MANCHESTER 1824

The University of Manchester

PHARMACOLOGICAL RESPONSE

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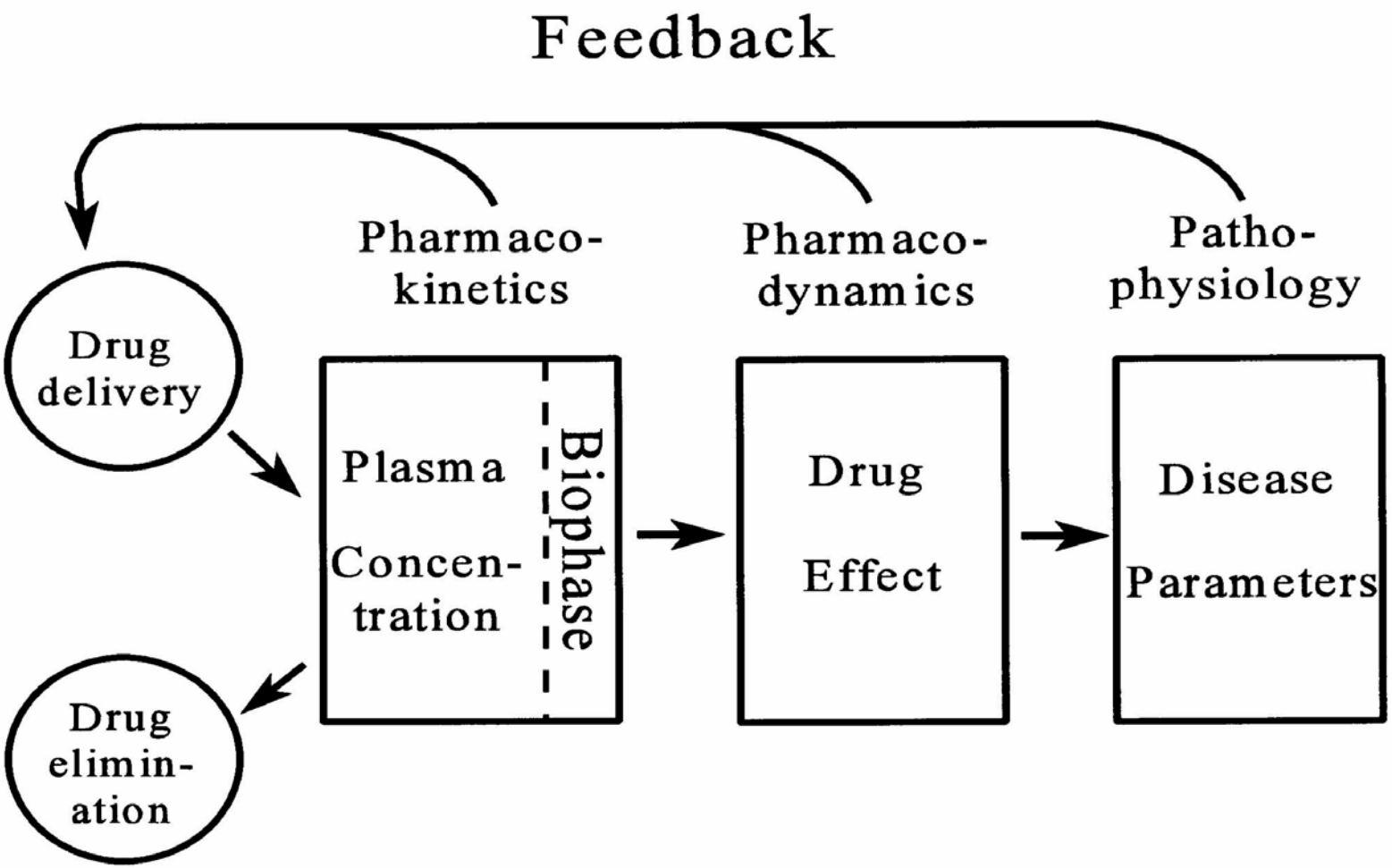
A. OBJECTIVES

- **Distinguish between quantal (all-or-none) and graded responses.**
- **Represent and graphically display quantal and graded responses.**
- **Understand the various models used to describe pharmacological effect.**
- **Explain why response often declines linearly with time when it lies in the region between 20 and 80 per cent of its maximum value.**
- **Detect time effects by plotting response against drug concentration.**
- **Evaluate the basic elements of a model that combines pharmacokinetic and pharmacodynamic data.**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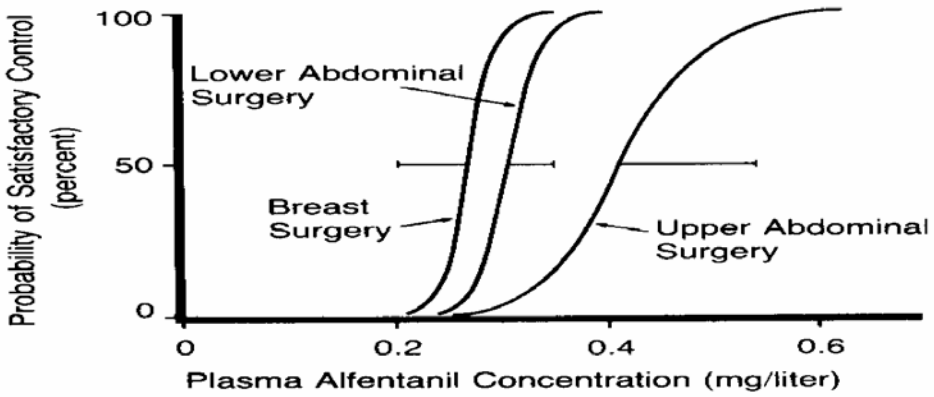
B. CONCENTRATION-RESPONSE RELATIONSHIPS

1. All-or-none (Quantal) Response

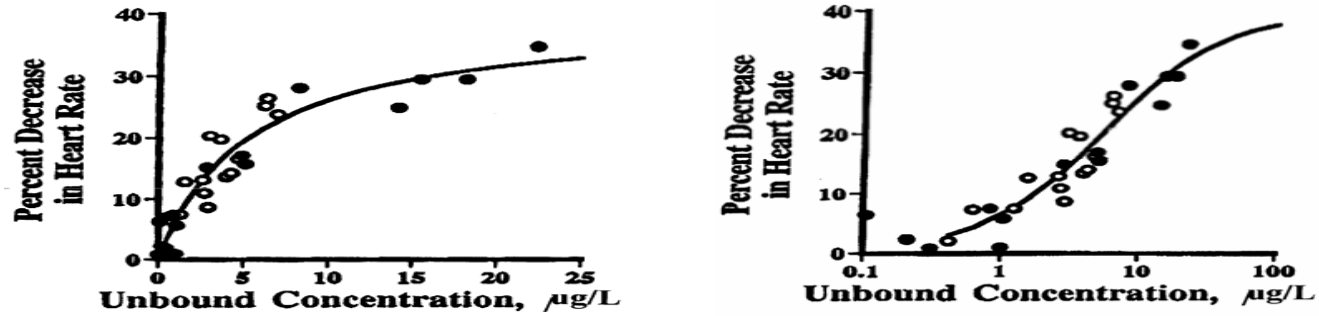
a. Response absent or present, *e.g.* toxicity or no toxicity.

b. Described by a plot of cumulative frequency distribution of effect *versus* concentration. Provides information on the probability that an effect occurs at or below a specified concentration.



2. Graded Response Intensity of effect (E) varies continuously with concentration within an individual, e.g. degree of muscle paralysis

a. Concentration-Response Relationship



A response, measured by the percent decrease in exercise-induced tachycardia, to propranolol increases with the unbound concentration of the drug in plasma. the data points represent measurements after single and multiple daily oral doses of two 80 mg tablets of propranolol (●) or a 160-mg sustained- release capsule (○) in an individual subject. The line is the fit of an Emax model to the data. The response appears to follow the Emax model with a γ of 1, an Emax of 40 per cent and an EC50 of 5,3 µg/L (redrawn from Lalonde *et al. Propranolol pharmacodynamic modelling using unbound and total concentrations in healthy volunteers. J. Pharmacokin Biopharm 15: 569-582, 1987)*

b. Assessment of Response

(1) Assumption is that at C = 0 , E = 0

(2) ***Baseline: Usually there is a basal value in the absence of drug, E_0.***

For some measurements baseline can vary appreciable with time e.g. blood pressure.

In addition, in clinical trials often see a significant placebo effect, so that

Measured = Drug (E) + Placebo + Baseline
Response Response Response

Sometimes *E is expressed as the increment above or decrement below a basal value, E_0*

Example: Increase in heart rate

$$E = E_{obs} - E_0$$

Note: When drug reduces observed measurement to zero $E_{max} = E_0$

Example: Complete paralysis (no muscle activity) with neuromuscular blocking agent.

