Time Course of Drug Action

Dr. Robert G. Lamb
Professor
Pharmacology & Toxicology

Introduction to Pharmacokinetics I

Drug effects are proportional to the level of drug in the plasma.

Drug in plasma is in equilibrium with drug at action site.

The time course of drug action is a function of drug absorption, distribution, metabolism and excretion (pharmacokinetics).

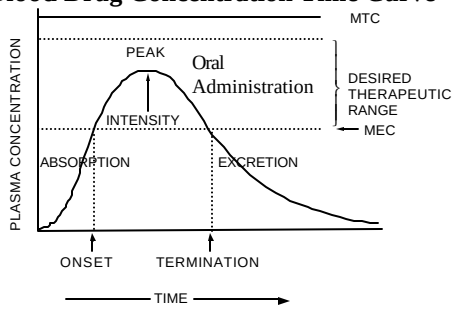
Introduction to Pharmacokinetics II

Changes in pharmacokinetics will alter drug effects.

Patient characteristics such as age, tissue function, living habits and nutrition will alter the pharmacokinetics of drugs.

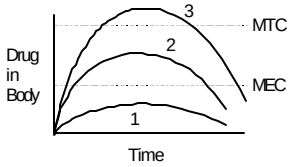
Drug dose, dose interval or both must be altered to compensate for changes in drug pharmacokinetics.

Blood-Drug Concentration Time Curve



Drug effect is proportional to level of drug in plasma.

Determining Drug Efficacy



Three Brands of Drug

Altered Bioavailability

2 is good 1&3 are not

MTC: [toxic level]

MEC: [effective level]

Zero-Order Reaction Kinetics I

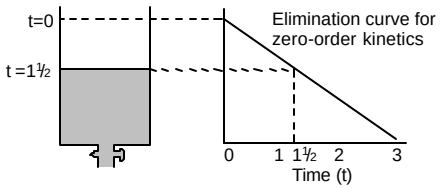
Saturable Processes: Enzymes and Transport Carriers

Constant Rate (zero-order) at saturation.

Rate independent of drug concentration at saturation.

Absorption: iv drip and iv infusion
implantation pellet
anesthetic gases
sustained release reparations

Zero-Order Reaction Kinetics II



iv infusion lowers drug level at constant rate which is independent of the level of drug.

Metabolism of Alcohol

Alcohol

– **Alcohol Dehydrogenase (slow)**

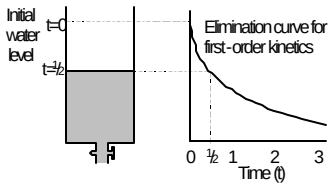
Acetaldehyde (toxic)

– **Acetaldehyde Dehydrogenase (fast)**

Acetate

clear 1 drink/h (constant)
input > 1 drink/h (drunk)
input = 1 drink/h (constant)
Input < 1 drink/h (sober)

First-Order Reaction Kinetics



Exponential Decline

Common Process

Changing Rate

Rate proportional to drug Concentration.

50 % every t ½

First-Order Kinetic Equations I

Half-life [t ½] = 0.693 / ke **

ke = first-order elimination rate constant

time to eliminate 50% of drug

Ke = Clearance / Vd **

Clearance (total body)

Vd (volume of distribution)

t ½ = [0.693][Vd] / Clearance

First-Order Kinetic Equations II

Vd = Q/Co**

Q = drug dose

Co = plasma drug concentration at time zero

Clearance = [ke][Vd]

Clearance = [0.693][Vd] / t ½

Vd = Clearance / ke

First-Order Kinetic Equations III

Ke = 0.693 / t ½

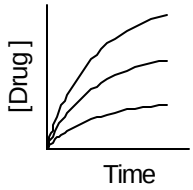
Co = Q/Vd

Q = [Co][Vd]

Be able to calculate:

Vd, t ½ , Clearance, ke, Co and Q

Drug Accumulation (Zero-Order CL)



Phenytoin cleared by liver.

CL is constant at high doses.

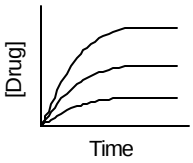
Saturation of liver enzymes.

Input > output = increase

Input = output = plateau

Does not plateau at all doses.

Drug Accumulation (First-Order CL)



Digoxin is cleared by kidney.

Clearance is non-saturable.

Clearance is dose-dependent.

50% in each t ½ interval.

Levels rise until input = output.

Plateau at all doses (7 t ½).

First-Order Elimination Time Course

T ½ intervals	Amount of Drug (mg) In Body	Eliminated
0	100	0
1	50	50
2	25	75
3	12.5	87.5
4	6	94***
5	3	97
6	1.5	98.5
7	0.75	99.3

Drug's t ½ = 4 h

Dose = 100 mg iv

94% of drug cleared at 4 t ½.

To accumulate dose interval must be less than 4 t ½.

It takes 7 t ½ to clear most of the drug.

