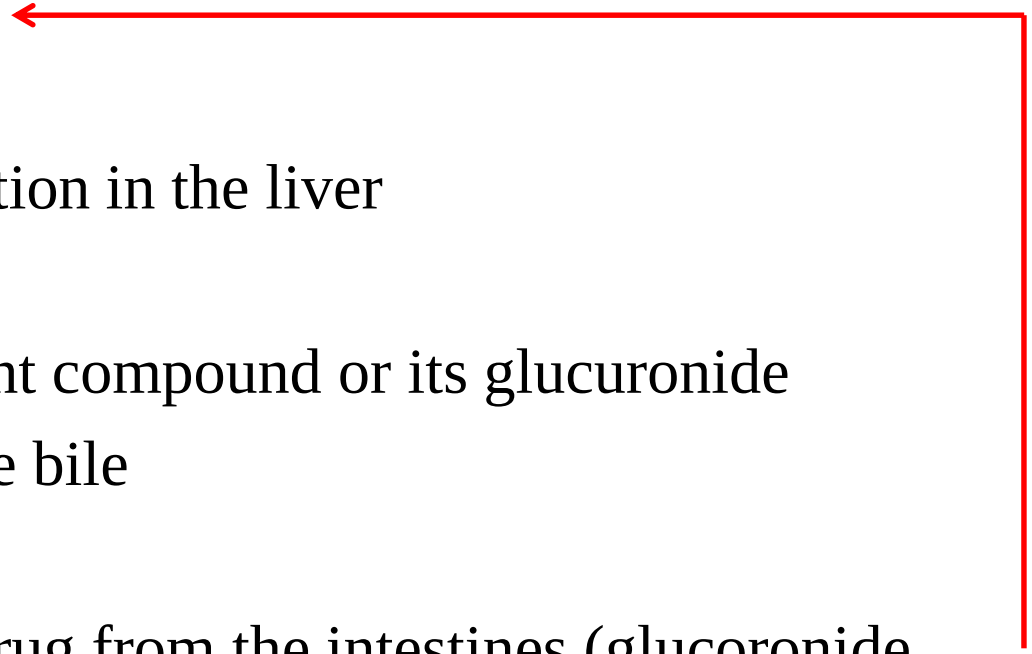
II. TUBULAR SECRETION – mediated by transporters in the BLM and BBM

- **Certainly involved if the renal clearance of a drug is > GFR (= $Cl_{KREATININE}$)**
- **Maximal renal clearance of a drug achievable is: RBF (= Cl_{PAH})**


Tight junction
Lateral membrane
Sinusoid
Sinusoid
MRPI
MRP3
(?)
MRP6
ATP
ADP
Organic
anions
OATP
Conjugation
2K+
Na+, K+-ATPase
3Na+
Na+
MRP2
(cMOAT)
cBST
(SPGP)
NTCP
Monovalent
bile salts
MDRI
MDR3
Organic
cations
OCTI
Phosphatidylcholine
Sinusoidal
membrane
Hepatocyte
Bile canalicular membrane
Bile canaliculus

Enterohepatic circulation (EHC)

1. drug absorption
   ↓
2. possible glucuronidation in the liver
   ↓
3. excretion of the parent compound or its glucuronide conjugate through the bile
   ↓
4. reabsorption of the drug from the intestines (glucoronide conjugates are commonly cleaved by the bacterial microflora resulting in the reappearance of the parent compound)



Consequence: slow elimination of the drug from the organism

Part A. ELIMINATION KINETICS

I. INTRODUCTION

Pharmacokinetic analysis deals with the
mathematical description of
- absorption,
- distribution, and
- elimination of drugs.

We will focus on the mathematical description of elimination, as that is most useful for us. For example, calculation of the clearance, an important descriptor of the elimination of a drug, allows us to determine the dose rate of the drug that is needed to reach a therapeutic concentration in the plasma.

Elimination (which includes excretion and biotransformation) is solely responsible for the **decline of the concentration of the drug in blood plasma** following distribution.

Therefore, the elimination of drugs can be mathematically described by analyzing the **plasma concentration versus time curve** (PC*vs*TC), i.e. the curve that depicts the disappearance of the drug from the plasma.

Disappearance of drugs from the blood plasma may follow two types of kinetics:

- **First-order kinetics** – called first-order because the change in plasma concentration (c) in time (t), i.e. the rate of elimination, is described by the following equation (where k is the rate constant):

  $\Delta c/\Delta t = -k \cdot c^1 = -k \cdot c$ That is: *the rate of elimination is concentration-dependent.*

  First-order kinetics characterizes the elimination of most drugs (when given in the therapeutic dose range).

- **Zero-order kinetics** – called 0-order because the change in plasma concentration (c) in time (t), i.e. the rate of elimination, is described by the following equation:

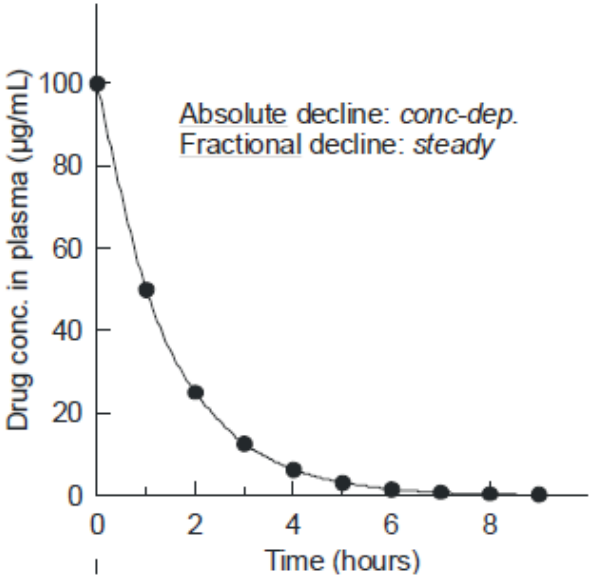
  $\Delta c/\Delta t = -k \cdot c^0 = -k$ That is: *the rate of elimination is concentration-independent.*

