BASIC PHARMACOKINETICS PRINCIPLES FOR T.I.V.A

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Pharmacology tries to clarify the relationship between drug-dose and drug-effect.
Although it is obvious that an increase in dose will be followed by an increase in effect, the relationship is less than simple and is complicated by the time dependency of the process. Furthermore, most drug concentrations can be measured in blood or plasma this in contrast to continuous measurement of drug effect. It is for these reasons that dose- effect relationships are divided in pharmacokinetics (= how the body effects the drug) and pharmacodynamics(=how the drug effects the body).
We have to realise that this approach was useful for research but not for clinical use of intravenous anaesthesia. Moreover, the assumption that blood or plasma concentration can be directly and proportionally related to the drug-effect appeared to be not true when the blood or plasma concentration is changing.
The increasing use of pharmacokinetic models has introduced some changes both in research as well in the clinical application of intravenous anaesthesia.
In research, appropriate pharmacokinetic models may reduce the necessity to measure blood concentrations while in clinical applications computer controlled infused systems may help to introduce the blood or effect-site concentration as an important clinical parameter.
This chapter may help to explain some pharmacokinetic principles and their use and limitations in clinical practice.

ABSORPTION DISTRIBUTION AND ELIMINATION.

Three important processes determine the fait of the drug in the body. In intravenous anaesthesia where drug is directly infused, absorption is obviously not important.
Elimination is assumed to follow first order exponential processes.
Consider a single compartment that represents the body. The volume(V) of this compartment can be calculated by measuring the concentration (C) immediately after a known dose (D). (1)
In a one-compartment model the decrease in blood concentration is solely dependent on elimination of the drug.
The fractional volume of this compartment being eliminated of the drug is constant in time. This is called the clearance. In formula: (2)
Where Kel is the elimination constant with unit 1/time or time-1 .Therefore the unit of clearance is volume per time. As drug is disappearing from the central volume the concentration will decrease.
Therefore the change of concentration ( ) is dependent on the concentration itself: the higher the concentration the more drug will be eliminated.
Integration of this equation yields (3)
If the dose(D) and the compartment-volume(V) is known than the initial concentration can be calculated. If the elimination constant is also known then at any time after the initial dose the concentration can be calculated, provided that the drug elimination is a first order process and can be modelled with a one compartment model. One can think of this compartment as a tube filled with fluid and a hole in the bottom. The higher the liquid level the higher the pressure and the more liquid will flow out. This is shown in figure 1. Figure 1 The time required for halving the intial concentration is expressed as by applying the natural logarithme(ln) this yields to (4).
From equation 3 it will be clear that the logarithm of such an exponential function will give a linear function. This is shown in figure 2.
Figure 2 Decay in a one compartment model
Unfortunately very few drugs can be fitted using a single exponential function. This becomes visible when measured blood concentrations are plotted on a logarithmic scale. If fitting into a single exponential function was possible then the straight line could be drawn through the data points(figure 2). Because drug is also lost from the central blood compartment to other tissues (distribution) the initial drop in the blood concentration is faster after an initial bolus resulting in

