Gerry's Real World Guide to Pharmacokinetics & Other Things teaches the basic elements of pharmacokinetics of anesthetic drugs in the form of conversations between a curmudgeonly older anesthesiologist and an anesthesia resident as they administer anesthesia.

Gerry's Real World Guide to Pharmacokinetics & Other Things

GERRY'S REAL WORLD GUIDE TO PHARMACOKINETICS & OTHER THINGS

By

G. M. Woerlee MBBS (W. Aust), FRCA (Lond.)

Anesthesiologist

Rijnland Hospital, Leiderdorp, the Netherlands

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"Looks like we've got a problem with an anatomical variation here," said Doctor Hawley Crippen in an agitated tone redolent of increasing desperation, as he applied the diathermy at maximum power to yet another piece of bleeding tissue deep in the pelvis of a woman undergoing a hysterectomy. The scrub nurse turned her head aside to avoid the clouds of acrid smoke rising from the depths of the pelvis, while rolling her eyes upwards as if beseeching celestial assistance to stop the bleeding. But the bleeding did not stop, so she handed Crippen yet another haemostatic clamp. Bob and Gerry looked at each other. They knew the signs. This gynecologist had already recited the complete litany of standard complaints during the last hour, such as: "The light isn't any good. This scalpel is blunt. The blades of these scissors don't close properly. The patient isn't relaxed. These retractors have the wrong curve. You aren't using the retractor correctly! The anesthetic is too deep." Crippen was going to take a very long time to finish this hysterectomy. Luckily Mrs. Elmore was the last patient on his operating list, and luckily for her, she was under general anesthesia.

Gerry walked around the operating table, assessed the amount of blood on the drapes and floor, as well as checking the volume of blood in the suction pots. Finally, he looked critically into the abdominal wound, saw a sight evoking imagery of a smoldering middle ages plague pit, sighed loudly and wearily, and looked upwards as if also seeking succor from the heavens. But just as with the scrub nurse, the much-desired heavenly intervention failed to arrive. He turned to Bob, and said in a voice clearly able to be heard by Crippen, "Well Bob, it looks like we have some time on our hands, so it's time to stretch your mind. Let's talk about intravenous anesthetic induction agents. We used 250 mg Thiopental to induce anesthesia in Mrs. Elmore. There is nothing unusual about this woman, except that she enjoys smoking about 20 cigarettes, as well as drinking at least three glasses of wine a day. There was also nothing unusual about her reaction to this perfectly standard induction dose. So if we administered no other drugs, how long would you expect her to remain asleep with this dose of Thiopental?"

"About ten minutes," replied Bob, "and perhaps even less, because she drinks three glasses of wine a day, so her liver will metabolize Thiopental more rapidly than that of a person who doesn't drink as much. Accordingly she will eliminate Thiopental quicker and wake up more rapidly than normal." Bob was quite pleased with this answer. It was physiologically oriented, and really did correspond with reality, because smoking cigarettes and drinking alcohol really do induce drug metabolizing liver enzymes. This explanation was what he had heard from everyone else, and could not fail to satisfy Gerry's lust for physiologically oriented answers.

Gerry appeared to be in pain, demonstratively clutched the anesthetic machine for support, and groaned, "Ohhhh, just as I was beginning to think the light of understanding was beginning to dawn in your mind, you start uttering pseudo-physiological

gibberish you must have heard from other people. Sadly, this is a popular delusion, even among people who should know better." Gerry assumed his lesson-giving stance. "Now Bob, you are quite correct, ten minutes to waking up after such a dose of Thiopental is perfectly normal for just about all adults. But as for the rest of your answer—what you said is true enough, but totally irrelevant in this context. After all, what you are actually telling me with your answer is that this woman, and all other people awaken after about ten minutes because of rapid elimination of Thiopental from their bodies. If you believe that, then you probably still believe in pixies, and that a good flogging together with exorcism of demons is a modern treatment for epilepsy. I see I'm going to have to do some work to correct this delusion. So let's begin with the basics. Tell me, what is the plasma elimination half-life of Thiopental? This plasma elimination half-life is no fantasy, but a product of real measurements of real Thiopental plasma concentrations made in real people. Look it up if you want (Appendix)."

Bob began to look uncertain, hauled his notebook out of his pocket, quickly leafed through to the pharmacokinetic datasheet, and replied, "Er, about 13 hours..."