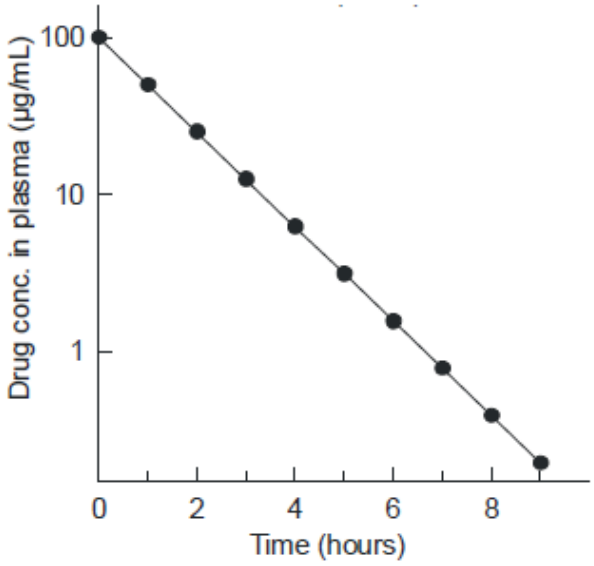
  Zero-order kinetics characterizes the elimination of a few drugs (when given in the therapeutic dose range, however, it is not uncommon in drug overdose).

FIRST-order elimination

The shape of the PC*vs*TC depends on how we plot the plasma concentration:

- on an **arithmetic** scale: monoexponential decline = concave line (figure: top left)
- on a **logarithmic** scale: linear decline = straight line (figure: bottom left)





The features of first-order elimination can be deduced from the PC*vs*TC:

1. The **absolute** decline in plasma concentration is concentration dependent, and it is directly related to the plasma concentration:

- Large decline – at high concentration (i.e., early after administration)
- Small decline – at low concentration (i.e., later after admin)

See the absolute declines in the figure (top left):
1st hr: **50 mg/L**, 2nd hr: **25 mg/L**, 3rd hr: **12.5 mg/L**.

This implies: **The rate of elimination is proportional to concentration of the drug.**

2. The **fractional** decline in plasma concentration is steady, concentration independent

See the fractional declines in the figure (top left):
1st hr: **50%**, 2nd hr: **50%**, 3rd hr: **50%**.

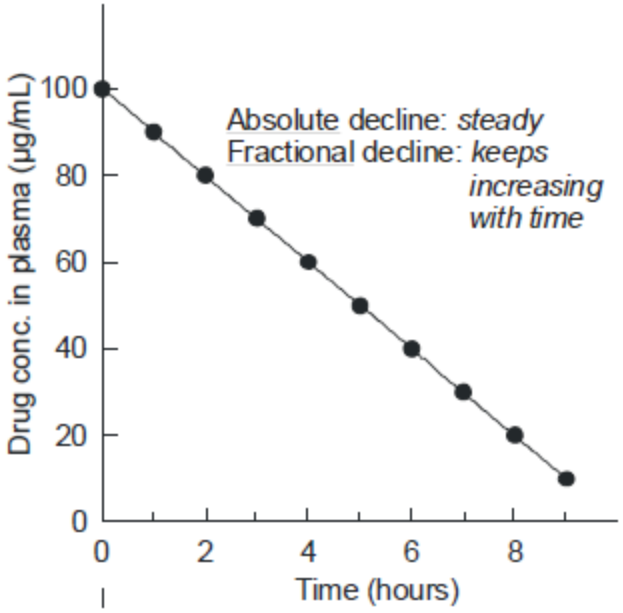
This implies: **The same fraction of the dose is eliminated in each unit of time.**

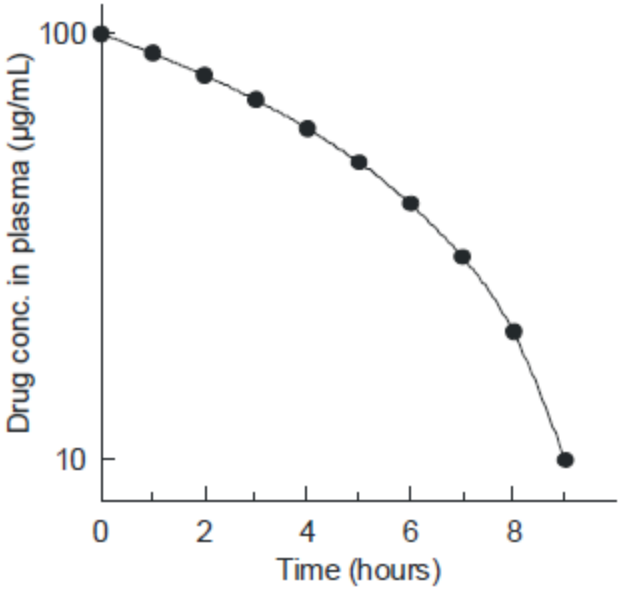
IN SUMMARY: **FIRST-order elimination is conc-dependent elimination.** Therefore, decreasing absolute amounts of the drug, but the same fraction of the dose in the body (body burden) is eliminated per unit of time as the time passes after dosing.

ZERO-order elimination

The shape of the PC*vs*TC, depends on how we plot the plasma concentration:

- on an **arithmetic** scale: straight line (figure: top right)
- on a **logarithmic** scale: convex line (figure: bottom right)





The features of ZERO-order elimination can be deduced from the PC*vs*TC:

1. The **absolute** decline in plasma concentration is steady (constant), and it is independent of the concentration.

See the absolute declines in the figure (top right):
1st hr: **10 mg/L**, 2nd hr: **10 mg/L**, 3rd hr: **10 mg/L**.