Plateau Principle [First-Order CL]

	Dosing interval 1		2		3		4		5		6		7	
	A	B	A	B	A	B	A	B	A	B	A	B	A	B
1g [Body]	1	.5	1.5	.75	1.75	.88	1.94	.97	1.97	.99	1.99	1	2	1
2g [Body]	2	1	3	1.5	3.5	1.75	3.75	1.88	3.88	1.94	3.94	2	4	2

T ½ = 4 h Dose Interval = 4 A = level of drug immediately after dose.

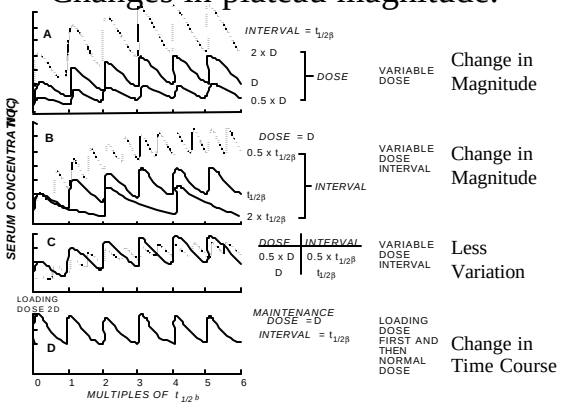
B = level of drug just before dose is give and drug cleared in each t ½ .

Drug accumulates until input = output (7 t ½) = plateau [all doses]

Time course of plateau is determined by drug's t ½ .

Loading dose (2g or 4g) then 1/2 at t ½ interval

Changes in plateau magnitude.



Alterations in Plateau Time Course

The plateau time course is a function of the drug's t ½ .

t ½ = 0.693 / ke (altered by excretion)

Increased excretion = decreased t ½ and time course.

Decreased excretion = increased t ½ and time course.

Loading Dose and then ½ LD at t ½ intervals produces rapid plateau.

Not altered by one change in dose or dose interval.

Alterations in Magnitude of Plateau

Proportional to changes in drug dose.

Inversely proportional to changes in dose interval.

Inversely proportional to changes in drug clearance (t ½).

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Application of Pharmacokinetic Principles

$$Css = \frac{F \times D}{ke \times Vd \times T}$$

Css = steady-state (plateau) level of drug in plasma

F = bioavailability T = dose interval (h)

D = dose administered (mg or g) iv

Ke = first-order elimination rate constant (1/min, h)

Vd = volume of distribution (L)

Clearance (CL) = ke x Vd (ml/min, L/h)

Pharmacokinetics of Theophylline I

Patient is a 70 kg male .

F =1 **D = 370 mg** **CL = 2.7 L/h**

T= 9 h **Vd = 35 L** **ke = 0.08 h^{-1}**

t ½ = 9 h **MEC = 10 mg/L** **MTC = 20 mg/L**

$$\textbf{Css} = \frac{F \times D}{CL \times T} = \frac{[1]\,[370\ mg]}{[2.7\ L/h][9h]} = 15\ mg/L$$

$$\textbf{Loading Dose} = \frac{Vd \times Css}{F} = \frac{[35L]\,[15\ mg/L]}{1} = 525\ mg$$

Pharmacokinetics of Theophylline II

Maintenance Dose = Css x CL x T / F

= [15 mg/L] [2.73 l/h] [9h] / 1 = 370 mg

t ½ = 0.693 / ke = 0.693 / .08 h -1 = 9 h

CL = 0.693 x Vd / t ½ = [0.693] [35L] /9 h = 2.70 L

Vd = t ½ x CL / 0.693 = [9h] [2.7 l/h] / 0.693 = 35 L

Pharmacokinetic Problems I

Principle: It takes 1, 2, 3, 4, 5, 6 and 7 t ½ s to clear and accumulate 50 75 88 94 97 99 and 100 % of drug.

When will a drug with a t ½ of 8 h reach 75% of Css if given every 4 h ?

What if drug is given every 12 h ?

Which situation gives the highest Css level?

Pharmacokinetic Problems II

Principle: It takes 1, 2, 3, 4, 5, 6 and 7 t ½ s to clear and accumulate 50 75 88 94 97 99 and 100 % of drug.

A drug was given iv and 24 h later 94% of the drug was excreted.What is the t ½ of this drug ?

Pharmacokinetic Problems III

Principle: It takes 1, 2, 3, 4, 5, 6 and 7 t ½ s to clear and accumulate 50 75 88 94 97 99 and 100 % of drug.

How long will it take to eliminate 750 mg of a 1000 mg iv dose, if this drug has a t ½ of 6 h ?

Pharmacokinetic Problems IV

Principle: It takes 1, 2, 3, 4, 5, 6 and 7 t ½ s to clear and accumulate 50 75 88 94 97 99 and 100 % of drug.

What is the t ½ of a drug if 940 mg of a 1000 mg iv dose is eliminated in 24 h?

Pharmacokinetic Problem V

What is the Css of a drug that is 100% bioavailable (F =1), When 250 mg of this drug is administered iv every 10 h to a Patient that clears this drug at a rate of 2.5 L/h ?

Css = F x D / CL x T = [1] [250 mg] / 2.5 L/h][10h] = 10 mg/L