"Well Bob, as you know, Thiopental is transported by the blood to the brainstem, where it diffuses out of the capillaries into the tissues of the brainstem to induce unconsciousness. The brainstem does not metabolize Thiopental, which means that brainstem tissue Thiopental concentration is determined by the plasma Thiopental concentration, because it is blood that transports Thiopental to and from the brainstem. Now, the Thiopental elimination half-life you just told me is the plasma elimination half-life, and not the half-life for elimination of Thiopental from the body (Chapters 1 and 3). So Bob, you're actually trying to tell me that people wake up about ten minutes after receiving a perfectly normal induction dose of Thiopental because rapid hepatic metabolism reduces the plasma concentration of Thiopental to a level

below that needed to keep them asleep. We're talking here about a drug with a plasma elimination half-life of 13 hours! How much Thiopental do you think this patient, or any other patient for that matter, will have eliminated from their plasma after ten minutes?"

"Not much."

"Quite right. Practically nothing. Within the time this woman, or any other patient awakens after an induction dose of an intravenous anesthetic induction agent, the entire drug dose is still present within the body. Very little, to no plasma elimination will have occurred within ten minutes."

"Then I guess people awaken for some other reason'

"Very good Bob, it seems you're learnt your lesson about plasma elimination half-lives well. So why do you think people wake up so rapidly after Thiopental? Look at your table of kinetic and dynamic data again (Appendix)."

Bob looked in his notebook again, and thought a few seconds before replying, "I guess it must be related to the plasma distribution half-life of Thiopental. After all that's very short, only about 3.3 minutes. If I apply the same reasoning to the plasma distribution half-life as we did with the plasma elimination half-life (Table 1.1), then the process of distribution will be almost complete (87.5% complete), after three plasma distribution half-lives = 3 x 3.3 = 9.9 minutes, which is about ten minutes. So this means people awaken ten minutes after an induction dose of Thiopental because distribution of this drug throughout the body is complete."

"You're getting quite good at this," was Gerry's answer. "You're quite correct. People wake up after a hypnotic dose of an induction agent because of distribution of drug throughout the body. But what do you mean by distribution? How do you see the relationship between distribution, the falling asleep, the awakening of the patient, and plasma elimination of Thiopental in this case, and all other drugs in general?"

"All I see are these complicated formulae and parameters in most books, and the relationship of these to physiology is not all that obvious to me. But I'm sure you would love to explain it to me."

"Don't know about that last bit, but I'll explain it anyway. First the basics," upon which Gerry expounded the following list.

- Consider what happens when a single intravenous bolus of a drug is administered. The injected drug mixes with the venous blood returning to the heart, and eventually the heart pumps this blood into the aorta, which conducts it to the arteries going to each organ and tissue of the body.
- Some organs, such as the brain, liver, and kidneys receive a high percentage of the cardiac output. Other organs such as muscles, intestines, and skin receive a lower percentage of the cardiac output. And others, such as fat and bone receive an even lower percentage of the cardiac output (Table 3.1).
- This means that much of an injected dose of a drug will initially diffuse into the tissues of organs with a high blood flow, such as the brain, kidneys, and liver. However, at the same time the circulation also transports drug into the capillary beds of the very much larger mass of organs with a lower blood flow, and drug also diffuses into the tissues of these organs.
- The result of all this is that drug concentrations are initially higher in the tissues of organs with a high blood flow such as brain, liver, and kidneys, than in the very much larger bulk of tissues with a lower blood flow, such as skin, muscle, bones, and fat.
- Diffusion of drug into the much larger mass of lower blood flow tissues continues. Eventually the plasma concentrations of drug in the blood drop below those in tis-

sues with a high blood flow, such as the brain. The result is that drug diffuses out of the tissues of the brain, and all other organs with a high blood flow back into the circulation. Continuing transportation of drug by the circulation to all tissues of the body means that drug diffuses into these organs and tissues, so reducing plasma drug concentrations even further. In the case of Thiopental, the plasma Thiopental concentration eventually falls below that required to induce, or to sustain unconsciousness.

- This process is called distribution, and as you correctly said or guessed, the speed of this distribution is given by the distribution half-life.

"This explains why Mrs. Elmore and all other people wake up so quickly after a normal induction dose of Thiopental, as well as after normal doses of all other intravenous induction agents. Is this clear?" asked Gerry.

"Very," was the curt response.

"Don't think you're going to get away this easily," said Gerry. "Now it's time to introduce a few concepts vital to your pharmacokinetic and pharmacodynamic development."