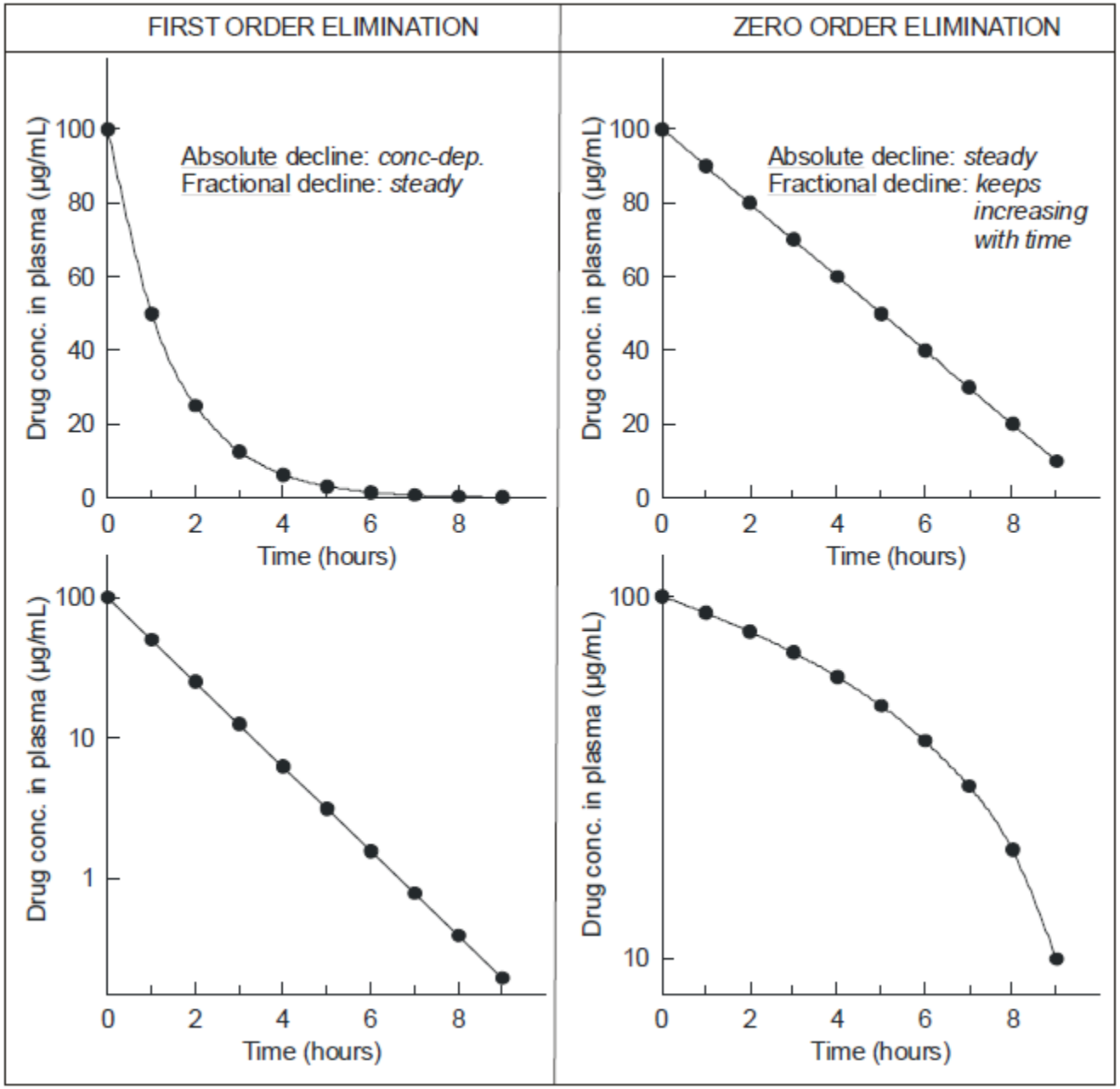
Implication: **The rate of elimination is steady (constant), i.e. concentration independent: the same amount of drug is eliminated at each unit of time.**

2. The **fractional** decline in plasma concentration is concentration-dependent and is inversely related to the plasma concentration.

See the fractional declines in the figure (top right):
1st hr: **10%** (from 100 to 90 μg/mL), 6th hr: **20%** (from 50 to 40 μg/mL).

Implication: **Increasingly larger fractions of the dose of the drug are eliminated with the passage of time after drug administration.**

IN SUMMARY: **ZERO-order elimination is a concentration-independent, capacity-limited elimination.** Therefore, the same absolute amount of the drug is eliminated in each unit of time, which represents larger and larger fractions of the dose in the body (body burden) as time passes after dosing.


FIRST ORDER ELIMINATION
ZERO ORDER ELIMINATION
Drug conc. in plasma (µg/mL)
100
80
60
40
20
0
Absolute decline: conc-dep.
Fractional decline: steady
0
2
4
6
8
Time (hours)
Absolute decline: steady
Fractional decline: keeps increasing with time
10
1

What determines the elimination kinetics of a drug?

The elimination kinetics depends on the mechanism of drug elimination:

- If the elimination mechanism is **concentration-dependent**, then the elimination of the drug follows **FIRST-order** kinetics.
- If the elimination mechanism is **capacity-limited** (concentration-independent), then the elimination of the drug follows **ZERO-order** kinetics.

