Drug Overdose
Another Perspective

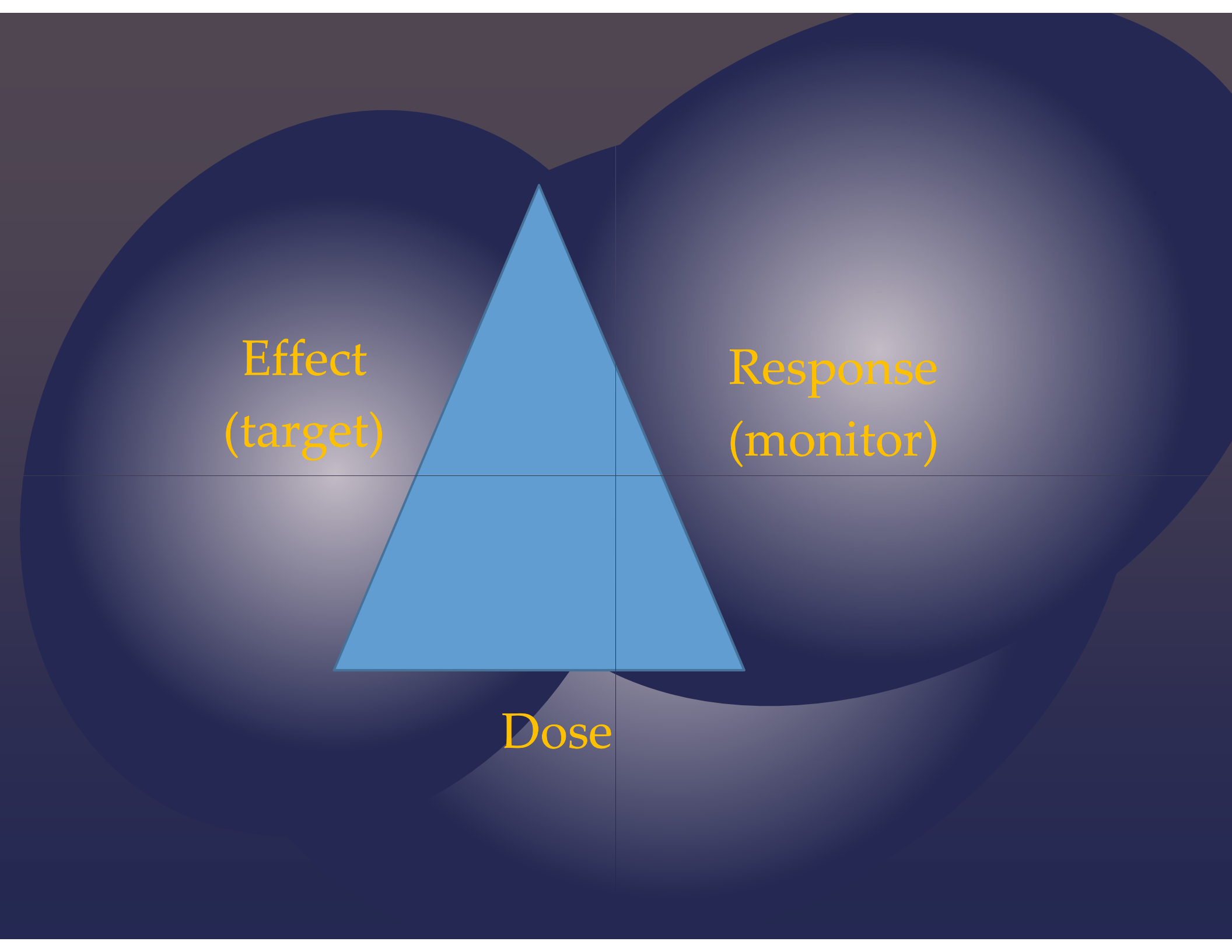
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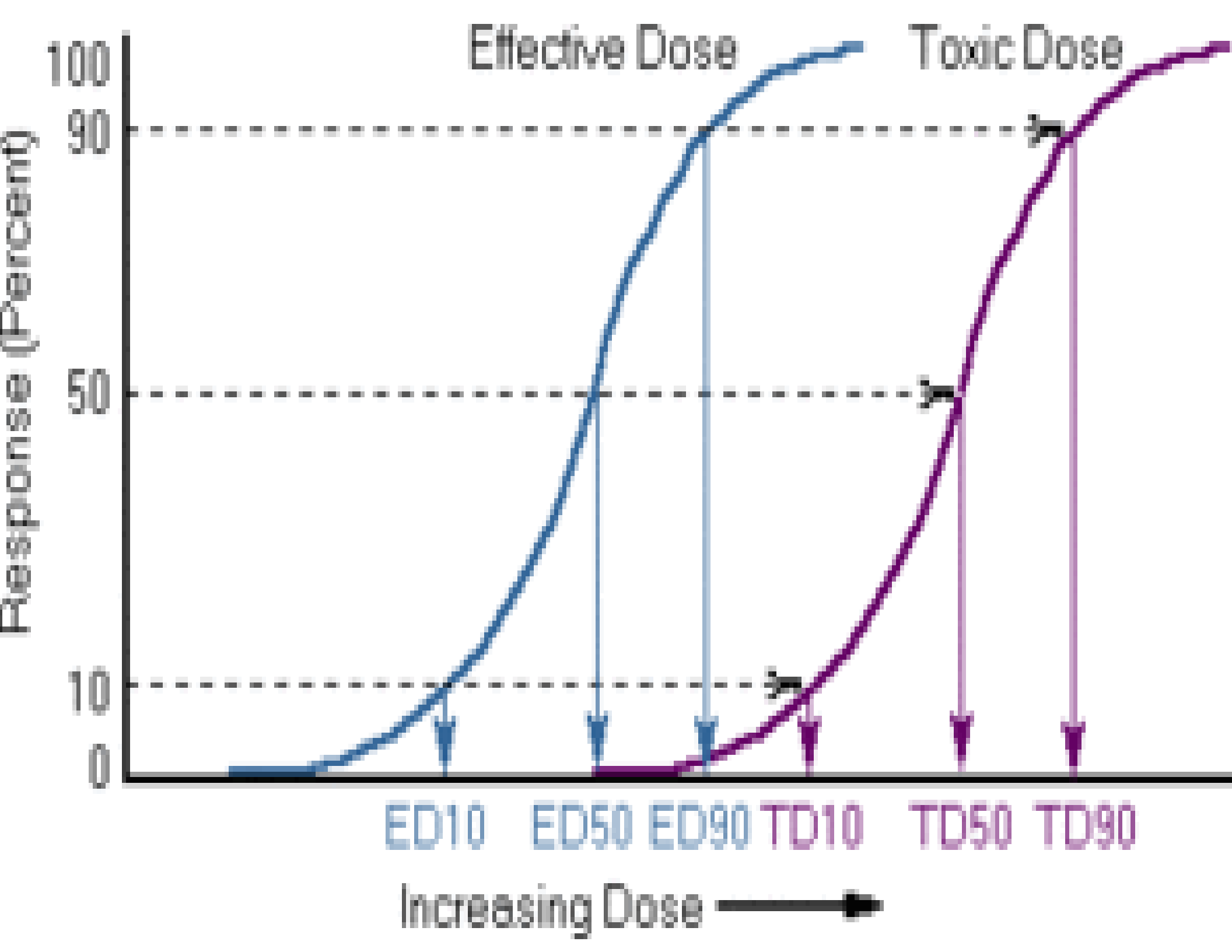
Risks Associated with Overdose Deep Anaesthesia

