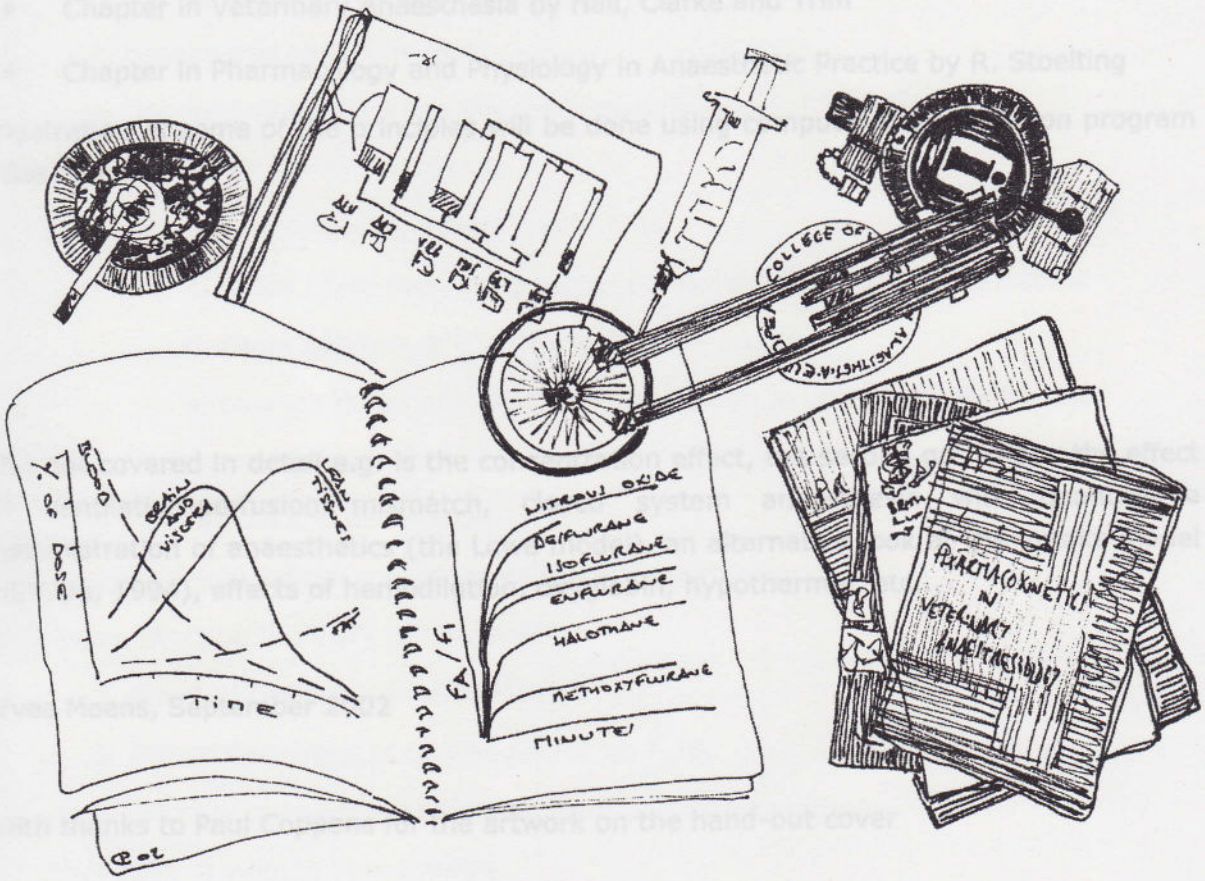
ASSOCIATION OF VETERINARY ANAESTHETISTS

EUROPEAN COLLEGE OF VETERINARY ANAESTHESIA

Autumn 2002 Meeting

Day Seminar on Pharmacokinetics



Crete, Greece

26 September 2002

UPTAKE AND DISTRIBUTION OF INHALATION ANAESTHETICS: THE BASICS

Notes for the Trainee-session at the 2002 Autumn Meeting of the Association of Veterinary Anaesthetists in Crete.

This is an introduction in the subject and there is much more material that cannot be covered during two sessions of one hour.

This notes are based on:

- Chapter in Lumb and Jones by E. Steffey
- Lectures of E. Eger presented in the serie "Distinguished Professor"
- Chapter in Veterinary Anaesthesia by Hall, Clarke and Trim
- Chapter in Pharmacology and Physiology in Anaesthetic Practice by R. Stoelting

Illustration of some of the principles will be done using computer the simulation program "Gas Man®"

PS: not covered in detail e.g. is the concentration effect, the second gas effect, the effect of ventilation-perfusion mismatch, closed system anaesthesia with quantitative administration of anaesthetics (the Lowe model), an alternative look at the uptake model (C.Y.Lin, 1994), effects of hemodilution, oxyglobin, hypothermia, etc...

Yves Moens, September 2002

with thanks to Paul Coppens for the artwork on the hand-out cover

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PHARMACOKINETICS OF IV AGENTS

1. Derivation of PK Parameters from Intercepts and Slopes

Example:

Propofol in the dog. Bolus dose of 4 mg/kg

Intercepts: $A = 7.68\ \mu g/ml$ $B = 0.92 \mu g/ml$

Slopes: $\alpha = 0.889/min$ $\beta = 0.00990/min$

C_0 (Concentration at time 0) = A + B = μg/ml

$$V_1 = \frac{\text{Dose}}{A+B} = \frac{4000 \mu g/kg}{\mu g/ml} = \text{ml/kg}$$

$$\text{Distribution } t_{1/2} = \frac{0.693}{\alpha} = \frac{0.693}{0.889/min} = \text{min}$$

$$\text{Elimination } t_{1/2} = \frac{0.693}{\beta} = \frac{0.693}{0.00990/min} = \text{min}$$

$k_{21} = (A\beta + B\alpha)/(A + B) = 0.1039/min$

$k_{10} = \alpha\beta/k21 = 0.0847/min$

$k_{12} = \alpha + \beta - k_{21} - k_{10} = 0.7103/min$

$$V_2 = V_1 (k_{12} / k_{21}) = V_1 \times \frac{0.7103}{0.1039} = V_1 \times 6.836 = 3179 \text{ ml/kg}$$

$Vss = V_1 + V_2 = 3644$ ml/kg

Cl (Clearance) $= k_{10} \times V_1 = 0.0847 \times V_1 = 39.4$ ml/min/kg

2. Influence of changes in inter-related parameters

A) Volume of Distribution

With a constant dose, the lower the measured concentration, the greater the volume of distribution:

V_1 = Dose/Concentration eg $\frac{4000}{8.6}$ = 465 ml/kg $\frac{4000}{4.3}$ = 930 ml/kg

$\frac{4000}{17.2}$ = 232.5 ml/kg

With a given volume of distribution, the concentration achieved at any given time is linearly related to the dose given:

Concentration = Dose/V_1 eg $\frac{4000}{465}$ = 8.6µg/ml $\frac{2000}{465}$ = 4.3µg/ml

B) Clearance is dependent on both the elimination rate constant (k_{10}) and V_1

$Cl = k_{10} \times V_1$

e.g. k_{10} = .0860/min. If V_1 = 465 ml/kg, Cl = 40 ml/min/kg

If V_1 = 232.5 ml/kg, Cl = ml/min/kg

e.g. V_1 = 465ml/kg If k_{10} = 0.0430/min, Cl = ml/min/kg

C) Half lives (Time required for concentration to fall by 50%) are dependent on both volume of distribution and clearance

Elimination $t_{1/2} = 0.693 \times \frac{V_D}{Cl}$

Elimination $t_{1/2}$ will be extended if V_D is increased or Cl decreased

Elimination $t_{1/2}$ will be shortened if V_D is decreased or Cl increased

How to Write a Case Report

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Introduction

One of the requirements of potential ECVA Diploma candidates is the submission of five case-reports, "published, or in a form suitable for publication of which the applicant is author or co-author". The case reports have to be relevant to anaesthesia, analgesia and, or intensive care. At least one report should be a large or a small animal case. That the candidate participated in the case described must be confirmed by the supervisor [1]. This year (2002) the ECVA examinations committee noted that the principal reason for application failure was related to the case reports. This article attempts to provide information that aims to resolve this problem.

The Case Report

A case report is a concise and sequential description of the medical management of a rare and, or interesting "event" which occurs (usually) in a single patient, and which is written with the intent to a) raise awareness of an "event" and b) educate the reader so that future encounters with the same "occurrence" are identified more rapidly and treated more effectively.

A verbal presentation of "what happened in this case" is probably the oldest method of communicating medical information. Undergraduate training in European and N. American Veterinary Schools often ensures that graduates have at least some experience in verbal case reporting by the time of graduation. While the written case report follows a similar format as the verbal presentation, rules are more stringent. The case report is often the postgraduates first venture into scholarly writing.

Case reports are an important vehicle for reporting unusual diseases, occurrences or presentations of disease and are probably the only means of surveillance for rare events. Their discussion *should* serve to elucidate the mechanisms of the "event" described and justify its treatment. However, their limitations must be recognised, and while they are a potentially rich source of hypotheses about disease or "event" frequency, risk, prognosis & treatment, they do not provide sufficient data to test the hypothesis because usually, only one case is involved. When the report involves more than ten subjects it becomes a case series (Smith 1988). Case series may provide information on the frequency of

findings in a given "medical event", but lack a control group, so are useless as estimates of risk.

Choosing a subject

Case report subject matter can fall into one of four categories: a) totally original, rare or highly unusual cases; b) cases presenting with features demanding conflicting management; c) accidents & incidents of major importance, i.e. high morbidity and, or mortality; d) cases with features which contradict or bring into doubt established practices or beliefs.

Whatever the topic, the case report must be interesting and convey a message. Interest motivates the reader to finish the article, and commit to memory the most important elements of the message. Thus a rare "occurrence" does not merit publication if there is no message, i.e. if the reader is left thinking, "So what?". Thus, case reports on drug combinations or techniques on very small numbers of an (uncommon) species may be worse than useless as they may convey the message that the technique is suitable, whereas it may later become established that the technique described kills 99% of recipients.

After reading a case report, the reader should know a) precisely what happened to the subject; b) the time course of events; and c) why management followed the lines that it did. The reader should then be able to d) diagnose more rapidly and e) manage more successfully a similar case should it arise in the reader's practice. In order to fulfil this, the case report must compare management techniques, identifying possible management errors and submitting alternatives. A good case report should offer clear recommendations for case management in future encounters.

Getting material for a case report

The longer a case-report is left unwritten, the harder it becomes to recover the detail required for a worthwhile submission. This creates a temptation to create, obfuscate or withhold details – or not to write the article at all. Consequently, writing a first draft should begin as soon as all the relevant details are amassed, perhaps within 24 hours. A prospective approach is advisable when a number of case-reports are required to meet examination requirements. Candidates in this situation should constantly endeavour to identify and participate in potentially reportable cases. That interesting and reportable events may arise unexpectedly indicates the importance of keeping a detailed anaesthetic record of all cases anaesthetized.

The priority during, or immediately after any situation, which may prove worth reporting is to record the temporal sequence of events and the time at which they occurred, or failing that, the approximate time interval between events. The second step is to record specific events in greater detail, e.g. drugs given, doses used, routes of administration, and the effects, which followed. All individuals who were present should be asked to confirm or correct personally recollected facts. Third, the medical record should be reviewed and all pertinent information copied.

Is it worth writing up?

The next step is to determine whether or not the material merits writing up. Initially, senior colleagues should be approached and the material "tested" for interest, educational and "rarity" value. The material should then be presented to a wider audience, e.g. at a resident's or departmental clinical seminar, with the presentation script being used as a template upon which a future paper may be founded. During these processes, the presenter should record any questions asked and criticisms made, intending later to address them fully within the body of the first draft. Such queries and criticisms are likely to be raised by future readers. These steps are taken first to avoid the third and laborious step of a literature review. This has two goals: a) to establish that the material is unique or extra-ordinary; and b) to collect background material for the case-report. Ethical obstacles to publication should also be resolved before too much work is performed. For example, it must be established that any material destined for inclusion in the final document does not contravene national or local animal care legislation, and prove (embarrassingly) to be grounds for manuscript rejection. In some cases client permission may be necessary.

During these stages the author must focus on the nature of the intended message and insodoing, question his or her own motives for writing the report. For unusual cases, or those involving complex management, self-aggrandisement must be avoided: the subject's case history should be interesting, not the author's skill at diagnosing, or managing complex problems. In rare cases and those involving accidents, the goals are to raise awareness and provide sound recommendations for the management or prevention of similar cases.

Writing up

The author must choose a journal to which submission will be made. The choice will depend on the nature and size of the journal's readership, its academic standing, the policy on case reporting and the duration of manuscript processing etc. However, the most important criterion for choice is based on the answers to two questions: "Who would benefit most from reading this work?" and then "Which journal do these people read?"

A recent copy of the chosen journal should then be examined for information on editorial policy concerning case reports, format and style issues. These will usually be specified under recent "Guidelines to contributors". Details are often less clear for material other than research articles, in which case the author might examine extended guidelines to the authors on the Journal's web-site. Alternatively, a case-report similar in nature to that being written and recently published in the target journal can be used as a template for format and style.

The paper should be written in clear unambiguous English and in a logical sequential fashion. Whilst the facts are being set down, the author should remain mindful of "the message". This helps to separate important from irrelevant material in the time it takes

to leave the authors consciousness and become established on paper (or disk). Irrelevant details should be discarded at all stages of manuscript development. Writing everything down under the illusion that this is the first draft, and that irrelevant material can be excluded later is a waste of time: large sections of useless text make it difficult to form a rational discussion; and most case reports are too long. The general format of the case report should be as follows.

Title

This should be concise and enticing. Excessively long and detailed titles might convince the reader that he or she has already gained all the information they need, causing them to read no further.

Authorship

No more than three authors are necessary for anaesthesia-based cases, as more than three people are rarely needed to anaesthetise an animal. Authorship should be restricted to those who made a material contribution to the management of the case as it is described in the report. There should be no acknowledgement of surgeons, primary clinicians, laboratory technicians or nurses if they were not major participants in management. Assistance with manuscript preparation should be acknowledged, but not form the basis of co-authorship. The inclusion of surgical or pathological details in a case-report does not warrant automatic co-authorship by surgeons or pathologists unless these, or other specialists, upon request by the author, submit an extra-ordinary report, i.e., more than that which would be routinely provided for the medical record.

It is a matter of professional etiquette to ask the primary clinician for permission to report the case. It is also a matter of professional etiquette that the primary clinician does not expect an automatic right to authorship if they fail to meet the criteria listed above.

Introduction

Should be very concise, put the case described in context, indicate its relevance and begin the process of interesting the reader. It should not include any type of background information.

Case description

Must be arrayed in chronological sequence.

signalement

presenting signs

relevant anamnesis

examination findings

investigation results

subject's progress the description should be full, but not submerged in irrelevances.

Diagrams are useful for presenting relevant physiological data. Photographs of what went wrong, i.e. a displaced catheter, or a damaged breathing system, which are clear enough to expedite recognition or recollection by the reader, are acceptable.

Discussion

The main purpose of the discussion is to explain how and why decisions were made and what lessons are to be learnt from this experience. The aim should be to refine and define the message for the reader, either what was done correctly (and what should be done in future) or what was mismanaged, and what should not be repeated. A good case report leaves the reader in little doubt about how similar cases should be managed should he or she encounter a similar case.

The discussion must not become a review, despite the temptation to write one in an attempt to justify the initial work involved in collecting information.

References

Only those that make a clear point should be included. Popular textbooks must be cited when accepted practice or knowledge is being challenged, in order to justify use of the word "accepted". Otherwise, only strongly supportive evidence, or directly contradictory material should be cited.

Acknowledgements

Criteria for acknowledgement are slightly less stringent than those for authorship. The author should ask, "Would the patient have managed without X?" and "Would the paper have been written without Y? If the answers are no, and X and Y are not co-authors, then their acknowledgement may be justified providing the reason is described, e.g. for technical assistance, for typing the manuscript etc. It is not appropriate to acknowledge routine assistance from nursing or surgical colleagues. It is essential to acknowledge all sources of financial assistance and any conflicts of interest.

Style Issues

Measures to avoid an unfavourable editorial response must be taken as a matter of priority: the editor will read the paper first and their impression may eventually prevail even though the reviewers may be more lenient. Before submission, "Guidelines to contributors" should be reviewed to ensure all requirements are met.

The author should pre-empt any questions asked by the reader and should ensure the information is in.

Within the strict framework outlined above, the author should be encouraged to use his or her literary skills to enhance the delivered message. For example, when describing accidents or emergencies, the author should attempt to make the reader glad that they were not involved, and intrigued at what happened – in addition to indicating future methods for prevention.

Poor English style and syntax are common reasons for alienating editors and submitted manuscripts. Leniency is given to case-reports whose authors do not use English as their first language. No leniency is given towards material whose authorship includes experienced English speakers who have not reviewed the manuscript.

References

[1] http://www.ecva.org.uk/guide.html#_Chapter_2

[2] http://www.ecva.org.uk/docs/case.pdf

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Yves Moens, september 2002

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    2. Influence of lung capacity
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F. Elimination of volatile anaesthetics
    1. Effect of duration of anaesthesia
    2. Effect of metabolism
G. Summary
H. GasMan

A. INTRODUCTION

1. The concept of MAC

When we anaesthetise an animal with a volatile agent we use the agent-vaporiser, a carrier gas (usually O_2) and a breathing circuit. The patient is breathing the anaesthetic mixture via a mask, a tracheal tube or is exposed to it in an induction chamber. When the vaporiser is located out-of-the-circuit we can control the concentration of the volatile agent introduced in the breathing circuit by using the dial setting calibrated in volume percent of one atmosphere (F_D)

The potency of inhalation agents can be compared using MAC.

MAC is the *minimum **alveolar** concentration* of an anaesthetic at one atmosphere that produces immobility in 50% of subjects exposed to a supramaximal noxious stimulus (Eger). The dose necessary to have 95% of the patiens anaesthetised is 1.2 to 1.4 MAC.

During administration of volatile anaesthesia it is convenient to measure, regulate and to communicate about the clinical dose using the concentration of the agent in volume percent (the vaporiser is set to deliver precise volume %). *The important aspect for the anaesthetic effect however is the partial pressure that the agent at this vol % exerts in the brain*.
The relationship in a gas-phase (not in blood or tissues, see later!) between concentration (C) in Vol% and partial pressure (P_{anaes}) is simple:

P_{anaes} = P_{bar} x fractional anaesthetic concentration (F_{anaes})

Fractional concentration = $C_{anaes}/100$. (e.g 100%=1; 50%=0.5, 2%=0.02 etc)

Thus the MAC expressed in concentration (vol%) may vary for a given agent according to barometric pressure (e.g . sea level versus mountains) but the P_{anaes} for MAC for a particular anaesthetic will always be the same.

2. The partial pressure Cascade

Controlling volatile anaesthesia is thus controlling the partial pressure of the agent in the brain.

It is still technically impossible to measure P_{anaes} in the brain, but thanks to the quick diffusion and equilibration at the level of the alveolar-capillary interface on one hand and at the brain/blood barrier on the other hand, one can consider (simplification!) that:

P_{anaes} alveolus = P_{anaes} arterial blood = P_{anaes} brain

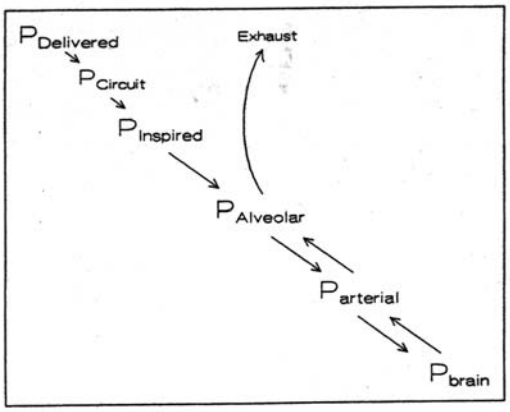
MAC represents alveolar concentration of the agent. Nowadays it is possible to measure accurately end-tidal concentration (and thus P_{anaes}) with properly calibrated anaesthetic agent analysers. In presence of normal capnograms % end-tidal = % alveolar or in other words: P_{anaes} end-tidal = P_{anaes} alveolus.

In this text we will use frequently fractional concentration of the agent: delivered (from the vaporiser), inspired and alveolar: respectively F_D, F_I and F_A.

Anaesthetic depth varies directly with P_{anaes} in brain tissue. Inhalational anaesthesia may be viewed as the development of a series of partial pressure gradients. The anaesthetic will always move from a higher pressure to a lower until equilibrium is reached.

Partial pressures may differ between:

-inflow and the circuit
-circuit and the alveoli
-alveoli and the blood
-blood, brain and other tissues



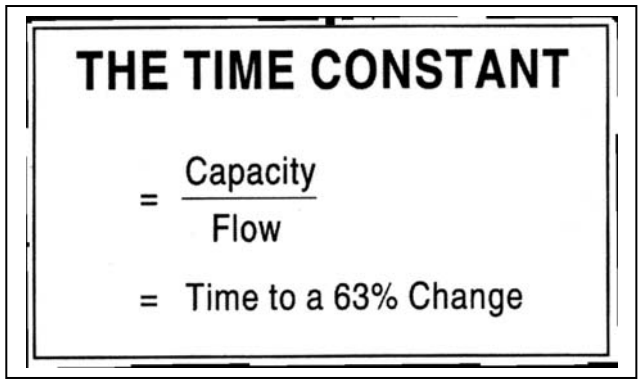
As P_A is the closest we can practically get to P_{brain} and thus a good index for the expected anaesthetic effect of our agent we will be interested in the actual P_A and also the speed with wich P_A changes. This will give us an idea of the depth of anaesthesia to be expected and the changes of P_A will dictate the speed of induction or recovery of inhalation anaesthesia. In the gas phase (lungs) we can for the discussion here conveniently consider the fractional concentrations (F_D, F_I, F_A) in stead of the partial pressures (also because we can conveniently measure concentrations in vol% and thus calculate fractions).

B. The relationship between F_D and F_{insp}

1. Influence of the patient breathing circuit: a time constant

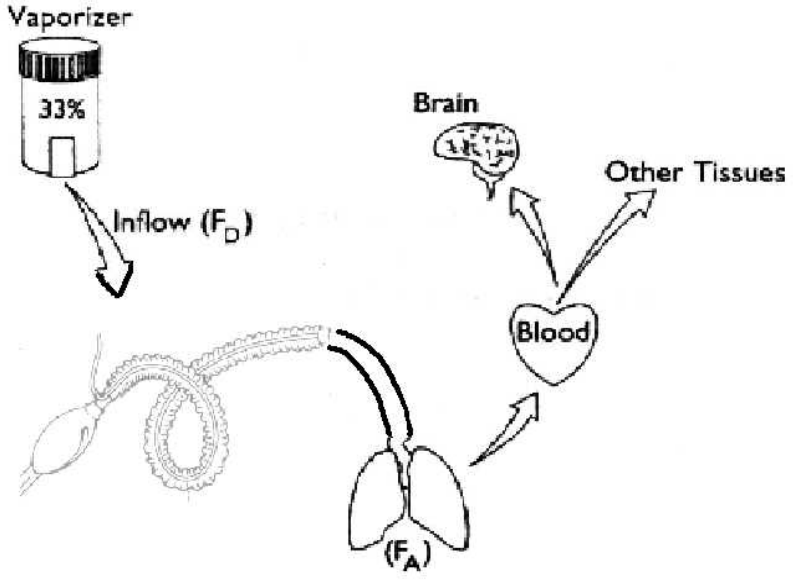
When we want to change F_A we will start with changing the F_D. The changes in F_A will follow **with a delay in time** depending on many factors
The patient circuit contains a gas volume that must be replaced ("washed out") with gas containing the desired anaesthetic concentration: it is a "buffer" to delay the rise of F_I. The rate at which F_I rises towards F_D in this system depends on the Time Constant of the system, this is: on the volume and the flow rate. The time constant is obtained by dividing the capacity of the system (here it is pure volume, see later time constants in tissues) by the flow through the system. The resulting time is one time constant and it is the time needed to produce a 63% change in the total possible change in concentration (this would be F_D on induction and 0 on elimination)

	0-100%	100%-0
1 Tc	63%	37%
2 Tc	86%	14%
3 Tc	95%	5%
4 Tc	98%	2%

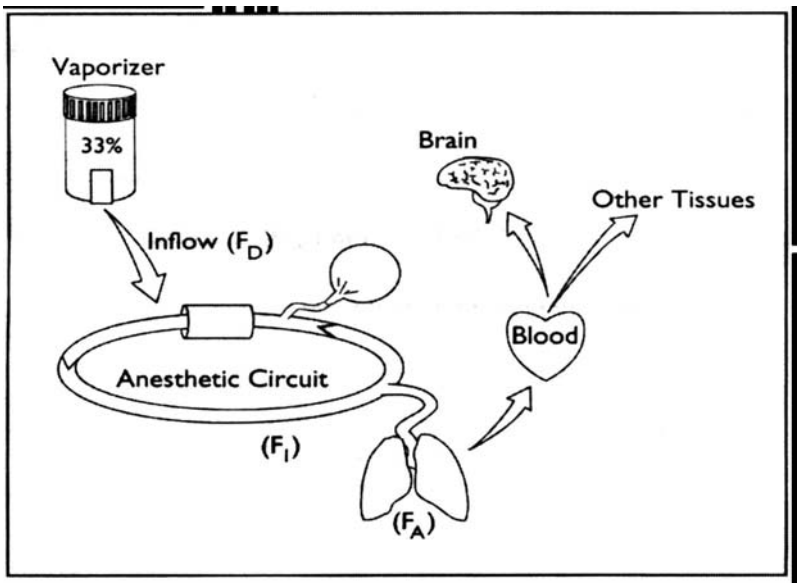


Depending on the volume and the flow you will have a *slow* or a *rapid* system:

When using a non rebreathings system (T-piece, Bain,…): inspired concentration almost immediately equals the vaporiser –dialed concentration ($F_{D=}$ F_I)

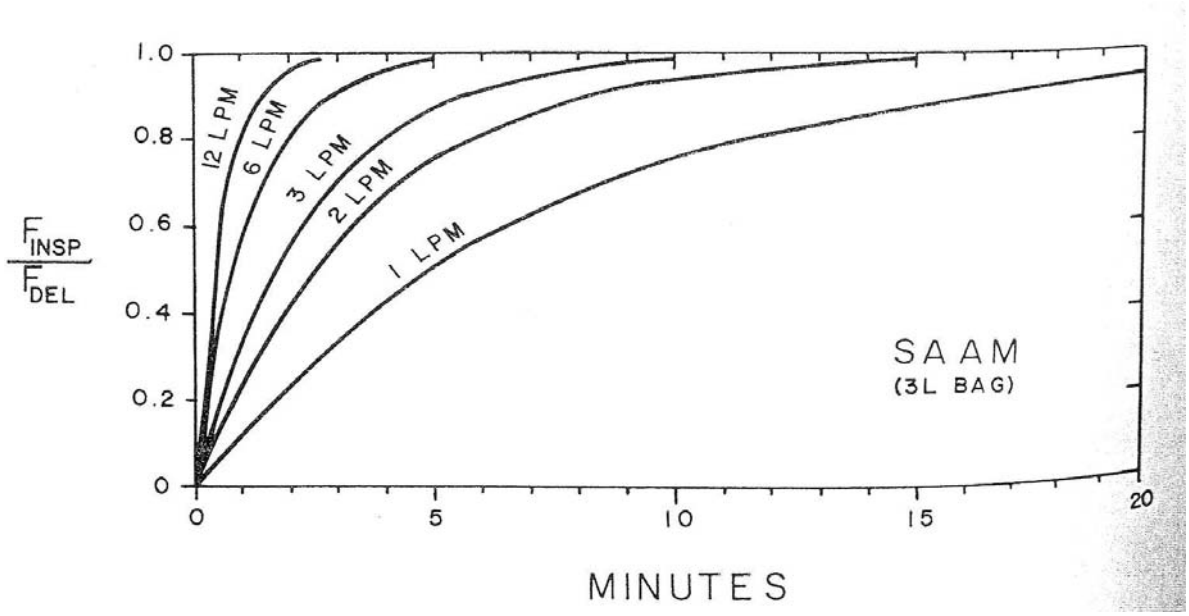


When using a rebreathing system (circle, to and fro). a delay will be present for two reasons:



1) depending on the inherent time constant of the system (importance of the size of the breathing bag, presence of one or two CO_2 absorbers, etc…).. In a slow system it will take a longer time before $F_I = F_D$. The higher the flow for a given volume the shorter the time constant the quicker the desired concentration is in theory inspired by the patient

2) once connected to a patient the circulating inspired gas consists of delivered gas from the vaporiser plus gas exhaled from the patient. This exhaled portion contains less anaesthetic because of anaesthetic uptake in the lung (see later). The higher the gas flow through the system, the less the rebreathed portion and the quicker F_I will increase to F_D.