Potency *versus* Efficacy

Potency is the concentration required to produce 50 per cent of maximum response, i.e. C_{50}. The lower C_{50} the more potent the drug

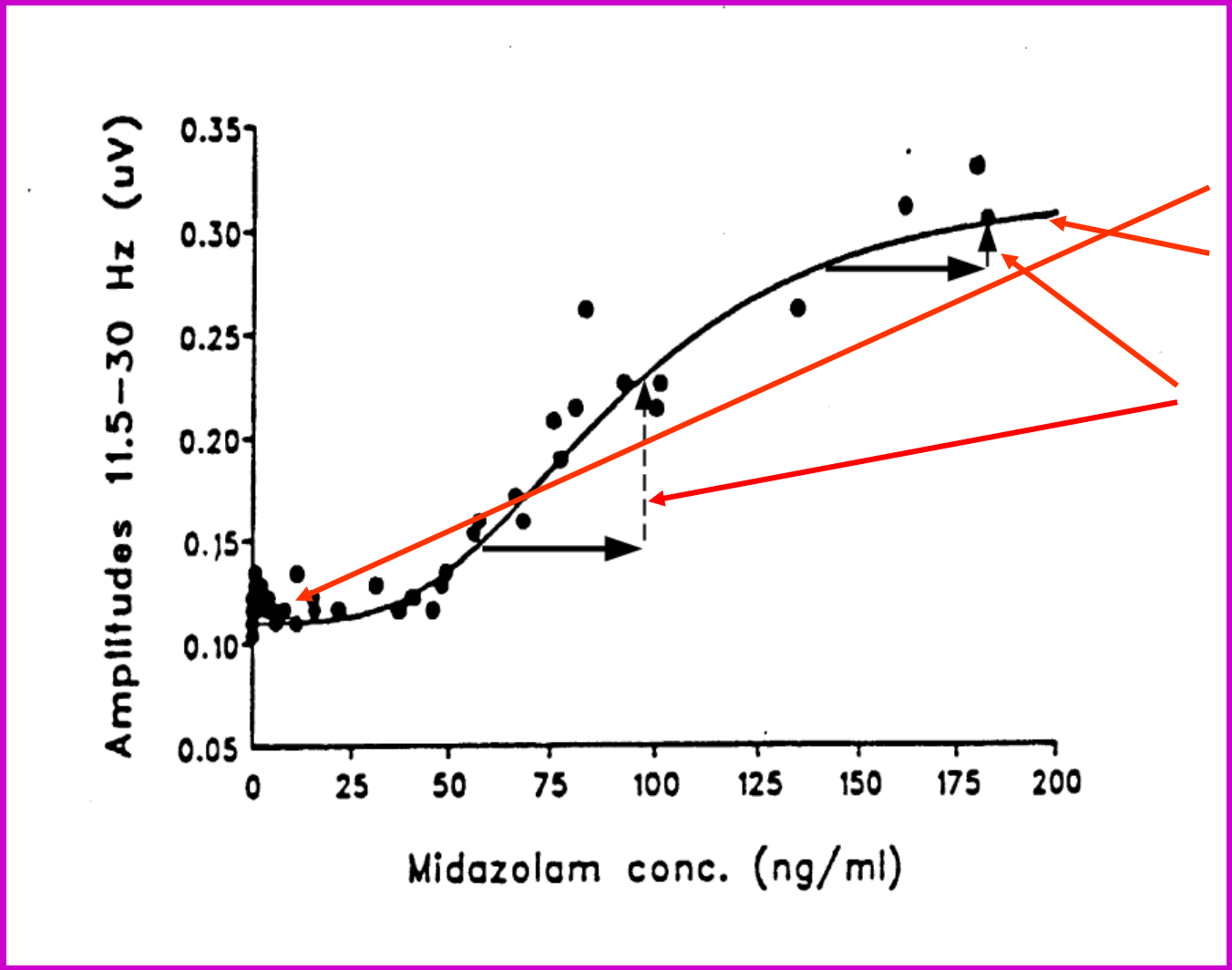
Efficacy is the maximum effect capable of being produced by a drug, i.e.E_{max}.

Drugs that produce the maximum possible effect are known as full agonists / antagonists. Some drugs cannot evoke the maximum effect, they are called partial agonists / antagonists.

Clinical Use. Together, selectivity (to minimise the likelihood of off-target adverse effects) and efficacy (rather than potency) are the more important parameters for clinical use.

Examples

Midazalom effect on EEG



Comment:

1. E = baseline at C = 0;E = maximum as C$\rightarrow \infty$.
2. This is a saturable system (law of diminishing returns).
3. A type of non-linear model (i.e., response not linearly proportional to stimulus).

Basic Empirical Model

Simplest form: Emax Model.

(Assume baseline = 0, for now).

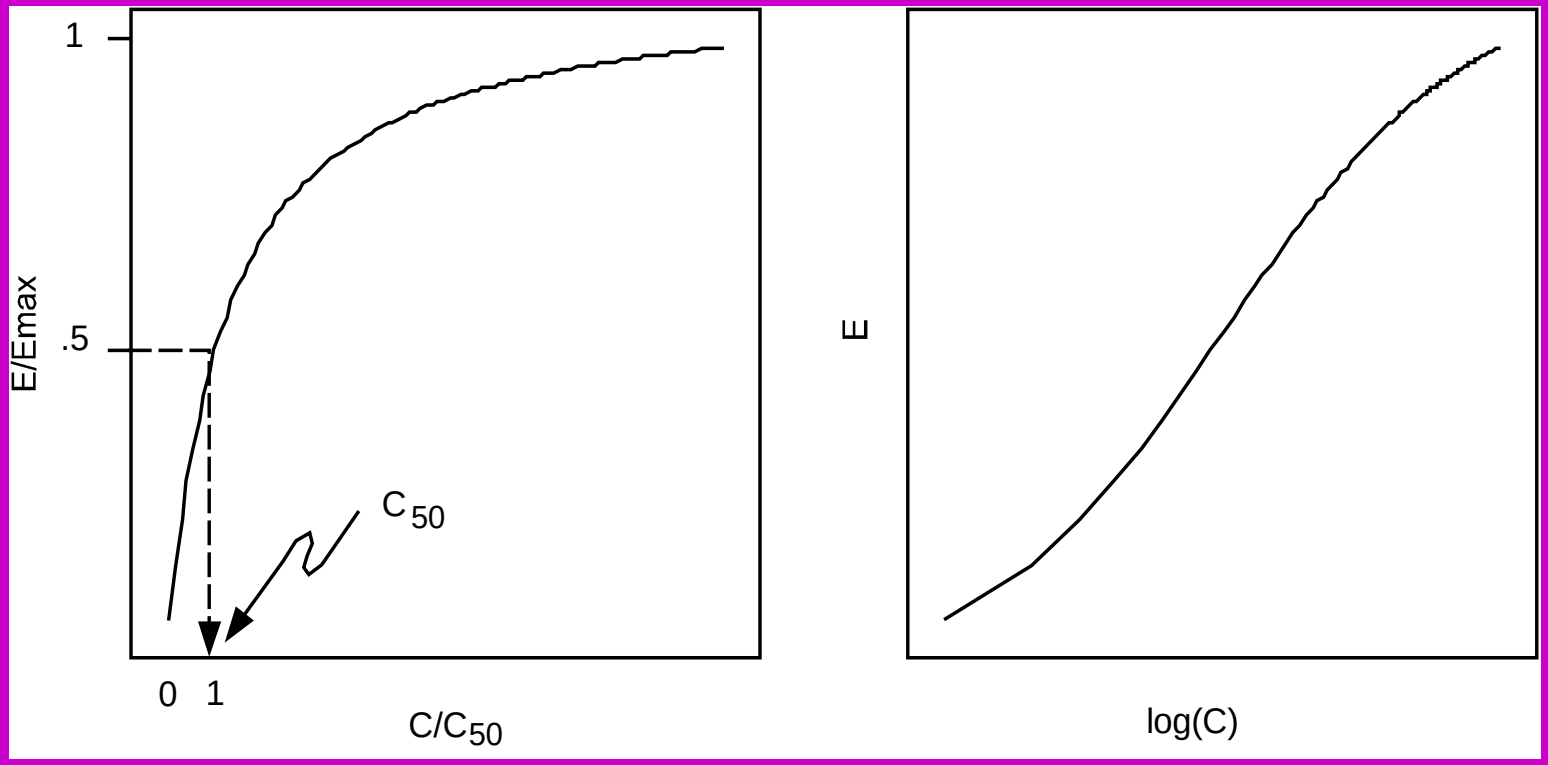
Hyperbola: 2 parameter model - "Emax model“

$$E = Emax\frac{C}{C + C_{50}} = Emax\frac{C/C_{50}}{1 + C/C_{50}} = Emax\frac{1}{1 + C_{50}/C},$$

where *Emax* is maximum E drug can produce; C_{50} is concentration yielding E=½Emax