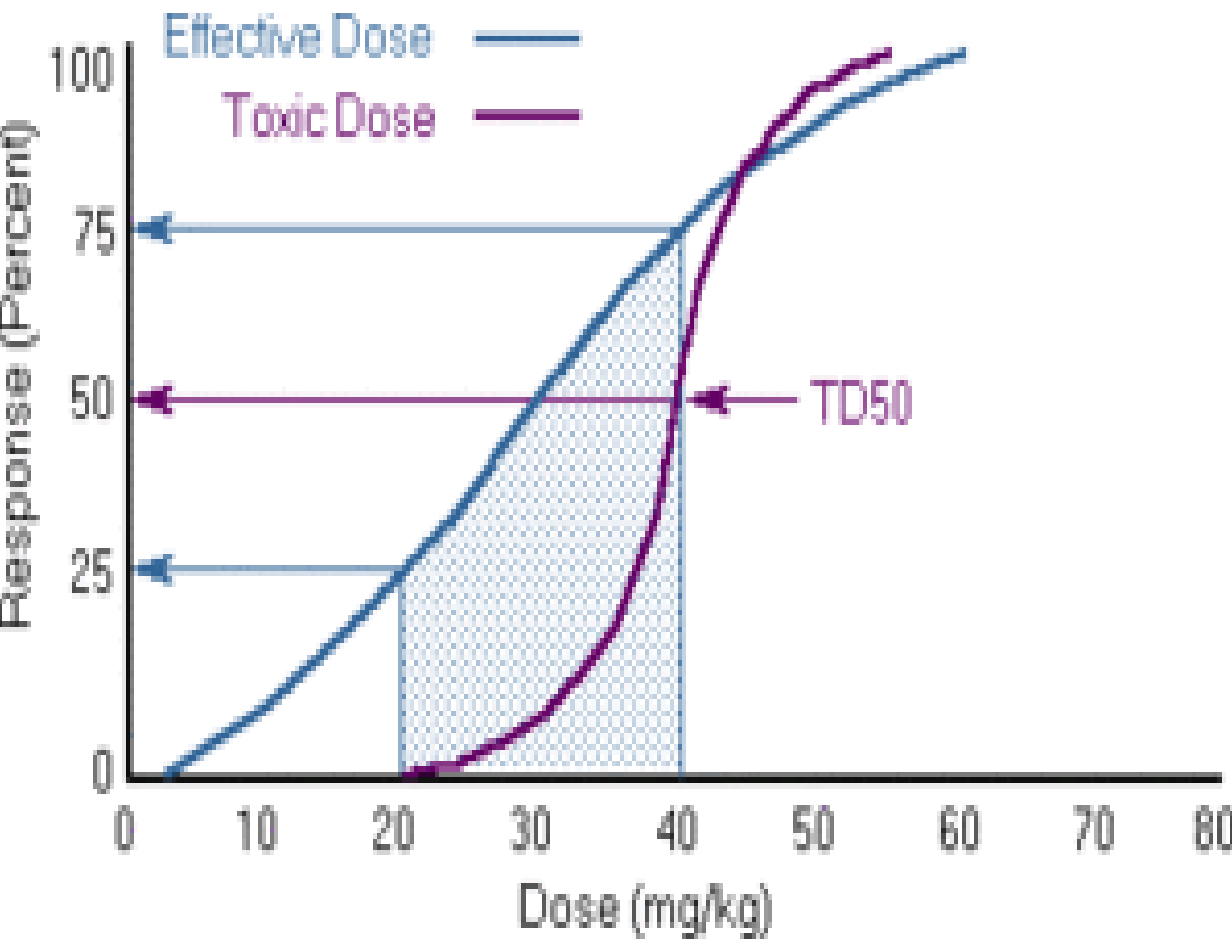
- ICU admission
- PACU late discharge
- Postoperative delirium
- Silent regurgitation
- Postoperative pulmonary complications
- Cardiovascular instability
- Neurogenic dysfunction
- Increases cost
- Mortality