With some anaesthetics (methoxyflurane, the solubility in rubber components decreases the rate of rise of the anaesthetic in the circuit)

2. Influence of long capacity: another time constant

If there would be no anaesthetic uptake the long volume (frc) can be regarded as a pure extension of the circuit volume and its time constant determined solely by the alveolar ventilation. The time constants of circuit and lung are then additive.

C. The relationship between F_A and F_I

1. Uptake and F_A/F_I

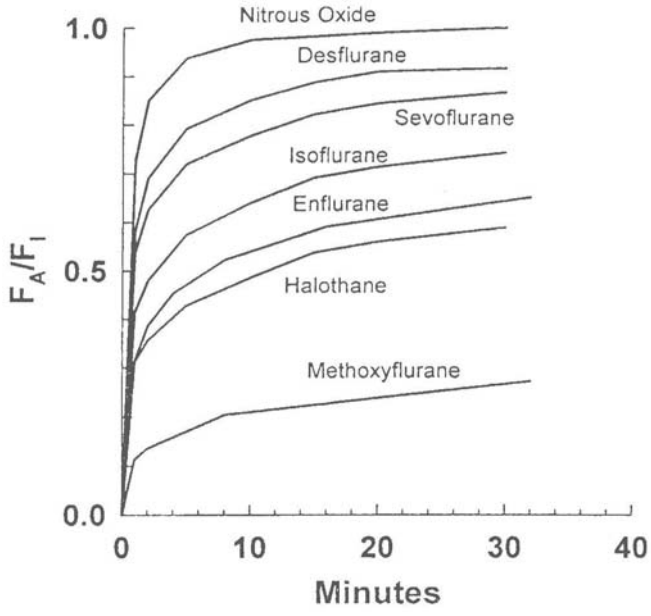
The relationship between the concentration of anaesthetic in the alveolar gas (F_A) and the concentration of anaesthetic in the inspired mixture (F_I) is important because F_A represents the partial pressure of anaesthetic going to the brain and tissues, and because F_I, can be easily controlled by 1)using a non rebreathing system or 2) by delivering F_D at a high inflow rate in a rebreathing system (limits rebreathing, F_D then rapidly equals F_I).

The figure shows the rate at which the alveolar concentration approaches the inspired concentration (the F_A/F_I ratio) for nitrous oxide, desflurane, sevoflurane, isoflurane, enflurane, halothane, and methoxyflurane.

Two characteristics are important:.

First, the curves for the anaesthetics differ in their position on the graph, nitrous oxide being at the top and methoxyflurane being at the bottom.

Second, all of these curves have the same shape, rising very rapidly to a first "knee," less rapidly to a second "knee," and more slowly thereafter



*The F_A of an anaesthetic (and thus P_A and thus anaesthetic depth) is a **balance** between anaesthetic input (delivery to the alveoli) and loss (uptake by blood and tissues).*

Uptake of anaesthetic opposes the effect of ventilation (increasing the concentration) and keeps the value for F_A/F_I from immediately reaching 1.
If one knows uptake, one can know the relationship between the alveolar and inspired concentrations of anaesthetic.
If uptake removes half the anaesthetic being brought into the lungs, F_A would be one half F_I; if uptake removes two thirds, F_A would be one third F_I.

The rapid rise or fall of F_A is associated with rapid changes in anaesthethic depth (induction, recovery, during maintenance,…).

2. Uptake and solubility

a. Uptake and solubility

Uptake is the product of three factors: solubility (λ), cardiac ouput (Q) and the difference between the partial pressures of anaesthetic in the alveolus (arterial blood) and venous blood.

$$\mathbf{UPTAKE = \lambda \times Q \times (A\text{-}v)}$$

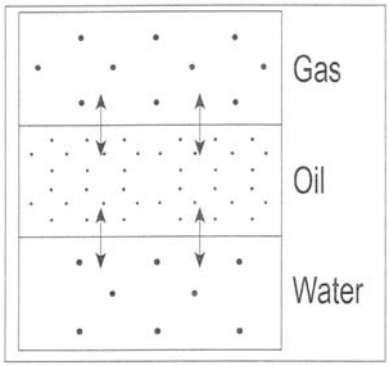
The extent to which gas will dissolve in a given solvent is expressed in terms of its solubility coefficient (λ) for inhalation agents mostly reported as *partition coefficient.*

*A **partition coefficient** describes how an inhalation anaesthetic distributes itself between two phases (e.g, gas and blood) or two solvents (e.g blood and muscle) once equilibrium is reached (when anaesthetic partial pressure is equal in both).*

Gas molecules will diffuse in the alveoli **from high partial pressure to lower partial pressure** and dissolve in the solvent (here blood) until no partial pressure difference exists and thus equilibrium is reached. The amount (nr of molecules) that dissolve in the solvent depend on: 1) the chemical nature of the gas 2) the partial pressure of the gas 3) the nature of the solvent 4) temperature (it is dissolving, not chemically binding!)

Vol diss = Solub x Part Press (Henry's Law, for a given temp).

The partial pressure is thus related to the disssolved amount but only an indirect indication of the the number of molecules present in blood or a tissue: this depends on λ (in contrast to gasphase where λ could be considered =1). For the calculation of time constants the volume of the tissue is better called "capacity" and is volume x λ (see later).
In the body there are also partitions between the blood and the different tissues. After equilibrium the partial pressures are the same but the total amount of molecules dissolved in each phase (tissue) is very different.



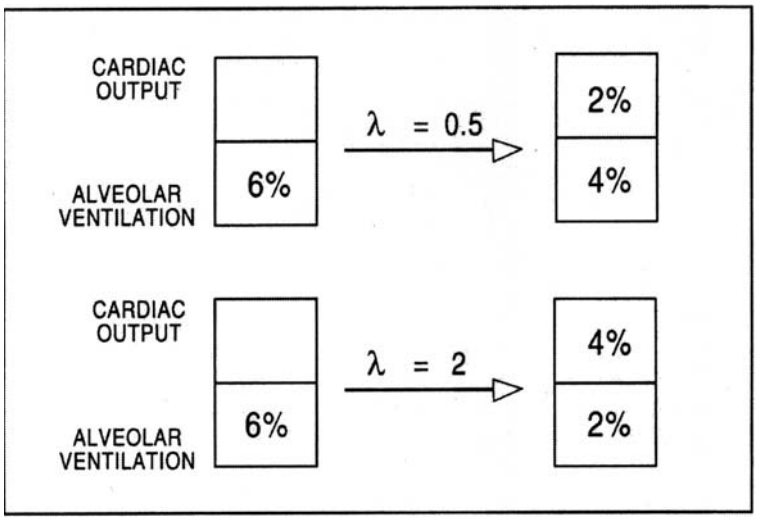
Based on blood/gas partition coefficients inhalation anaesthetics fall into three general ranges of blood solubility. Desflurane, nitrous oxide, and sevoflurane have blood/gas partition coefficients of approximately 0.5. Isoflurane, enflurane, and halothane have partition coefficients of about 2. Methoxyflurane, now obsolete, represents very soluble anaesthetics and has a blood/gas partition coefficient of 15. At equilibrium, a 1% concentration of methoxyflurane in the alveoli would produce a 15% concentration in the blood.

BLOOD SOLUBILITY

Desflurane	0.45
Nitrous Oxide	0.47
Sevoflurane	0.65
Isoflurane	1.4
Enflurane	1.9
Halothane	2.4
Methoxyflurane	15.0

b. the effect of λ on F_A/F_I during washin of the anaesthetic

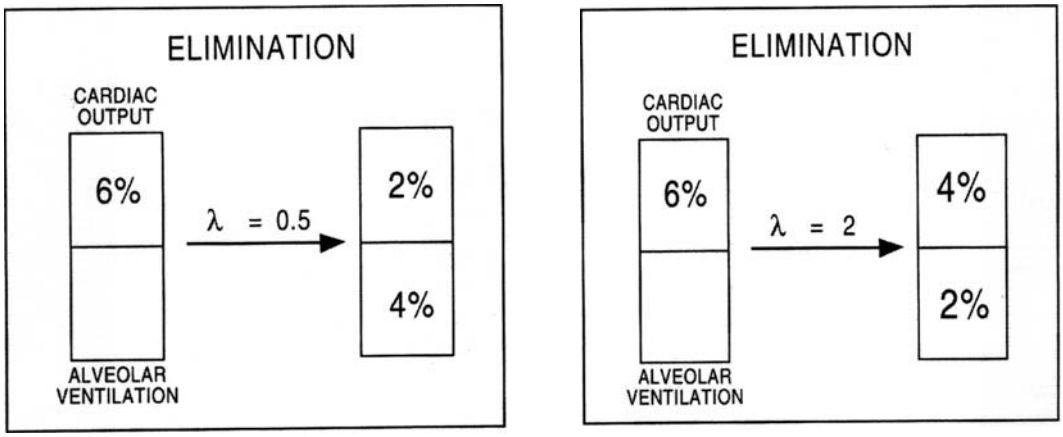
Solubility as a predictor of increase in F_A during the first few minutes of anaesthesia:
Figure : a lung, represented by a box marked "alveolar ventilation," receives 6% of some anaesthetic. Another box of equal size represents cardiac output, which is equal to alveolar ventilation in liters per minute. The anaesthetic has a blood/gas **partition coefficient of 0.5**. At equilibrium, 2% of the anaesthetic would have moved into the blood and 4% would remain in the lung. For this anaesthetic, F_A/F_I would be 4/6, in other words the alveolar concentration of anaesthetic would be 67% of the inspired concentration (F_A/F_I =0.67) .
What happens when solubility quadruples: **partition coefficient of 2**? Again, 6% of an anaesthetic is introduced into the lungs, but now 4% moves into the blood and 2% remains behind. F_A rises to only 33% (2/6) of F_I.



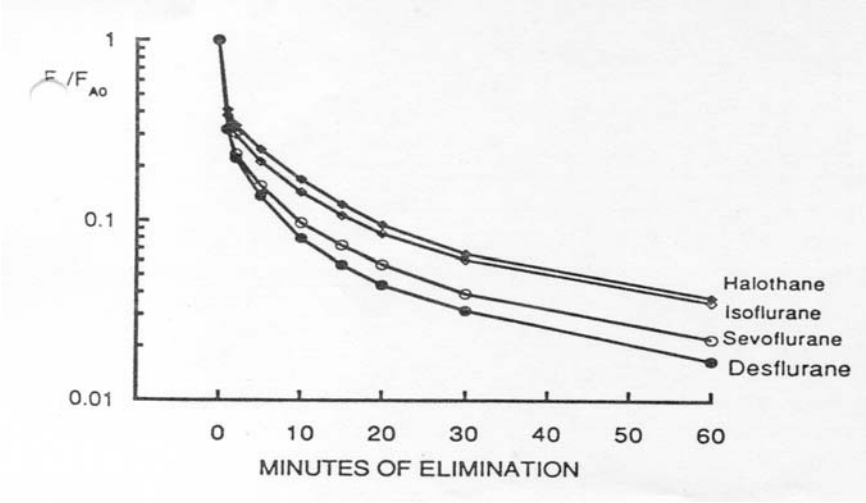
In summary: when solubility is low (blood/gas partition coefficient of 0.5), two thirds of the way to equilibrium (4/6) is reached on induction. When solubility quadruples, only one third (2 /6)of the way to equilibrium is reached. These box examples allow us to predict the course of F_A/F_I in the first 1 minute to 3 minutes of anaesthesia: with a poorly soluble anaesthetic (blood/gas partition coefficient of 0.5), F_A/F_I would reach 67% in that time; and with a moderately soluble anaesthetic (blood/ gas partition coefficient of 2), F_A/F_I would reach only 33%. This determines for a part the induction time.

c. the effect of solubility on F_A/F_I during elimination of anaesthetic.

Recovery from inhalation anaesthesia results from the elimination of anaesthetic from the brain. This begins with a decrease in alveolar partial pressure (F_A) which provokes a decrease in arterial and subsequently in brain partial pressure. Factors influencing recovery are in essence the same as induction: ventilation and the factors that dictate elimination: in the first place solubility, cardiac output and the (A-v) partial pressure difference.Washout curves are in essence inverses of the washin curves. Washout is more rapid for the less soluble agent. Elimination of anaesthetic is more rapid with a less soluble anaesthetic than with a more soluble anaesthetic.
Following represent recovery from an anaesthetic with different solubilities.



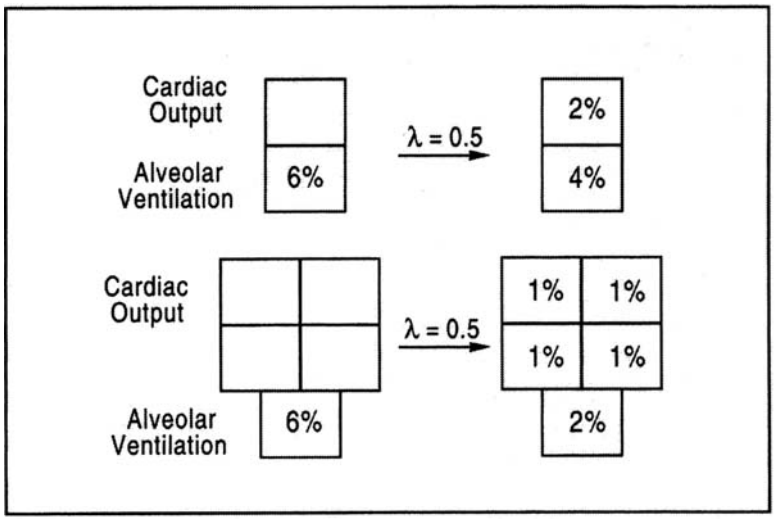
The anaesthetic is now only in the blood because the patient has been given only oxygen to breathe, and no anaesthetic is being brought to the alveoli. Two thirds of the (λ=0.5) anaesthetic (4/6) will be washed from the blood. That is, blood returning from the lungs to the brain will have lost two thirds of its anaesthetic towards the lung and one third goes to the brain. Less anaesthetic leaves the blood if the anaesthetic is more soluble (λ=2). When solubility quadruples only one third of the anaesthetic leaves the blood (2/6), and two thirds remains for recirculation to the brain.



Elimination of anaesthetic is more rapid with a less soluble anaesthetic than with a more soluble anaesthetic

3. Uptake and cardiac output

We have seen that λ affects uptake. The second factor is cardiac output as demonstrated by the box examples in the figure. The top half of the figure reviews earlier findings: that a blood/gas partition coefficient of 0.5 would move 2% of anaesthetic into the blood, and that 4% would remain in the lungs for an inspired concentration of 6% (67% of F_I).



The four boxes in the bottom half of the figure represent a quadrupling of cardiac output with no change in solubility. We see that the 1% concentration in each box satisfies the blood-gas partition coefficient:the ratio of concentrations is 1% ÷ 2%, or 0.5 Although the amount of blood has quadrupled the amount of anaesthetic in the blood has only doubled. *Quadrupling cardiac output (with no change in solubility) has the same effect on uptake as quadrupling solubility: this is* ***a decrease of F_A/F_I*** *from 4/6 (67% of F_I) to 2/6 (33% of F_I).*

4. Uptake and the alveolar (or arterial)-to-venous partial pressure difference

a. uptake by the tissues

The factors affecting uptake of anaesthetic by tissues are the same as for uptake by blood in the lungs. Translated to the tissue level, uptake of anaesthetic by tissue is the product of the tissue/blood partition coefficient (λ_t), blood flow to the tissue (Q_t) and the difference between the partial pressures of anaesthetic in arterial blood and in the tissue (a-t).

$$\text{Tissue Uptake} = \lambda_t \times \dot{Q}_t \times (a\text{-}t)$$

Where λ_t = Tissue/Blood Partition Coefficient
$\dot{Q}_t$ = Blood Flow to that Tissue
a-t = Arterial to Tissue Anesthetic Partial Pressure Difference

b. blood/gas vs tissue/blood partition coefficients for six anaesthetics

Tissue/blood partition coefficients fall into two easy-to-remember categories.
(1) The coefficients for lean tissue such as the brain are roughly 1 to 2, going below 1 for a few anaesthetics, such as nitrous oxide, and as high as 2 or 3 for other anaesthetics in muscle.
(2) For fat, the tissue/blood partition coefficients for all of the anaesthetics except nitrous oxide are very high. *In summary, it's 1 to 2 for lean tissues and "very high" for fat.*

PARTITION COEFFICIENTS
(Middle-Aged Adults, 37°C)

	Blood/Gas	Brain/Blood	Fat/Blood
Desflurane	0.45	1.3	27
Nitrous Oxide	0.47	1.1	2.3
Sevoflurane	0.65	1.7	47
Isoflurane	1.4	1.7	56
Enflurane	1.9	1.3	46
Halothane	2.4	1.9	67

(Data from Yasuda et al,[1] Lerman et al,[2] and Eger.[3])

c. tissue blood flow, arterial-to-tissue partial pressure difference and time constants

The next two determinants of tissue uptake (tissue blood flow and the arterial-to-tissue anaesthetic partial pressure difference) cannot be analyzed in isolation, as one affects the other. When Q_t is high, the arterial- to-tissue anaesthetic partial pressure difference narrows quickly with time. Four examples demonstrate these principles. (see also Gas Man® simulations)

Tissue/Blood Flow Per 100 mL Tissue	Tissue/Blood Partititon Coefficient	Time Constant (Minutes)
100 mL/min	1	1
3 mL/min	1	33
100 mL/min	2	2
2 mL/min	50	2500

The four rows of data in the figure describe blood flows, solubilities and time constants for 100 mL volume of each of four tissues.

Knowing tissue solubility and blood flow to the tissues allows determination of their time constants (time constant = capacity÷flow).

In the first example (the first line) it is apparent that the tissue is lean (because of the low tissue/blood partition coefficient) and highly perfused (such as the brain, liver, kidney, or heart:the "vessel-rich group") with 100 mL per minute blood flow per 100 mL volume of tissue. *The time constant is therefore 1 minute.* Within 1 minute, the tissue will have gone 63% of the way to equilibrium; within 2 minutes, 86%; and within 4 minutes, 98%. At 4 minutes, the arterial-to-tissue anaesthetic partial pressure difference will have narrowed to 2% of its initial value, and uptake by that tissue will be essentially zero. So, because a large volume of anaesthetic is being delivered (high perfusion), a highly perfused tissue absorbs a lot of anaesthetic initially but ceases to take up anaesthetic shortly thereafter.

The second line represents a tissue (such as muscle) that is not so highly perfused (3 mL of blood flow per minute for each 100 mL of tissue). Again, the tissue/blood partition coefficient is 1. The *time constant for this tissue would be 33 minutes* to reach 63% of the way to equilibrium, 66 minutes for 86% of equilibrium, and 132 minutes to reach 98% of equilibrium or four time constants. Muscle would take up anaesthetic 33 times as long as the brain to undergo the same decrease in the arterial-to-tissue anaesthetic partial pressure-difference.

The third example resembles the first in several ways, with one difference. Both tissues are highly perfused (perhaps brain). Both are lean, as shown by low tissue/blood partition coefficients. The anaesthetic in example-row 1 (perhaps nitrous oxide) is a less soluble agent (λ_t =1) than the agent in example 3 (perhaps halothane, λ_t =2). Solubility influences capacity. Capacity is defined not only by the volume of the tissue but also by the affinity of the tissue for the anaesthetic, relative to the affinity of blood for that anaesthetic. In example 3, the tissue in question has twice the capacity for halothane as the blood. Therefore, 100 mL of brain would absorb the same amount of anaesthetic as 200 mL of blood and that accounts for the time constant of 2 minutes in example 3. It would take 8 minutes to reach 98% of equilibrium (compared to 4 minutes).

The fourth example represents fat. It has a very low blood flow (2 mL/minute per 100 mL tissue) and a very high tissue/blood partition coefficient of 50. *The time constant is 2,500 minutes*, almost 2 days! For whatever this anaesthetic might be (e.g., halothane), more than a

day of anaesthesia would be required for the fat to be half way toward equilibrium. Therefore, equilibrium with the fat will not occur in the course of any reasonable anaesthetic.

d. characteristics of the four tissue groups

All of the possible different tissues of the body could be analyzed as in the previous figure, tallying their effects to determine total uptake of anaesthetic. However, such a detailed undertaking is not necessary, because *the body tissues fall into* ***four groups based on their time constants****: the vessel-rich group (VRG), the muscle group (MG), the fat group (FG), and the vessel-poor group (VPG).*

The vessel-rich group
consists of highly perfused tissues-the brain, heart, liver, and kidney- that make up only 9% of the body mass but receive 75% of the cardiac output. When cardiac output is 5.4 liters per minute, the vessel-rich group receives approximately 4 liters per minute. If the tissue/blood partition coefficient for this tissue group is 1 (lean tissue) and blood flow is 75% or 4 liters per minute (flowing through 6 liters of tissue), the time constant would be 1.5 minutes. For the vessel-rich group, equilibrium is 63% complete in 1.5 minutes (one time constant), 95% complete in 4.5 minutes (three time constants) and 98% complete in 6 minutes (four time constants). *Within 4 to 6 minutes, blood returning to the lungs from this tissue group has almost equilibrated*. Thus, three quarters of the cardiac output returning to the lungs would now be incapable of taking up anaesthetic because the partial pressure of the anaesthetic in the (venous) blood returning from this group would be equal to the partial pressure of arterial blood and in turn this would equal partial pressure in the alveoli (no partial pressure difference). The same proportions are valid for animals.

CHARACTERISTICS OF TISSUE GROUPS

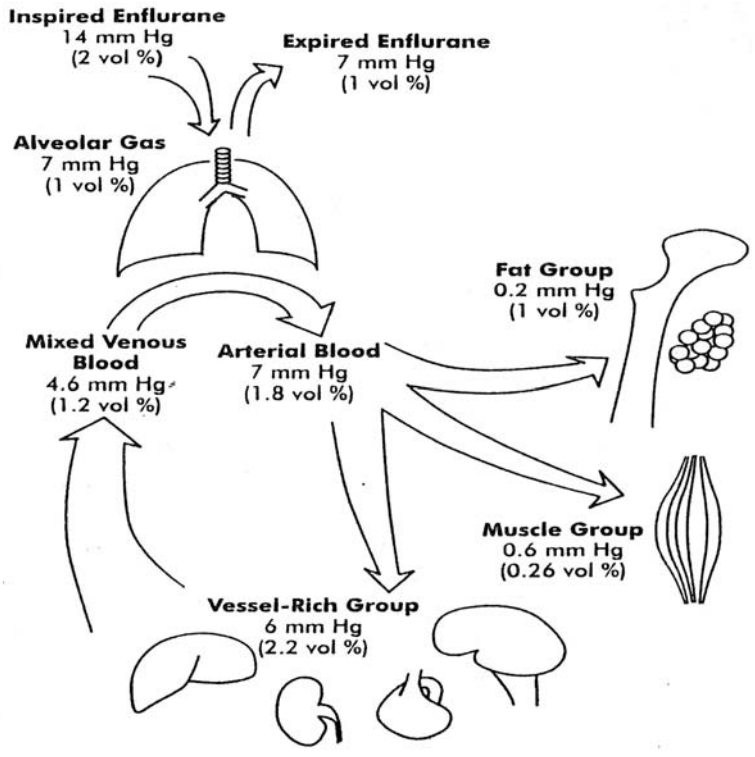
	VRG	MG	FG	VPG
% Body Mass	9	50	19	22
Liters/70 kg	6	33	14	12
% of Cardiac Output*	75	18	7	0
Liters/Min	4.0	1.0	0.4	0

*Cardiac Output = 5.4 Liters/Min

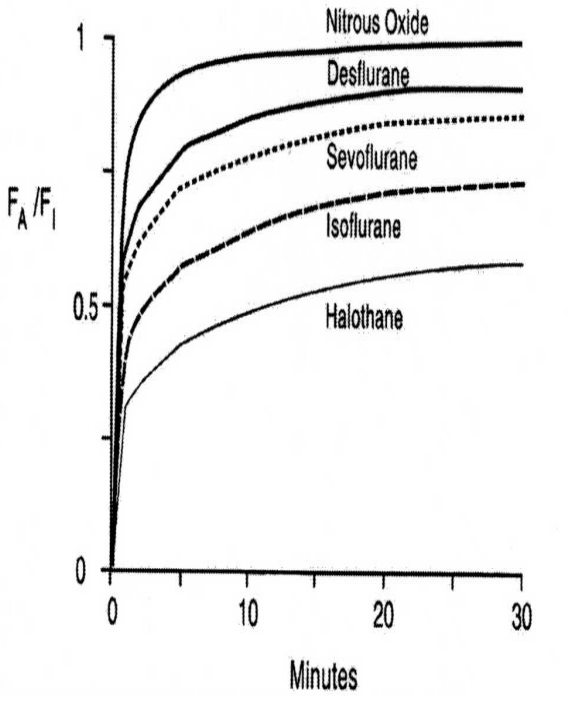
The muscle group
is made up not only of muscle but also skin, which has the same perfusion and solubility characteristics (the same time constant) as muscle. In a lean person, the muscle group constitutes half of the body mass but receives only 18% of the cardiac output. Tissue blood flow would be 1 liter per minute (flowing through 33 liters of tissue). Tissue/blood partition coefficients tend to be higher for the muscle group than for the vessel-rich group because muscle contains fat. For this tissue group, a tissue/blood partition coefficient of 1 produces a time constant of 33 minutes; a coefficient of 2, a time constant of 66 minutes; and a coefficient of 3, a time constant of 99 minutes. *Equilibration is to be expected after 2 to 7 hours.*
The fat group
In a lean person, fat makes up about 20% of body mass and receives approximately 7% of the cardiac output, or 0.4 liters per minute. Although perfusion (per liter) of fat does not differ substantially from perfusion of muscle, the solubility of anaesthetic differs greatly for these two types of tissue. Because solubility is much higher for fat, its time constant is much longer than that for muscle (capacity is much greater). *Thus, equilibration would take longer than 24 hours and most likely not be realized during a normal anaesthetic*.

The vessel-poor group
consists of tissues receiving no perfusion: bones, ligaments, tendons, and cartilage. Although these tissues make up 22% of body mass, they do not absorb anaesthetic. Where there is no perfusion, there can be no uptake. Therefore, only three tissue groups (VRG, MG, and FG) absorb any significant amount of anaesthetic.

Distribution of partial pressures (mmHg) and concentration (vol%) for enflurane in body tissues calculated for 10 minutes after beginning ventilation with 2% enflurane in the inspired gas. At this time the alveolar gas concentration and partial pressure are about half that of inspired gas. Anasthetic flow is in direction of decreasing partial pressure, and this is indicated quantitatively by size and direction of arrows. The partial pressure show that the vessel rich group of tissues is close to equilibrium with blood and the muscle and the aft group are still far from equilibrium. Note that the concentration (vol%) of enflurane depends on partition coefficients



e. characteristics of the F_A/F_I curves for anaesthetics



All the curves have the same characteristics: a rapid upswing to a first knee, a slower rise to a second knee, and a still slower third ascent. The initial upswing results because the difference between the alveolar and venous anaesthetic partial pressures is zero at the start, as no anaesthetic occupies the alveoli. Thus, no anaesthetic is being taken up to oppose the tendency of alveolar ventilation to produce a rapid increase in F_A, which rises accordingly. The first knee represents the point at which uptake counteracts the input of anaesthetic by ventilation. E.g. if F_A/F_I is one third, this would be the moment where uptake by all the tissue groups would be two thirds of the input by ventilation. Thereafter, F_A/F_I rises slowly, primarily because of decreasing uptake by the vessel-rich group. This decrease continues to the second knee, which occurs 4 to 8 minutes into anaesthesia (three or four time constants for the vessel-rich group). After the second knee, the rise is very slow, as uptake by muscle is gradually diminishing. Uptake by fat is not decreasing but slightly increasing, because the arterial partial pressure of anaesthetic is rising, and the partial pressure of anaesthetic for fat is rising at a slower rate.