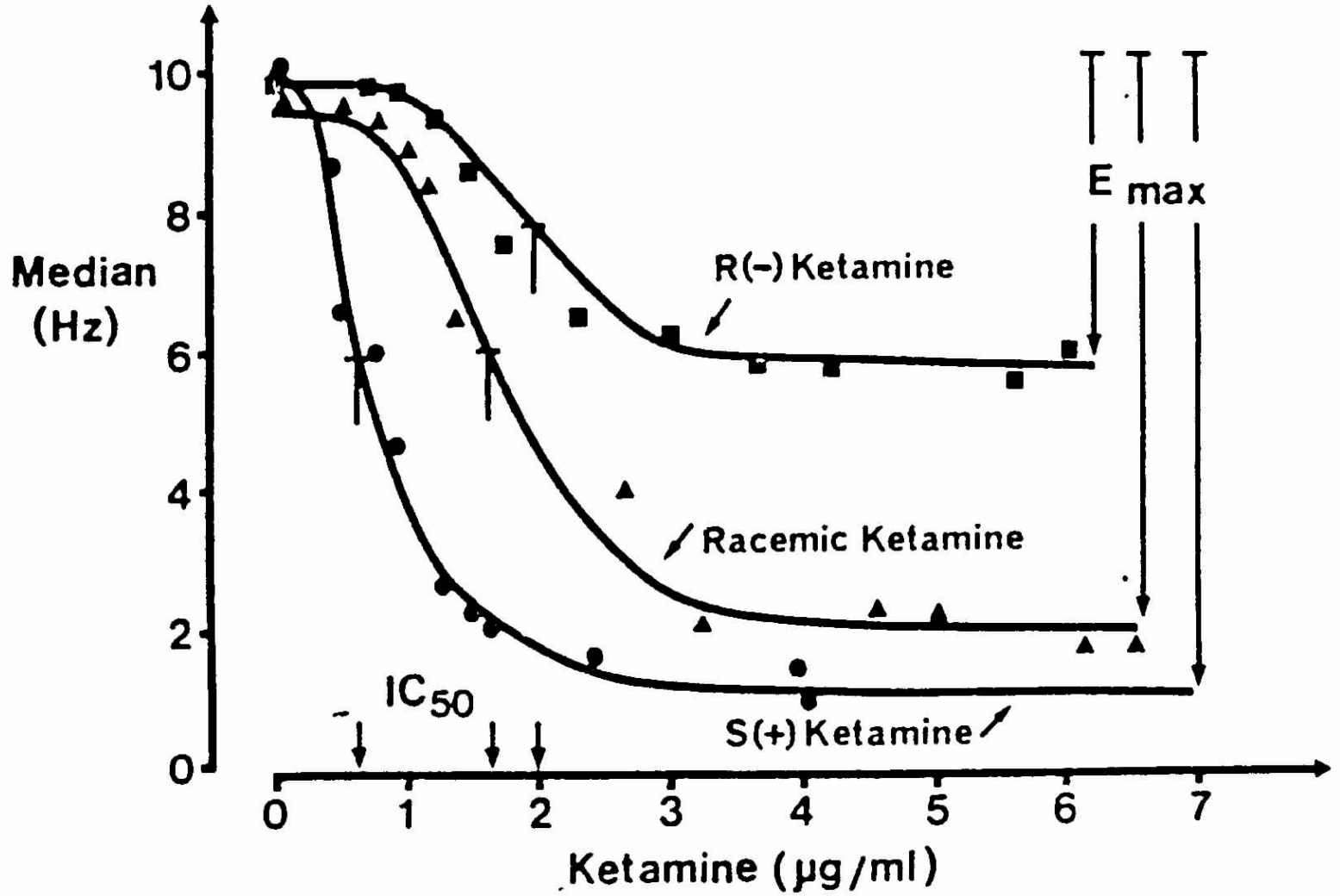
Graphical

Left panel: E vs. C, standard axes;
Right panel: E vs. log C = "sigmoid" shape



E vs log (C) only looks sigmoid; actually dE/dC is max as C←0

Sigmoid E_{max} model - Example



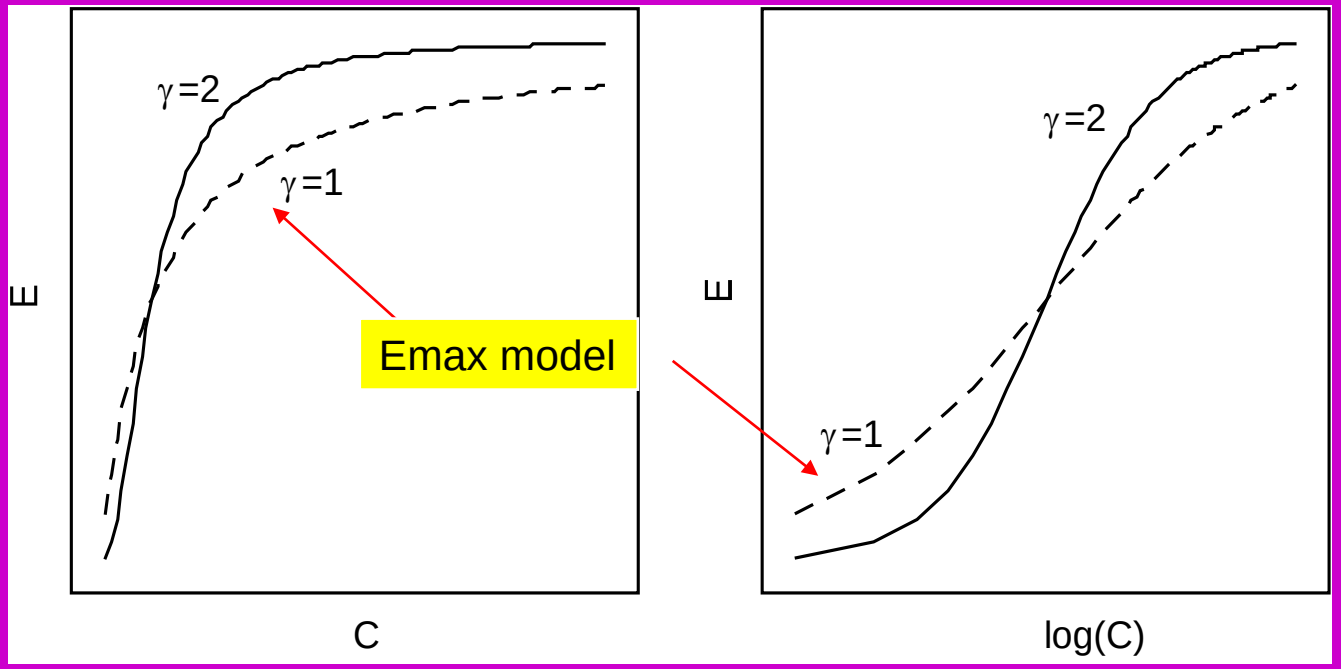
- Concentration-EEG effect relationship of the intravenous anesthetic ketamine and its two enantiomers. The median frequency of the EEG is used as drug effect measure. The solid lines represent the best fits according to the sigmoid E_{max} model. The maximal effect (E_{max}) and concentration required to produce 50% of the maximal effect (EC_{50} or IC_{50}) are indicated. from: Schüttler et al. J. Pharmacokin. Biopharm. 15:241-253, 1987.

Sigmoid-Emax Model

Empirically transformed $C \rightarrow C^{\gamma}$, adds 3rd parameter, γ:

$$E = Emax\frac{C^{\gamma}}{C^{\gamma} + C^{\gamma}_{50}} = Emax\frac{(C/C_{50})^{\gamma}}{1+(C/C_{50})^{\gamma}} = Emax\frac{1}{1+(C_{50}/C)^{\gamma}}$$