An anaesthetist is a special clinical pharmacologist who uses drugs in a rational, safe, and effective way.

Our aim is to give the "right dose" to avoid under/over medications i.e. the effective dose.


Effect
(target)
Response
(monitor)
Dose


Effective Dose
Toxic Dose
100
90
50
10
0
Response (Percent)
ED10
ED50
ED90
TD10
TD50
TD90
Increasing Dose


Effective Dose
Toxic Dose
100
75
50
25
0
TD50
Response (Percent)
0
10
20
30
40
50
60
70
80
Dose (mg/kg)

Therapeutic range is translated in anaesthesia as a patient's response to the dose given.

How do we overdose?

- Pharmacokinetics

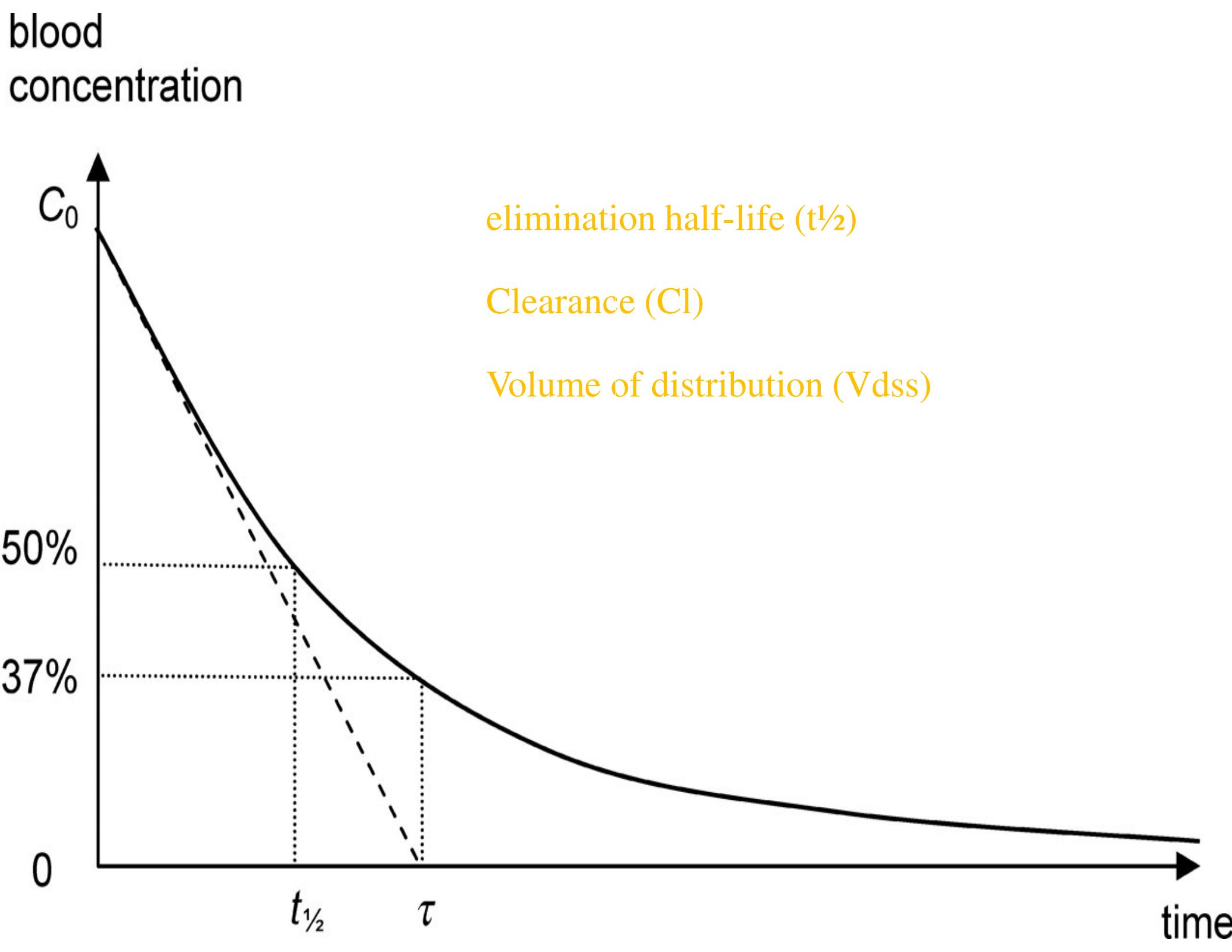
explains what happens to a drug in the body