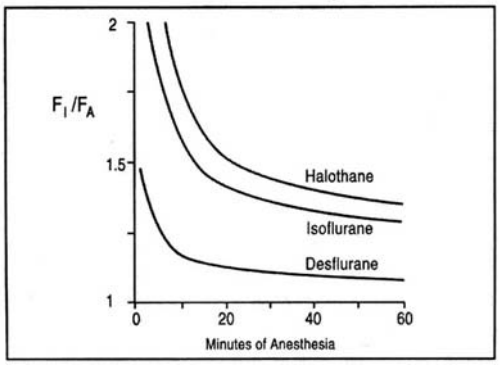
5. Effect of Inspired concentration on F_A/F_I (concentration effect)

Inspired concentration must be added to the factors affecting F_A/F_I. A.comparison of F_A/F_I curves for 70% nitrous oxide and 2% desflurane (see figure above) shows the effect of F_I on the rate of rise of F_A, i.e., the *concentration effect*. Despite similar blood solubilities, F_A rises more quickly with 70% nitrous oxide than with 2% desflurane. According to the concentration effect, the higher the F_I, the less the impact of uptake on F_A, When F_I is 100%, the rate at which F_A rises towards F_I is the same for all anaesthetics, and uptake will not affect F_A. The alveolar rate of rise would then be determined by the time constant of the lung.

D. The Overpressure technique-Maintenance of anaesthesia

The anaesthetist develops an anaesthetising partial pressure, causing the concentration of inhaled anaesthetic in the lungs to rise at different rates for different agents. The more soluble the anaesthetic, the slower the rise in F_A/F_I. Solubility does not influence the shape of the F_A/F_I curves for anaesthetics. These curves all have the same shape because the factors influencing the time constants for the tissues are approximately the same for all anaesthetics. However when F_I from the beginning would be e.g. only one MAC-equivalent, induction would take a very long time specially with soluble agents (and even more so in a rebreathing system with a low gas flow). In order to establish rapidly the desired partial pressure in the alveoli (F_A) its inspired partial pressure (F_I) may be adjusted to a value that is severalfold greater than the desired alveolar partial pressure (=overpressure technique). For example if the target F_A is 1% the F_I could be adjusted to 3%. During the early period of anaesthesia F_A/F_I increases rapidly, reaching rapidly a ratio of 0.3 and thus achieving the goal of F_A 1%. Because of the subsequent decrease in uptake, F_I is then decreased progressively by decreasing the delivered concentration F_D. The challenge during the maintenance of anaesthesia, then, is keeping F_A at a particular target level. Uptake of anaesthetic creates the

need to replenish anaesthetic in the alveoli, if the alveolar concentration of anaesthetic is to be kept at a constant level. That is, for maintenance of anaesthesia, an F_I must be supplied that is sufficient (relative to F_A) to compensate for uptake. The relative positions of the curves on the graph (= during maintenance, F_A e.g. 1 MAC) depend on solubility: the least soluble agent, desflurane, produces the lowest value tor F_I/F_A.

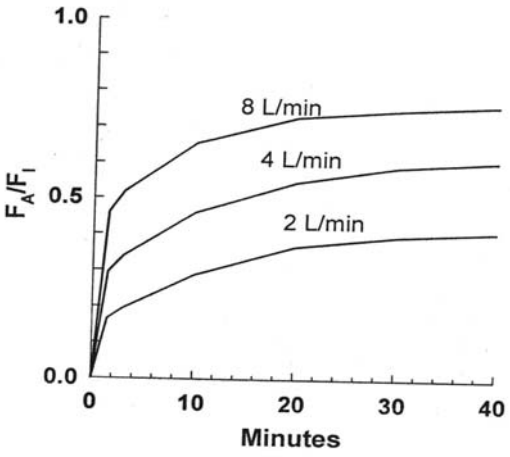


The value for F_D/F_A will equal the value for F_I/F_A only when high inflow rates are used (no rebeathing). At lower inflow rates F_D must exceed F_I to compensate for the uptake of anaesthetic from the rebreathed gases. The difference between F_D and F_A will be higher when lower inflow rates and more soluble anaesthetics are used.

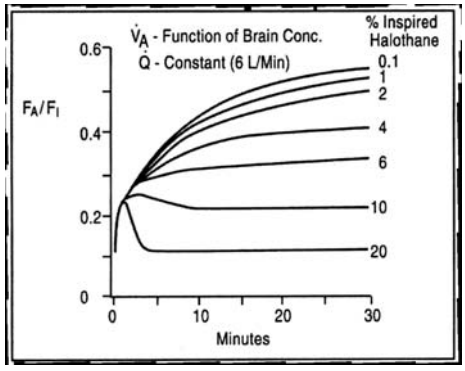
E. Factors affecting the F_A/F_I relationship

1. Effect of changing ventilation on F_A/F_I

Many events can change ventilation, e.g., actions by the anaesthetist (ippv) and use of inhaled anaesthetics and certain drugs. *An increase in ventilation increases F_A/F_I of an inhalation agent (see figure).*This will be more so with a more soluble anaesthetic than with a less soluble anaesthetic For nitrous oxide, an agent of very low solubility, F_A always rises rapidly toward F_I, even at an alveolar ventilation of 2 liters per minute. As a result, the F_A/F_I curve for nitrous oxide is not capable of increasing much more rapidly, no matter what the increase in ventilation. Ether, a very soluble agent (blood/gas partition coefficient of 12), represents the other extreme, as doubling ventilation almost doubles the F_A of ether. When a very soluble anaesthetic is given, almost all of the anaesthetic moves into the blood; if the amount in the blood doubles, the partial pressure would also double, reflecting the doubling that also must occur in the alveoli.

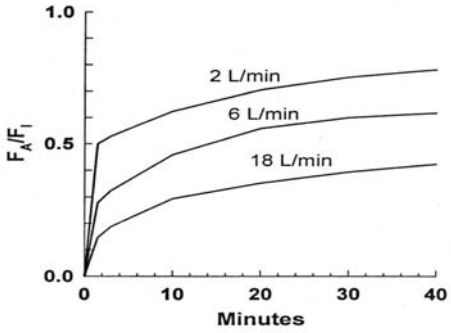


A decrease of ventilation decreases F_A/F_I.
This decrease can also be due to the effects of the volatile anaesthetic itself. As the dose (partial pressure)of anaesthetic increases, spontaneous ventilation decreases. Therefore, the higher the F_A for the anaestetic, the lower the ventilation and, consequently, the F_A/F_I ratio (see figure). Therefore, increasing F_I, does not increase F_A proportionally. The limit to the increase in F_A as F_I increases produces a **negative feedback** system that protects against the development of excessive concentrations of anaesthetic during spontaneous ventilation.

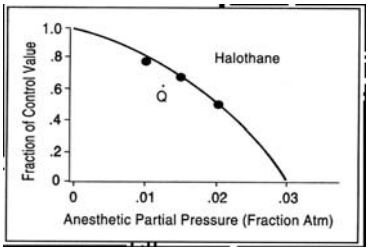


2. Effect of changes in cardiac output on F_A/F_I

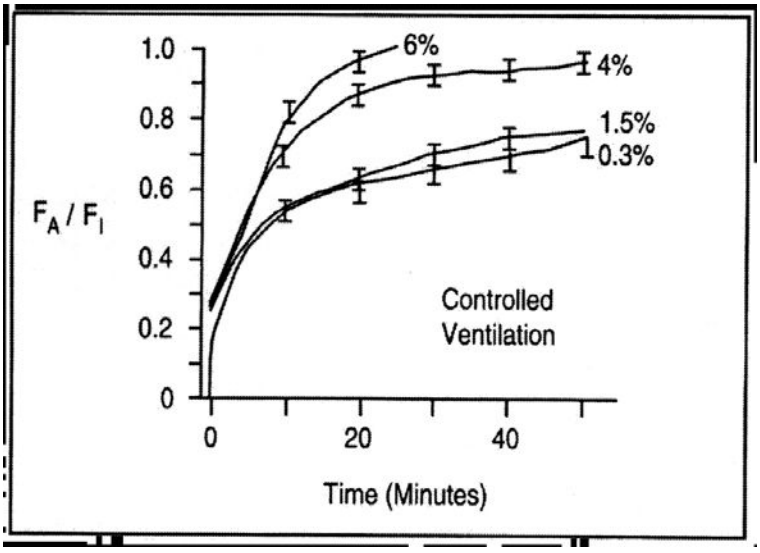
Increasing cardiac output decreases F_A/F_I. The effect is, again, greatest with the most soluble anaesthetic. Because various events in surgery (blood loss, changes in surgical stimulation) can affect cardiac output, the anaesthetist may need to increase or decrease the F_D of anaesthetic to compensate for changes in F_A that would otherwise occur. Such changes in the anaesthetic concentration may have their own pharmacological effects.



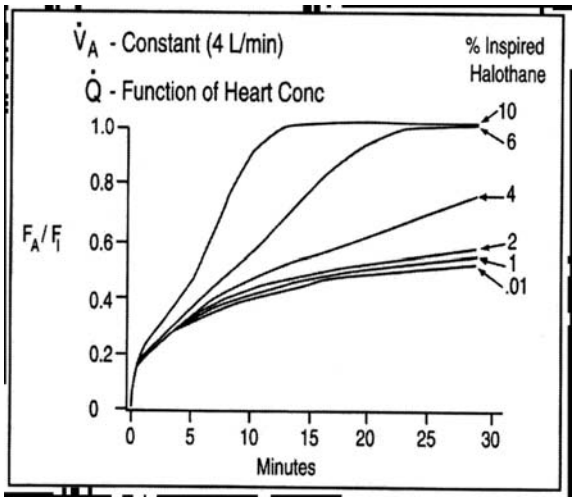
Some anaesthetics do routinely change cardiac output: halothane affects cardiac output in a more dose-related manner than does isoflurane or desflurane
The figur shows the progressive decrease in cardiac output that occurs when increasing concentrations of halothane are given to volunteers (i.e., when no surgical stimulation is present). As mentioned, decreasing ventilation with **spontaneous breathing** during the administration of increased concentrations of halothane provides *negative feedback* that protects against overdosing the patient



However, the use of **controlled ventilation** during increased concentrations of halothane produces *positive feedback*. That is, the higher the concentration, the greater the depression in cardiac output. This greater depression decreases uptake and further increases the alveolar concentration of halothane (increase of F_A/F_I). Studies in dogs illustrate the positive feedback and associated risks of increasing the concentration of halothane while controlling ventilation. Concentrations of 0.3% and 1.5% halothane produce similar rates of rise in F_A/F_I, but 4% and 6% produce accelerated rates of rise in association with cardiovascular collapse.

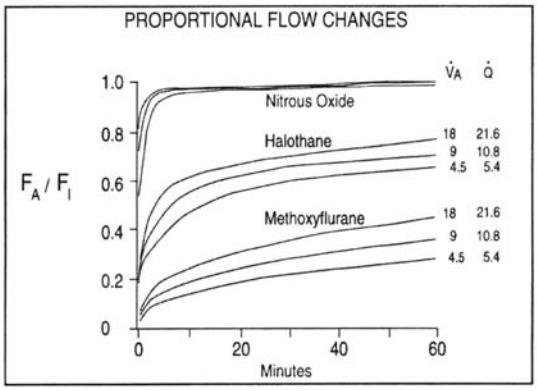


The results of computer simulations illustrated in the figure demonstrate the changes in F_A/F_I at various percentages of inspired halothane when ventilation is kept constant at 4 liters per minute. As F_I increases, the rate of rise of F_A also increases. The sudden and sharp increase in the rate of rise that occurs in the 10% curve at an F_A/F_I of approximately 0.5 represents the point at which cardiac output decreases dramatically, i.e., to zero.

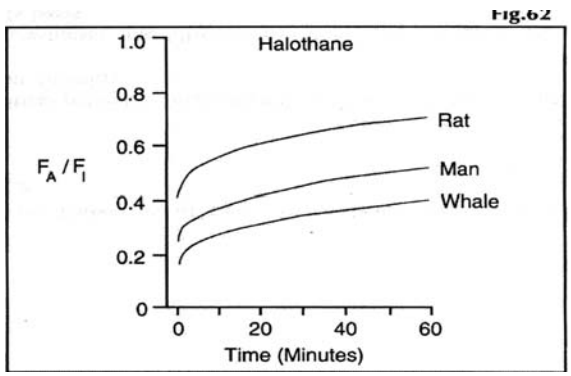


3. Effect of an increase in both Cardiac Output and Ventilation on F_A/F_I

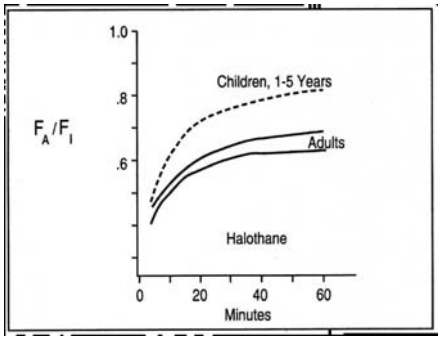
So far, we have changed ventilation while keeping cardiac output constant, then we controlled ventilation and cardiac output was changed. Now, what happens to the F_A/F_I ratio when both ventilation and cardiac output increase? If nothing else changed, doubling both ventilation and cardiac output would double both input and removal of anaesthetic, so that F_A/F_I should not change (assuming that any increase in blood flow is distributed proportionately to all tissues). However F_A/F_I ratios for three anaesthetics of differing solubilities all increase, but not much, as both ventilation and cardiac output are first doubled and then quadrupled (fig.). In actuality, doubling cardiac output decreases the time constants for all tissues, which in turn decreases the alveolar- to-venous partial pressure difference by decreasing tissue uptake. Thus, *uptake does not increase in proportion to the increase in cardiac output*. The result is a more rapid rise in F_A/F_I. Conditions that might increase both ventilation and cardiac output with proportional increases in tissue blood flow are those characterized by increases in metabolic rate, such as hyperthermia or hyperthyroidism



Increases in metabolic rate (and, therefore, in ventilation and circulation) do increase the rate of rise of F_A. These changes in ventilation and circulation *relate to body size*, because metabolism per kilogram of tissue decreases as body size increases.The figure shows the rate of rise of F_A/F_I for halothane given to rats, human beings, and Gigi, a California grey whale. The changes are as predicted but are not very large, considering that the difference in body weight is approximately four orders of magnitude (rats vs. whales).



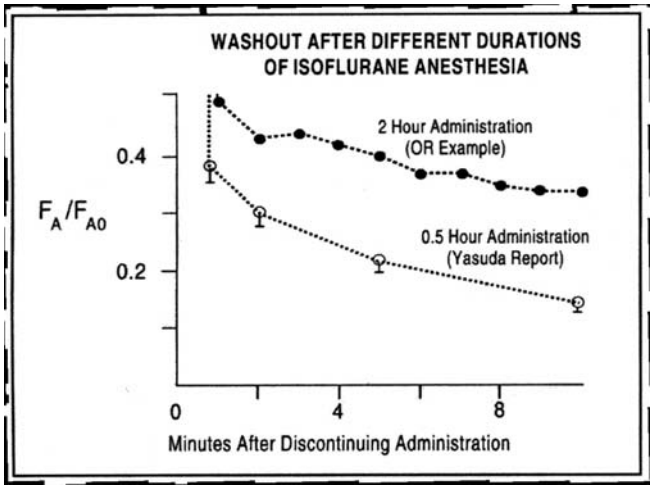
Rate of rise of F_A/F_I of halothane in children vs adults:
the rate of rise of the F_A/F_I of halothane is lower in adult patients than in children (data from two studies in adults). (fig.) This effect partly accounts for the faster induction of anaesthesia in children, even though MAC for halothane is higher for children than adults. In addition, because blood *flow to the brain is higher* in children, the time constant for the brain is shorter; it therefore takes longer for a particular concentration of anaesthetic to develop in the brain of an adult than in the brain of a child

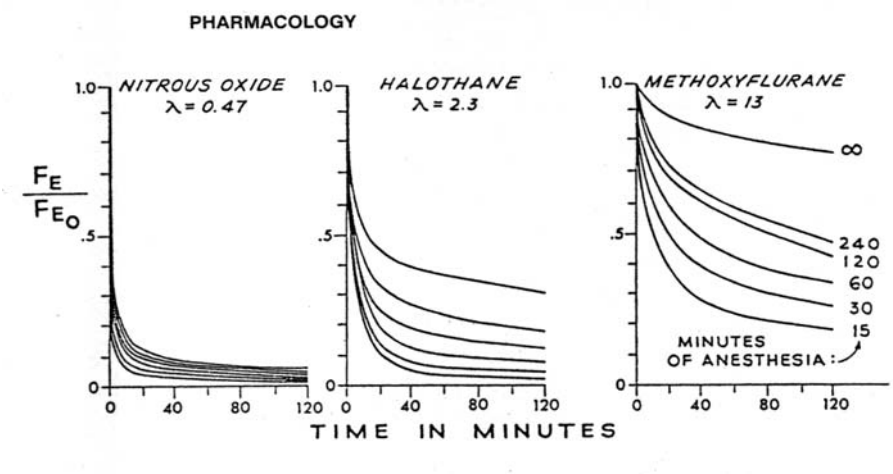


F: Elimination of volatile anaesthetics

1. Effect of duration of anaesthesia

Washout is more rapid for the less soluble agent (see earlier). However, the duration of anaesthesia is also important for washout. As anaesthesia lengthens, washout is prolonged, i.e.., the F_A/F_{AO} curve (F_{AO} is the final alveolar concentration of an anaesthetic during its administration, at the moment when F_D is turned to zero) sits higher on the graph. The longer anaesthesia continues, the greater the total amount of anaesthetic taken up, the more anaesthetic in the reservoirs, and the more anaesthetic that must leave the body. Therefore, the longer anaesthesia continues, the higher the alveolar concentration of anaesthetic is sustained during recovery. This effect is greater with a more soluble anaesthetic (figure under).

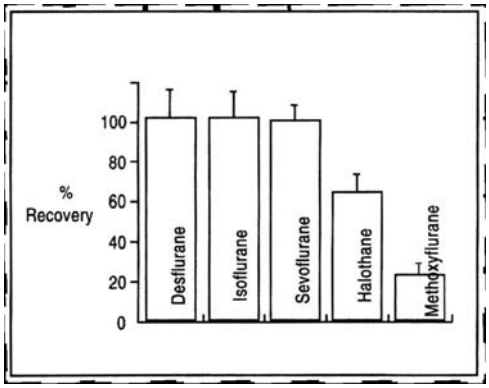




If a rebreathing circuit is used and the animal not disconnected, the circuit will reduce the rate of recovery (as during induction). The use of high flows of anaesthetic free gas will reduce this effect.

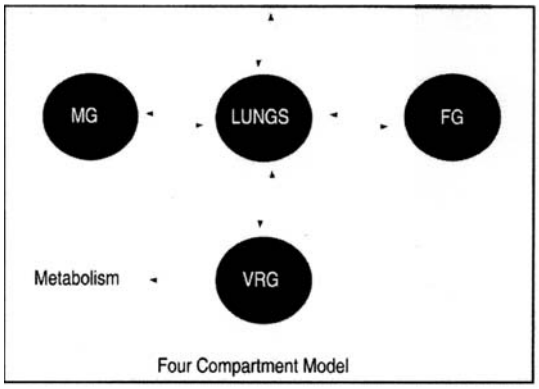
2. The effect of metabolism on kinetics

The principles discussed so far presume a simple model of uptake and distribution . The *lungs* accept gases from, and returns gases to the *breathing circuit*. Gases also travel from the lungs to, and return from, the *vessel-rich group, the musc1e group and the fat group* by the circu1ating *blood*



Investigators analyzed metabolism of several anaesthetics in patients by first measuring how much anaesthetic was taken up and then measuring the total amount exhaled. The figure. shows that all of the desflurane, isoflurane, and sevoflurane that was taken up was recovered. However, 40% of the halothane and 75% of the methoxyflurane were not recovered. Metabolism can affect FA significantly. It is likely to play a role during prolonged anaesthesia.

Thus we must add **metabolism** to the model representing the factors governing uptake



G. SUMMARY

Summary of Relevance of Solubility to Uptake, Distribution and Clinical Management

During induction and maintenance of anaesthesia there will be a variable discrepancy between vaporiser setting (F_D) and inspired concentration (F_I) and end-tidal concentration (F_A). This discrepancy is greatest in the induction phase and becomes smaller during maintenance. F_I will be higher than F_{ET} (F_A) during maintenance because of uptake. This difference is greater for a soluble agent than a less soluble and is likely to become smaller but subsist during anaesthesia. During recovery from anaesthesia this process reverses.

The shorter the time constant of the circuit the more rapid F_I will come closer to F_D (= vaporizer setting) and the more precise control of anaesthesia will be. This can be influenced by the type of circuit and the flow rate used

The higher the solubility of the anaesthetic, the slower the increase in the alveolar concentration (F_A or F_{ET}) toward the inspired concentration (F_I). Induction is quicker with a less soluble agent and the degree of overpressure needed is less.

Elimination of anaesthetic is more rapid with a less soluble anaesthetic than with a more soluble anaesthetic.

Changes in physiologic variables (e.g., ventilation or cardiac output) will have much less of an impact on depth of anaesthesia (F_A) when a poorly soluble agent is given than when a more soluble agent is given.

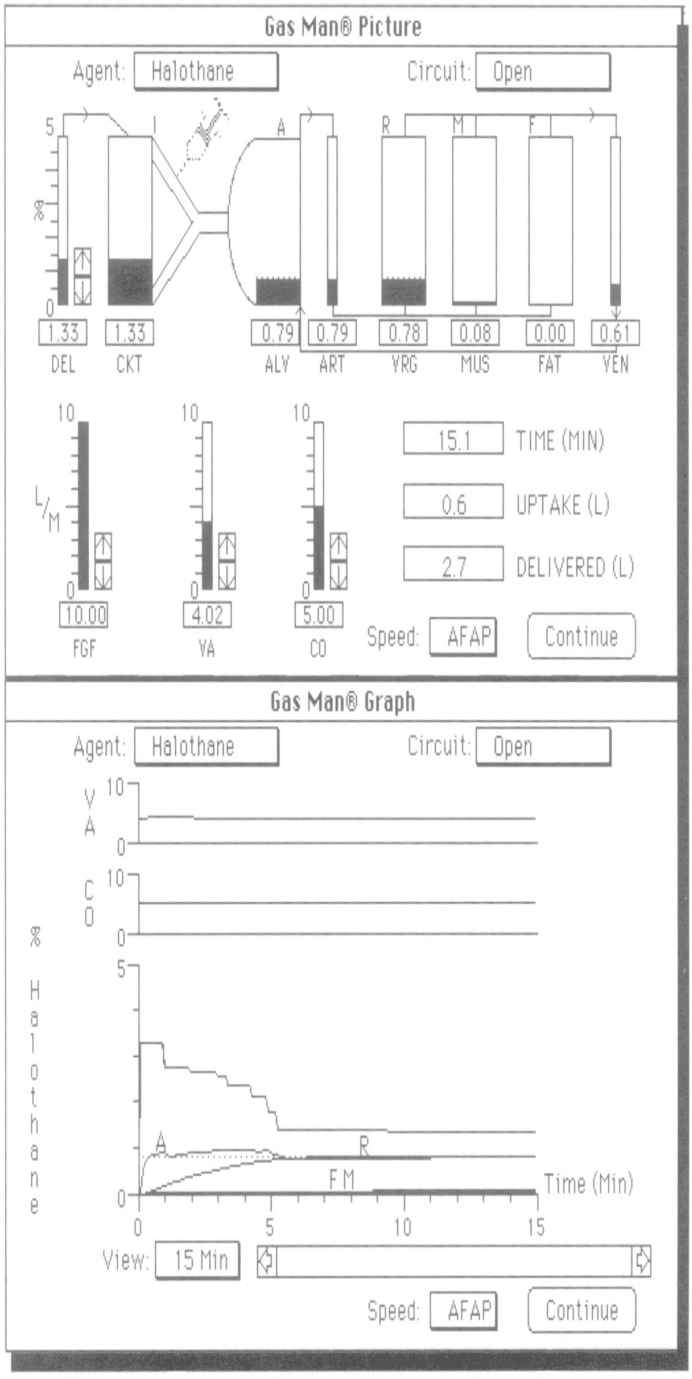
Changes in anaesthesia made to compensate for varying surgical stimulation occur more quickly with a less soluble anaesthetic.