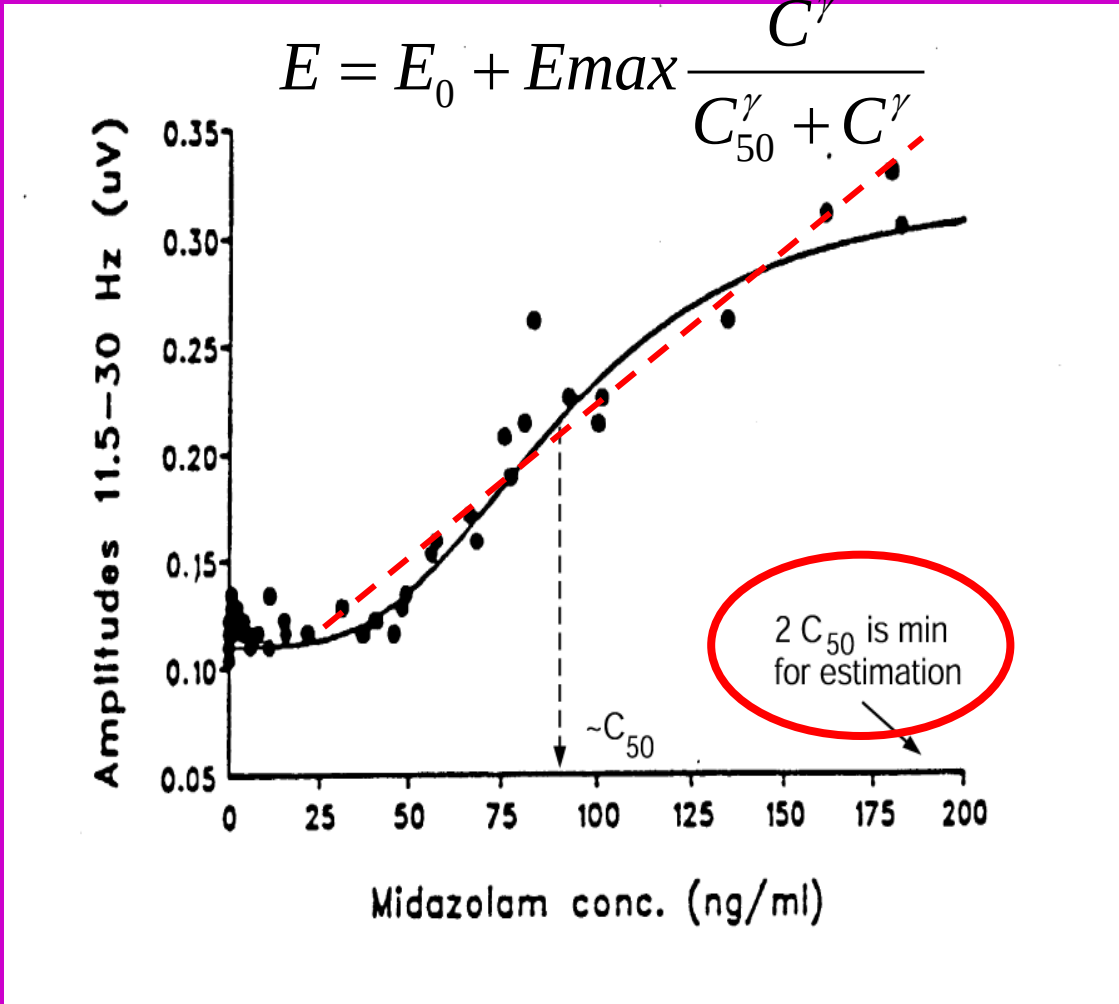
$\gamma=\infty \Rightarrow$ "square wave"



Midazolam Example*

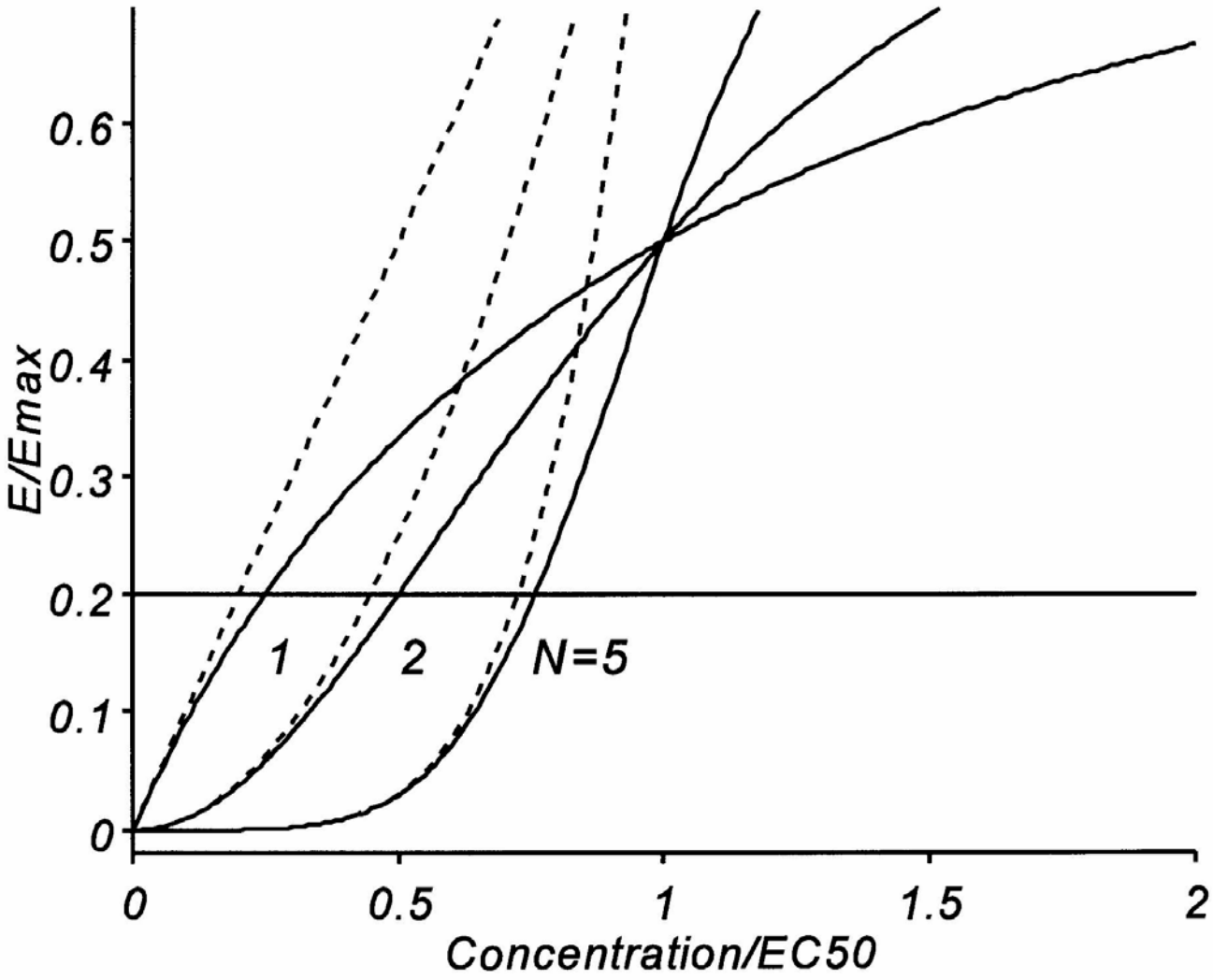
- Midazolam .1 mg/kg infused for 15 min, frequent C (venous plasma) and EEG recorded.

- PD is average amplitude (square root of power) in 11.5 - 30 Hz frequency band of EEG.
- Figure has data from 1 subject, fitted by Sigmoid Emax model (with baseline).



* Mandema et al, Clin Pharm Ther 51: 715-28, 1992

Linear and power model



Linear model :

$$E = E_o + S \cdot C$$

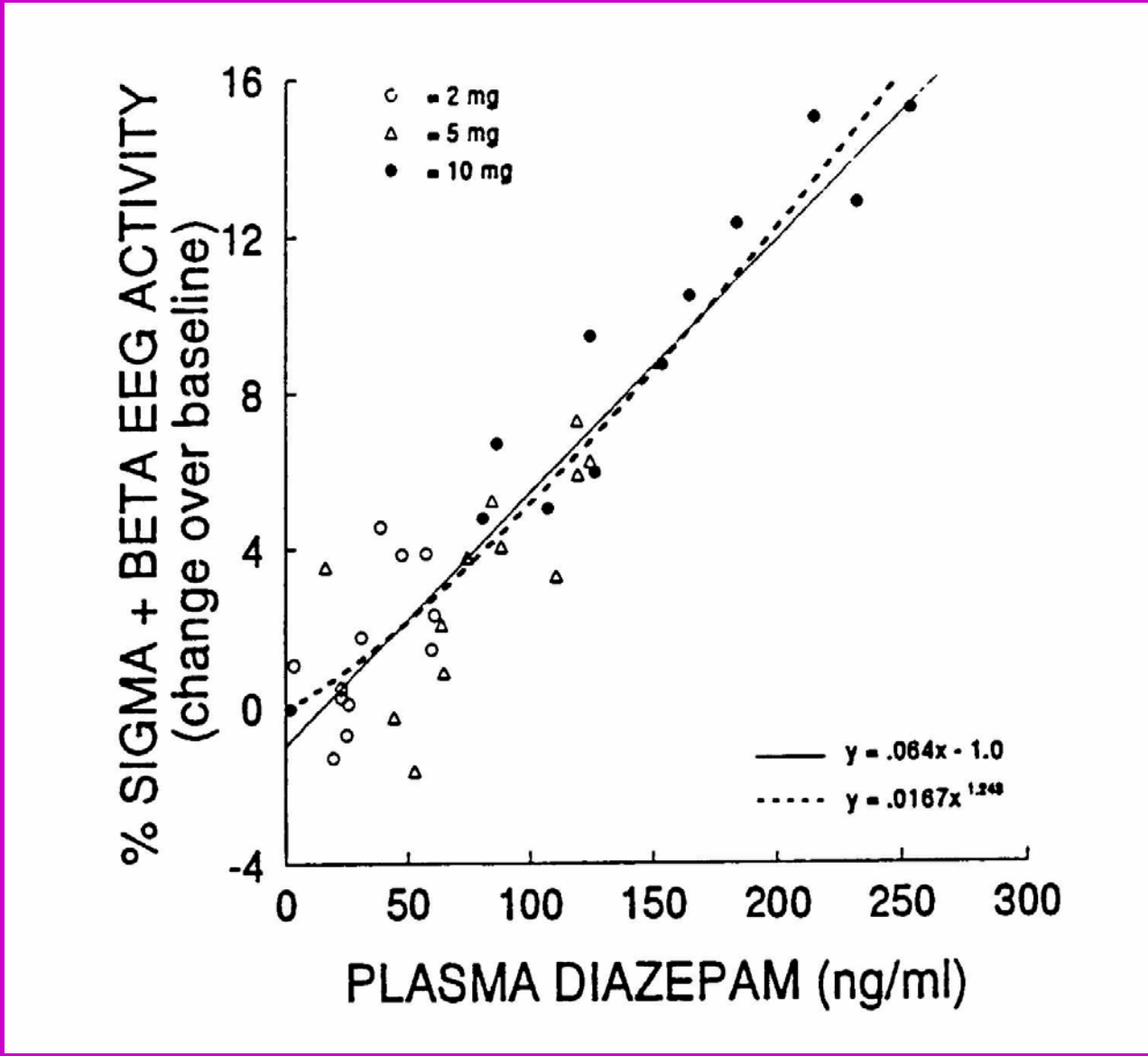
Power model :