Three possible cases: 1, 2a, 2b

1. For drugs that are eliminated only by diffusion or filtration (which are conc-dependent processes), **the elimination will follow FIRST-order kinetics.**

N_2O (nitrous oxide): is eliminated by exhalation (i.e., diffusion across the alveolar cells), which is a concentration-driven process → **FIRST-order elimination**

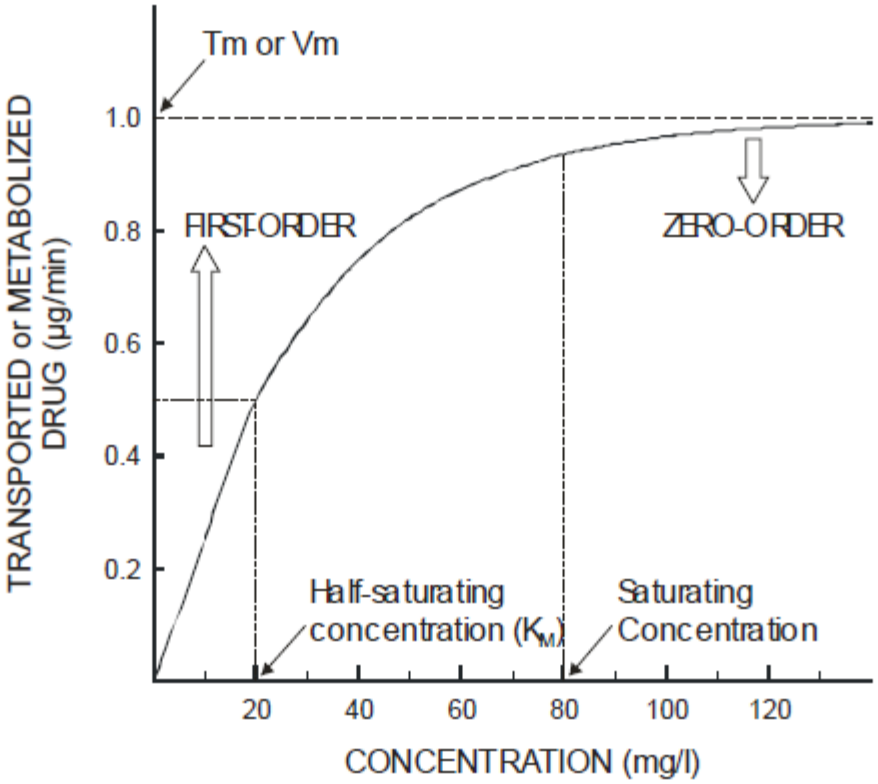
Aminoglycoside antibiotics: are eliminated by glomerular filtration, the rate of which is dependent on the plasma concentration → **FIRST-order elimination**

2. **For drugs that are eliminated via**

- **excretion by carrier-mediated transport** (tubular secretion, biliary excretion), or
- **enzyme-catalyzed biotransformation, the elimination kinetics depends on the *concentration of the drug*** in the vicinity of the transporter or the enzyme.

  (a) If the drug conc is around or below the K_M → **FIRST-order elimination** occurs, because then the transport rate or the metabolite formation rate is concentration-dependent (see figure)

  (b) If the drug conc is much higher than the K_M and is close or above the *saturating concentration* → **ZERO-order elimination** occurs, because then the transport rate or the metabolite formation rate is steady (constant), concentration-independent and capacity-limited (see figure)



Ad 2a. Examples:

Penicillin:

Elimination mechanism: tubular secretion by OAT1 → MRP2

OAT1 has high capacity (3 M units/hr/person), low affinity (high Km)
The usual dose (concentration) of penicillin (1 M units/day) does not saturate OAT1

→ **concentration-dependent, FIRST-order elimination**

Lidocaine:

Elimination mechanism: N-deethylation by CYP3A4

High amount of CYP3A4 is in human liver + it has high capacity, low affinity (high Km)
The therapeutic dose (concentration) of lidocaine, does not saturate CYP3A4

→ **concentration-dependent, FIRST-order elimination**

Ad 2b. Examples for drugs whose elimination is conc-independent = capacity limited, therefore their elimination follows **ZERO-order kinetics**.

Phenytoin:
Elimination mechanism: 4-hydroxylation by **CYP2C9**

- CYP2C9 is present in low amounts in human liver.
- The Km CYP2C9 for phenytoin is 6 mg/L, its therapeutic conc is 10-20 mg/L.

If the dose of phenytoin is >300 mg, then its concentration >15 mg/L (higher than Km), and then CYP2C9 becomes saturated:
the metabolite formation rate becomes limited by the capacity of CYP2C9
→ **capacity-limited, concentration-independent, ZERO-order elimination**

Salicylic acid:
Elimination mechanism: **conjug. with glycine** to form salicyl-glycine (salicyluric acid)