"Uh oh," thought Bob. "This could turn out to be a long teaching session. And I'm still not quite awake after the party last night." But he knew how to play this game, so he said aloud, "Do you mean the relationship between pharmacokinetics, pharmacodynamics, and physiology?"

"Absolutely. These are core concepts integrating the seemingly different aspects of physiology, pharmacokinetics, and pharmacodynamics. Practical application of these basic ideas will give you the ability to use existing drugs much better than before, as well as the ability to predict the behavior of new drugs. So let's begin."

Table 3.1

Organ weight and blood flow

Organ	Organ blood flow (ml/100 g/min)	Organ weight (% body weight)
Kidneys	340	0.5
Liver	100	2
Heart	69	0.4
Brain	54	2.3
Skeletal muscle	10-12	43
Skin	11	7
Adipose tissue	2-7	16-36

A harried bleating rose from the other side of the sterile drape separating anesthesia territory from that of the gynecology, "I want some silence in MY operating theater." Crippen continued, "Get out, or be quiet. I'm trying to perform a difficult operation, and your cackling is so distracting that I can't work properly."

Gerry looked over the sterile sheet into gynecology territory and saw the eyes of one scrub nurse rolling, while the other nurse looked desperately above. But as before, no angelic forms descended from the heavens to miraculously cure the patient and whisk them all away from this place. Mrs Elmore, Doctor Crippen, and the scrub nurses would have to do it together with some help from the anesthesiologist. Gerry fleetingly wondered if you could get periorbital muscle cramps or spasms from excessive eyeball rolling as he exclaimed, "What a good idea Hawley! It's time to indulge my caffeine addiction after working so hard. I'm off to relax and drink a delicious cup of coffee. So I'll leave you to get on with it. Bob, ask Bert to take over here for a while, and join me in the coffee room. We'll continue this lesson there."

Compartmentalized & distributed

Shortly afterwards, Bob joined Gerry in the otherwise empty coffee room. After taking a sip of black coffee, Gerry pulled a scrap of paper out of a pocket, found a pen, and began talking. "After you inject a single dose of a drug into the body, the blood transports it to all parts of the body where it diffuses into the tissues and organs of all parts of the body. At the same time, some of the organs and tissues into which the injected drug diffuses remove the drug from the body, either by excretion of the unchanged drug, or by metabolism of the drug. This latter is the process of elimination. When you look at it like this, you can say the volume of the body into which the drug is injected and is eliminated is a single volume. This is called a one-compartment model, and can be drawn as in Figure 3.1. In this model the drug is distributed throughout the distribution volume labeled V_d The equation describing the plasma drug concentration with time after intravenous injection of a single bolus dose of a drug into the body is given below."

$$\mathbf{C = Be^{-\beta t}}$$

- C = plasma drug concentration.
- B = a drug-specific constant.
- e = a transcendental mathematical constant with the value 2.718.
- t = elapsed time after drug administration.
- β = a drug-specific constant whose value is given by: $\beta = 0.693/t_{1/2\beta}$, where $t_{1/2\beta}$ = plasma elimination half-life of the drug.

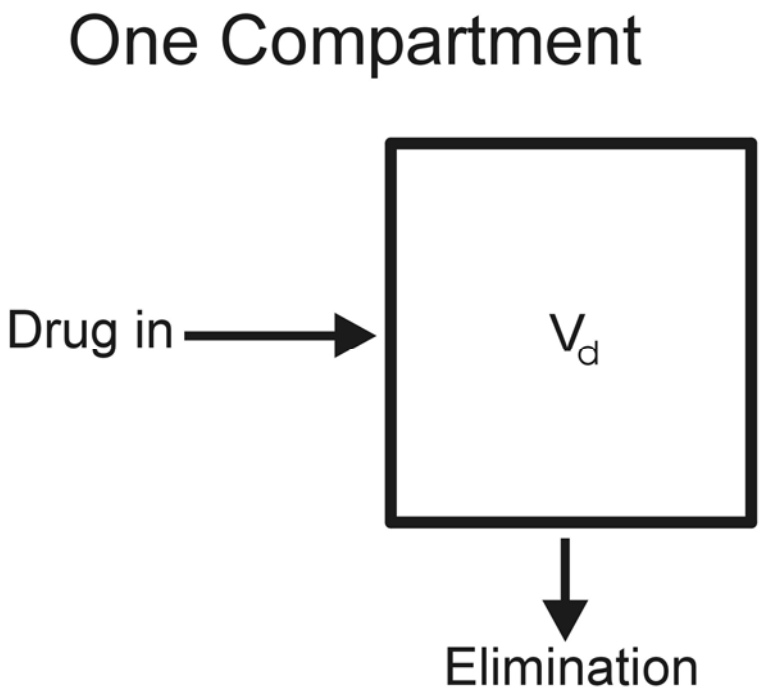

Figure 3.1: A single compartment pharmacokinetic model where the administered drug theoretically mixes within one compartment and is eliminated from that same compartment.