$$E = E_o + S \cdot C^n$$

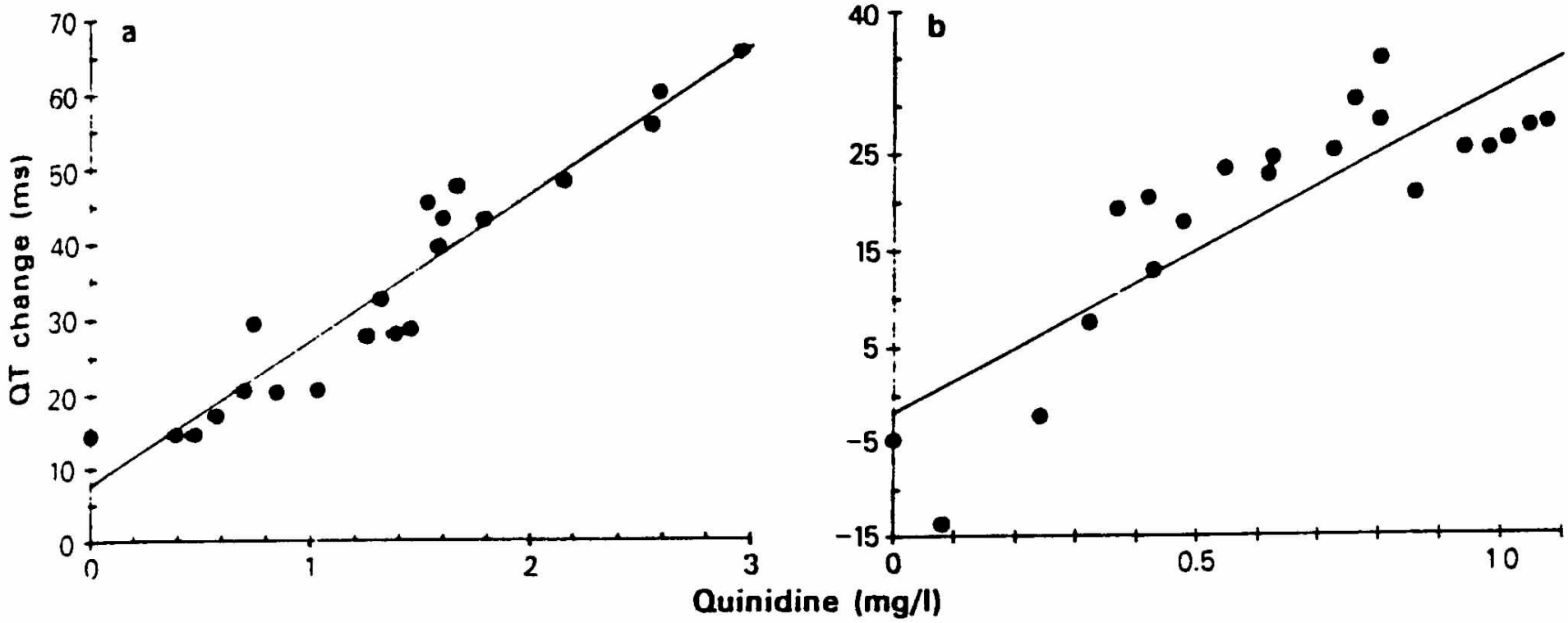
These models are valid for the lower end of the sigmoid E_{max} (power model) and E_{max} (linear model) concentration-effect relationship. S is the slope (approximately E_{max}/EC_{50}^n)

Linear and power model - Example

Relation between mean plasma diazepam concentrations and the mean change over baseline in the percentage of amplitudes falling in the 13 to 30 Hz frequency range of the EEG. Solid line was determined by fitting to a linear model. Dashed line was obtained by fitting the power model to the data. From: Friedman et al. Clin. Pharmacol. Ther. 52:139-150, 1992.

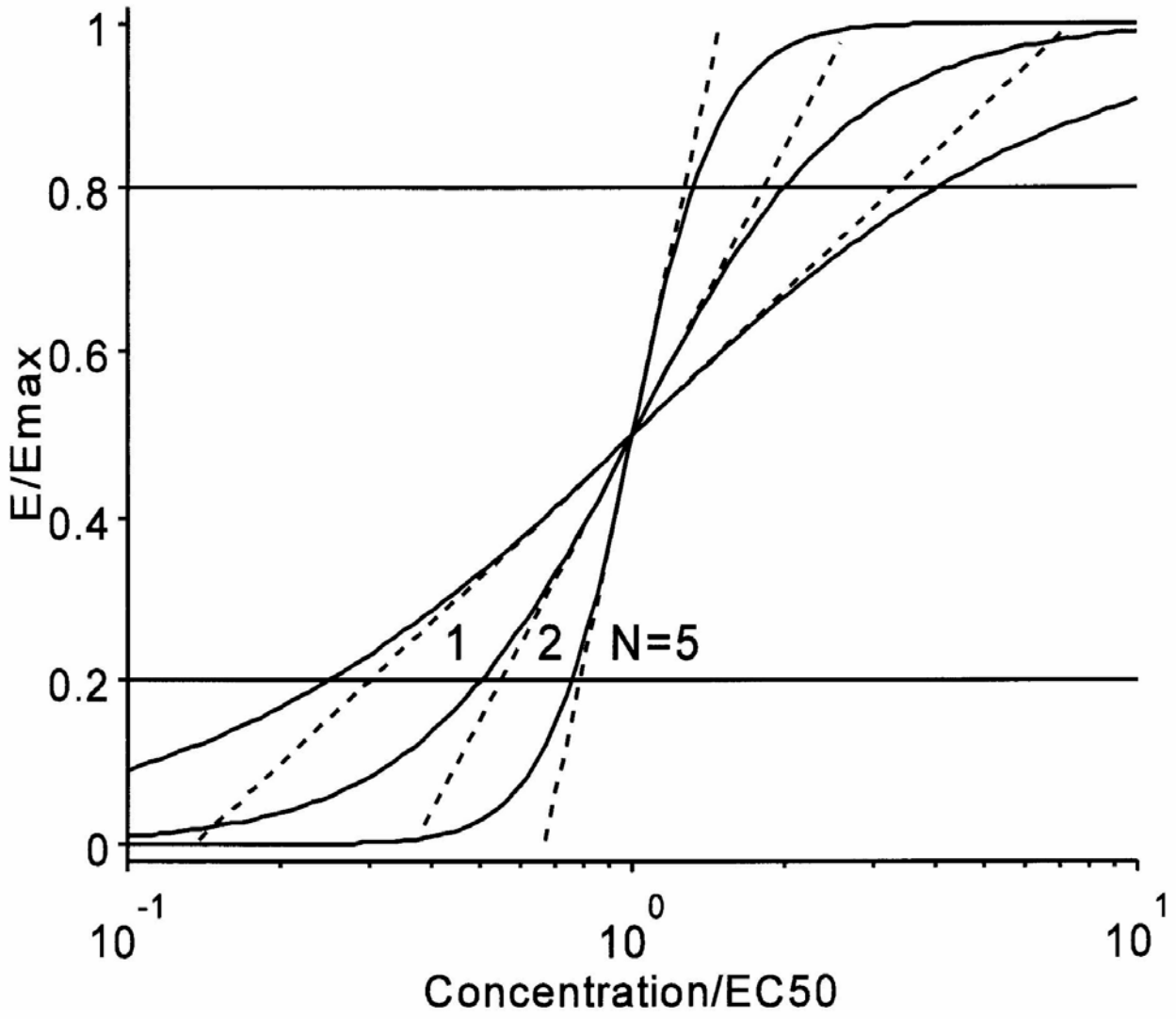


Linear model - Example



Change in QT interval of the electrocardiogram after intravenous infusion (left panel) and oral administration (right panel) of quinidine. The solid lines represent the fit of the linear PD model to the data. From: Holford et al, Br. J. Clin. Pharmacol. 11:187-195, 1981.