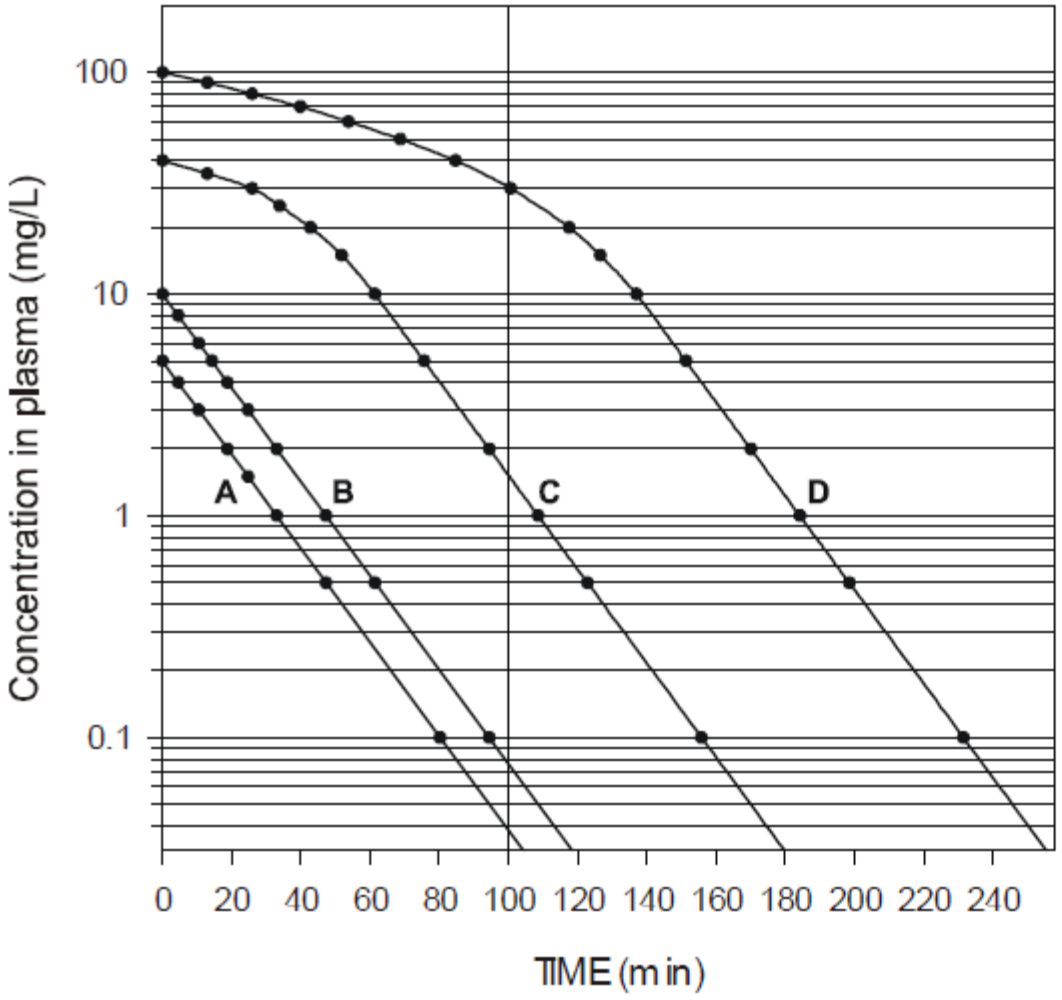
Glycine availability limits the capacity of conjugation if dose of aspirin is >2 g
→ **capacity-limited, concentration-independent, ZERO-order elimination**

Ethanol:
Elimination mechanism: **NAD-dependent dehydrogenation by ADH**

NAD availability limits the capacity alcohol dehydrogenation
NAD availability is limited by reoxidation of NADH to NAD
→ **capacity-limited, concentration-independent, ZERO-order elimination**

Capacity: 10 g ethanol/hr/adult man,
The fall in blood ethanol level is steady: 0.15 – 0.20 g/L

V. Change in the kinetics of elimination from first-order to zero-order



DOSE mg/kg	C_0 mg/L	C_{100} mg/L
5	5	0.038
10	10	0.076
40	40	1.7 !
100	100	30 !

The consequence of the change in the kinetics of elimination from 1st to 0-order:

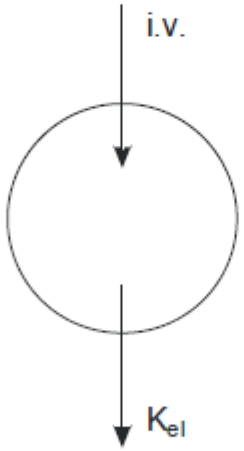
- As long as the elimination remains FIRST order,
  the plasma concentration at all time points increases **proportionally** to the dose,
  which is commonly expected.

- As soon as the elimination becomes ZERO order,
  the plasma conc. at later time points increases **disproportionally** with the dose.

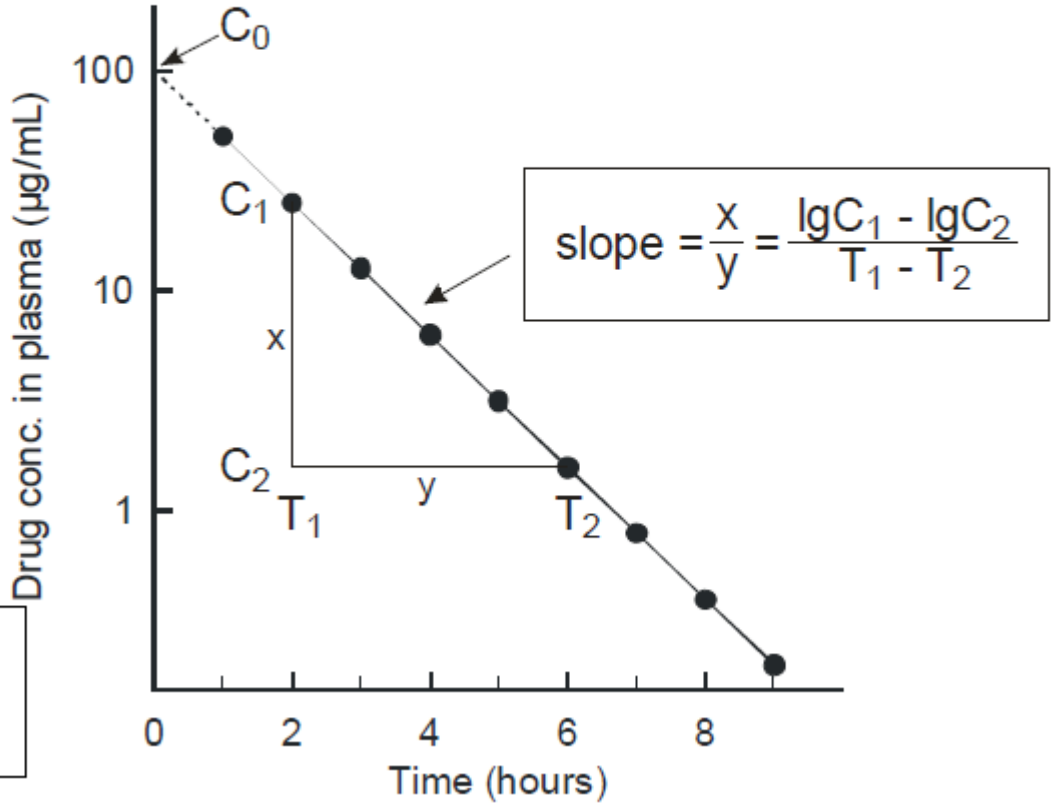
  Therefore, the drug concentration in the plasma remains high for a long time
  → The drug may cause, unexpectedly, **toxic effects**! For example, phenytoin,
  whose elimination becomes 0-order at a dose of 300 mg, may cause sedation,
  nystagmus, cerebellar ataxia, ophthalmoparesis, and paradoxically, seizures.