Changes in vital functions (both ventilation and circulation) influence anaesthetic depth (F_A) to a greater degree when a more soluble anaesthetic is given than when a poorly soluble anaesthetic is given

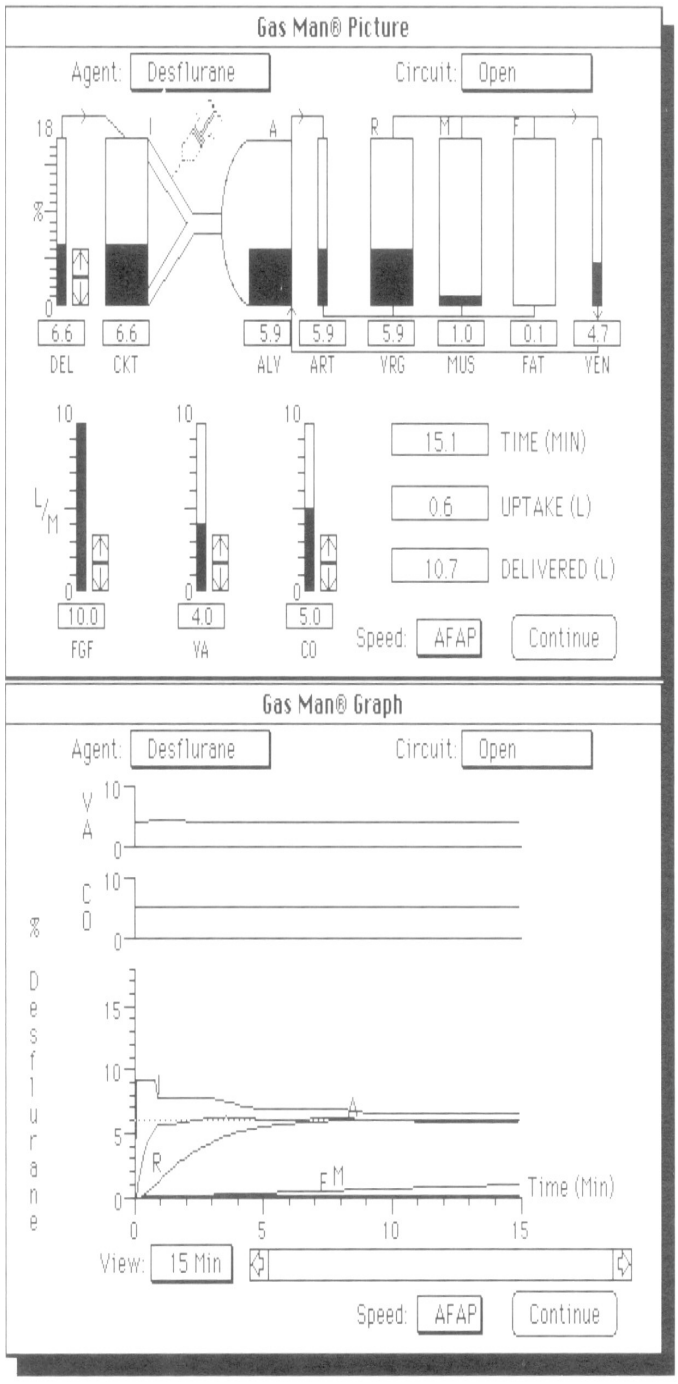
Controlled ventilation with high inspired volatile concentrations can lead quickly to a high F_A/F_I ratio

H. GAS Man®

Registered trademark of Med Man Stimulations. It is a computer tool for teaching, simulating and experimenting with anaesthesia uptake and distribution developed by James H. Philip, MD. The Gas Man® computer model graphically simulates the pharmacokinetics of anaesthesia administration. It shows the time course of anaesthesia uptake in each compartment of the body-lungs, heart, brain- as well the breathing circuit and vaporizer (http://www.gasmanweb.com).



example halothane (overpressure induction)



example desflurane (no overpressure)

PHARMACOKINETICS: INJECTABLE AGENTS : 1

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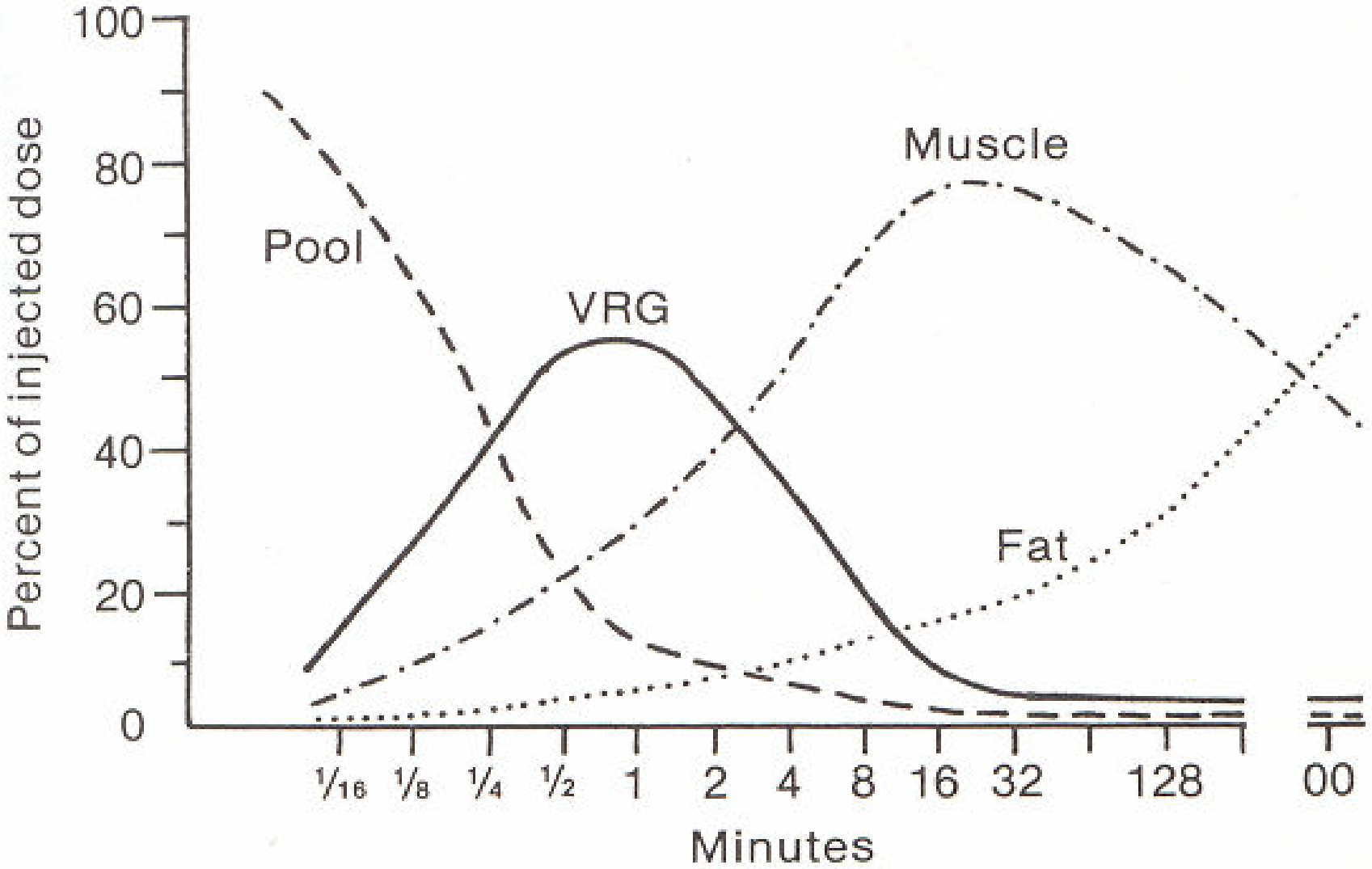
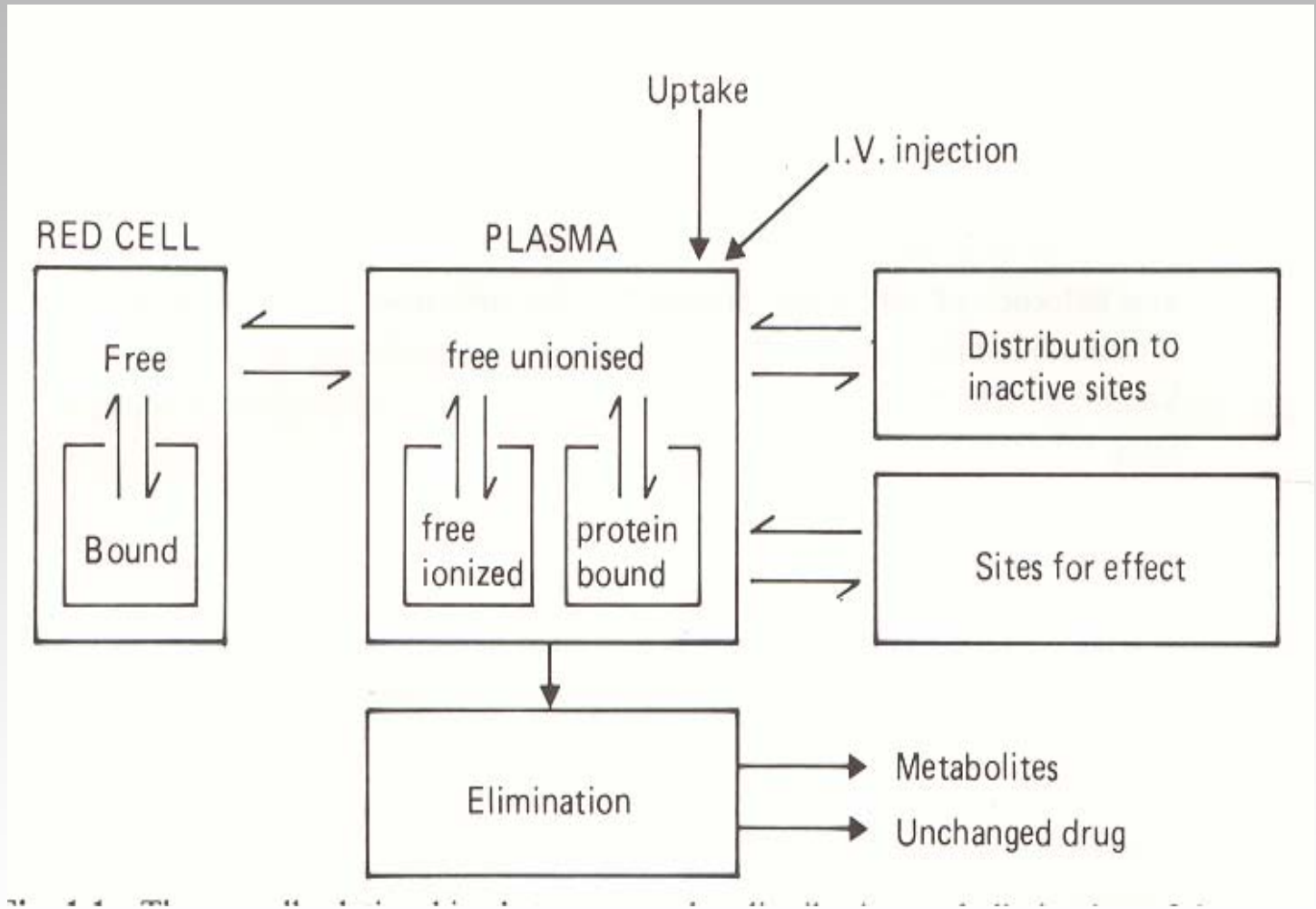
Glen Pharma Ltd, Knutsford, UK

Redistribution of Thiopentone (Price et al. 1960)



Distribution and Elimination of Drugs



Pharmacokinetic Concepts and Analysis

- Process of pharmacokinetic analysis
- Compartmental models
- Derivation of PK parameters
- Volumes of distribution
- Clearance
- Half lives
- Context-sensitive half time
- Effect-site equilibration time

Pharmacokinetic Analysis : Aims

- Obtain information on drug distribution and elimination
- Development of dosing guidelines
- Understand possible sources of PK variability

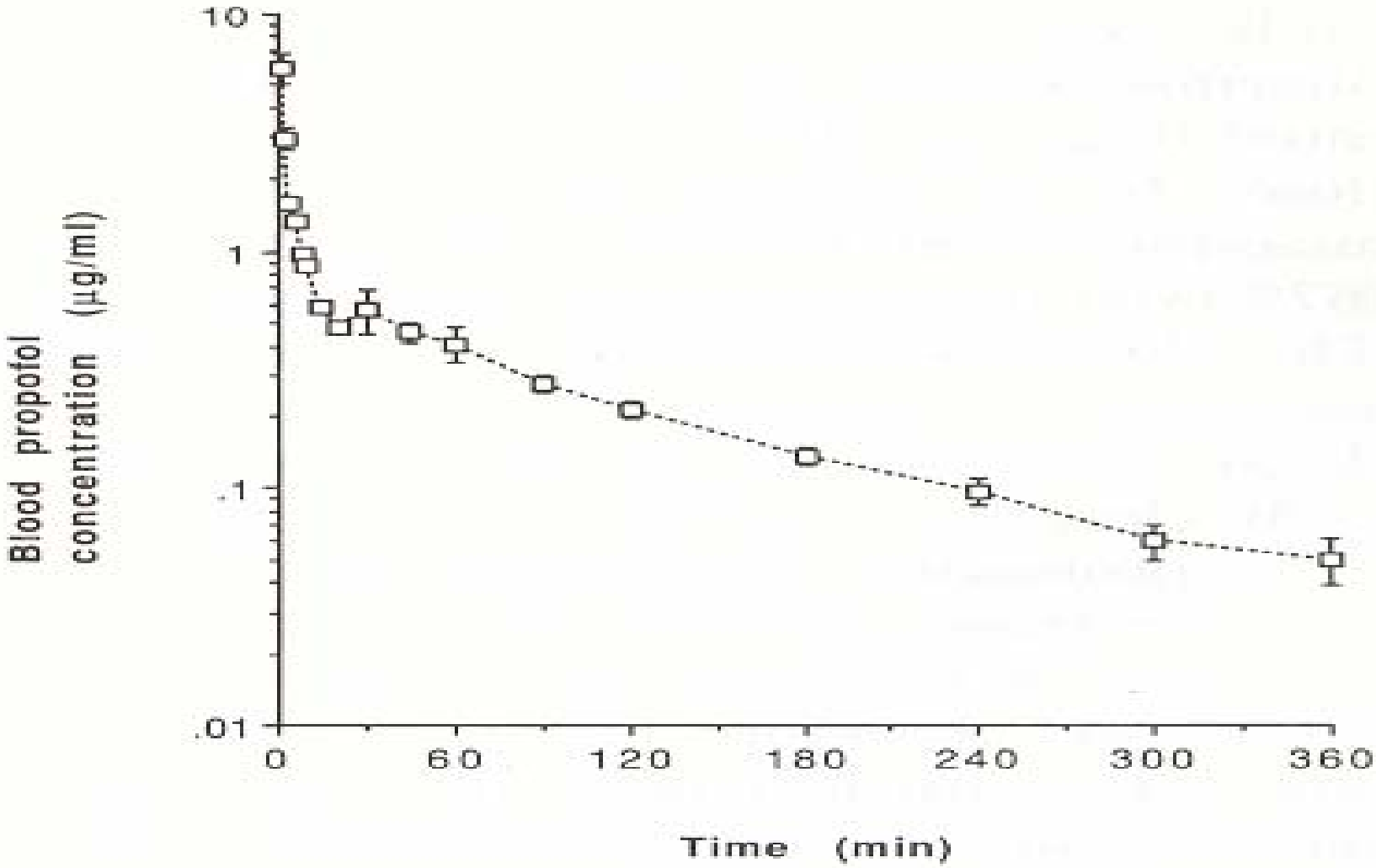
Pharmacokinetic Analysis : Process

- Establish blood level assay with suitable sensitivity
- Understand stability of active agent
- Suitable method for collection and storage of samples
- Administer known amount of drug
- Collect blood samples at timed intervals
- Plot concentrations (log scale) v time

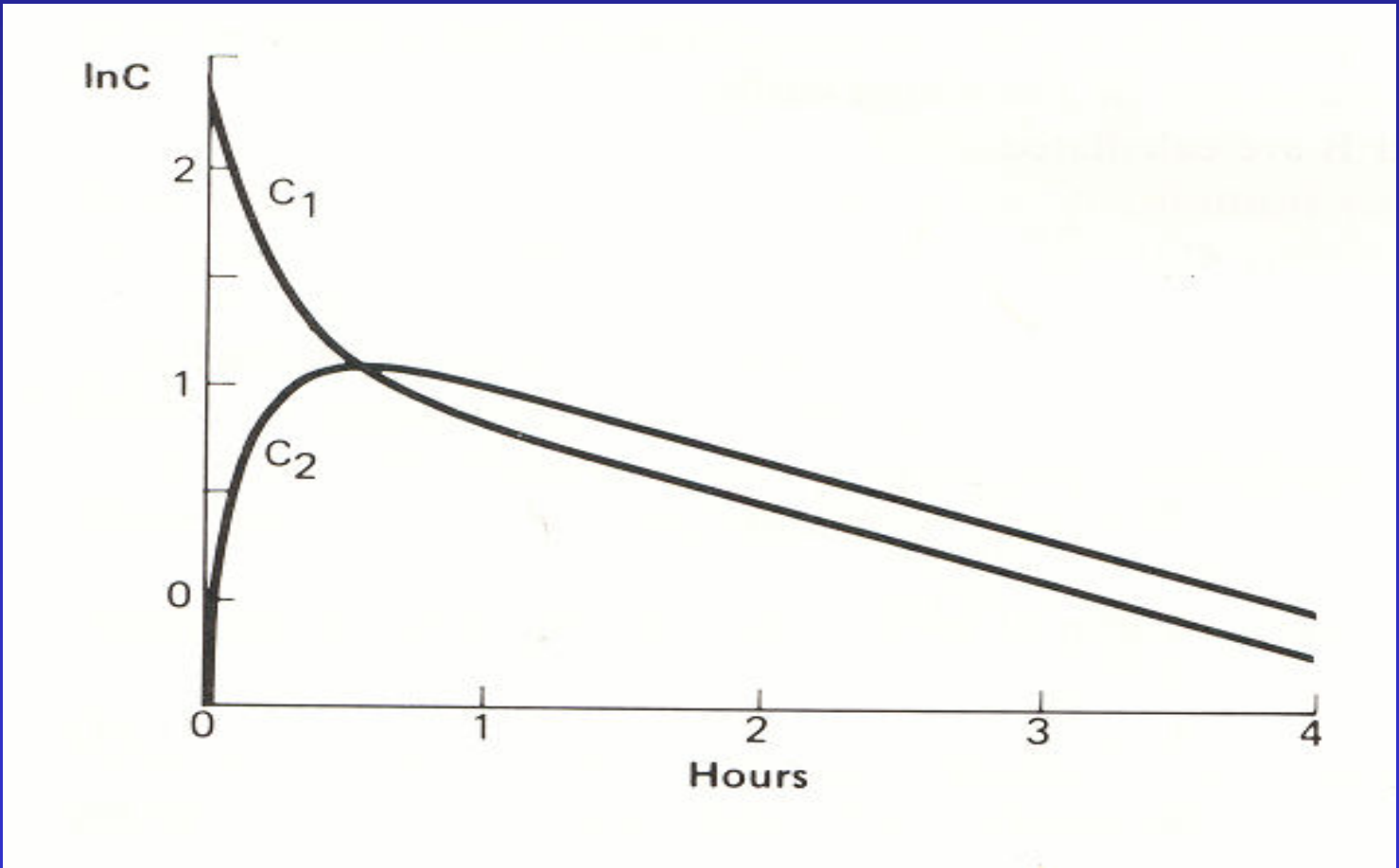
Concept of 'Compartments'

- Refers to organs or tissues for which the rates of uptake and clearance are similar
- Not anatomical compartments
- Number (usually 2 or 3) indicated by the number of exponentials required to describe the blood concentration – time curve

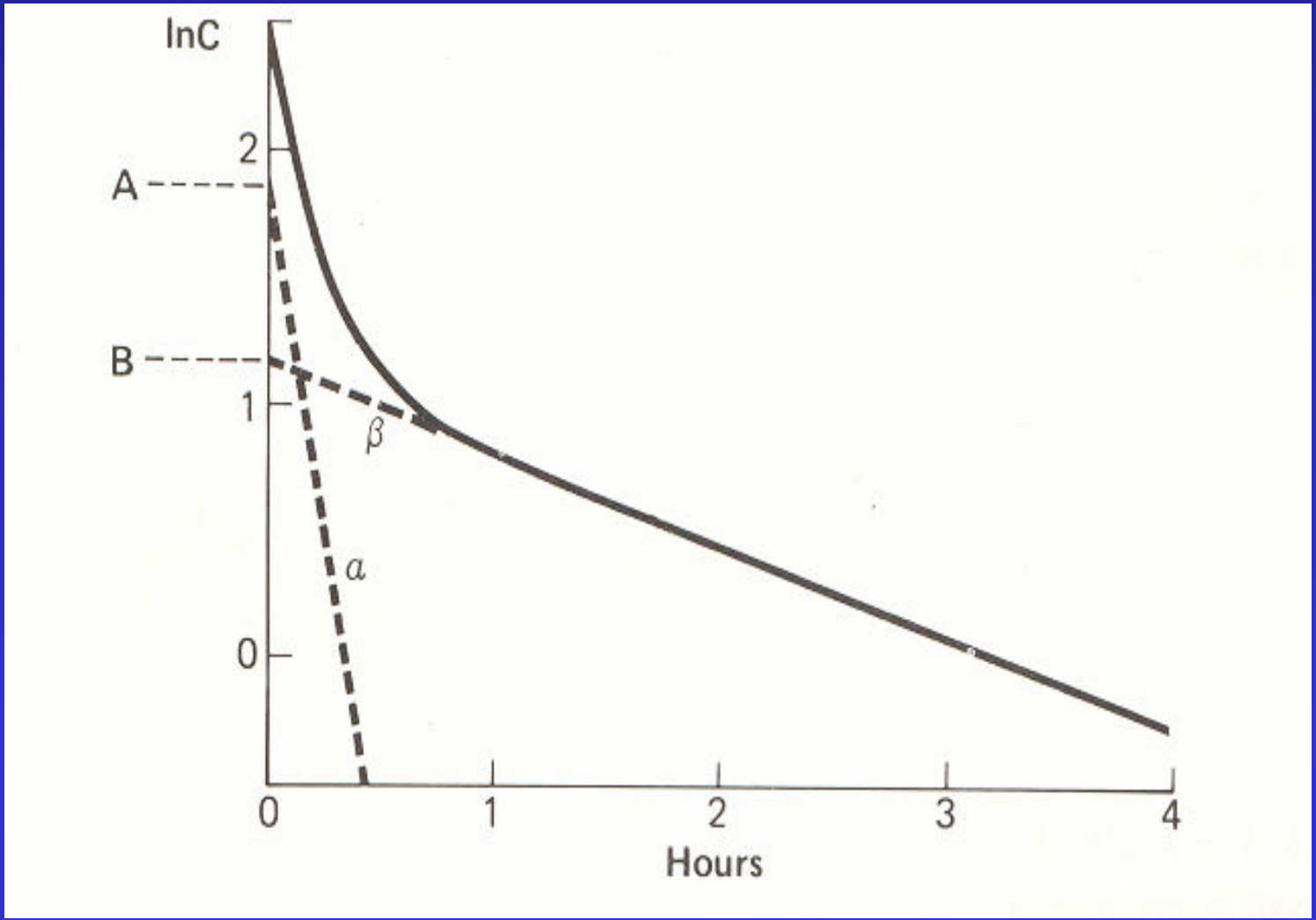
Propofol Concentrations following bolus 4mg/kg: Dog



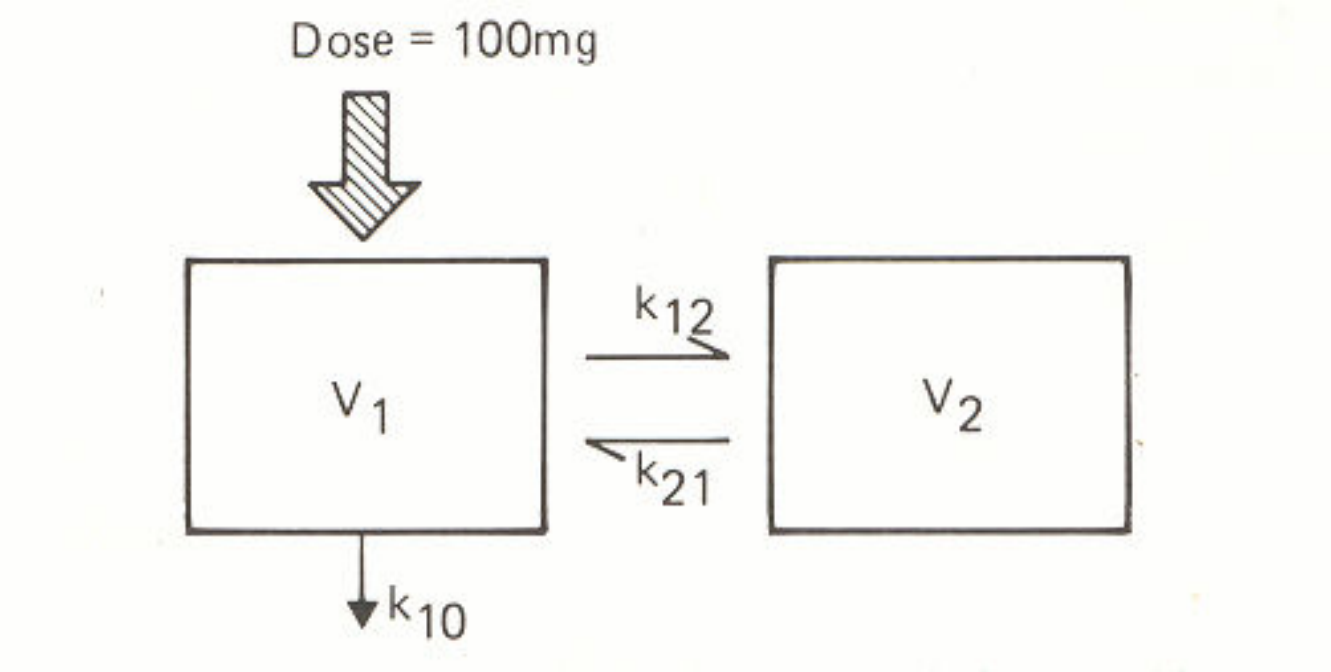
Log concentrations in both compartments of a 2-compartment model following a bolus dose



Analysis of bi-exponential curve by method of residuals

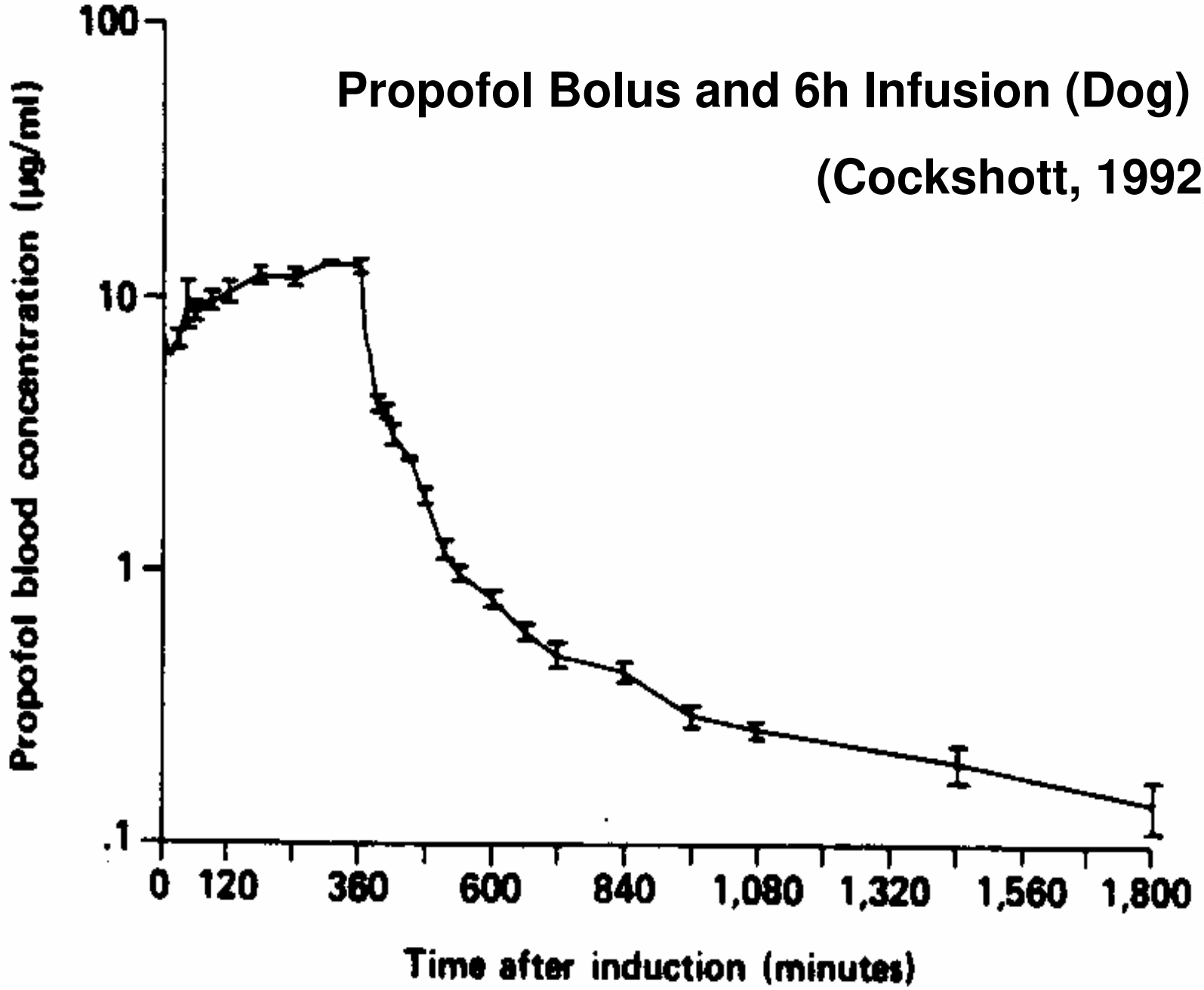


Two Compartment Model

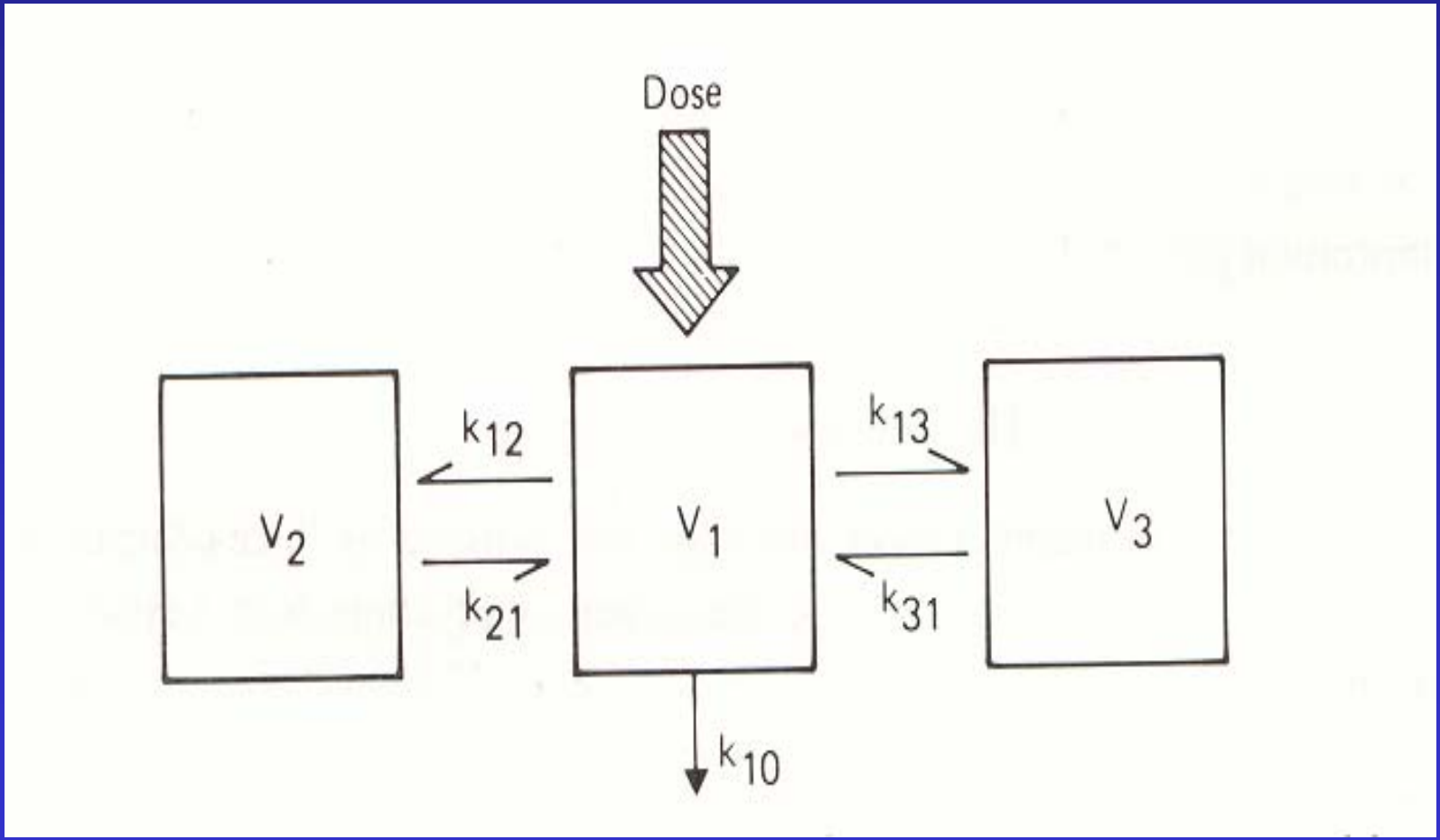


Propofol Bolus and 6h Infusion (Dog)