a non linear change in decrease. By adding additional exponential functions the curve can be fitted again.
By definition is γ the smallest of the exponential constants. When expressed as a half-live (see equation 4) it is called the terminal elimination half live. Although it will give some idea on the duration of the elimination process it will be clear that this term has nothing to do with halving the concentration.
Just as the single exponential function can be represented by one compartment, the bi- or tri-exponential function can be represented by two or three compartments.
The parameters used in the compartment model (see table 1) are not the same as in equation 5 but they are mathematically related and can be converted. Figure 4 displays the 3-compartment models for Remifentanil and Fentanyl. These two drugs represents the extremes in the group of opioids usable for intravenous anaesthesia in terms of distribution and elimination.
Three compartment models of the example drugs used in the equations. Volumes and clearances are drawn in scale.
Blood concentration measurements can be fitted to a pharmacokinetic model but it is still not possible to relate the effect of a drug to the concentration of this model without constructing a separate compartment where drug-effect is supposed to take place. With fast changing concentration for example after a bolus the effect will lag behind on the increase of the concentration. The effect site compartment that will allow modelling of this delay is in a sense a 'patch' on the model. It does not have a volume like the other compartments because its function is not to be a part of the distribution process but merely to explain the delay between increase in concentration and increase in effect. Figure 5 tries to visualise the concept.
The exponential constant that determines the delay between central compartment is called the keo or if expressed as a halflive the thalf-keo6. This thalf keo usually is in the order of several minutes. This may not be of importance for example in the dosing of antibiotics, for intravenous anaesthesia this is a very important determinant for the development of dosing schemes as will be shown later on.
APPLYING PHARMACOKINETICS FOR DOSING INTRAVENOUS DRUGS
Although with pharmacokinetics it is possible to describe the concentration as de result of drug administration, their usefulness in the reverse of this process namely calculating the required dose to obtain a concentration is fairly limited without the help of a computer. This is probably the reason that practitioners work with receipts, intuition and experience, because they are unable to use for example the population pharmacokinetics that have been developed in the recent years for many intravenous drugs. There are however some very simple pharmacokinetic principles that may be usable in the initial estimation of required drug dosage. In addendum a two examples have been worked out with two completely different drugs: Remifentanil and Fentanil
The infusion required to obtain a given concentration at steady state
As pointed out above in a first order system the elimination is dependent on the concentration of the drug. If a infusion rate is started then initially the elimination of the drug is zero. As the concentration is increasing the elimination will increase until at a certain moment in time the input by drug infusion equals the output by elimination. The amount of drug being eliminated is concentration X volume X elimination constant.
An example of calculating this rate is given in the addendum: Example 1.
Where C¬¬ss is the concentration where this balance between input and output is established. This is true in a single compartment model, or in a multi-compartment model if the distribution to the other compartments has terminated: the moment where the concentration is equal in all compartments. The model is said to be in steady state.
Every drug that follows first order elimination will reach steady state at a certain point in time. The role of distribution in this process is that it will influence the shape of the curve and the moment when the steady state is achieved. Figure 6 shows the the concentration curves for some

anaesthetic drugs when the concentration is expressed as a percentage of the steady state concentration C¬¬ss.

First and zero order elimination

As explained above: in a first order process the elimination rate is a function of one concentration. If in contrary a fixed amount of drug is eliminated in time it is called a zero order process. The elimination process for most drugs is complex. The drug can leave the body by passive passage through biologic barriers as the guts, the biliary or renal system. Passive processes are concentration gradient dependent and therefore have first order characteristics by nature. Active processes usually require metabolisation by enzyme systems, which can be saturated or inhibited. When the amount of drug available for metabolisation exceeds the maximum capacity then a first order process will become a zero order process1. If drug input (infusion rate) exceeds the fixed maximum capacity then the concentration will not stabilise at an expected concentration but will increase indefinitely or stabilise at the equilibrium concentration of another slower elimination process. This is called accumulation. This rise in concentration should be discriminated from the 'normal' rise of concentration that is the effect of the distribution of the drug. Sometimes this kind of drug concentration increase is also mistakenly called accumulation.

Before drugs are released on the market they have been tested on the risks of accumulation. This risk is dependent on the potency of the drug and the drug response curve (this determines the amount of drug and the maximum and minimum concentration required for the effect) and the difference between this effective concentration and the maximum concentration that can be handled by the main metabolisation process. Drugs that are usually relative short acting may become extremely long acting in certain other patients that are ill, old or use drugs that inhibit the metabolisation system.

The Cytochrom P450 system and subsystems is an enzyme system that is involved in the metabolisation of many drugs. Unfortunately this system can be easily inhibitated and compromised.

With less potency, the drug concentration must be higher to achieve an effect.

Knowledge of such pharmacokinetic properties should influence the drug selection in clinical practice. Unfortunately this is not the case. Drug selection is usually based on tradition rather than common sense.

Another consideration in selecting drugs is the role of active metabolites. The pharmacokinetic properties of these metabolites may be completely different.

The loading bolus dose, time to peak effect

It will be clear that applying only a fixed infusion rate will not be sufficient in intravenous anesthesia. A too high infusion rate will decrease the time between infusion start and noticeable effect but will also create an effect overshoot. An infusion rate calculated to achieve an effect at steady state will create this effect after a too long period.

With pharmacokinetics the appropriate loading dose by bolus can be calculated. There are two classical approaches that are not sufficient for most drugs for IV anaesthesia:

1.The loading dose based on the central volume: this will give a to small bolus that will not bring the concentration in the effect compartment on the required level2. (Example 2).