I. ANALYSIS OF FIRST ORDER DRUG ELIMINATION

– i.v. administration, one-compartment model



Let us characterize the elimination with meaningful parameters: **C_0, V_d, $T_{1/2}$, and Cl**



$$\text{slope} = \frac{x}{y} = \frac{\lg C_1 - \lg C_2}{T_1 - T_2}$$

C_0 = the apparent conc. of the drug at time 0. Determine it by extrapolation to time 0.

Vd = Volume of distribution

Vd is an apparent volume in which the drug is distributed. It can be determined by:

$$V_d = \frac{D_{iv}}{C_0}$$

At time 0: - the whole dose is in the body
- the plasma concentration is C_0

Why is Vd meaningful?

1. The size of V_d influences the **duration of elimination**: The larger the V_d in which a drug is distributed, the longer the time its elimination from the body takes.
See under Clearance: $T_{1/2}$ is directly related to V_d (and inversely to Cl).

2. The value of Vd may indicate the **water space** in which the drug is distributed and whether the drug accumulates in tissue(s).

Volume of distribution (Vd) of some drugs.

The table also contains the Vd of some model compounds whose Vd value is the measure of a water space in the body.

Chemical/Drug	Vd (L/kg)	Distribution space
Dextran	*0.04*	*Plasma water space*
Heparin	0.06	
Furosemide	0.13	
Leflunomide	0.13	
Aspirin	0.15	
Inulin	*0.17*	*EC. water space*
Carbenicillin	0.18	
Gentamicin	0.28	
Ethanol	*0.57*	*Total-water space*
Phenytoin	0.64	
Paracetamol	0.95	
Diazepam	1.10	
Thiopental	3	
Digoxin	6	
Donepezil	12	Tissue
Imipramine	18	accumulation
Amiodarone	66	
Chloroquine	200	

Kel = Elimination rate constant

Kel is the fraction of dose in the body (=body burden) that is eliminated per unit of time. (Kel is constant for each unit of time if the drug is eliminated by a 1st-order process.)

Kel can be calculated:

$$K_{el} = - \text{slope} \cdot 2.3$$

$$\text{slope} = \frac{x}{y} = \frac{\lg C_1 - \lg C_2}{T_1 - T_2}$$

Determine the **slope** of the PCvsTC plotted in a semilog graph by fitting a rectangular triangle to the straight line that represents the PCvsTC . The slope is the tangent (x/y) of the triangle. The slope has a negative value, because it is a downward slope.

Kel has a unit of hr^{-1}. Kel = 0.1 hr^{-1} means that 10% drug is eliminated hourly.

$T_{1/2}$ = elimination half-life

$T_{1/2}$ is the time during which the plasma concentration of the drug decreases by 50%.

Determination: - graphically (from the graph)
- by calculation:

$$T_{½} = \frac{0.693}{K_{el}}$$

For a drug that is eliminated by a first order process, the $T_{1/2}$ is constant (i.e., independent of the time and the dose).

NOTE: For a drug that is eliminated by a zero order process, the $T_{1/2}$ is NOT constant, as the $T_{1/2}$ decreases with time after dosing and increases when the dose is increased. Thus, a drug that has a 0-order elimination, does not have a true $T_{1/2}$.

Why is $T_{1/2}$ meaningful?

1. The $T_{1/2}$ indicates **when the drug becomes eliminated from the body**.

Practically, a drug is eliminated in 4-5 half-lives:

TIME AFTER DRUG ADMINISTRATION	DOSE REMAINING IN THE BODY (%)	DOSE ELIMINATED FROM THE BODY (%)
1 $T_{1/2}$	50	50
2 $T_{1/2}$	25	75
3 $T_{1/2}$	12.5	87.5
4 $T_{1/2}$	6.25	93.75

Theoretically, the drug is never eliminated completely.

2. The $T_{1/2}$ is also related to **the duration of action of the drug**.

EXAMPLE: An imaginary intravenous general anesthetic.
Does doubling of its dose double its duration of action?

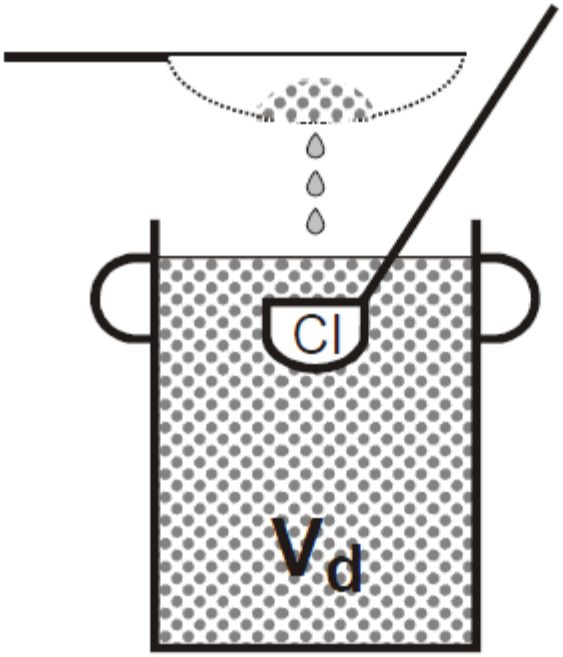
DOSE (mg iv)	$T_{1/2}$ (min)	Awakening	Duration of action
100	10	When 12.5 mg Remains in the body	? min
200	10		? min

Conclusion: Doubling of the dose increases the duration of action only by 1 half-life!