$V = X/C$

$Q = kV$

- Pharmacodynamics

describes the actions produced by the drug on the body

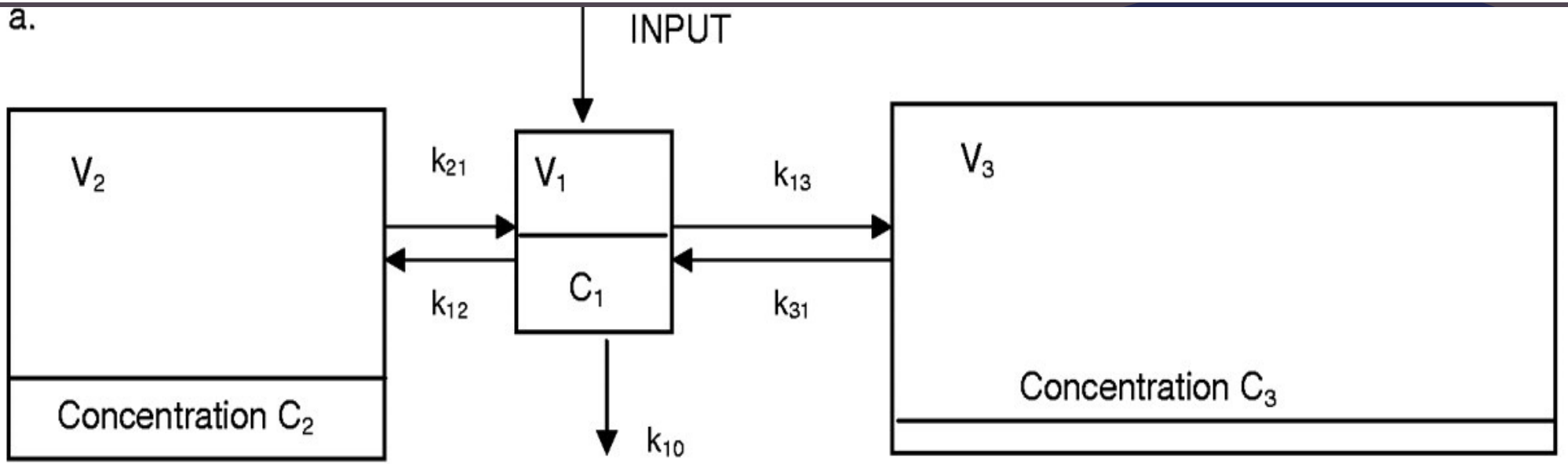


elimination half-life (t½)

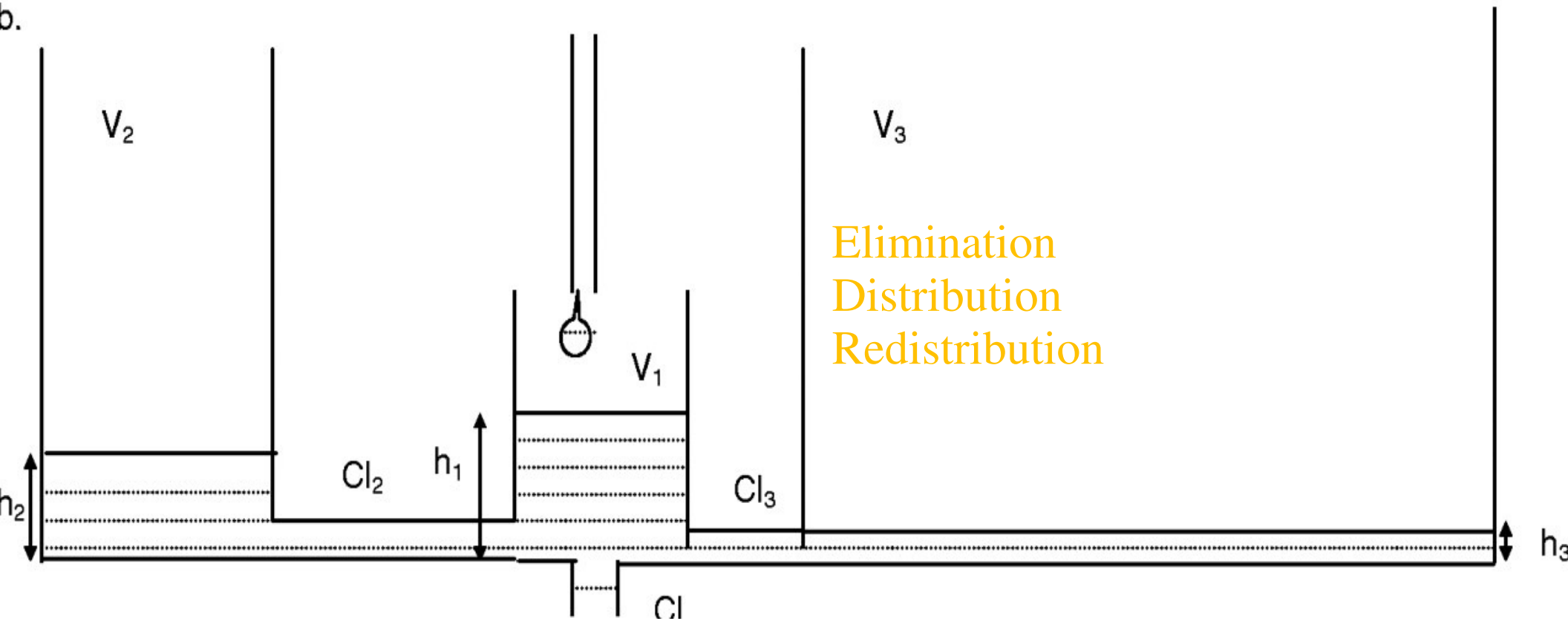
Clearance (Cl)