Log-linear model



$$E = I + S \cdot \log(C)$$

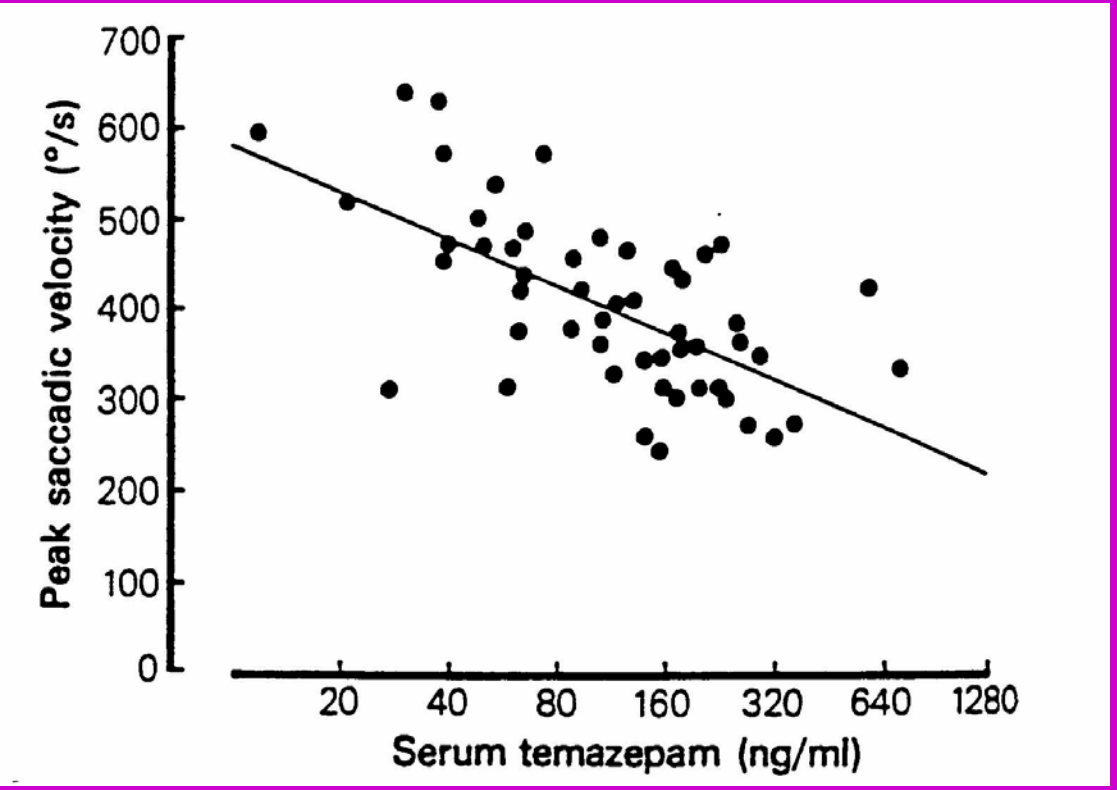
This model is valid for the middle part of the sigmoidal concentration-effect relationship from 20 to 80% of the maximal effect, independently of n.

S is the slope (approximately $nE_{max}/4$),

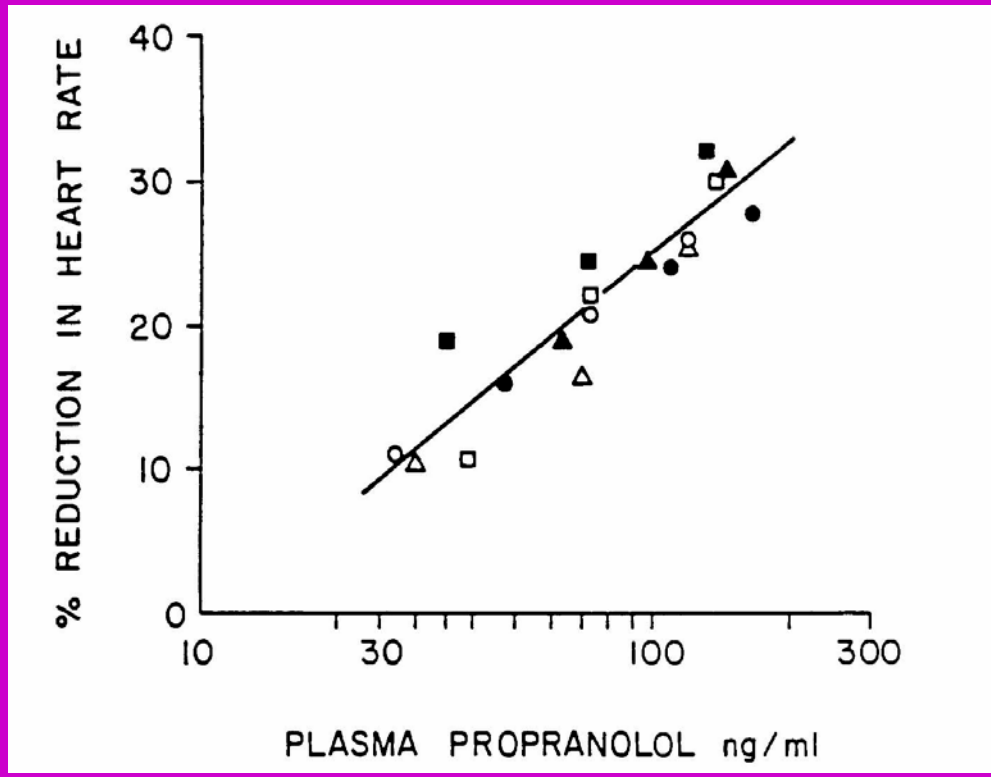
I is the effect when C=1.

The line intercepts the x-axis at $C=EC_{50}\exp(-2/n)$.

Log-linear model - Examples



Relationship between serum temazepam concentrations and peak saccadic velocity in six healthy volunteers who received 20 mg oral temazepam. From: Bittencourt et al. Brit. J. Clin. Pharmacol. 12:523-533, 1981.



Relationship between % reduction in exercise tachycardia and plasma propranolol concentrations. The solid line is the best fit according to the log-linear PD model. Each symbol denotes an observations in a single subject. From: McDevitt and Shand, Clin. Pharmacol. Ther. 18:708-713, 1975.

Linear and Log linear models - Caveats

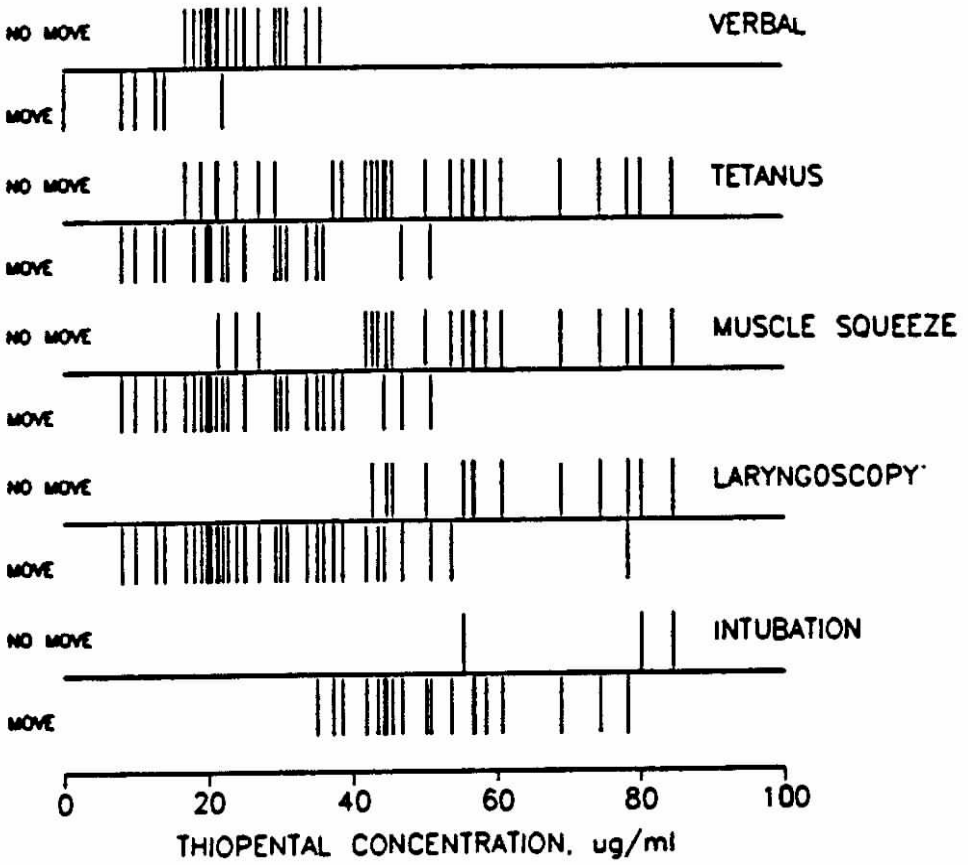
- **The linear and log-linear models are often used as approximations for the description of concentration-effect relationships in human studies when:**
  1. **the occurrence of side-effects prevents the administration of high doses.**
  2. **the drug has a long half-life, resulting in a narrow concentration range being studied**
- **The linear and log-linear model are useful for interpolation not extrapolation. Both models predict no E_{max} and the log-linear model suggests a threshold concentration below which no effect occurs.**