"All these things mean that the speed with which the plasma drug concentration declines is solely determined by the rate of elimination of the drug from the plasma, in this case the plasma elimination half-life. Do you follow me Bob?"

Bob looked vacantly at the equation. His only comment was, "Er...yes."

"I knew you would be excited. I always think it's wonderful how natural logarithms and transcendental numbers describe so many aspects of body function. Something mystical there. Makes

you think there is some sort of grand order in the universe. So let's proceed further."

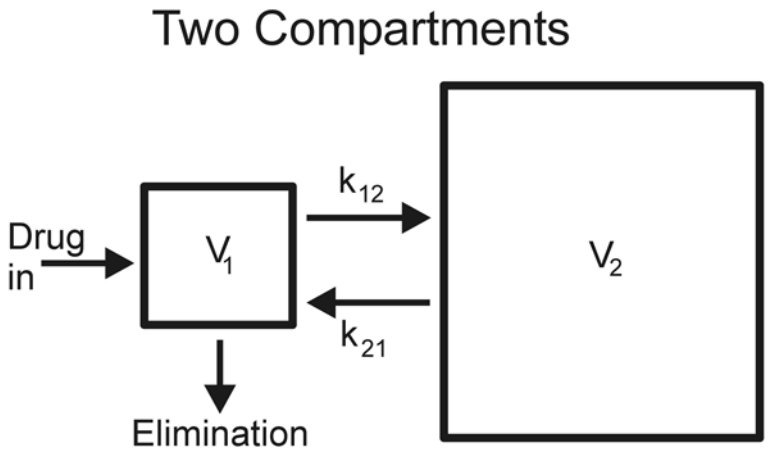

Figure 3.2: A two-compartment pharmacokinetic model where drug enters into, and is eliminated from a central compartment, as well as distributing into, and out of a second parallel peripheral compartment.

Totally disregarding the ever more vacant expression on the face of Bob, Gerry proceeded further. "As you know, the human body is not homogenous, so you must have realized immediately that this single compartment model of drug distribution is woefully inadequate. After all, the circulation transports intravenously administered drugs to body tissues of enormously variable composition. Some organs and tissues are mainly composed of fat, there is muscle tissue, there are all sorts of different organs with very diverse compositions, there are bones, and there is a lot of gooey stuff inside and between all these things. In addition to

differences between the compositions of different tissues, the blood flow per unit weight of each tissue and organ also differs considerably (Table 3.1). This latter explains why an intravenously administered drug initially mainly diffuses into organs with higher blood flows before a significant amount of the drug diffuses into the tissues of organs with lower blood flows. Accordingly, you can conceive of drugs being distributed to higher and lower blood flow tissues, or two functional compartments. This is the physiological basis of the two-compartment model of drug pharmacokinetics. One compartment is the so-called central compartment, which is composed of blood, perivascular extracellular space, and the tissues of high blood flow organs. The second compartment is called the peripheral, or deep compartment, and comprises the larger part of the body mass which is composed of lower blood flow organs and tissues. This can be drawn schematically as in Figure 3.2. According to this two-compartment model, the plasma drug concentration decreases according to the equation below after intravenous injection of a single bolus dose of a drug. However, the pharmacokinetic properties of many anesthetic drugs are often better described with models using more than two compartments, such as the popular three-compartment model shown by figure 3.3. Models with even more compartments exist, but their clinical relevance is somewhat dubious."

$$\mathbf{C = Ae^{-\alpha t} + Be^{-\beta t}}$$

- C = plasma drug concentration.
- A = a drug-specific constant.
- B = a drug-specific constant.
- e = a transcendental mathematical constant with the value 2.718.
- t = elapsed time after drug administration,

- α = a drug-specific constant whose value is given by: $\alpha = 0.693/t_{1/2\alpha}$, where $t_{1/2\alpha}$ = the plasma distribution half-life of the drug.
- β = a drug-specific constant whose value is given by: $\beta = 0.693/t_{1/2\beta}$, where $t_{1/2\beta}$ = plasma elimination half-life of the drug.