Volume of distribution (Vdss)

a.



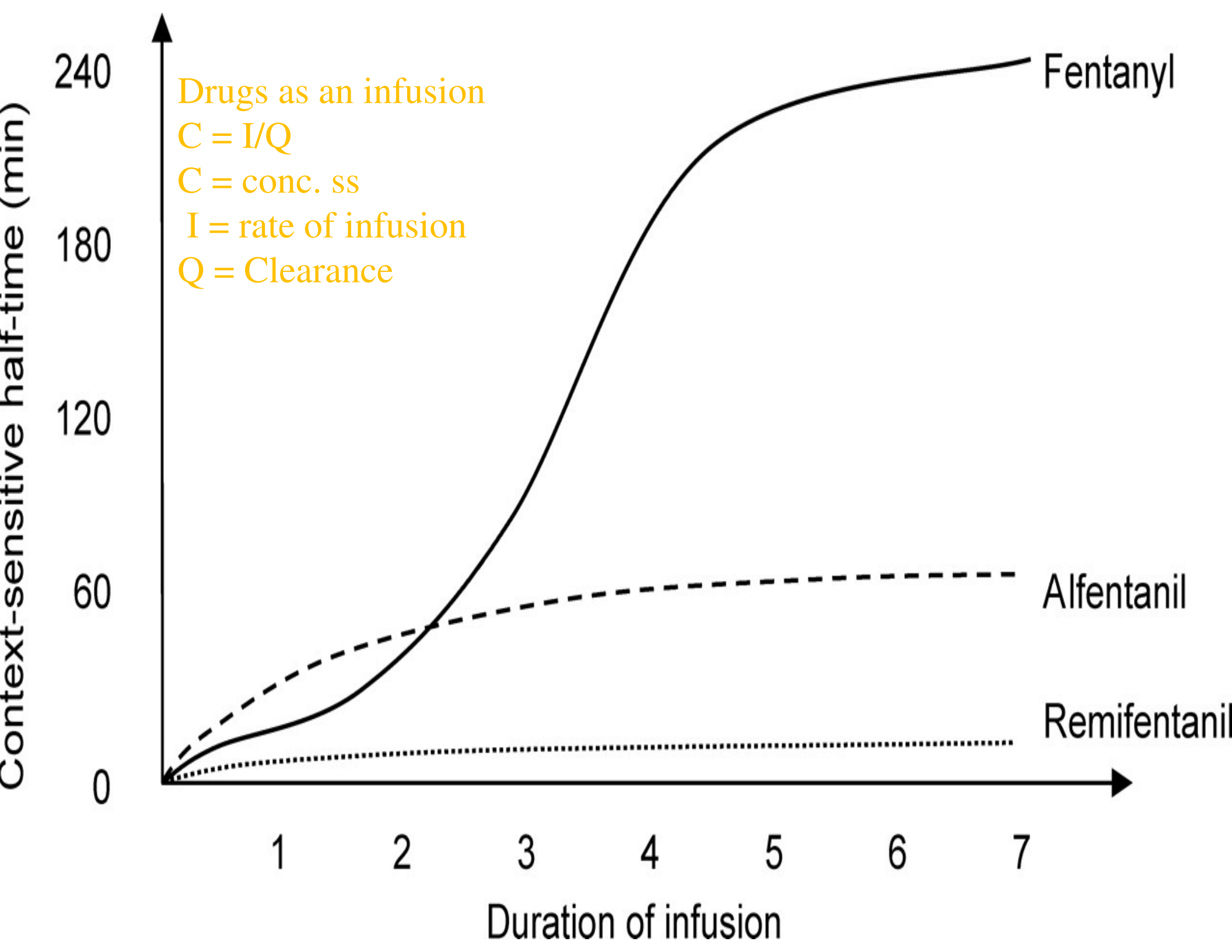
b.