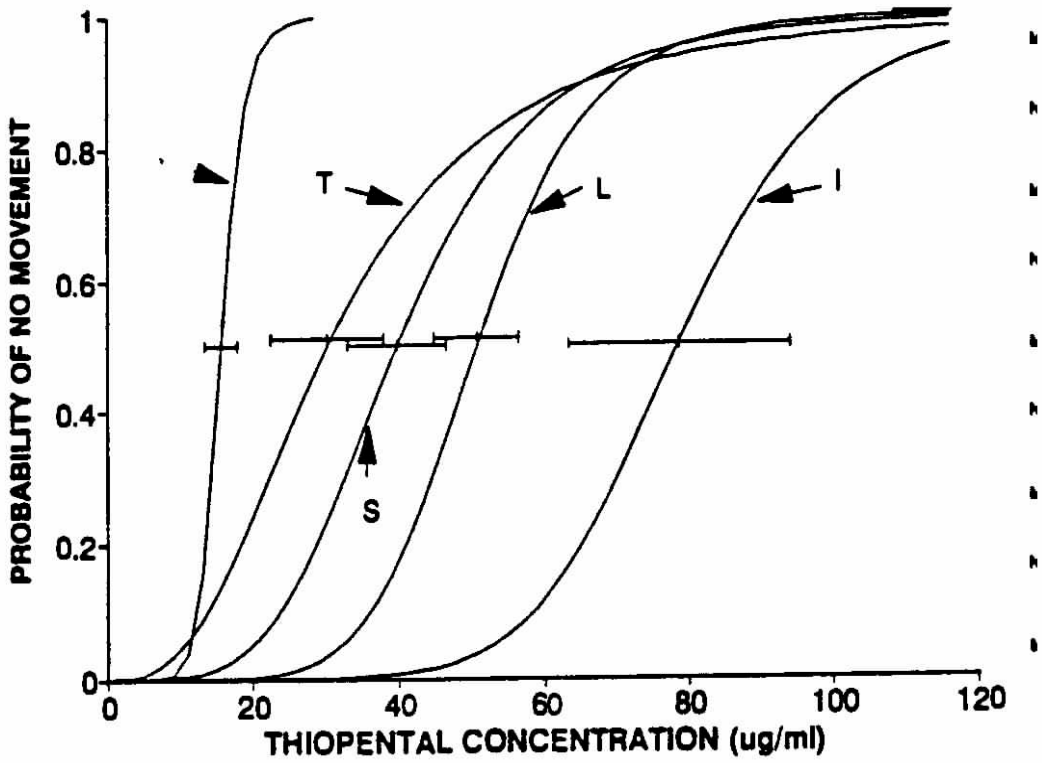
Binary response or Logistic model

$$P(Y=1)=\frac{C^n}{C^n+EC_{50}{}^n}$$

- The logistic model relates drug concentrations to an effect which may be either present or absent (binary response, Y=0 or 1) where:
  - P(Y=1) is the probability that the response will occur,
  - EC_{50} is the drug concentration that will produce 50% probability of response, i.e. elicit the effect in 50% of the population,
  - n is a constant expressing the steepness of the concentration-effect relationship, which reflects the interindividual variability in the measured effect.

Binary response - Example

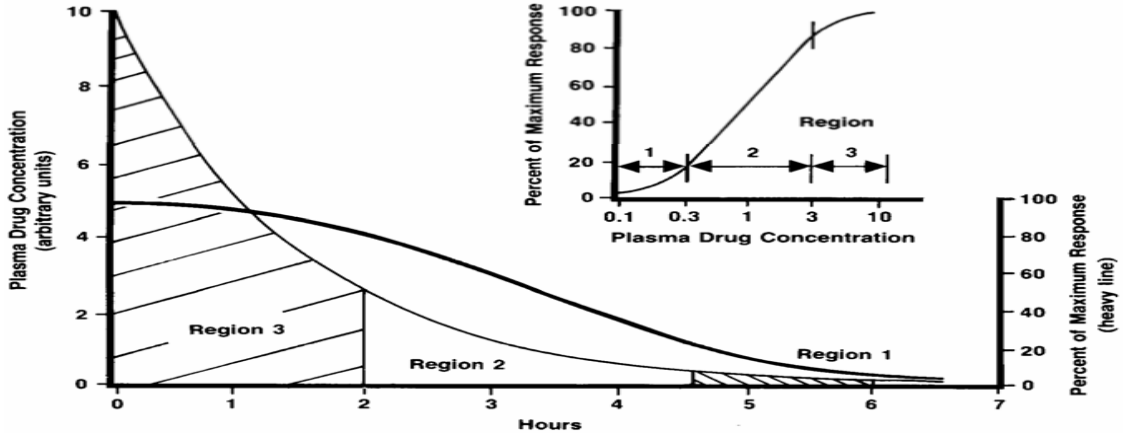




The left panel shows the relationship between serum concentration of thiopental and response/ no response to five different clinical stimuli. Each bar indicates the serum thiopental concentration and response to the stimulus applied to an individual patient. The right panel shows the predicted probability of no movement versus serum thiopental concentrations, obtained using logistic regression of the data shown in the top panel. The bars indicate the 95% confidence bounds of the estimate of the serum thiopental concentration producing a 50% probability of no movement to the applied stimuli. V = verbal; T = tetanic nerve stimulation; S = trapezius muscle squeeze; L = laryngoscopy; I = laryngoscopy and intubation. From: Hung et al. Anesthesiology 77:237-244, 1992.

C. COMBINING PHARMACOKINETICS AND PHARMACO-DYNAMICS

1. Decline of Activity



If response lies between 20 and 80 per cent of E_{max} and simple one-compartment kinetics pertain, response declines <u>linearly with time</u>.

$$Intensity = m \cdot \ln C + b$$

$$C = C_0 e^{-k.t}$$

$$Intensity = \left(m \cdot \ln C + b \right) - m \cdot k \cdot$$

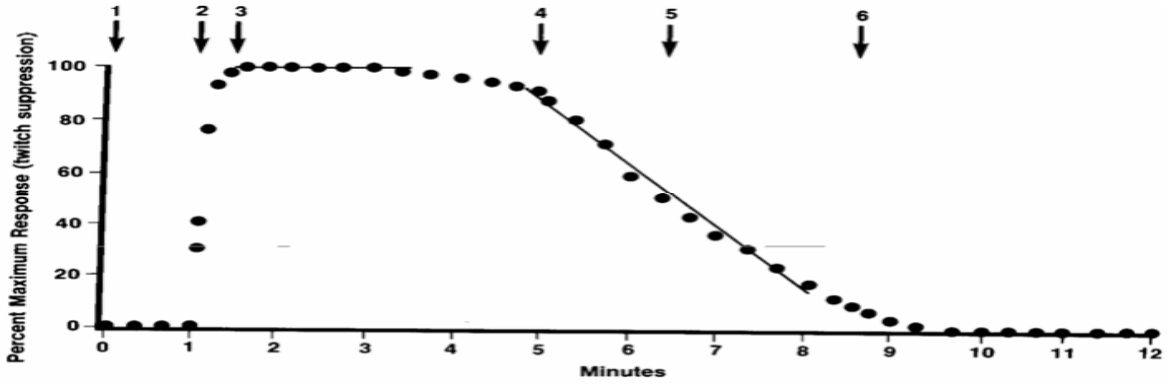
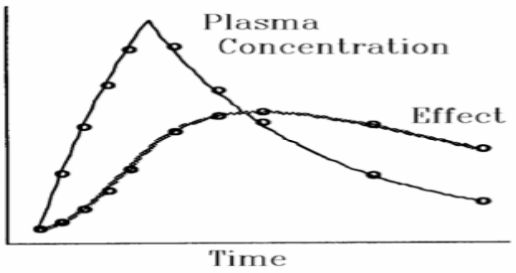
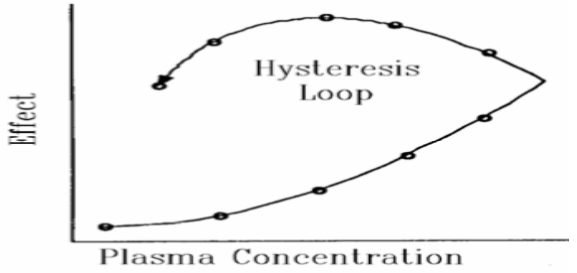