2.The loading dose based on the distribution volume. Theoretically this is the amount of drug present in the body at steady state, unfortunately this amount has to pass the central compartment causing effect overshoot and side effects3. (Example 3).

As explained above, a fast change in the blood concentration will not be followed by a fast change in the effect. To model this delay between concentration and effect a hypothetical effect compartment has been added to the model. The delay is represented by a single parameter the Keo or Thalfkeo if expressed as a half-life. Drug concentration in this compartment is following the blood concetration but with a delay. After a bolus the bloodconcetration will increase steeply and decrease thereafter dependent on the distribution and elimination of the drug. The

concentration in the effect compartment will rise more slowly until effect concentration equals the decreasing blood concentration. Thereafter the blood concentration is lower than the effect concentration causing the effect concentration to decrease also. The moment where effect-concentration and blood-concentration cross is called the time to peak effect. This time not only dependent on the keo but also on distribution and for some drugs even elimination. Because these are all fixed parameters the overshoot fraction is initially (when there is no drug in the body) constant for all drugs. This fraction is listed for some drugs in table 2
With the help of this fraction the optimal loading dose now can be calculated that will give an effect site concentration without overshoot (Example 4).
With the principles explained here the two extremes of IV drug dosing can be calculated: the initial bolus and the final infusion for maintenance at steady state. Most drugs require in between a down stepping infusion scheme to compensate for drug that is distributed to other compartments in the body. Without the help of computer simulation programmes these infusion schemes cannot be calculated or estimated (Example 5). But even if a dosing regimen is applied that would give a theoretical constant effect site concentration than this approach would neglect the fact that not only every patient needs a different bloodconcentration but also every different surgical stimulus is associated with different requirements. Added to this the complexity of interaction between (intravenous) drugs used in anaesthesia4 and it will be clear that what without the help of special infusion devices like Target Controlled Infusion it will be impossible to use the advances in pharmacokinetic/pharmacodynamic modelling and research.
Drug decay, Context Sensitive Decrement time.
As long as no steady state has been reached the concentration decay after stopping drug administration is dependent on the amount of drug lost to other compartments by distribution and the elimination to the outside minus the drug gained from other compartments by redistribution. As time progresses the contribution of the distribution to the decay process diminishes and the contribution of redistribution increases. So before steady state the time to decrease to a certain concentration is dependent on the amount of drug present in the compartments which is dependent on the context in which the drugs are administered. If the concentration in the central compartment is kept constant for example with a computer controlled infusion : a so called Target Controlled Infusion, the decrement time to a percentage of this concentration can be calculated: the context sensitive decrement time7. This context sensitive decrement time is dependent on the duration of the infusion. This is graphically explained in figure 7.
Figure 7 The context sensitive decrement time and the relation to the infusion duration.
There are large differences between the drugs. Also the shape of the decay curve is different between drugs. Even a well recognised long acting opioid like Fentanyl has a fast initial decay caused by the relation between the volume of the central compartment, elimination and (re) distribution.
If only a 10% decrease is necessary at the end of the operation than even Fentanyl will behave like a short acting drug after prolonged administration. If a 10% decrease is sufficient is dependent on the steepness of the dose response curve in other words how much the concentration of adequate anaesthesia differs from the concentration that is save and adequate in the post operative period. This also depends on the interaction with other drugs. This is to illustrate that the separation between pharmacodynamics and pharmacokinetics is highly artificial for clinical practice. Figure 8 illustrates the complexity of drug dosing. In this example the effectsite concentration is maintained at 3 ng/ml using bolus of the same amount of drug. Notice that the interval of the bolus slowely increases over time.
Figure 8 The effect of bolus technique on decrement time.
Many anesthesiologists believe that using a bolus technique will prevent overdosing and increasing time to recovery. The example shows that this is only partially true. If the patient would regain the drive for adequate ventilation at 2 ng/ml then the influence of prolonged

admistration is minimal. If the required postoperative concentration is 1 ng/ml then the recovery period may take up to 4 hours after an anaesthetic procedure that lasted 1.5 hr.
The often published terminal elimination half live that only incorporates the elimination characteristic is therefore artificial and does not predict the moment of halving the concentration even not at steady state.
For example the terminal elimination half live of Fentanyl with given parameters in table 1 is 8hr. In reality the moment of halving the concentration starting from steady state is 'only' 4.55 hr. Figure 8..14 sow the context sensitive decrement times for different TIVA drugs. Please notice the differences in the time axis scaling.
Most drugs apart from remifentanil have large differences between 10% and 90% decrement. The properties described by these curves open possibilities. For example combinations of a short acting opioid like remifentanil with longer acting opioids such as fentanyl or sufentanil may provide optimal controllability intraoperatively and a reasonable starting plateau for postoperative pain control.