Elimination
Distribution
Redistribution

Context - sensitive half-time

Time required for 50% decrease in plasma drug concentration during continuous infusion


Drugs as an infusion
C = I/Q
C = conc. ss
I = rate of infusion
Q = Clearance
Context-sensitive half-time (min)
240
180
120
60
0
Fentanyl
Alfentanil
Remifentanil
1
2
3
4
5
6
7
Duration of infusion

The Biophase:

Plasma is not the site of drug action.

Drugs effect at the "biophase" i.e. effect site

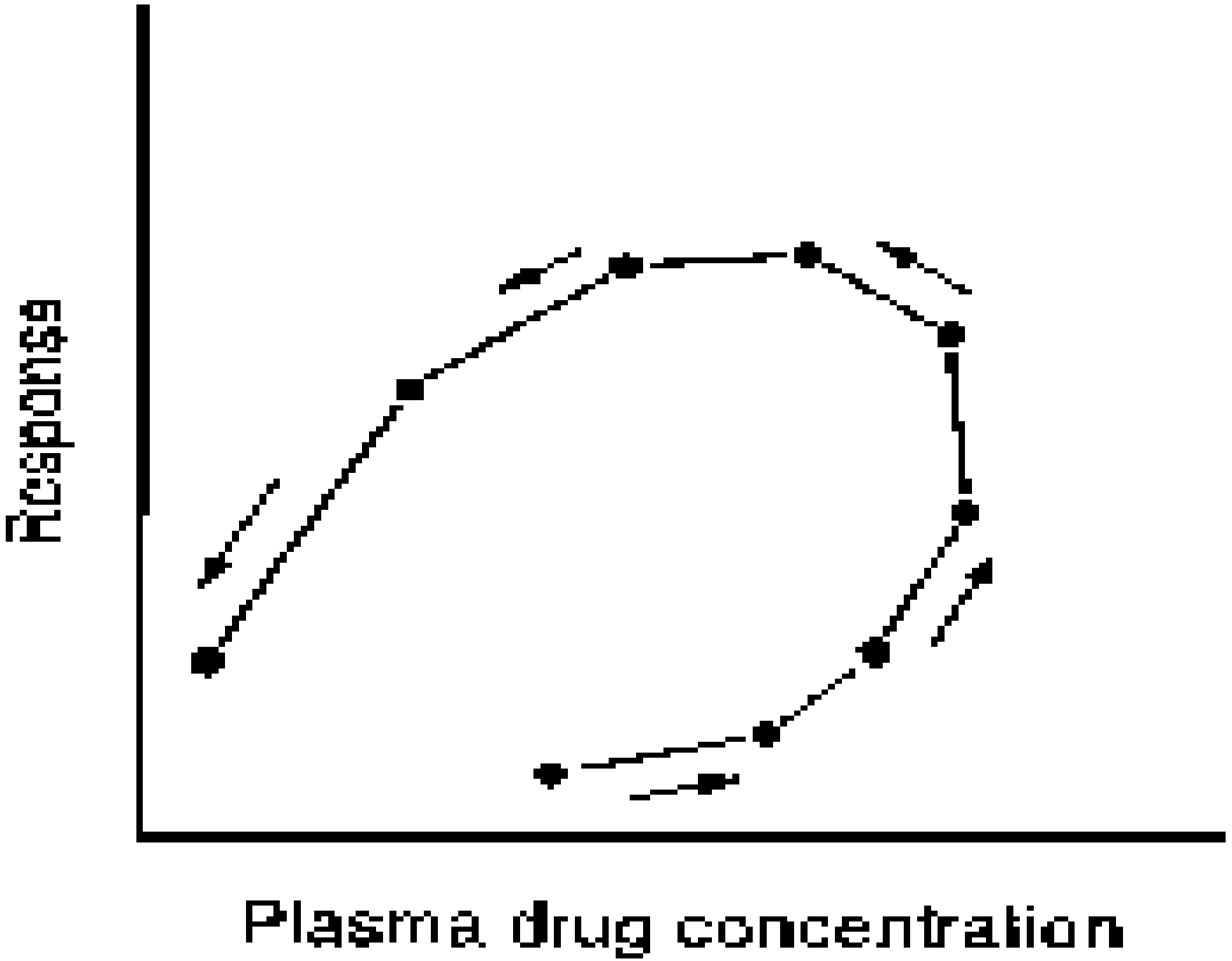
Ke0

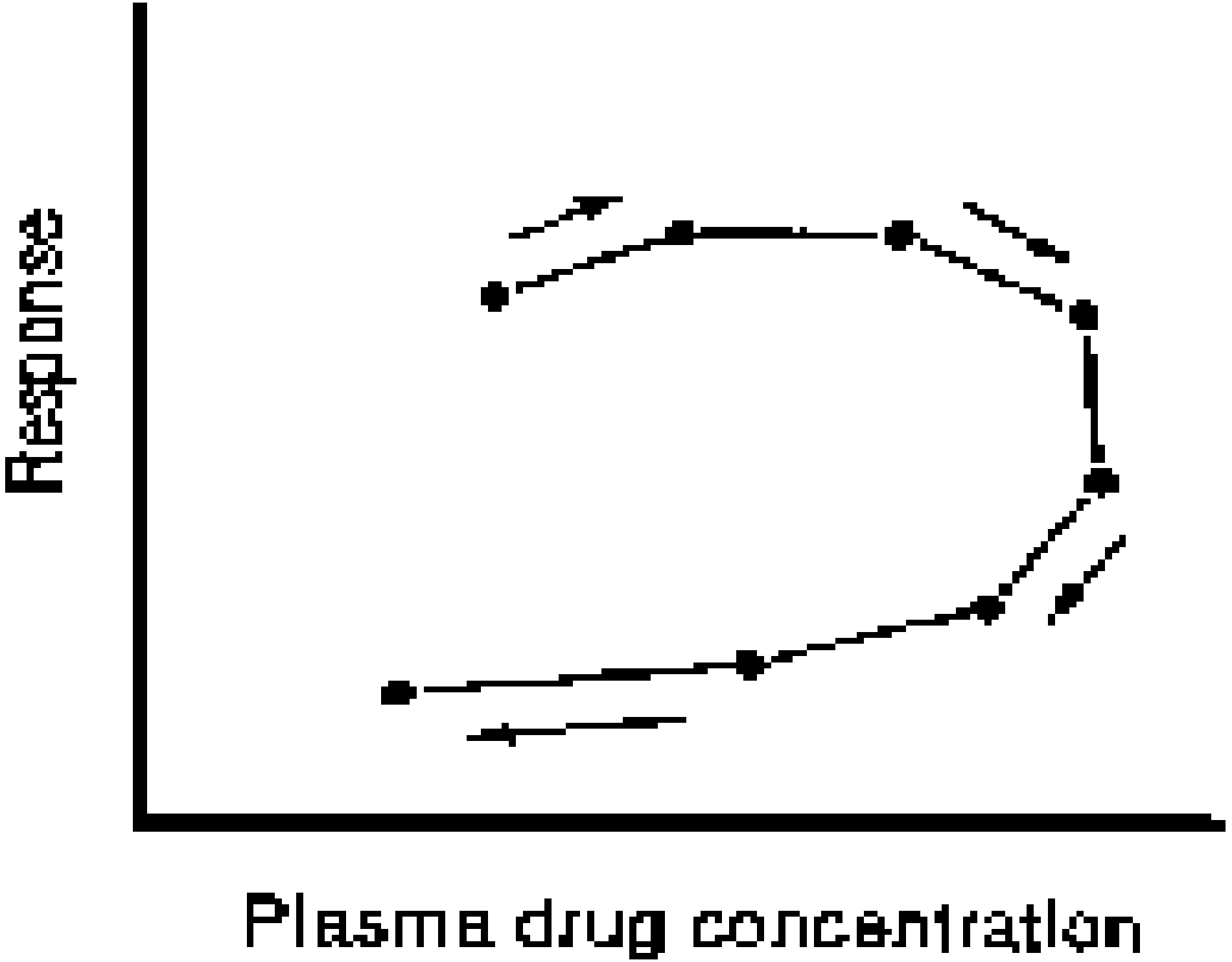
Is the rate constant of drug elimination from the effect site