(Cockshott, 1992)

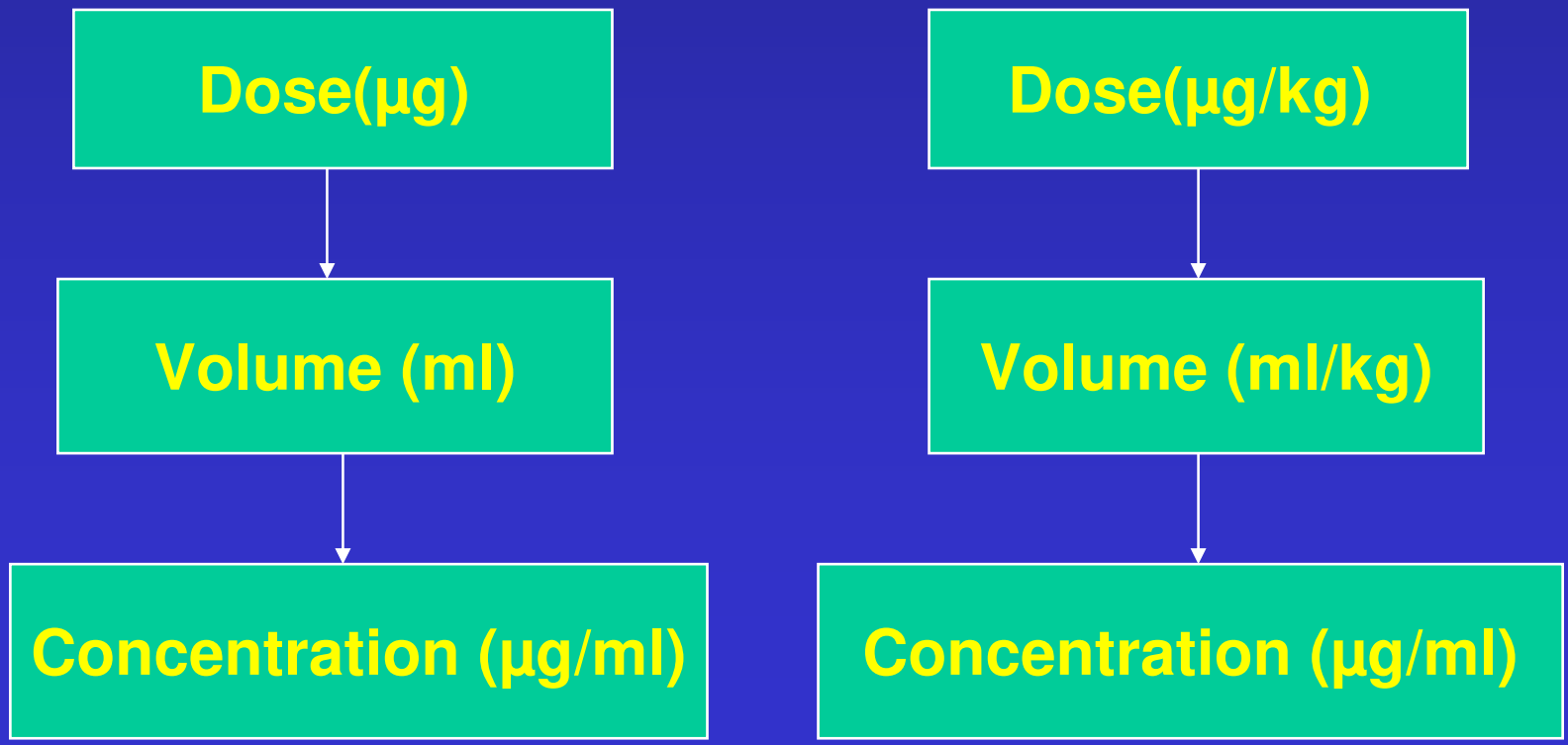


Three-compartment model



Volumes of Distribution

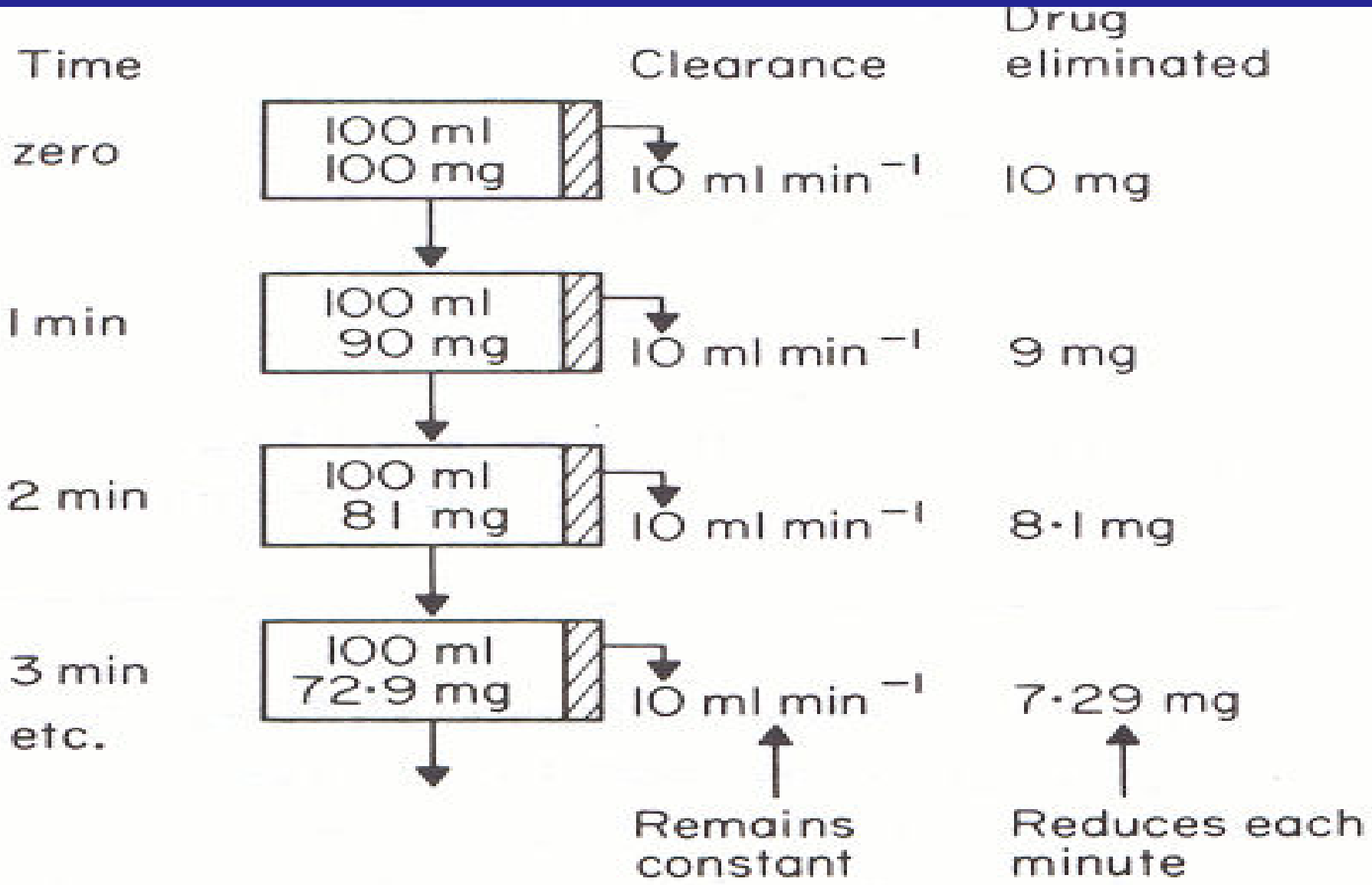
$$\text{Measured concentration} = \frac{\text{Dose administered}}{\text{Vol of Distribution}}$$



Clearance

- Process whereby active drug is removed-
  - Hepatic metabolism or renal excretion
- Expressed in units of volume/time
- Defined as the hypothetical volume of blood from which a substance is completely removed per unit time.
- Clearance (ml/kg/min) = V1 (ml/kg)x k_{10}/min

The Concept of Clearance



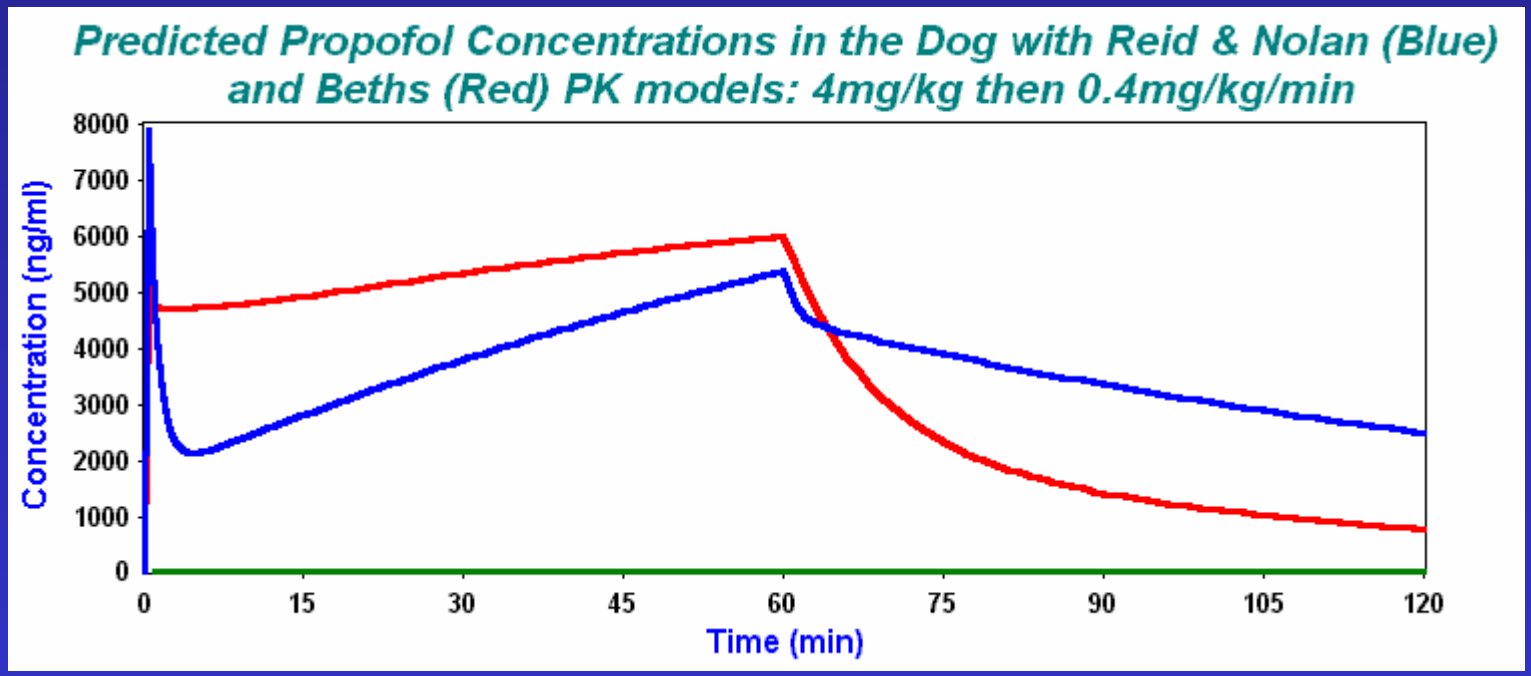
Derivation of PK Parameters from Intercepts and Slopes

- C_0 Concentration at time 0
- V_1 Central volume of distribution
- Elimination half lives
- Intercompartmental distribution rate constants
- Clearance
- V_{ss} Volume of Distribution at steady state

Propofol in the Dog: 2 and 3 Comp Models

- 2-Comp Model
  (Reid&Nolan, 1993)
- V1 465ml/kg
- K10 0.0847
- K12 0.7103
- K21 0.1039
- (Cl 39.3 ml/min/kg)
- (Vss 3644 ml/kg)

- 3-Comp Model
  (Beths et al, 2001)
- V1 780ml/kg
- K10 0.07
- K12 0.0365
- K21 0.0312
- K13 0.0049
- K31 0.0011
- (Cl 54.6 ml/min/kg)
- (Vss 5167 ml/kg)

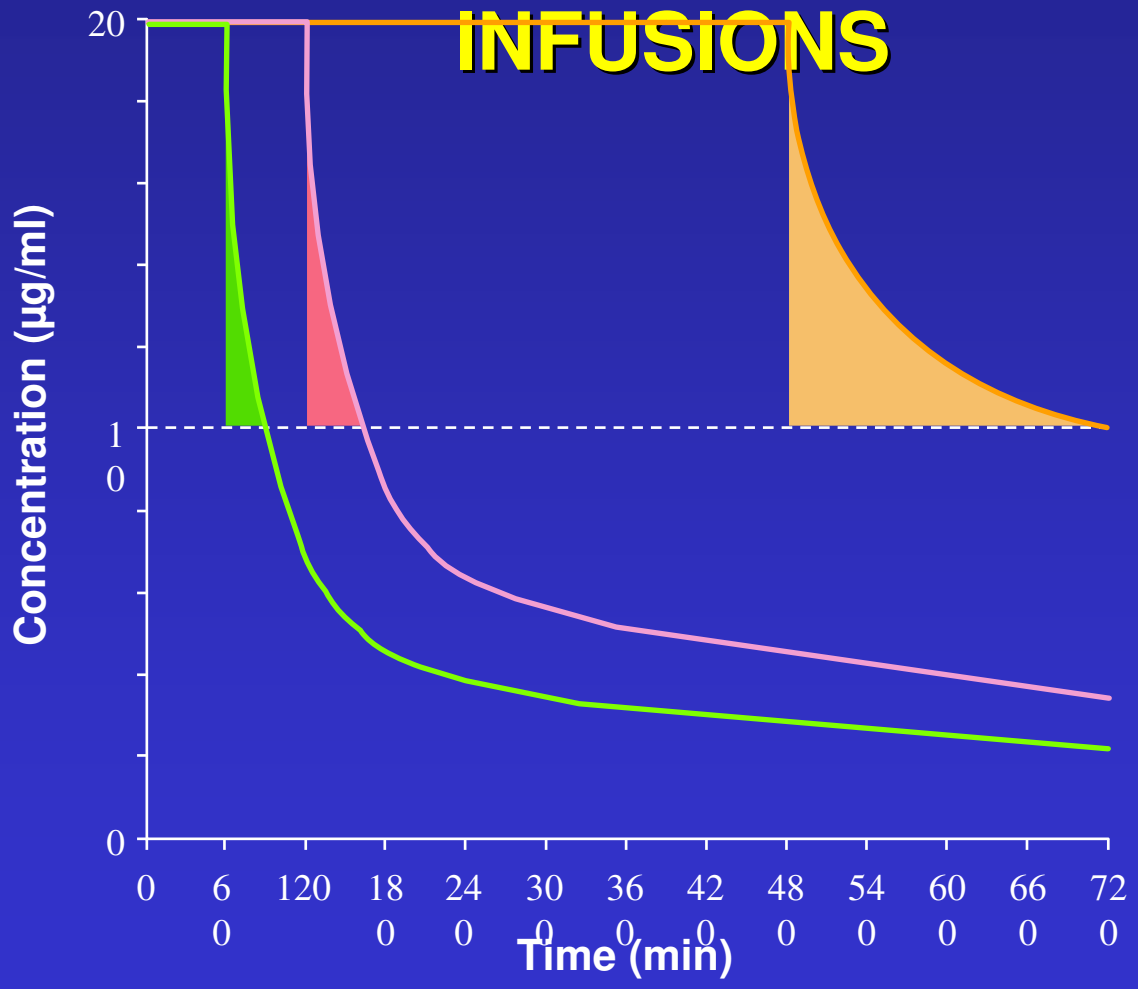

Predicted Propofol Concentrations in the Dog with Reid & Nolan (Blue) and Beths (Red) PK models: 4mg/kg then 0.4mg/kg/min
Concentration (ng/ml)
8000
7000
6000
5000
4000
3000
2000
1000
0
0
15
30
45
60
75
90
105
120
Time (min)

CONTEXT SENSITIVE HALF TIME

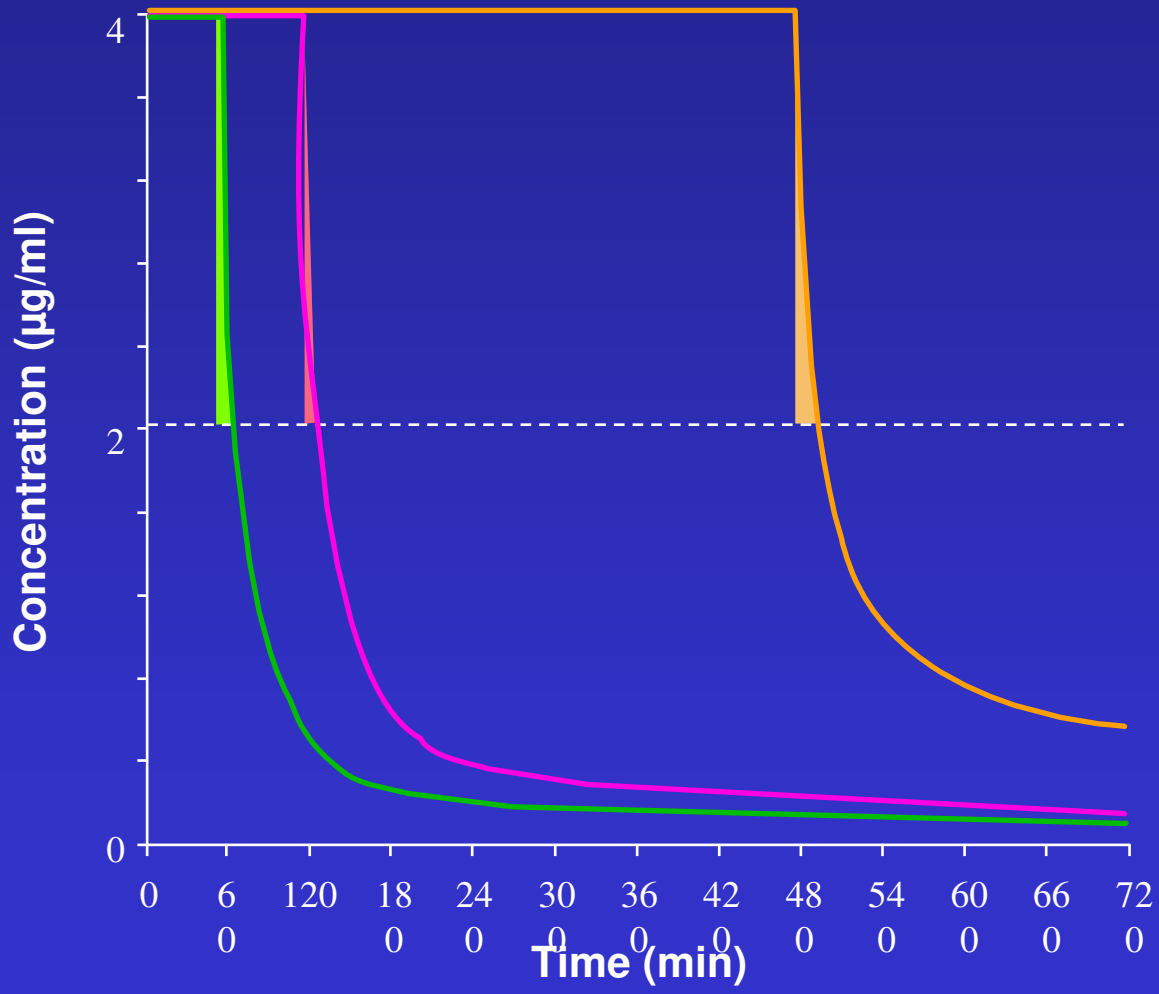
- The time required for the central compartment drug concentration to decrease to 50% of that achieved at the end of an infusion regimen designed to maintain a constant plasma concentration for a specific period of time
- For most drugs half-time increases markedly as the duration of infusion is extended