Cl = Clearance

Cl is a volume, a part of the Vd, which is cleared from the drug per unit of time (L/hr).

Illustration of clearance:



Clearance mechanism = dipper + strainer. They represent organs that can eliminate the drug (e.g., liver, kidney, etc.). The pot represents the body, enclosing the Vd that is filled with drug molecules (beads).

The dipper and the strainer remove the beads (drug molecules) from the pot (body, Vd). With continuous operation, the dipper clears a small volume (Cl) of the pot of the beads (drug) that is equivalent with the volume of the dipper.

The volume of the dipper represents the clearance.

Determination of Cl – by two methods:

Method 1 is based on the definition: As Kel is the fraction of the dose eliminated per unit of time, a Kel fraction of the volume of distribution is cleared in each unit of time.

$$Cl = V_d \cdot K_{el} \Rightarrow Cl = V_d \cdot \frac{0.693}{T_{1/2}} \Rightarrow T_{1/2} = 0.693 \cdot \frac{V_d}{Cl}$$

Method 2 is analogous to the calculation of urinary (or renal) clearance (C_p is the plasma conc of the drug at mid time of the urine collection period):

Renal clearance = $\dfrac{\text{Amount of drug excreted in urine}}{C_p}$

Total body clearance (Cl): Divide the iv dose (D_{iv}; i.e. the amount of drug eliminated from time 0 to infinity) by the area under the PCvsTC from time 0 to infinity ($AUC_{0-\infty}$):

$$Cl = \frac{D_{iv}}{AUC_{0-\infty}}$$

What is the practical use of the clearance?

If the Cl of the drug is known, we can calculate:

1. The dose rate (DR) that is necessary to reach and maintain an average steady-state concentration between dosing times (see in detail under repeated dosing).

If Cl is a volume within the volume of distribution of the drug which is cleared of the drug per unit of time, and if one wants to maintain an average concentration (Cav) in that volume, then the amount of drug to be administered per unit of time (DR) equals:

$$DR = Cl \cdot C_{av}$$

2. The average steady-state concentration (Cav) that can be reached when the drug is administered at a certain dose rate (DR).

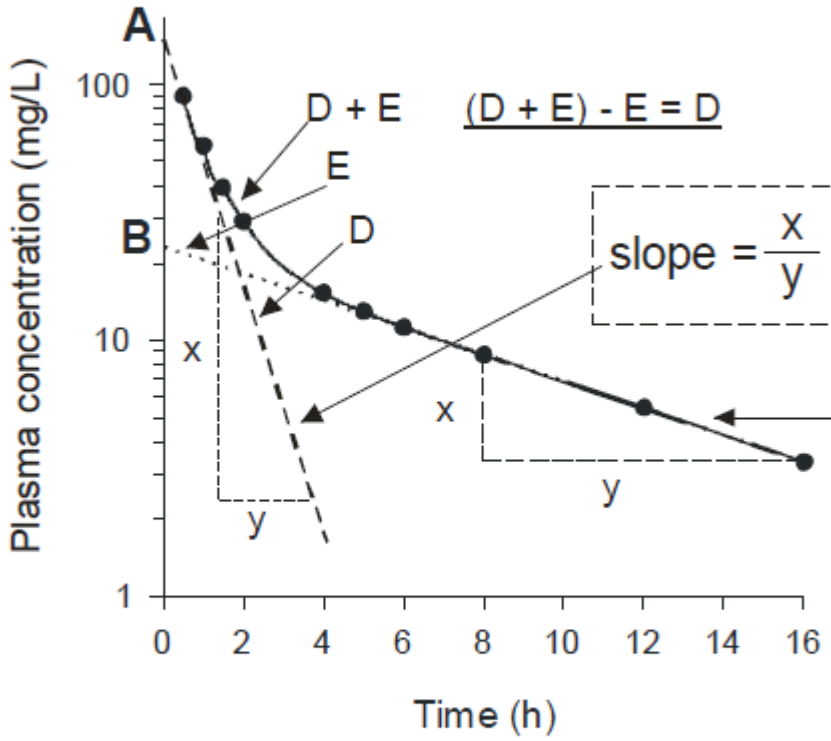
$$C_{av} = \frac{DR}{Cl}$$

The formula above can be used for determination of the clearance of a drug by infusing the drug, in the following rearranged form:

$$Cl = \frac{DR}{C_{av}}$$

Method: The drug is infused at a known rate (DR) and the conc of the drug in plasma is measured periodically. When the steady-state concentration is reached the known DR (mg/min) is divided by this concentration (Cav; mg/L) to obtain the Cl (L/min).