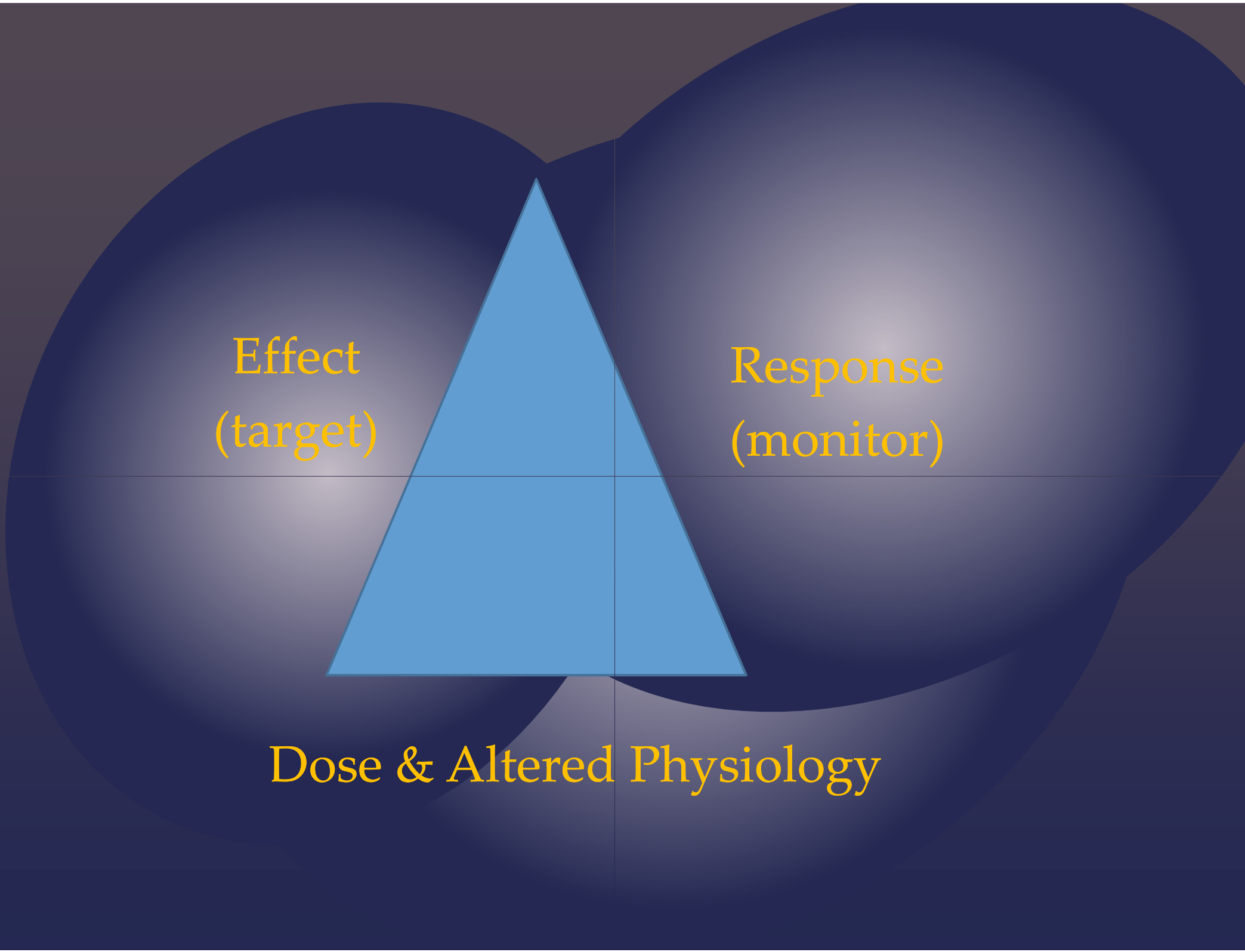
t1/2Ke0

Time required to for the biophase concentration to reach 50% of plasma concentration

= o.693 / Ke0


Response
Plasma drug concentration


Response
Plasma drug concentration


Effect
(target)
Response
(monitor)
Dose & Altered Physiology

High Cardiac Output

> The effective volume of blood initially diluted
> Lower peak concentration
> Reach quickly to the vessel-rich tissues
> Fast onset of action

Low Cardiac Output

> A higher initial peak concentration
> Mixed with a smaller volume of blood
> Take longer to reach its target site

Low Cardiac Output

> decrease HBF causing decrease Cl-h
> decrease RBF causing decrease Cl-r
> decrease tissue perfusion causing decrease Vd

Drug Metabolism

Hepatic drug clearance depends on

- ER = Cin – Cout / Cin
- HBF

i.e. Hepatic clearance = HBF * ER

Drug Metabolism

- 50% reduction for high Cl-h drugs
- 25% reduction for low Cl-h drugs

Renal Elimination

- fu = 1, drug elimination entirely by the kidneys
- fu = 0, drugs eliminated by metabolism
- fu = 0.5, total dose should be 75% of normal

Renal Elimination

- drugs doses should be reduced in direct proportion to the degree of impairment in CrCl
- if CrCl is half normal , doses should be half normal

Pharmacogenetics

- Poor metabolizer (no active CYP2D6)
codeine > No pain relieve but bad constipation

- Pseudocholinestrase deficiency
1 : 3000 > prolonged ventilation

Age

Elderly (pharmacokinetics)

- drugs Cl of drugs with high fu is consistently impaired
- drug Cl of metabolized drugs is usually impaired

Age

Elderly (pharmacodynamics)

- Homeostatic adaptation is less efficient
- Target organ sensitivity is blunted
- Impaired cholinergic and adrenergic function

Age

Children (Pharmacokinetics)
Cl

- Functional maturity is reached between 6 months to 1 year
- After that it is greater than that of adults and relate better to surface area

Age

Children (Pharmacokinetics)
Vd

- Infants has more body water, 85% of BW (Increase Vd for water soluble drugs)
- Less fat % (Decrease Vd for lipid soluble drugs)

Age

Children (Pharmacokinetics)

PB

- Decreased albumin
- Decreased binding capacity
- Presence of displacers (FFA & Bilirubin)
- Effects on concentration
- Little significance

Age

Children (Pharmacodynamics)

- More sensitive to drugs effect
- BBB is slow to develop
- May be paradoxical reactions

Conclusion

- Recommended drug doses is derived from average values in population studies
- Provide no certainty of response in a specific individual
- Drug administration should be based on a measured patient response

Patient's profile
(age, weight, sex, race, allergies, H/O smoking, alcohol, diseases, pregnancy, current therapy)

Drug's profile
(class, action, kinetics, interactions, side effects, monitoring)



Thank You