Hughes et al, 1992

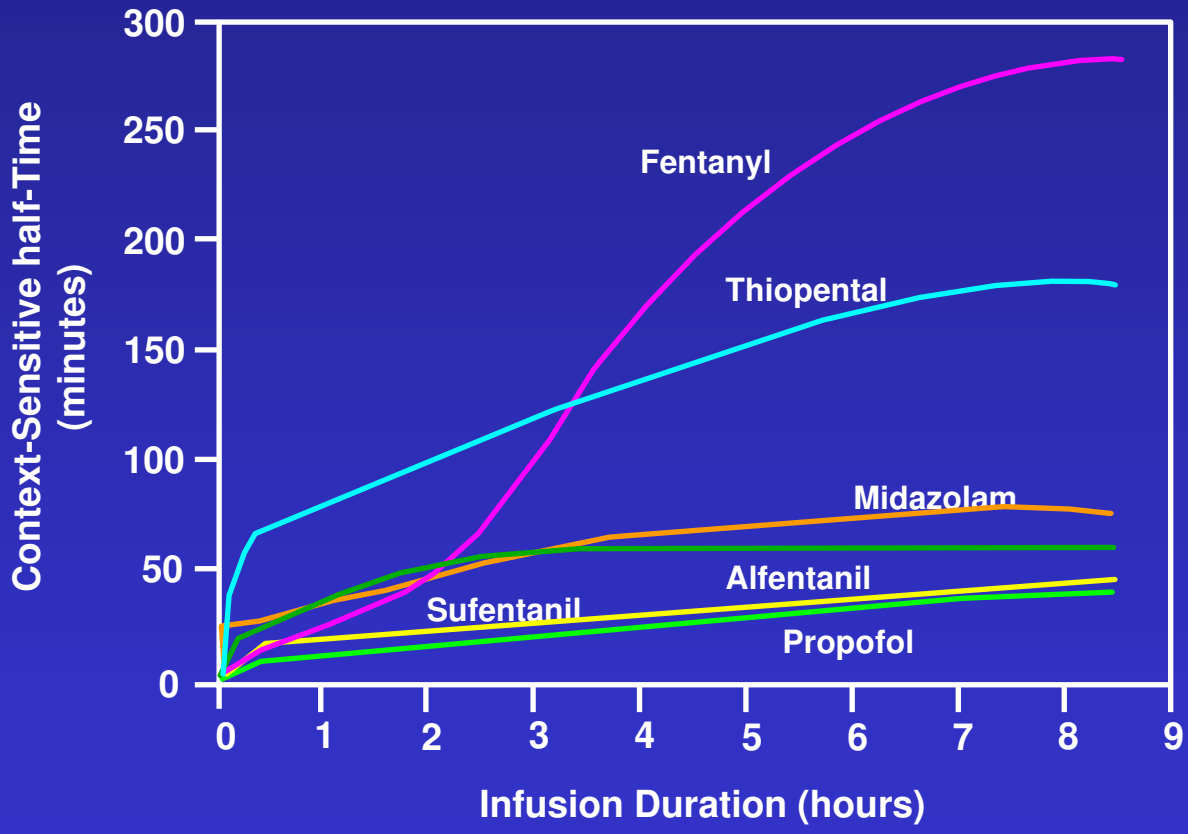
CONTEXT SENSITIVE HALF-TIMES: THIOPENTONE 1, 2 AND 8 HOUR INFUSIONS



CONTEXT SENSITIVE HALF-TIMES: PROPOFOL 1, 2 AND 8 HOUR INFUSIONS

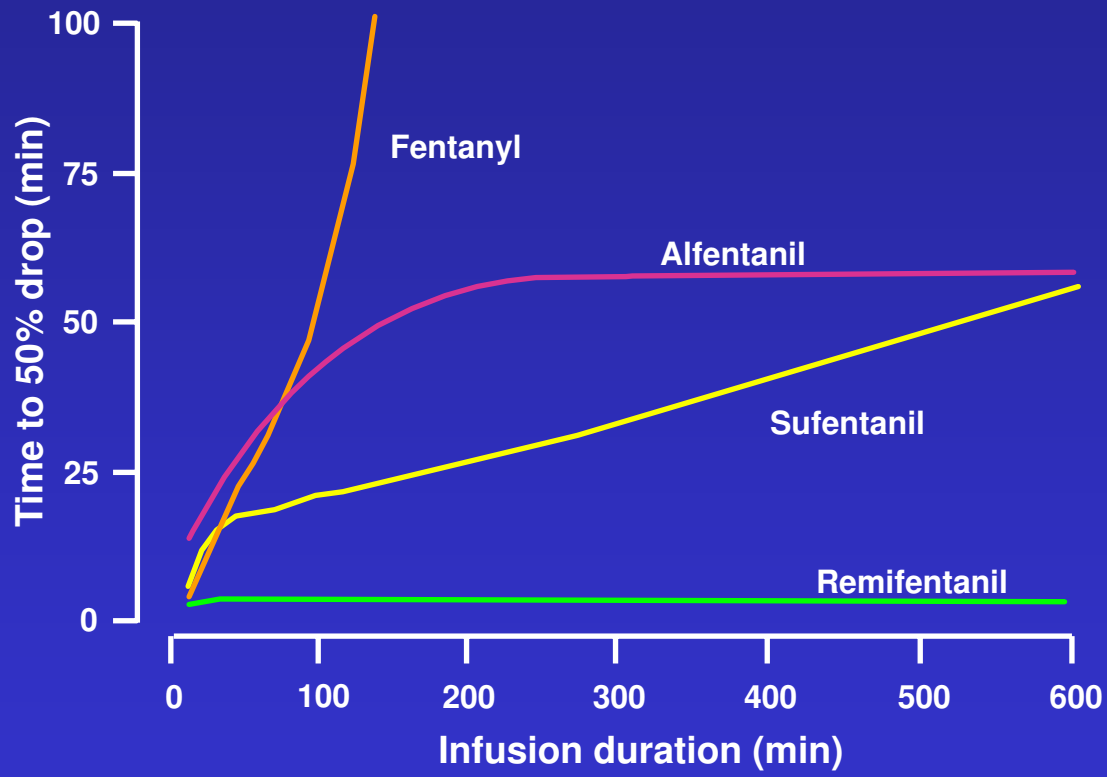


CONTEXT-SENSITIVE HALF-TIMES OF I.V. AGENTS



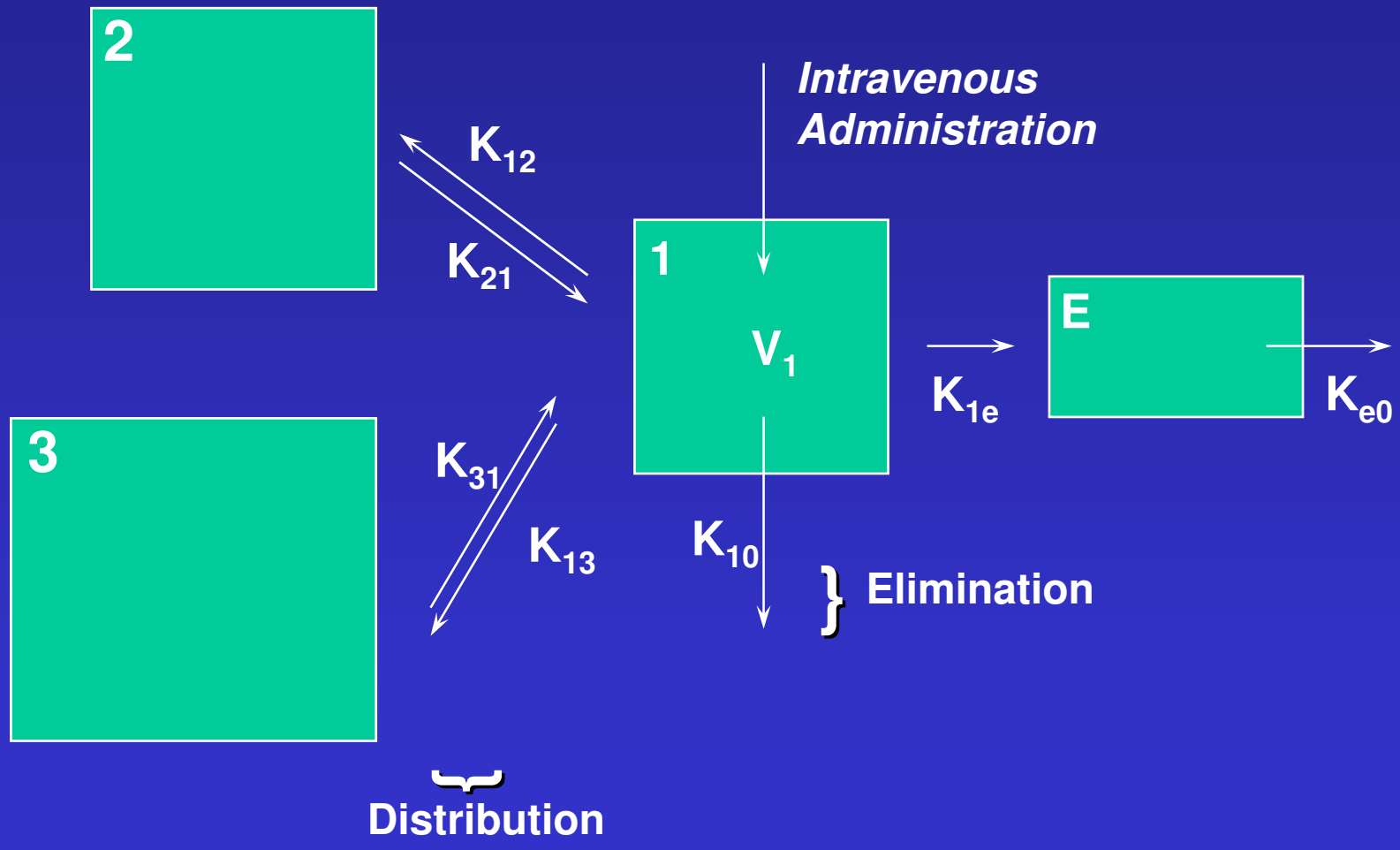
(Hughes et al 1992)

CONTEXT-SENSITIVE HALF TIMES OF I.V. ANALGESICS

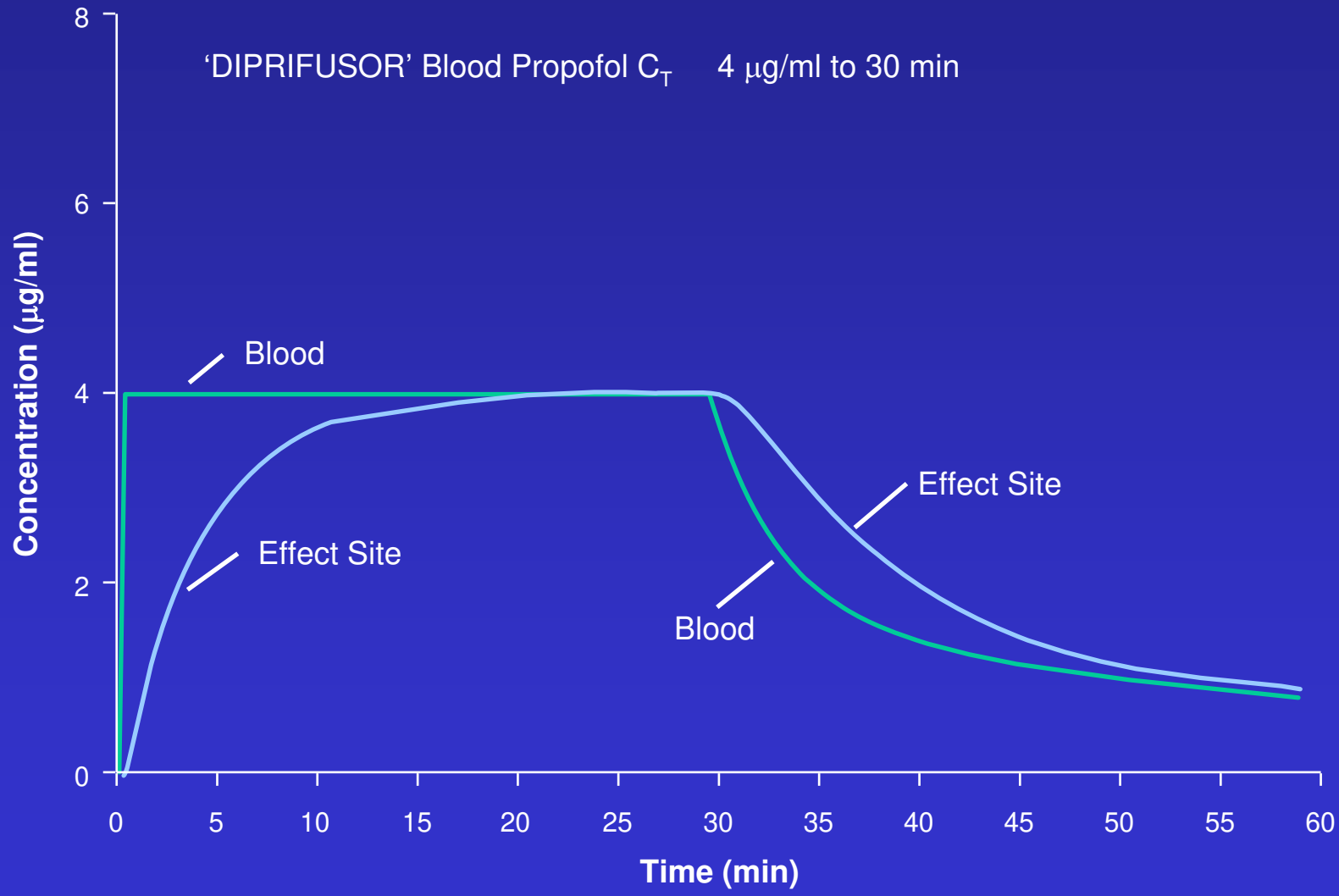


(Egan et al 1993)

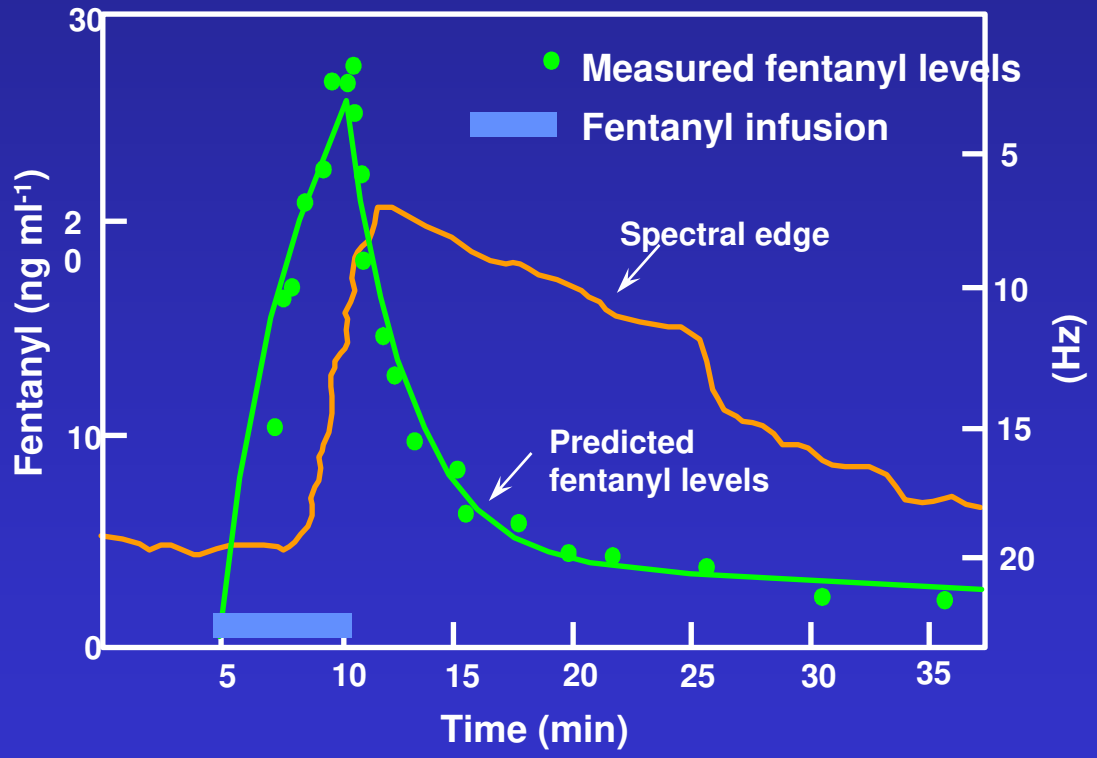
3-COMPARTMENT MODEL LINKED TO AN EFFECT COMPARTMENT



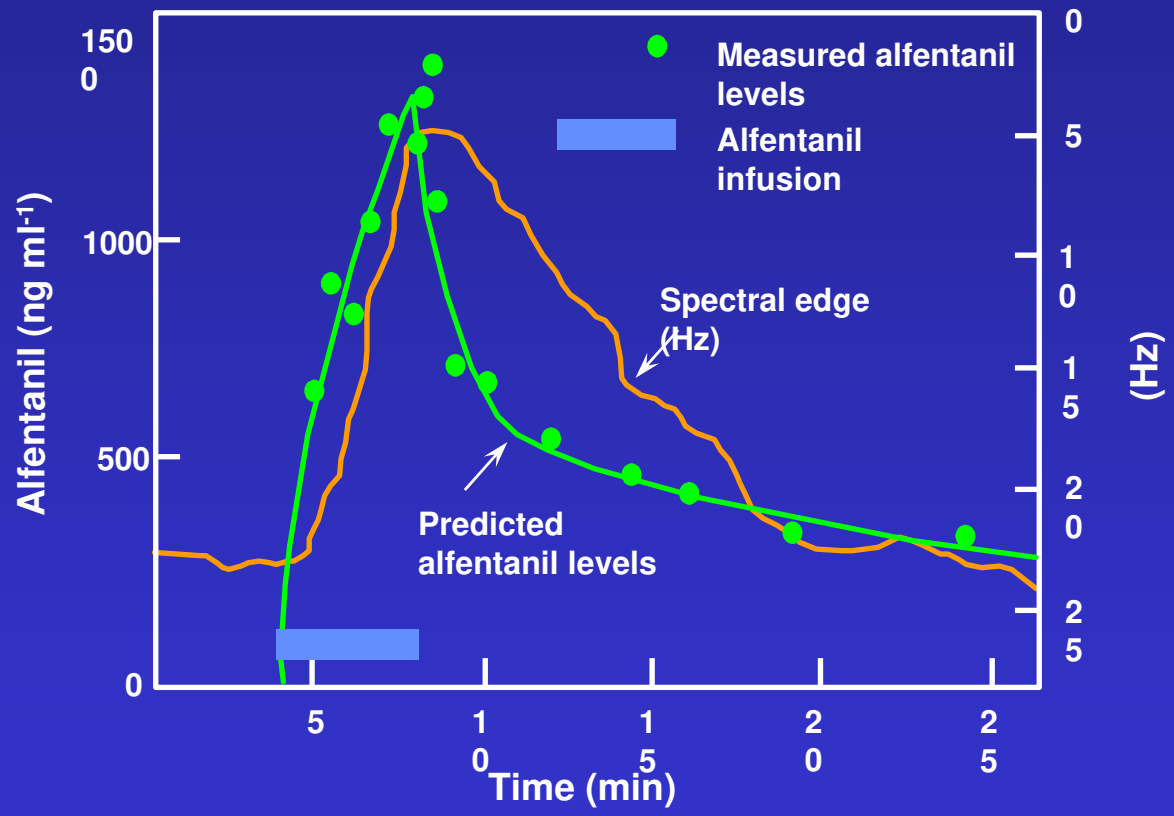
PROPOFOL PREDICTED CONCENTRATIONS



CONCENTRATION-EFFECT HYSTERESIS FOR THE EEG EFFECTS OF FENTANYL

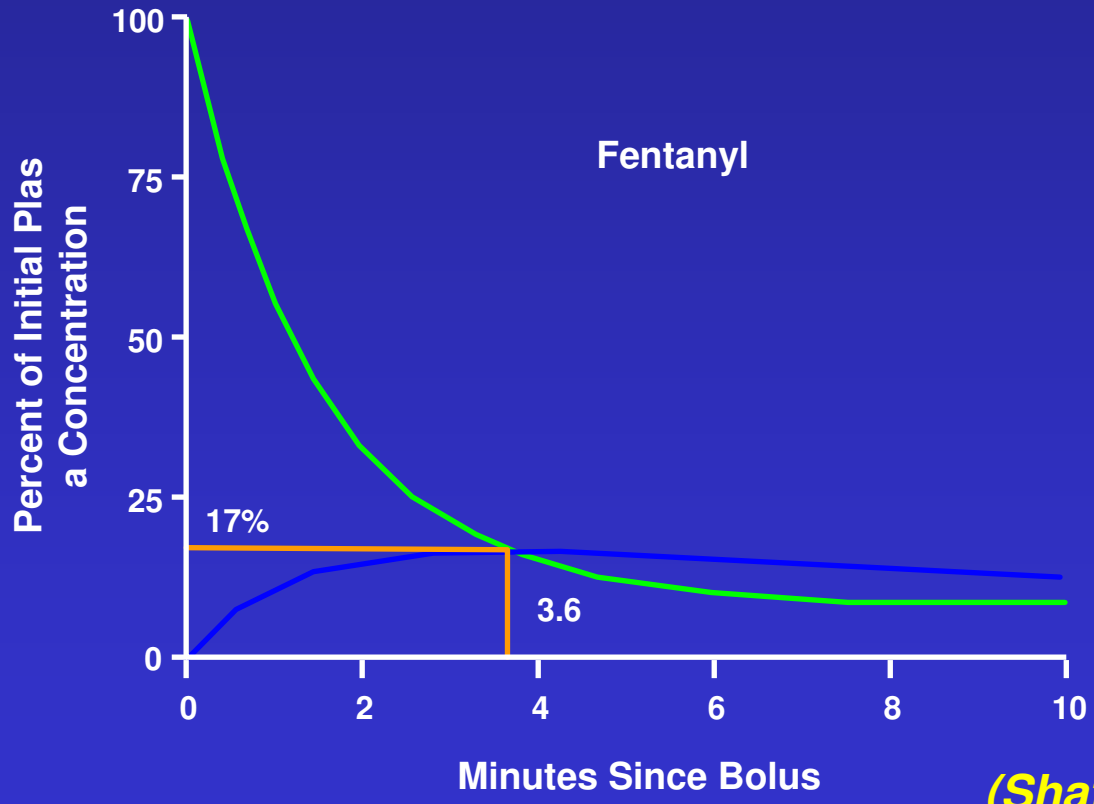


CONCENTRATION EFFECT HYSTERESIS FOR THE EEG EFFECTS OF ALFENTANIL

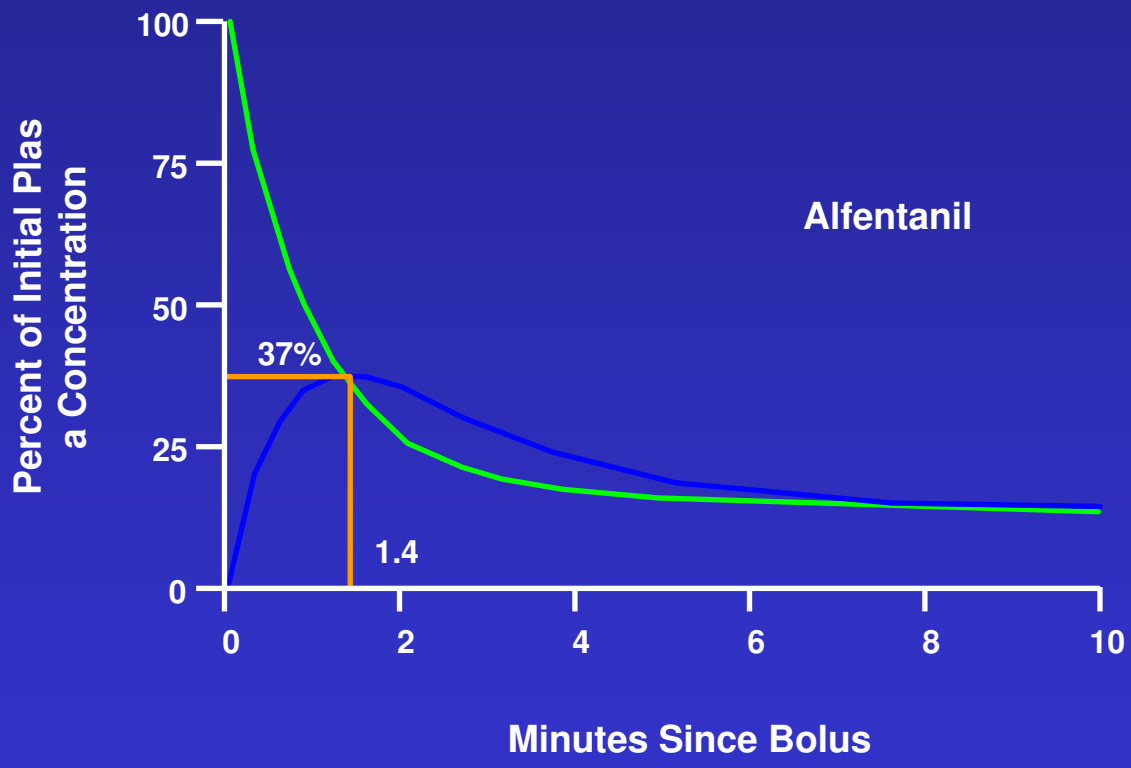


(Scott et al, 1985)

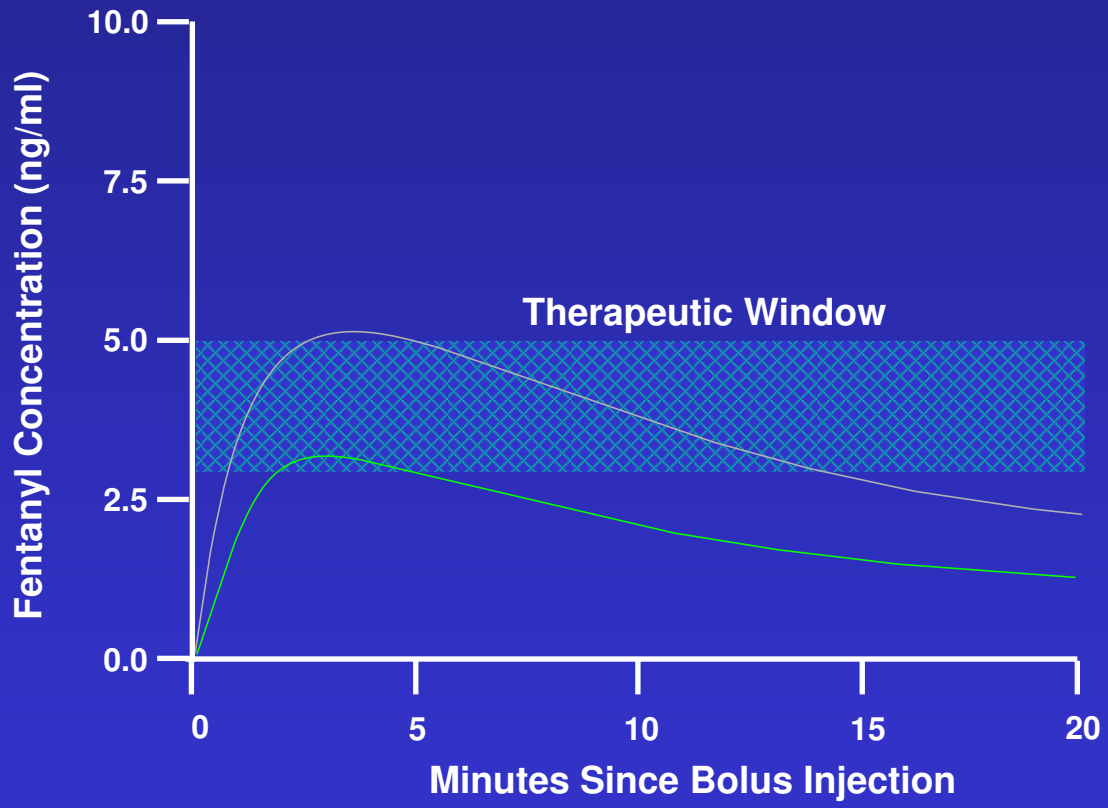
PLASMA AND EFFECT SITE CONCENTRATIONS FOLLOWING AN IV BOLUS OF FENTANYL OR ALFENTANIL



(Shafer et al 1991)


Percent of Initial Plas
a Concentration
100
75
50
25
0
37%
1.4
Alfentanil
0
2
4
6
8
10
Minutes Since Bolus

THE BIOPHASE CONCENTRATIONS AFTER TWO DIFFERENT BOLUS DOSES OF FENTANYL.



(Shafer, 1993)

Pharmacokinetic Concepts and Analysis

- Process of pharmacokinetic analysis
- Compartmental models
- Derivation of PK parameters
- Volumes of distribution
- Clearance
- Half lives
- Context-sensitive half time
- Effect-site equilibration time

PHARMACOKINETICS: INJECTABLE AGENTS: 2

Dr J B (Iain) Glen
Glen Pharma Ltd, Knutsford, UK

Application of Pharmacokinetic Information

- Derivation of dosing strategies
- Use of computer simulation techniques
- Understanding differences between agents
- Understanding sources of PK variability
- Target controlled infusion (TCI)

Manual administration of Drugs

- Titrate dose to effect
- Estimate loading and maintenance dose from PK parameters
- Look at ‘what if’ scenarios with computer simulation

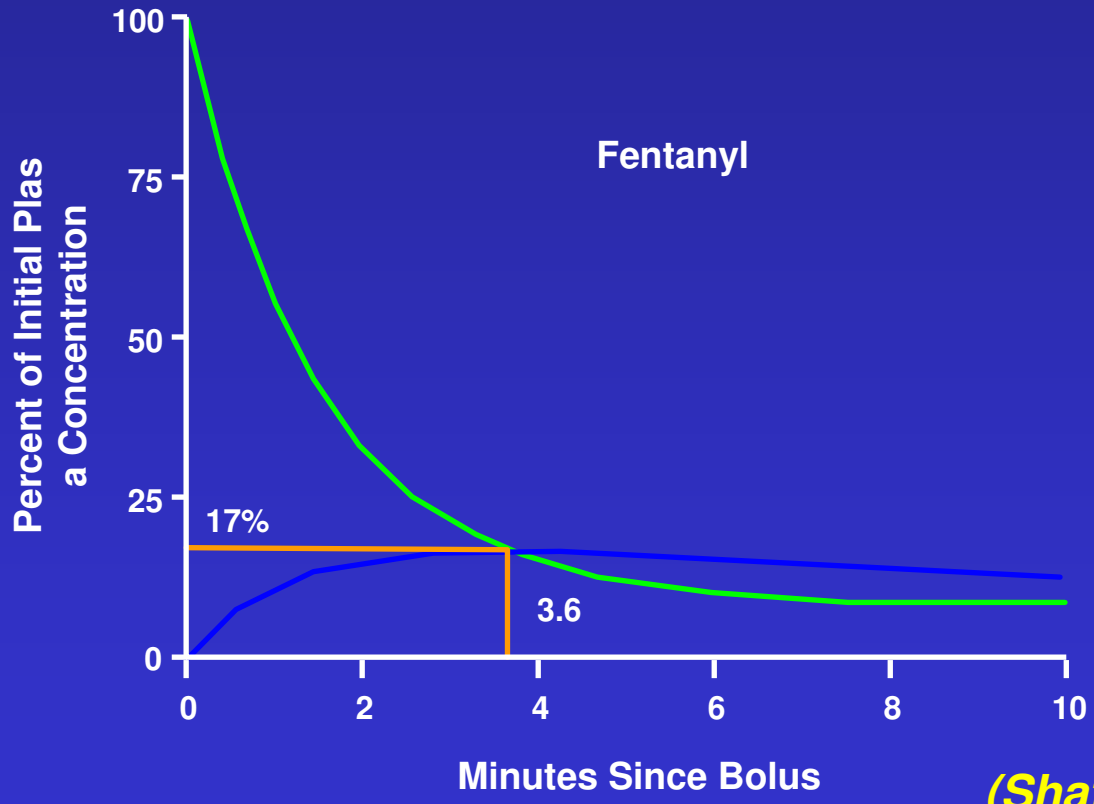
Estimation of Loading dose

- Loading dose = desired concentration x V1
- Loading dose = desired concentration x Vss
- Loading dose = desired concentration x Vd at time of peak effect

Estimation of Loading Dose to achieve a concentration of 2ng/ml Fentanyl

- V1 = 12.7L : LD = 2 x 12.7= 25.4 µg
- Vss = 358L : LD = 2 x 358 = 716 µg

PLASMA AND EFFECT SITE CONCENTRATIONS FOLLOWING AN IV BOLUS OF FENTANYL OR ALFENTANIL



(Shafer et al 1991)

Loading dose of Fentanyl based on Vd (peak effect)

- Vd (peak effect) = V1 / % concentration remaining at time of peak effect

12.7 / 17% = 75L : LD = 2 x 75 = 150µg

Vd(peak effect) for some iv agents (Stanski, Shafer & Kern 1990)

Drug	V1(litres)	Time of Peak Effect (min)	% of Peak Concn	Vd (peak effect) (litres)
Fentanyl	12.7	3.6	17%	75
Alfentanil	2.19	1.4	37%	5.9
Sufentanil	17.8	5.6	20%	89
Propofol	11.1	2.0	47%	24

Calculation of Infusion Rate

- With multi-compartment models the infusion rate to achieve a given concentration changes over time