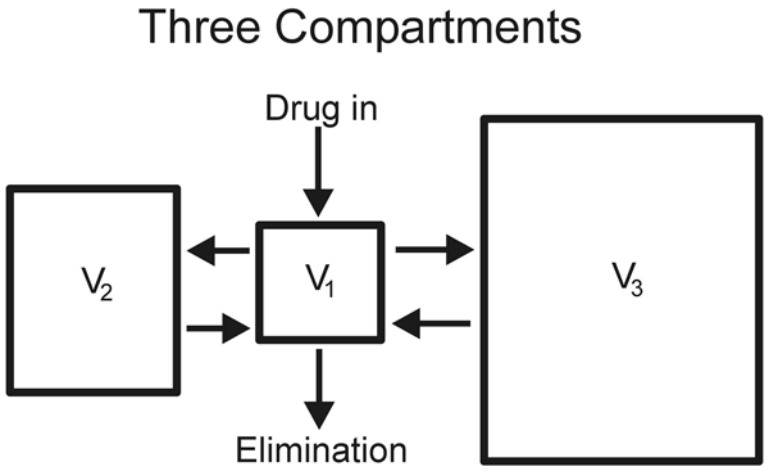

Figure 3.3: The most common form of a 3-compartment pharmacokinetic model. Drug enters into, and is eliminated from a central compartment (C_1), while at the same time distributing into, and out of two parallel peripheral compartments. One of these peripheral compartments (C_2) has an intermediate rate of exchange with the central compartment. The third, or deep peripheral compartment (C_3) has a much slower rate of drug exchange with the central compartment.

By now it was evident that a cup of strong coffee had not been sufficient to arouse Bob. This was totally lost on Gerry, who

regarded Bob's vacant staring at these models and equations as proof he was almost cataplexic with excitement. Bob made an almost superhuman effort to arouse himself to ask a pertinent question. "Why don't we simply use a physiological mathematical model instead of all these complicated equations and unphysiological models which don't really seem to relate all that well to the structure and function of the body?"

"To begin with, a physiological model requires a set of constants for each organ and tissue of the body. Obtaining such data for each drug means serial biopsies of each and every organ and tissue in the body after administration of a drug. This would have to be done for several persons for each drug for which we want to obtain data. However, there are surprisingly few people willing to subject themselves to being biopsied to death for the sake of pharmacokinetic data. Physiological models have been constructed using deficient animal tissue drug data, but because of these deficient data they are no more accurate than empirical multi-compartment pharmacokinetic models based only on blood data. After all, blood is a tissue easily obtained from humans, and you can do that repeatedly without harming the volunteers from whom pharmacokinetic data are obtained. This is why all pharmacokinetic data in current use are based upon data obtained from serial blood sampling.

Bob barely concealed a yawn, and interrupted, "Thrilling stuff, but what is the clinical relevance to me? Are these equations and concepts useful in my clinical practice?"

"Actually, all these multicompartment equations are totally useless in clinical practice. They are too complex to be useful, and no-one carries a pocket computer to calculate drug doses and regimens while administering anesthesia, because practical clinical experience always yields a better result. However, the concepts associated with these models and parameters yield extraordinarily useful practical insights. These insights make drug ad-

ministration predictable, give you understanding of how you use current drugs, how you can use them in new ways, how you can solve clinical problems related to drug use, as well as how you can use new drugs with which you have no experience at all. I'll explain how by beginning with the basics. To begin with, it is certainly true that the three-compartment model is a more accurate mathematical model for many anesthetic drugs, but as I said, is too complex for simple calculations. So I will restrict myself to the two-compartment model, which while not as accurate as the three-compartment model, is a model that is very easy to use without recourse to complicated calculations. Furthermore, it is a model providing valuable clinical insights, and calculations based on this model yield usable results that are sufficiently accurate for clinical practice. Here are the relevant parameters for the two compartment pharmacokinetic model."