Figure 5 Changes in the degree of muscle paralysis (assessed as the suppression of a twitch produced in response to ulnar nerve stimulation) following an intravenous bolus dose of 0.5 mg/kg succinylcholine to a subject. 1, Time of injection; 2, onset of twitch suppression; 3. complete twitch suppression; 4, 5 and 6, recovery of twitch to 10 per cent (T_{10}), 50 per cent (T_{50}), and 90 per cent (T_{90}) of the maximum twitch height. The straight lines cover the regions of maximum response (horizontal line) and where the response declines (between 4 and 6) essentially linearly with time. (modified from LF Walts and JB Dillon: *Anesthesiology* 28: 372-376, 1967)

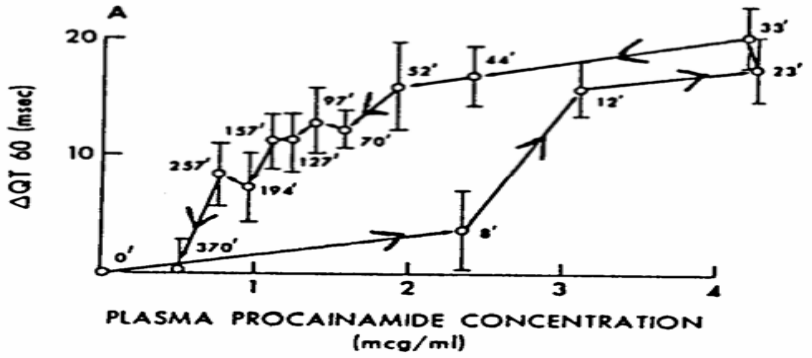
Situation is more complicated if response declines over a wider range of response, and if takes significant time for drug to distribute to target tissue.

2. Detecting Time Effects - Hysteresis Curves





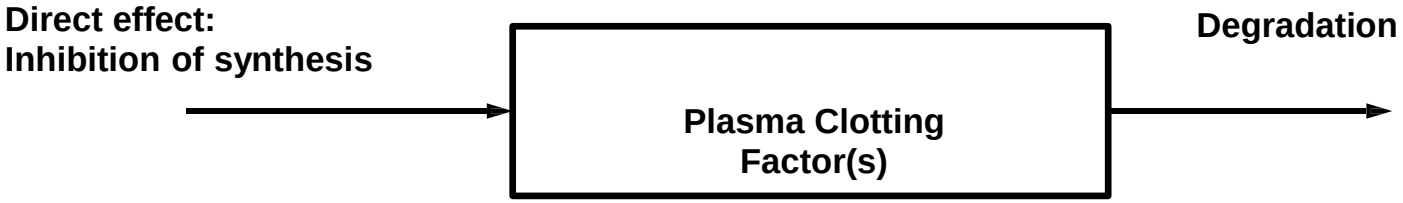
Plot response against plasma drug concentration and join points in chronological order. Commonly observe a counter-clockwise hysteresis.



Other explanations: Sequential events between interaction with receptor and response, occurrence of an active metabolite, or indirect effect.

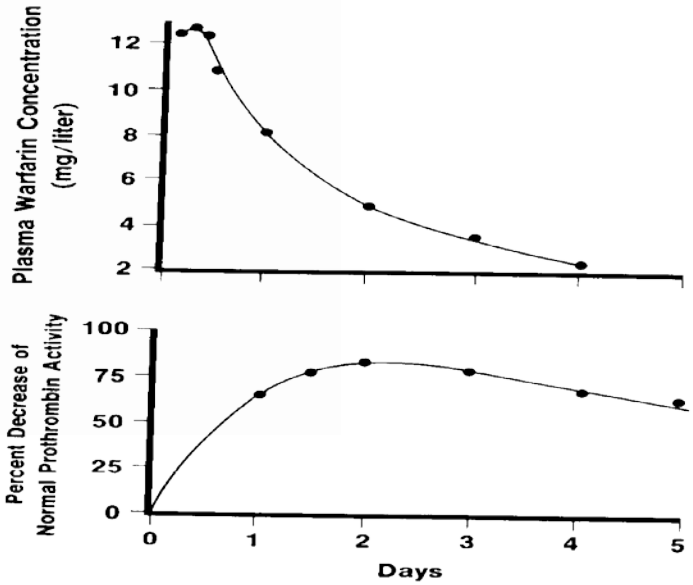
3. Indirect Response. For many drugs, the observed response is an indirect measure of the direct effect.

***Example*. Warfarin. The direct effect of this oral anticoagulant is inhibition of synthesis of clotting factors of the prothrombin complex. The observed effect is the change in the plasma concentration of these clotting factors**



Even if synthesis totally blocked (maximum effect), fall in clotting factors will be controlled by their half lives (7hrs – 4 days)

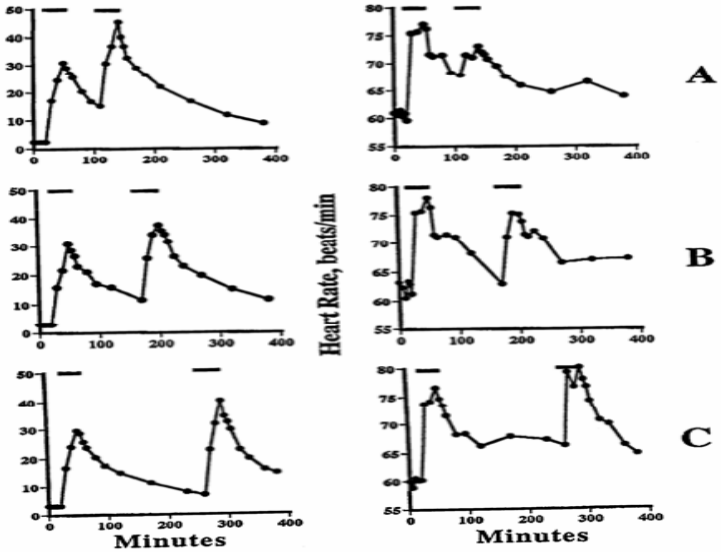
The sluggish response in the plasma prothrombin complex activity to inhibition of its synthesis by warfarin reflects the slow elimination of this complex. For the first two days after giving warfarin, the complex activity steadily decreases. During the first day, the concentration of warfarin is sufficient to almost completely block complex synthesis. As warfarin levels fall, the synthesis rate of the complex increases and by 48 hr equals the rate of degradation of the complex. Thereafter, with the synthesis rate exceeding the rate of degradation, the complex activity rises and eventually, when all the warfarin has been eliminated, it will return to the normal pre-warfarin steady-state level. The data points are the average following the oral administration of 1.5 mg warfarin sodium / kg body weight in 5 male volunteers. (from R Nagashima et al: Kinetics of pharmacologic effects in man: The anti-coagulant action of warfarin. *Clin Pharmacol Ther* 10: 22-35, 1969)



D. SOME COMPLEXITIES

1. Tolerance

The diminished response to a given concentration / dose on repetitive administration. Example - tolerance to nicotine



Mean blood concentration of nicotine (left panels) and the corresponding mean heart rate (right panels) in eight subjects are two 30 min IV infusions of 25 µg/min per kg separated by 1 hr (top two panels), 2 hr (middle two panels) and 3.5 hr (bottom two panels). The short lines at the top of each graph indicate the periods during which nicotine was infused. The longer the separation between the doses, the smaller is the increase in the plasma concentration following the second dose, but the greater the maximum response to the second dose. The effect on heart rate is clearly diminished when the doses quickly follow each other, a phenomenon called *tolerance*. (adapted & redrawn from HC Porchet et al: Pharmacodynamic model of tolerance: Application to nicotine. *J Pharmacol Exp Ther* 244: 231-236, 1988)

<u>Note</u>: The degree of tolerance depends on the dose of drug producing it and the frequency of drug administration; the less frequent drug administration, the less tolerance developed.

2. Active Metabolites

Active metabolites can be discovered by plotting response against drug concentration following oral and intravenous administration of the drug (particularly when formed substantially during drug absorption), or following single and multiple dosing (if metabolite accumulates extensively).

SUMMARY

- **Drug response may be quantal or graded.**
- **On increasing concentration, E_{max}, response increases to a maximum value.**
- **For graded response, the concentration-response relationship is characterised by C_{50}, E_{max} and γ.**
- **For simple one-compartmental kinetics, intensity declines linearly with time after an intravenous bolus dose.**
- **Time delays in the concentration-response relationship may be due to either measurement of an indirect effect, time for distribution to occur, or delay between receptor occupation and response produced. Methods exist for abstracting the underlying concentration-response relationship.**
- **Complexities in the concentration-time-response relationship include:**
  - **i) development of tolerance**
  - **ii) active metabolites**