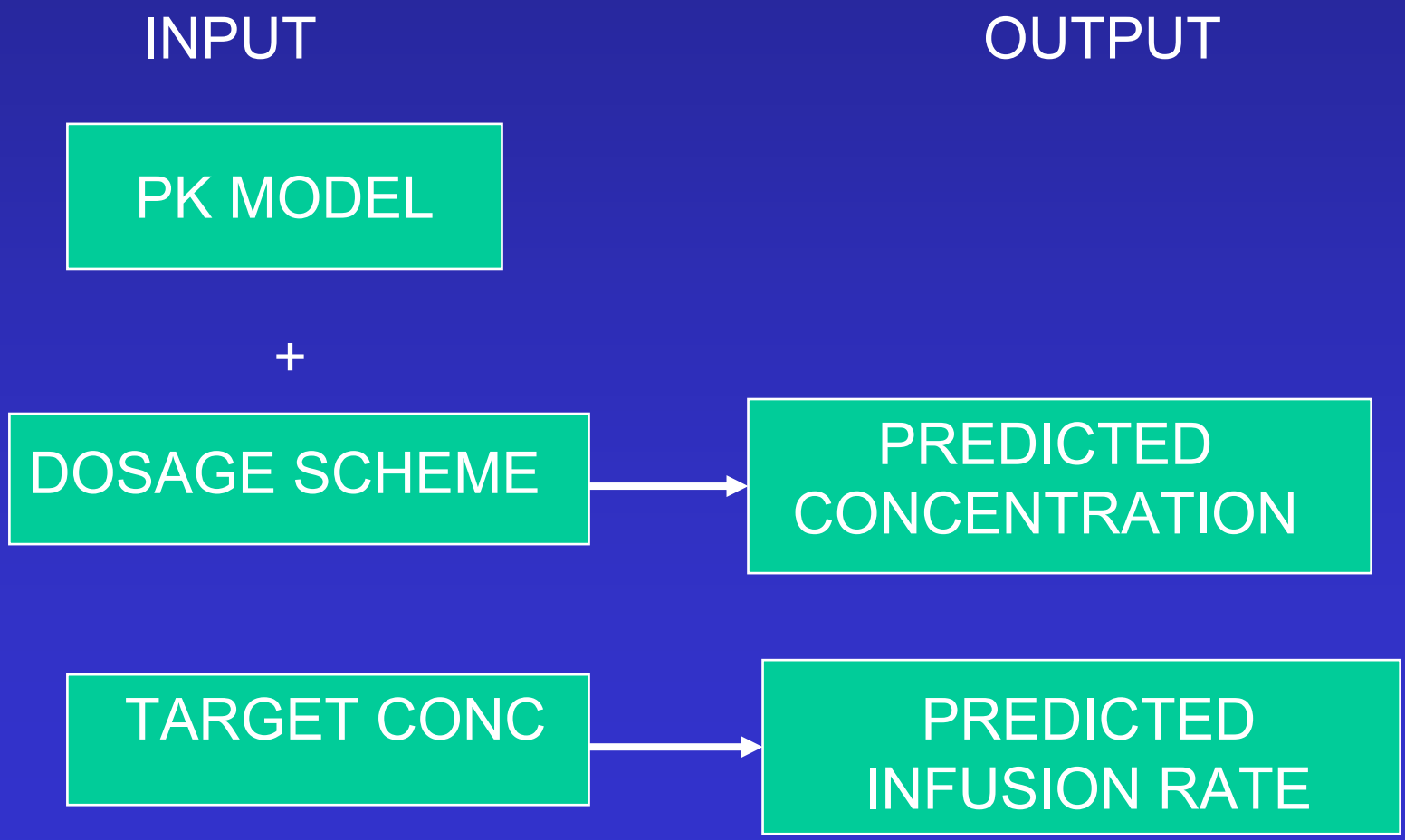
- At steady state,

  Concentration x Clearance = Rate of infusion

  e.g. 2µg / ml x 1500 ml/min = 3000 µg/min

  (Measurement of Css at known rate of infusion can also be used to estimate clearance)

Computer Simulation of Pharmacokinetics

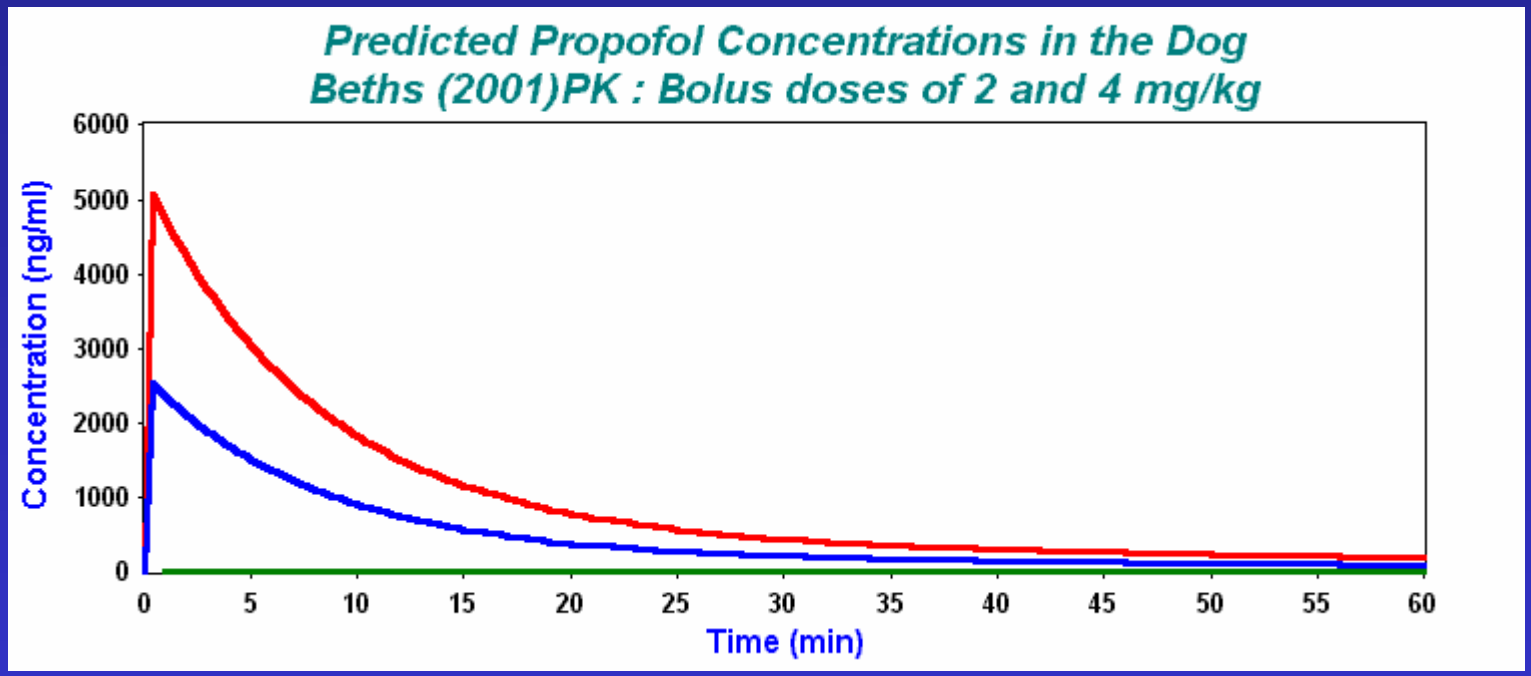


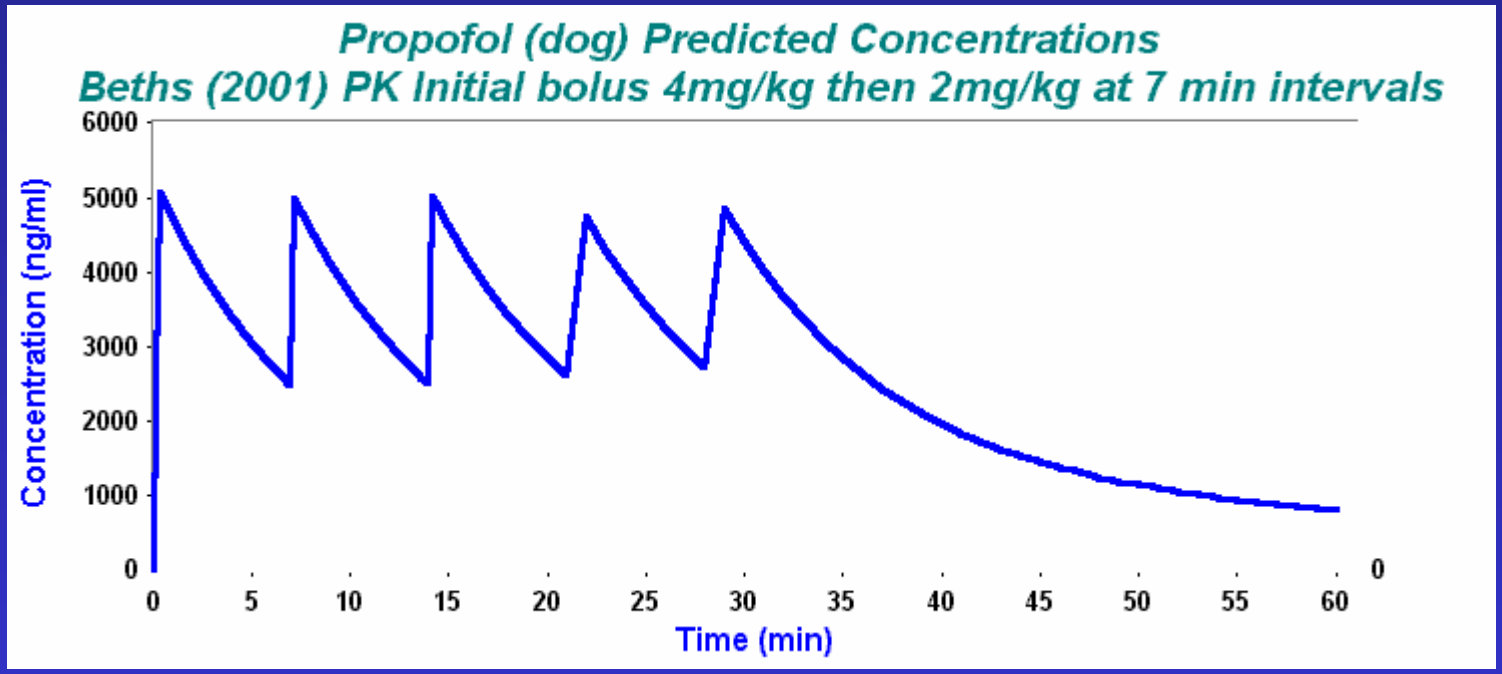
PK Computer Simulation Programs

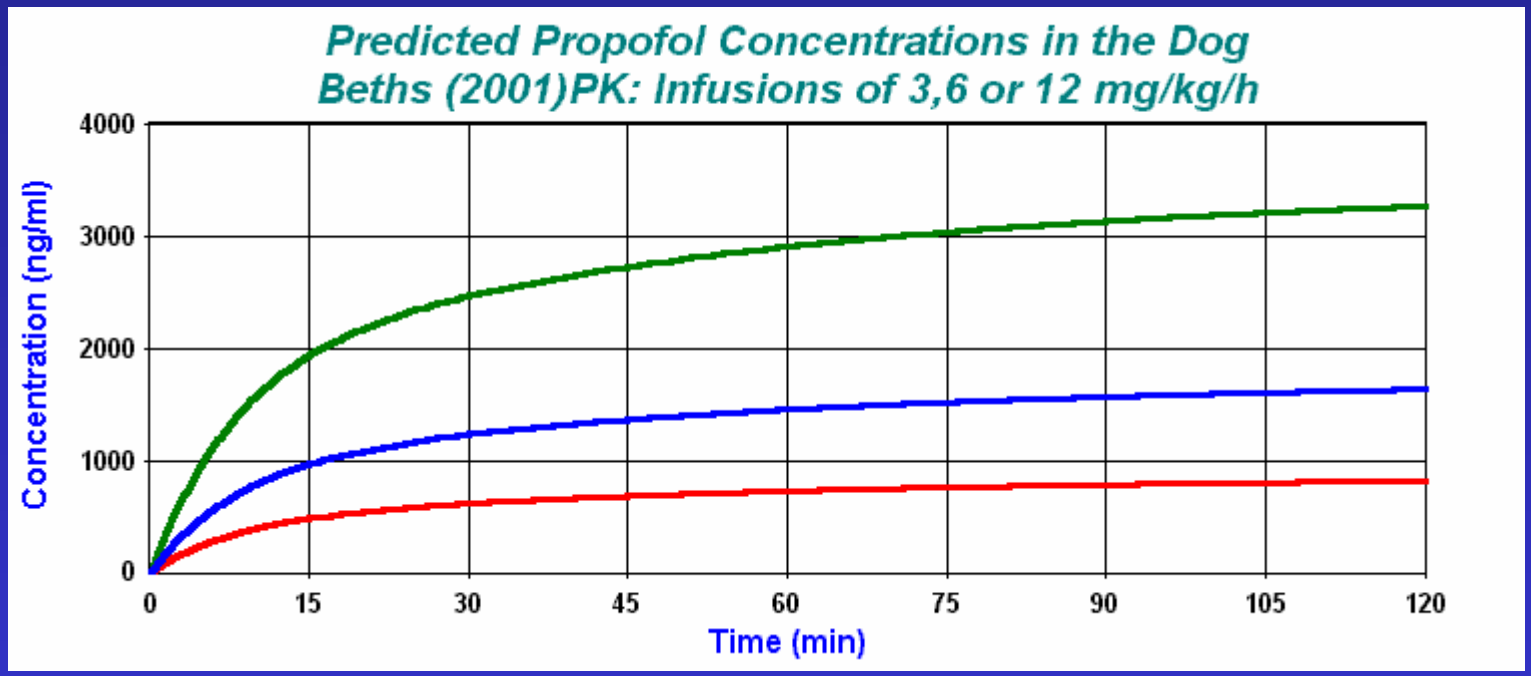
- http://anesthesia.stanford.edu/pkpd
  - PK-SIM (R Epstein, US)
  - RUGLOOP (M Struys, Belgium)
  - STANPUMP (S Shafer, US)
  - STELPUMP (J Coetzee, SA)
- www.eurosiva.org
  - TIVA TRAINER (F Engbers,NL)

Computer Simulation of bolus and infusion doses: Propofol in the Dog

- 3-Comp Model (Beths et al, 2001)
- V1 780ml/kg
- K10 0.07
- K12 0.0365
- K21 0.0312
- K13 0.0049
- K31 0.0011
- (Cl 54.6 ml/min/kg)
- (Vss 5167 ml/kg)


Predicted Propofol Concentrations in the Dog
Beths (2001)PK : Bolus doses of 2 and 4 mg/kg
Concentration (ng/ml)
6000
5000
4000
3000
2000
1000
0
0
5
10
15
20
25
30
35
40
45
50
55
60
Time (min)


Propofol (dog) Predicted Concentrations
Beths (2001) PK Initial bolus 4mg/kg then 2mg/kg at 7 min intervals
Concentration (ng/ml)
6000
5000
4000
3000
2000
1000
0
0
5
10
15
20
25
30
35
40
45
50
55
60
0
Time (min)


Predicted Propofol Concentrations in the Dog
Beths (2001)PK: Infusions of 3,6 or 12 mg/kg/h
Concentration (ng/ml)
4000
3000
2000
1000
0
0
15
30
45
60
75
90
105
120
Time (min)

Understanding Differences Between Agents

- Physicochemical chemical properties
  - Lipid-soluble drugs have greater Vss than water soluble agents
  - pKa. Only unionised form can cross membranes
- Protein Binding
  - Only unbound form can cross membranes
- Rate of metabolism

Understanding Sources of PK Variability

Dose → Blood Concentration → Effect

Pharmacokinetic variation

- Absorption
- Distribution
- Metabolism
- Excretion

Pharmacodynamic variation

- Receptor sensitivity
- Receptor density
- Tolerance

Factors influencing drug distribution

- Muscle and adipose tissue mass
- Cardiac output
  - Increase $\Rightarrow$ more rapid initial distribution, lower peak concentration
- Protein binding
  - Increased free drug $\Rightarrow$ more rapid and extensive distribution, increase in Vss

Factors Influencing Hepatic Clearance

Highly extracted drugs

Cl = HBF

eg. Propranolol

Poorly extracted drugs

Cl << HBF

eg. Warfarin

Clearance affected by changes in HBF

Enzyme induction/inhibition or changes in protein binding have minimal effect

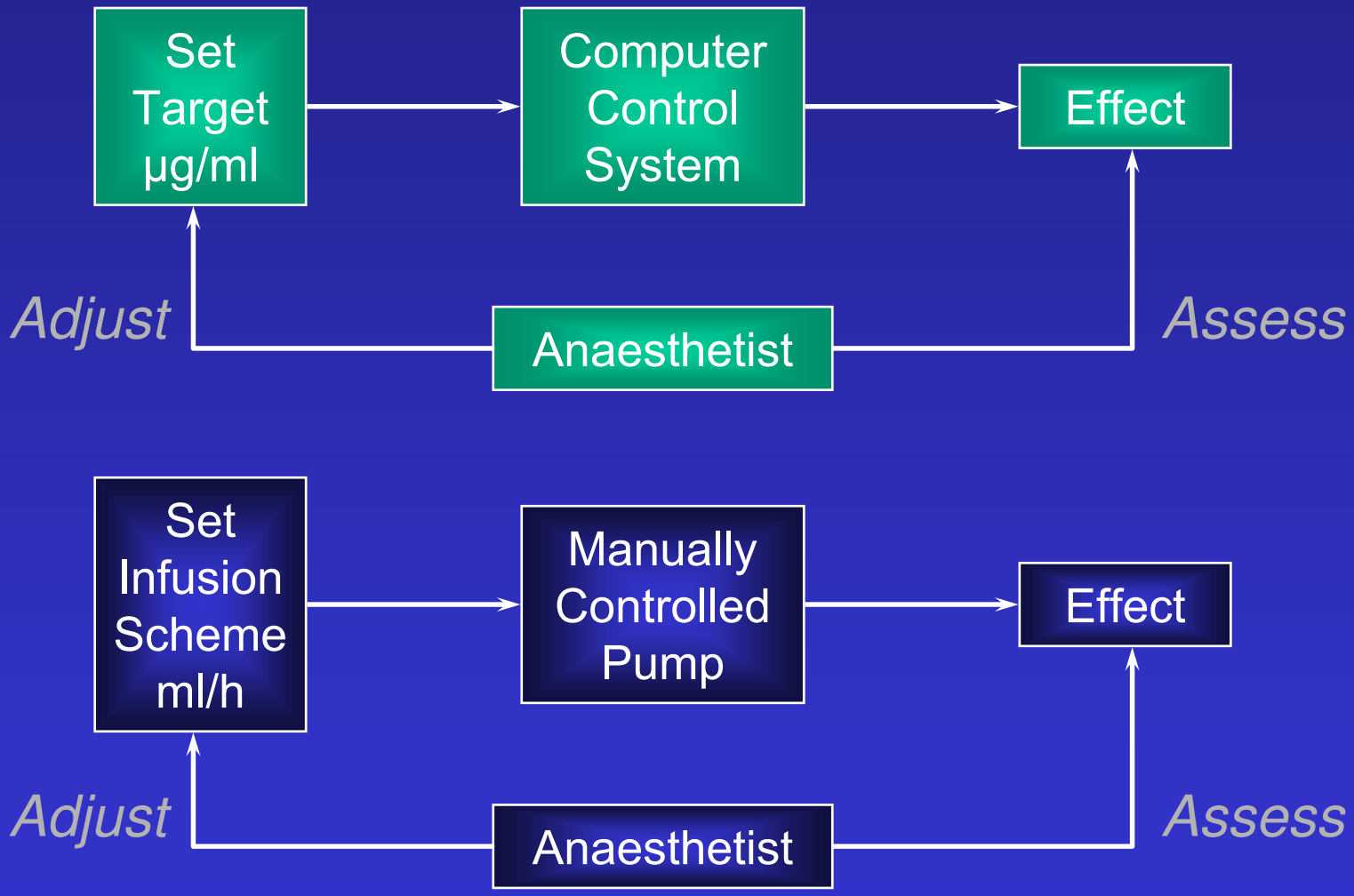
Clearance affected by changes in hepatic metabolic activity,enzyme induction or inhibition.

Changes in protein binding may affect clearance

Target Controlled Infusion (TCI)

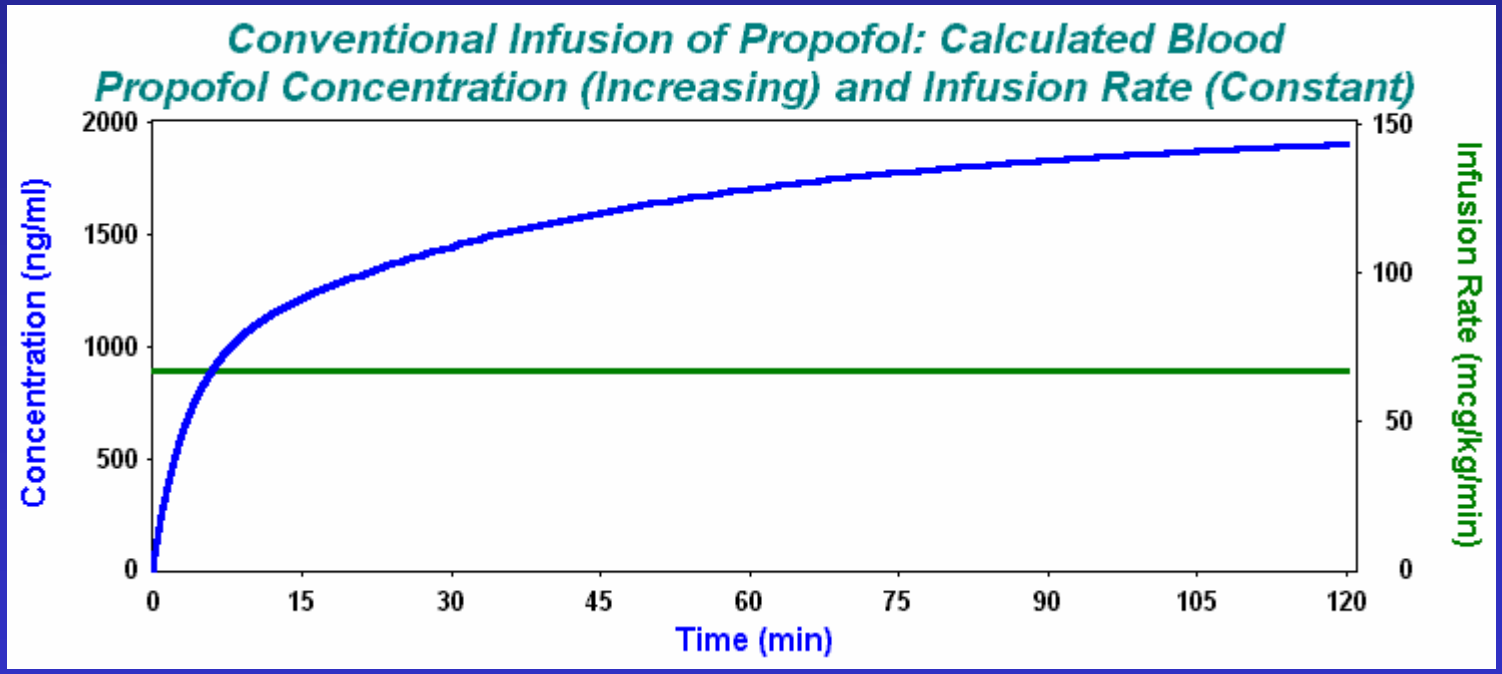
- The concept of TCI (Target Controlled Infusion)
- Advantages of TCI
- The development of a prototype TCI system for use in dogs

Computer vs Manual Control



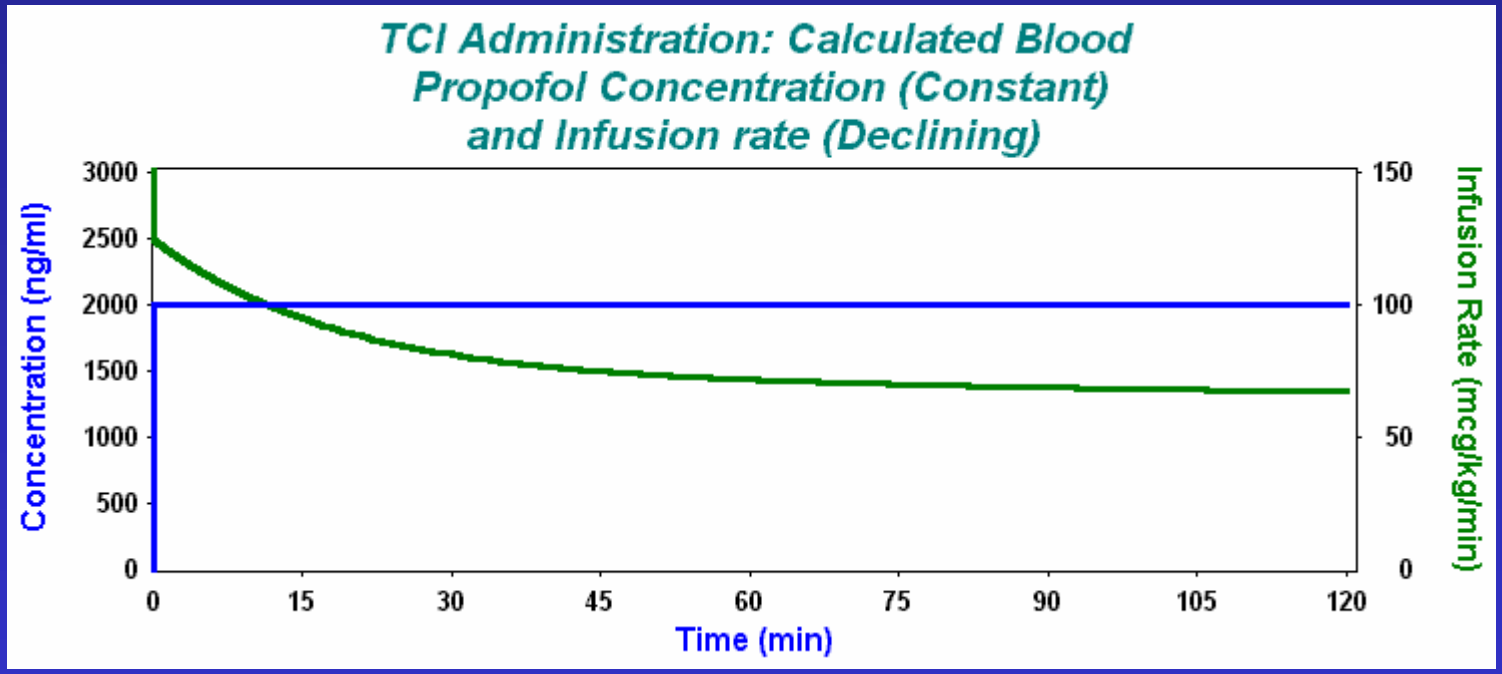
Conventional infusion techniques

- Constant infusion rate over time
- Blood concentration increases over time
- Effect achieved depends on duration of infusion
- Lag time when titrating infusion rate to effect


Conventional Infusion of Propofol: Calculated Blood Propofol Concentration (Increasing) and Infusion Rate (Constant)
Concentration (ng/ml)
2000
1500
1000
500
0
Infusion Rate (mcg/kg/min)
150
100
50
0
0
15
30
45
60
75
90
105
120
Time (min)