Table 1

	Vc(L)	V2(L)	V3(L)	C
Propofol	15.9	32.4	202	1
Midazolam	31.5	53	245	2
Thiopentone	5.53	33.7	152.1	1
Fentanyl	7.35	33.94	275.6	3
Alfentanil	7.77	12.0	10.5	2
Sufentanil	11.48	25.1	88.3	6
Remifentanil	5.122	9.9	5.4	1

Subject: 70 kg 40 yr Male

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Table 2

	peak plasma concentration/peak effect concentration(Fce)	Time to peak effect(mm:ss))
Propofol	2.7	4:00
Midazolam	1.75	13:10
Tiopentone	2.73	1:40
Fentanyl	8.5	3:40
Alfentanil	1.58	3:00
Sufentanil	5.67	6:00
Remifentanil	3.34	1:30

REFERENCES

1. D.R.Stanski, F.G.Mihm, M.H.Rosenthal and S.M.Kalman, Pharmacokinetics of high-dose thiopental used in cerebral resuscitation Anesthesiology 53: 169–71 (1980
2. R.N.Boyes, D.B.Scott, P.J.Jebson, M.J.Godman and D.G.Julian, Pharmacokinetics of lidocaine in man. Clin Pharmacol Ther; 12:105-15; (1971)
3. P.O.Mitenko and R.I.Olgilvie. Rapidly achieved plasma concentrations plateaus with observations on theophylinne kinetics. Clin Pharmacol Ther;13:329-35 (1971).
4. J.Vuyk, T.Lim, F.H.M. Engbers, A.G.Burm, A.A.Vletter and J.G.Bovill, The pharmacodynamic interaction of propofol and alfentanil during lower abdominal surgery in women, Anesthesiology 83(1): 8-22 (1995)
5. C.F. Minto, Th.W.Schnider, T.D.Egan, E.Youngs, H.J.Lemmens,P.L.Gambus, V.Billard, J.F.Hoke, K.H.Moore, D.J.Hermann, K.T.Muir, J.W.Mandema and S.L.Shafer. Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil: I. Model development, Anesthesiology 86: 10-23 (1997).
6. M. White, M.J.Schenkels and F.H.M.Engbers, Effect-site modelling of propofol using auditory evoked potentials, Br J Anaesth 82(3): 333-910 (1999).

7.M.A.Hughes, P.S.A.Glass and J.R.Jacobs, Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs. Anesthesiology;76:334-341 (1992).
8. J.F.Coetzee, J.B.Glen, C.A.Wium and L.Boshoff, Pharmacokinetic Model Selection for Target Controlled Infusions of Propofol. Anesthesiology 82: 1328-1345 (1995).
9. K. Zomorodi, A. Donner, J. Somma, J. Barr, R. Sladen, J. Ramsay, E. Geller, S.L. Shafer, Population pharmacokinetics of midazolam administered by target controlled infusion for sedation following coronary artery bypass grafting. Anesthesiology 89 (6): 1418-29 (1998).
10. D.R. Stanski and P.O.Maitre, Population pharmacokinetics and pharmacodynamics of thiopental:the effect of age revisited. Anesthesiology 72:412-422 (1990).
11. P.O.Maitre, S.Vozeh,J.Heykants, D.A. Thomson and D.R.Stanski, Population pharmacokinetics of alfentanil: the average dose-plasma concentration relationship and interindividual variability in patients, Anesthesiology 66:3-12 (1987).
12. S.L. Shafer, J.R. Varvel, Pharmacokinetics, pharmacodynamics, and rational opioid selection. Anesthesiology 74 (1): 53-63 (1991).
13. J.G. Bovill, P.S. Sebel, C.L. Blackburn, C.L. Oei-Lim, J.J. Heykants, The pharmacokinetics of sufentanil in surgical patients, Anesthesiology
*Tivatrainer Simulation software, Guttabv, Aerdenhout.
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