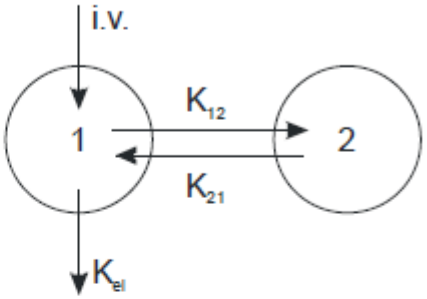
III. ANALYSIS OF FIRST ORDER DRUG ELIMINATION
– i.v. administration – two-compartment model



(D + E) - E = D

$$\text{slope} = \frac{x}{y} = \frac{\lg C_1 - \lg C_2}{T_1 - T_2}$$

$$\text{slope} = \frac{x}{y} = \frac{\lg C_1 - \lg C_2}{T_1 - T_2}$$



Distribution phase = α-phase

Disposition phase = β-phase

α and β are hybrid rate constants.

$$\alpha = - \text{slope} \cdot 2.3$$

$$\beta = - \text{slope} \cdot 2.3$$

Calculations:

- Calculate **hybrid rate constants:**
  - **α** from the slope of the derived dashed line in the α phase (see figure)
  - **β** from the slope of the straight section of the PC*vs*TC (solid line) in the β phase: fig

$$K_{el} = \frac{A + B}{(A/\alpha) + (B/\beta)}$$

$$K_{21} = \frac{A\beta + B\alpha}{A + B}$$

$$K_{12} = \alpha + \beta - K_{21} - K_{el}$$

* $$T_{1/2\beta} = \frac{0.693}{\beta}$$

* $$V_d = \frac{D_{iv}}{B}$$

$$Cl = \frac{D_{iv}}{AUC_{0-\infty}}$$

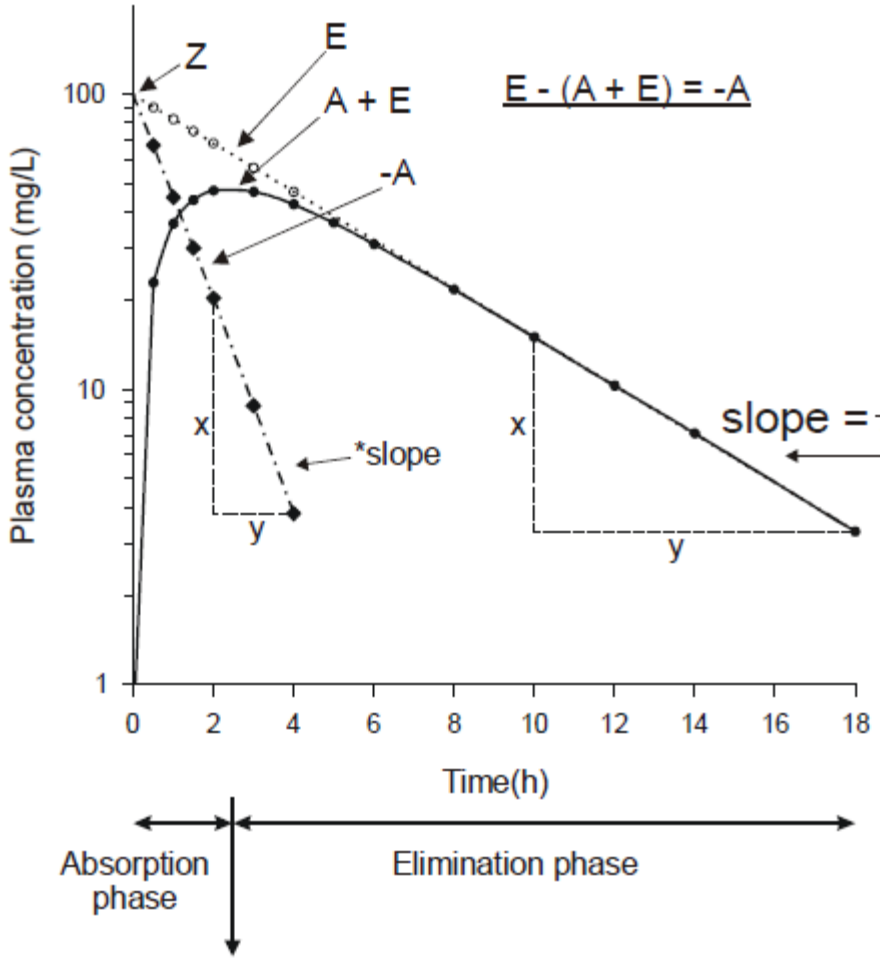
$$AUC_{0-\infty} = \frac{A}{\alpha} + \frac{B}{\beta}$$ or graphically

Note that the larger amount of drug accumulates in the peripheral compartment, the lower will be the **B** value (the intercept on the Y axis) and the larger will be the **Vd**. This explains the extremely high Vd values for some drugs (e.g., amiodarone, chloroquine).

II. ANALYSIS OF FIRST ORDER DRUG ELIMINATION – oral administration, one-compartment model

The PCvsTC after oral administration is composed of two phases (sections):

- the absorptive phase – analyzed to obtain the absorption parameters
- the elimination phase – analyzed to obtain the elimination parameters



$$*slope = \frac{x}{y} = \frac{lgC_1 - lgC_2}{T_1 - T_2}$$

$$K_{ab} = - slope \cdot 2.3$$

$$T_{1/2} = \frac{0.693}{K_{ab}}$$

A>>E A>E A=E A<E A<<E

Analysis of the elimination of the drug:

For calculating the descriptors for elimination (i.e., Kel and $T_{1/2\ el}$), the slope of the elimination section of the PCvsTC should be determined. For this purpose, a rectangular triangle is fitted to this section of the curve and the slope is calculated by the formula in the figure. After obtaining the slope, **Kel** and $\mathbf{T_{1/2\ el}}$ can be calculated as follows:

$$K_{el} = - \text{slope} \cdot 2.3$$

$$T_{1/2} = \frac{0.693}{K_{el}}$$

For calculation of **Cl**, the following formula is used:

$$Cl = \frac{F \cdot D_{p.o.}}{AUC_{0-\infty}}$$

F is oral bioavailability (= the fraction of the oral dose that reaches the systemic circulation – see also under Absorption of drugs), which is determined as follows:

$$F = \frac{AUC_{p.o.}}{AUC_{i.v.}}$$