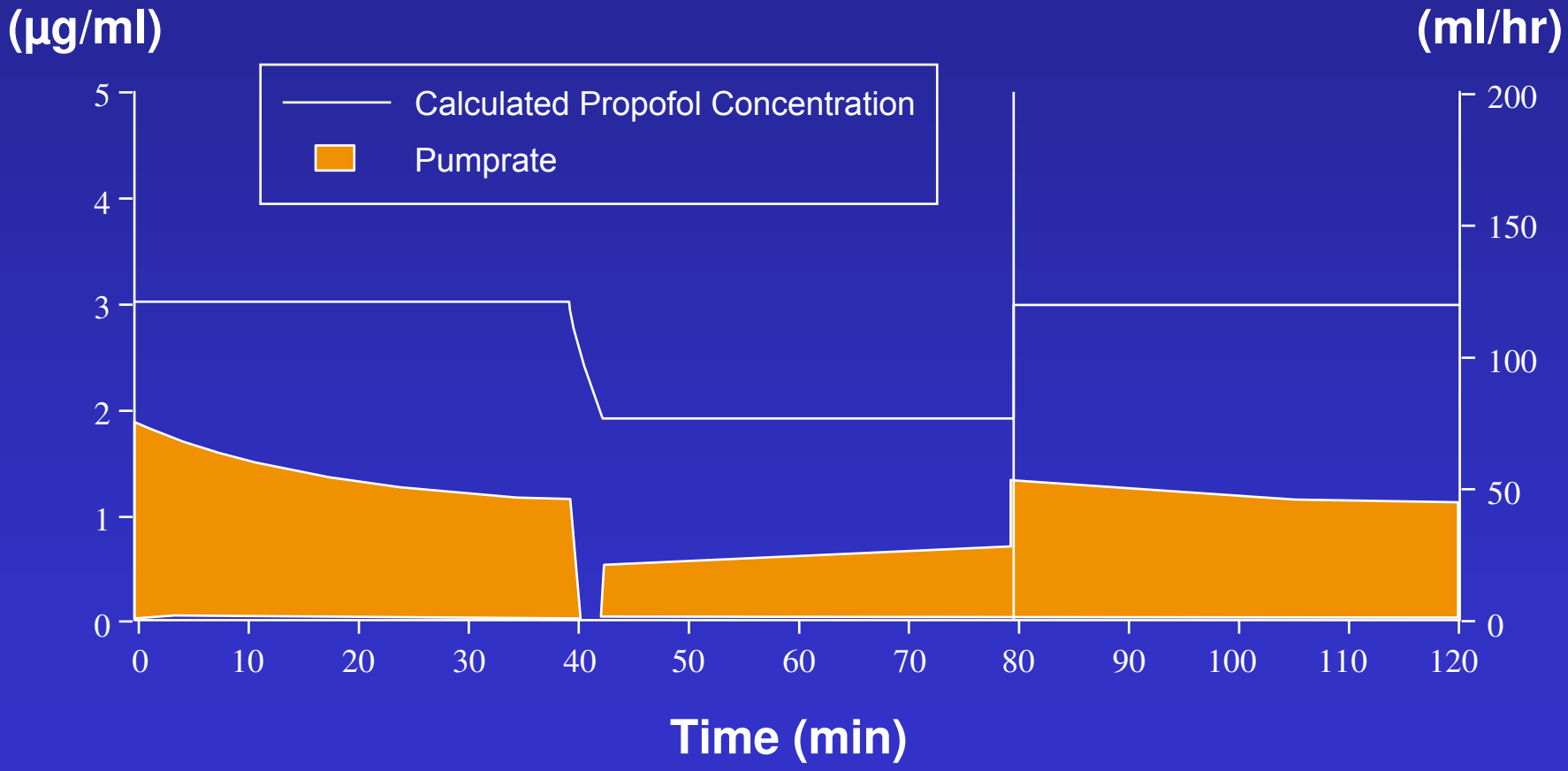
Target Controlled Infusion (TCI)

- Target blood concentration is attained rapidly and held constant
- Pump automatically reduces infusion rate with time to achieve this
- Rapid response to a change in target setting


TCI Administration: Calculated Blood Propofol Concentration (Constant) and Infusion rate (Declining)
Concentration (ng/ml)
3000
2500
2000
1500
1000
500
0
Infusion Rate (mcg/kg/min)
150
100
50
0
0
15
30
45
60
75
90
105
120
Time (min)

Target Controlled Infusion

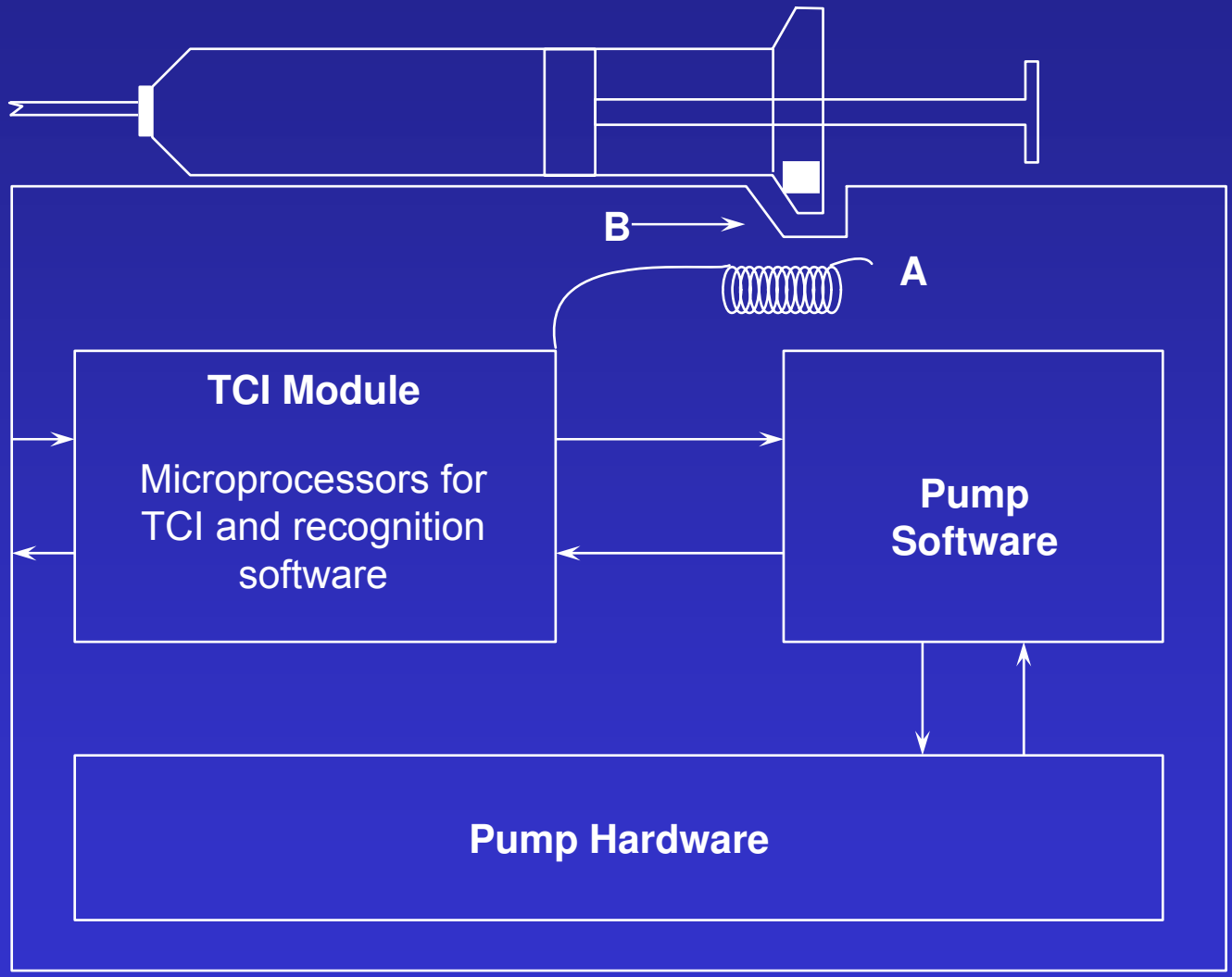
Target concentrations of 3 µg/ml, 2 µg/ml, and back to 3 µg/ml



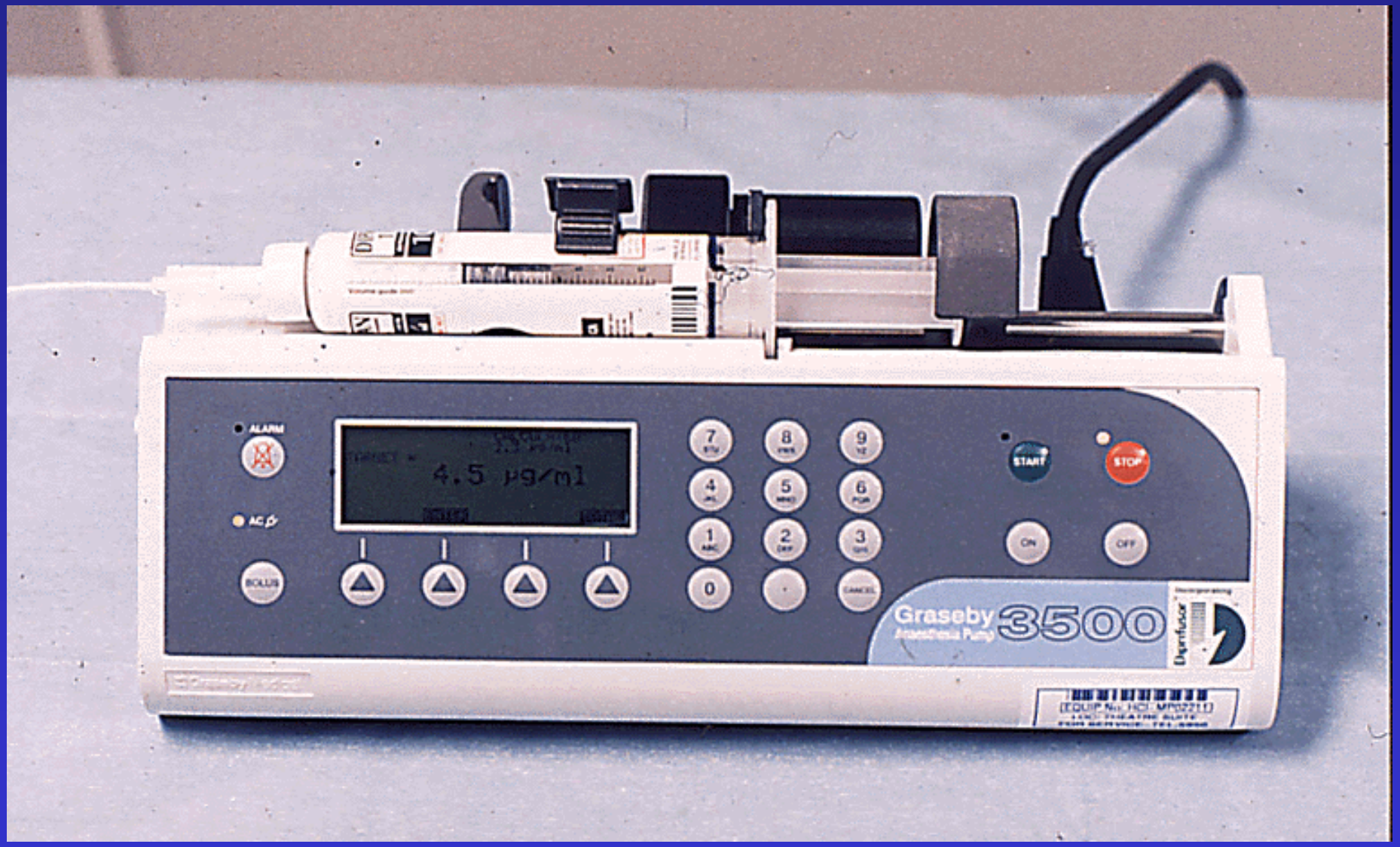
DIPRIFUSOR MODULE

- Electronic component ("Accessory") for incorporation in standard pumps
- Converts normal pump to a TCI pump
- Standardized p/k model and delivery performance
- Linkage to Diprivan labelling
- Zeneca responsibility

AN INTEGRATED 'DIPRIFUSOR' SYSTEM



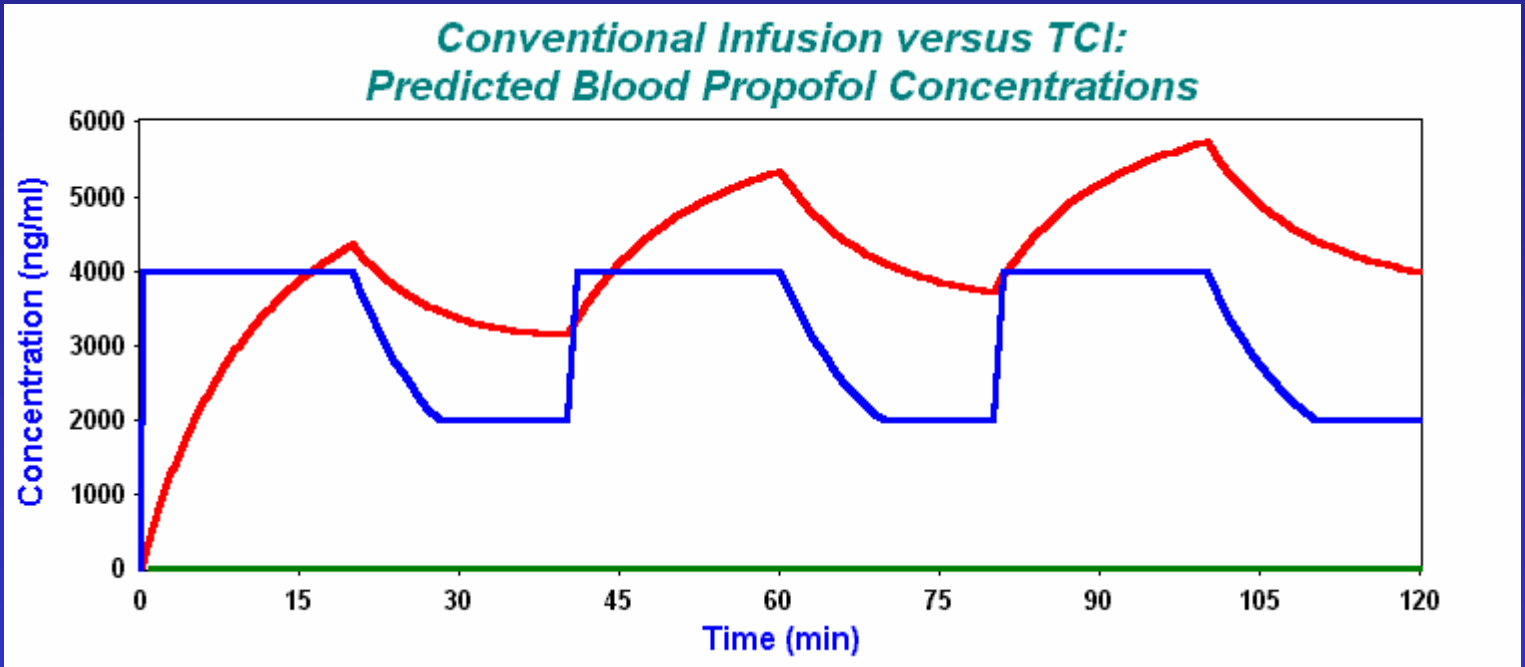
A = aerial **B** = syringe tag identification system


ALARM
4.5 µg/ml
START
STOP
ON
OFF
Graseby 3500
Anaesthesia Pump
Dymed

Advantages of TCI

- Rapid achievement of desired blood concentration
- Avoidance of ‘overshoot’ seen with bolus administration
- Ability to make proportional increases or decreases in blood concentrations
- Advisory information on calculated blood and effect-site concentrations
- Ability to predict waking time
- Compensation for any interruption to an infusion

Response to halving or doubling infusion rate (red) or target concentration (blue)



Development of a Prototype TCI System for Dogs

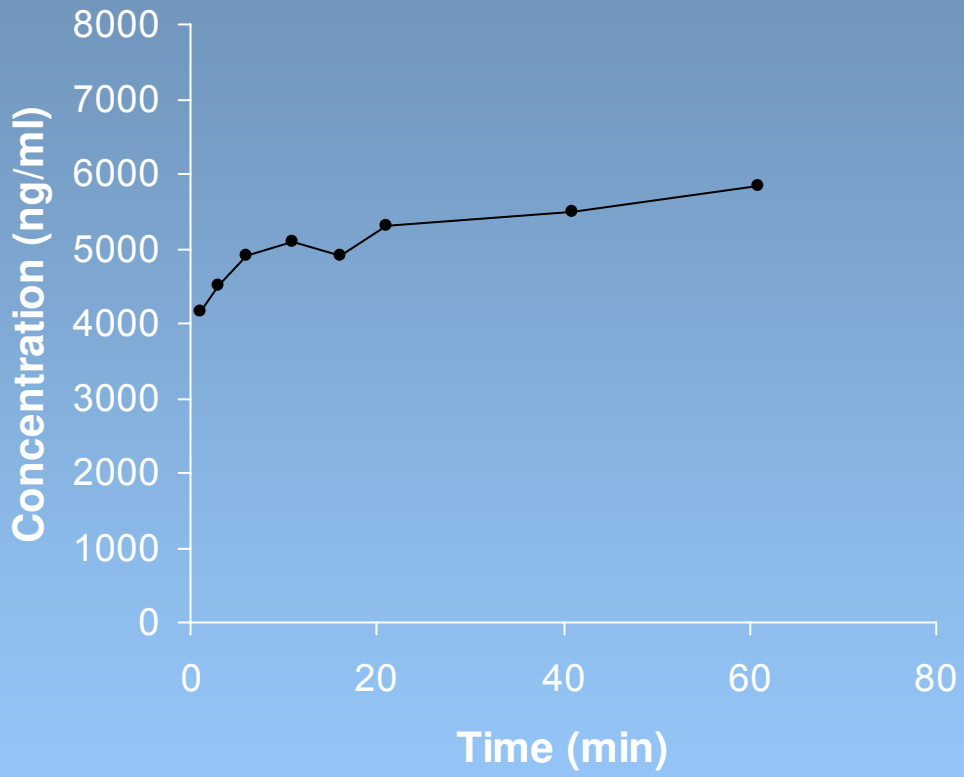
- Review of published PK parameters for propofol in dogs
- Computer simulation studies to compare and refine parameters
- Incorporation of dog parameters in TCI module
- Clinical validation studies

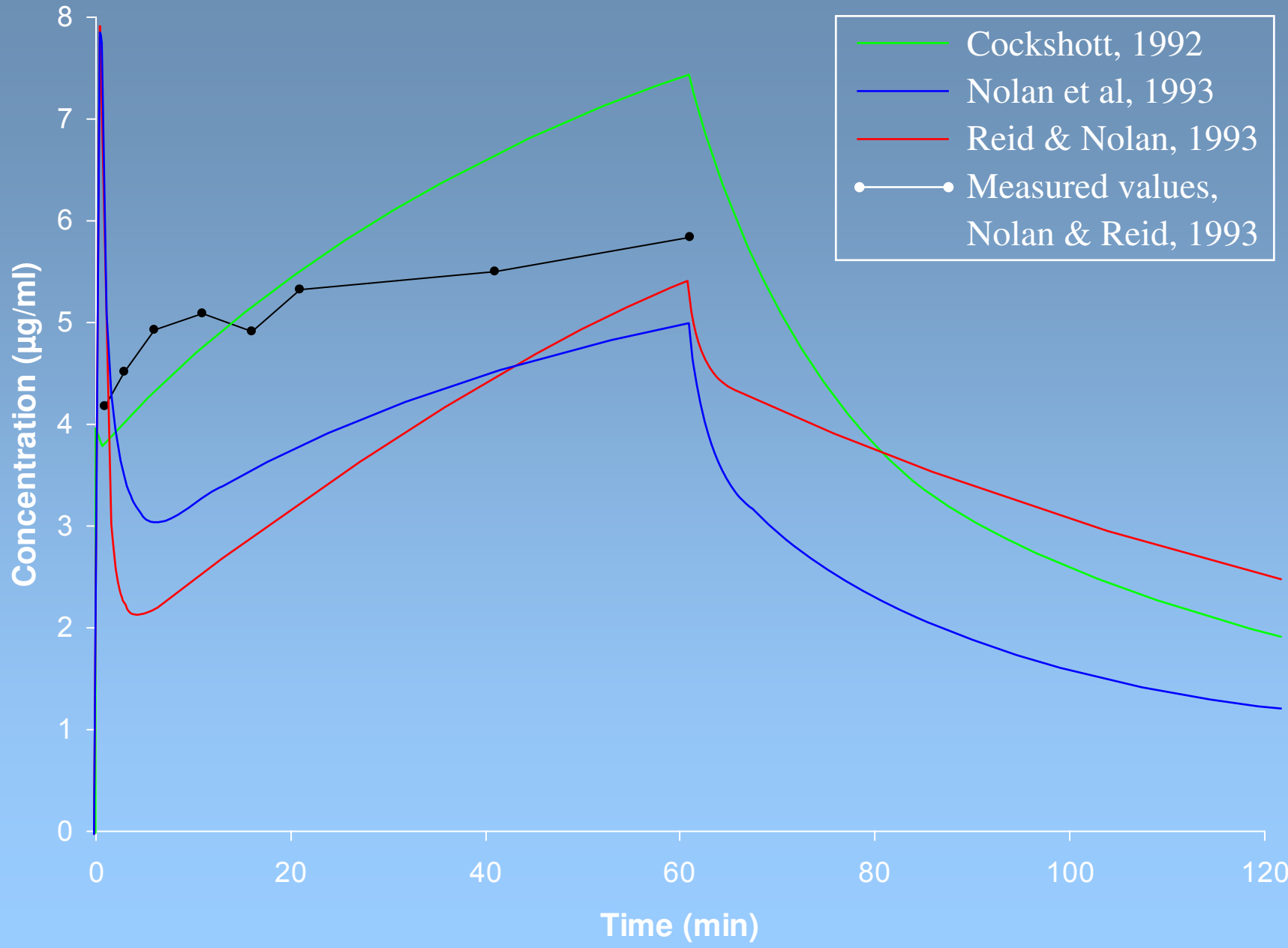
Published PK Parameters for Propofol in Dogs

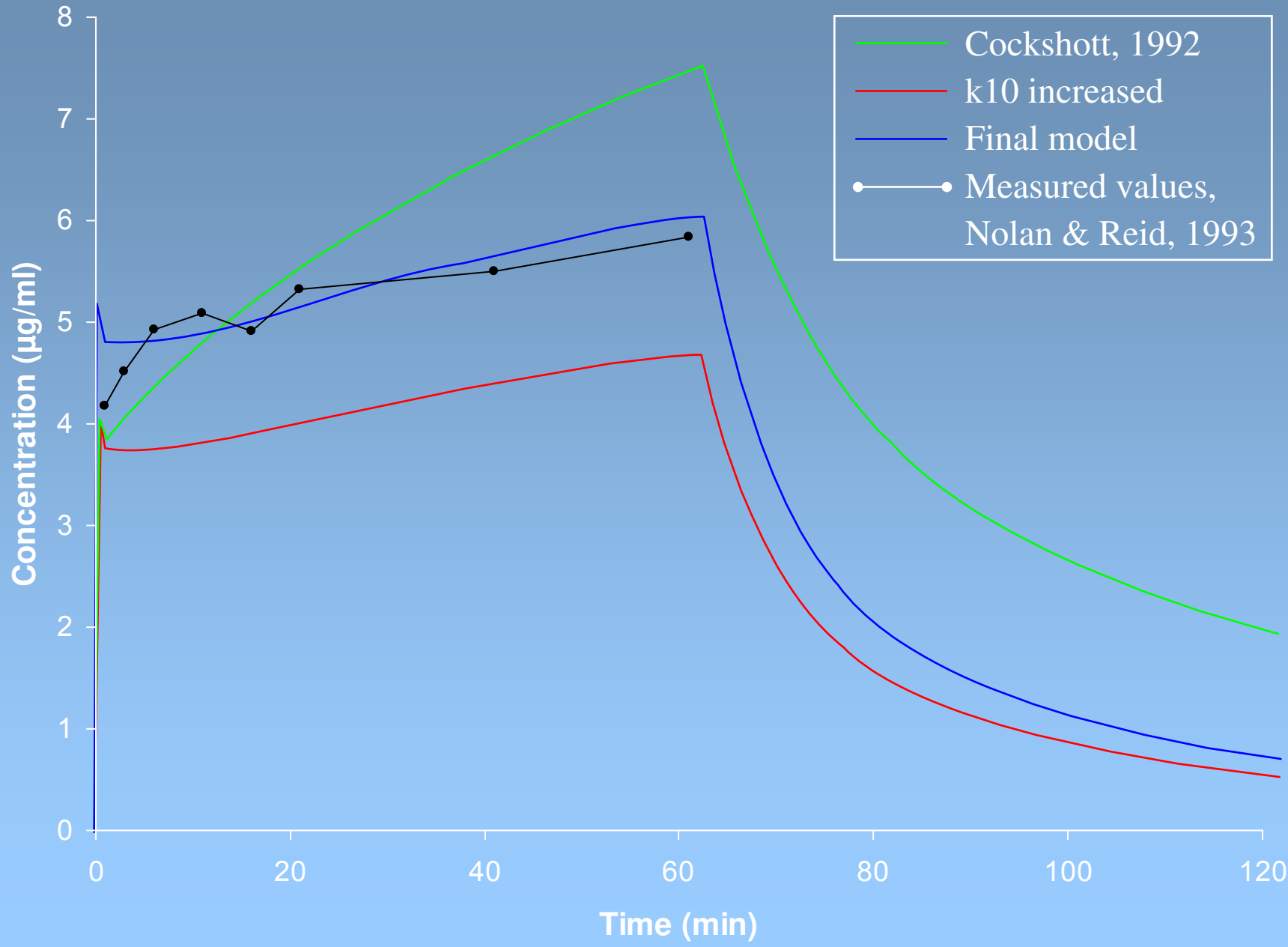
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
t½ λ_1 (min)	1.2	0.78	7.4		7.6		
t½ λ_2 (min)	14	70	53	74	122	486	322
t½ λ_3 (min)	96		725	48			
Cl_{TB} (ml/min/kg)	51	40	34	40	115	34	50
V_1 (ml/kg)	486	466	1000	48	1817		
V_{SS} (ml/kg)	4384	3589	6600	2460	9748	6040	6510

(1) Nolan et al, 1993. Bolus or Bolus/Infusion (n=7)
(2) Reid & Nolan, 1993. Bolus (n=7)
(3) Cockshott et al, 1992. Bolus/Infusion (n=3)
(4) Mandsager et al, 1995. Bolus/Infusion (n=5: greyhounds)
(5) Zoran et al, 1993. Bolus (n=8: mixed breed dogs)
(6) Hall et al, 1994. Bolus/Infusion (n=6)
(7) Nolan & Reid, 1993. Bolus/Infusion (n=7)

Measured Propofol Concentrations with Bolus of 4mg/kg and infusion of 0.4mg/kg/min (Reid & Nolan)




Cockshott, 1992
Nolan et al, 1993
Reid & Nolan, 1993
Measured values, Nolan & Reid, 1993
Concentration (µg/ml)
Time (min)
0
1
2
3
4
5
6
7
8
0
20
40
60
80
100
120


Cockshott, 1992
k10 increased
Final model
Measured values, Nolan & Reid, 1993
Concentration (µg/ml)
Time (min)
0
1
2
3
4
5
6
7
8
0
20
40
60
80
100
120

Empirical Refinement of Final Model

	Cockshott et al 1992	k_{10} increased	Final model, k_{10} increased and V_1 decreased
V_1 (l/kg)	1000	1000	780
Cl_{TB} (ml/min/kg)	34	(70)	(54.6)
k_{10} (min^{-1})	0.034	0.07	0.07
k_{12} (min^{-1})	(0.0365)	0.0365	0.0365
k_{21} (min^{-1})	(0.0312)	0.0312	0.0312
k_{13} (min^{-1})	(0.0049)	0.0049	0.0049
k_{31} (min^{-1})	(0.0011)	0.0011	0.0011

Application of Pharmacokinetic Information

- Derivation of dosing strategies
- Use of computer simulation techniques
- Understanding differences between agents
- Understanding sources of PK variability
- Target controlled infusion (TCI)

REFERENCES

- Clark B, Smith DE. An Introduction to Pharmacokinetics.2nd Ed. Blackwell Scientific Publications, Oxford,1993
- Hull CJ. Pharmacokinetics for Anaesthresia, Butterworth Heinemann, Oxford,1991
- Glen I. Anaesthesia & intensive care medicine, Vol 3,263-269,2002
- Questions by E-mail jbg@glenpharma.com