- V_1 or V_c = central compartment volume in liters per kilogram body weight. I will use liters per kilogram body weight as the unit of volume in this book.
- V_2 = peripheral compartment volume, otherwise also known as the deep compartment volume, in liters per kilogram body weight.
- V_d = total volume of distribution in liters per kilogram body weight = $V_1 + V_2$. There are actually several other definitions of V_d too, but while these are relevant when considering detailed mathematical analysis, they are irrelevant in this book because no precise calculations are made. The interested reader is advised to consult relevant textbooks on pharmacokinetics.
- Distribution of drugs between higher flow and lower flow tissues is a reasonably rapid process. This process of distribution is characterized by a rapid decline of plasma drug concentrations in the period immediately after intra-

venous bolus administration. This period is called the distribution phase (Figure 3.4). The speed with which this process of distribution of drug throughout the body occurs is expressed by the plasma distribution half-life.

- $t_{1/2\alpha}$ = plasma distribution half-life in minutes. Throughout the rest of this book, I will use the term distribution half-life to actually mean the plasma distribution half-life. This is standard terminology for all pharmacokinetic data of anesthetic drugs.
- After the process of distribution slows down, a second phase characterized by a slower decline in plasma drug concentration becomes evident. This slower rate of decline of plasma drug concentration is due to diffusion of drug into volumes of tissue with a low blood flow, as well as being due to metabolism and elimination of the drug from the body. It is should be noted that these processes also begin immediately after drug administration, but their effects on the plasma drug concentration only become evident after the distribution phase is complete. This phase is called the elimination phase (Figure 3.4). Even so, the term elimination phase only means that drug is eliminated from the plasma—it does not mean that drug is eliminated from the body. The speed with which this process of drug elimination from the plasma occurs is given by the plasma elimination half-life.
- $t_{1/2\beta}$ = plasma elimination half-life in minutes. Throughout the rest of this book, I will use the term elimination half-life to actually mean the plasma elimination half-life. This is standard terminology for all pharmacokinetic data of anesthetic drugs. Again, it cannot be emphasized enough that the elimination half-life is not necessarily the speed with which a drug is eliminated from the body—it only

describes the rate of change of plasma drug concentration during the elimination phase.
- D = drug dose in milligrams per kilogram body weight.
- C = plasma drug concentration in milligrams/liter.
- 2-compartment pharmacokinetic data for many anesthetic drugs are listed in the appendix.

"So let's apply 2-compartment pharmacokinetic principles to answer the question I asked earlier. How long will it take for Mrs. Elmore to awaken after a normal 250 mg intravenous dose of Thiopental if nothing is done to keep her asleep? Look up the relevant parameters for me and we'll put them in a list (see data in Appendix)." Without any further ado, Gerry and Bob made the following list.

- Body weight of Mrs. Elmore = 50 kg.
- Dose of Thiopental = 250 mg = 5 mg/kg body weight.
- Thiopental is very fat-soluble which is why you can say that plasma and blood Thiopental concentrations are approximately equal.
- Volume of blood with which drug mixes before emerging into her aorta after the first passage through her heart =1.5 liters (see Chapter 2).
- V_c = 0.128 l/kg.
- V_d = 3.5 l/kg.
- $t_{1/2\alpha}$ = 3.3 min.
- $t_{1/2\beta}$ = 781 min = 13 hours.
- Plasma Thiopental concentration causing myocardial depression = 70 mg/1 (Table 2.1).
- Plasma Thiopental concentration causing hypnosis =10 mg/1 (Table 2.1).

Bob looked at the list of pharmacokinetic parameters and began to look dissatisfied, unhappy even. He interrupted. "There's something wrong with the volume of distribution. The V_d in this list is 3.5 l/kg. Now I know the specific gravity of the human body is almost equal to one kilogram per liter body volume (actually somewhere between 0.99 to 1.07 kg/1), which is why people can float more easily in seawater (specific gravity 1.03 kg/1), than in fresh water (specific gravity 1.0 kg/1). So a volume of distribution like this means that for each kilogram or liter of body volume, Thiopental occupies a volume of 3.5 liters! This can't be right! When I look at the tables of pharmacokinetic data in the appendix, I also see many other ridiculously improbable volumes of distribution. You talk about the mathematical phantasmagoria of pharmacokinetics—well this looks like a good example. How can such volumes be possible?"

"Bob, I'm a doctor, and I'm your mentor. Would I lie to you? So believe me when I say these volumes are true. I'll explain why very shortly. In the meantime, suspend your disbelief, and we can start doing some calculations for Mrs. Elmore," said Gerry, upon which he proceeded to make the following list.

- The volume of blood with which Thiopental mixes on the first passage through the heart and lungs is about 1.5 liters (Chapter 2). So Mrs. Elmore's initial aortic blood Thiopental concentration based upon the volume of blood with which drugs mix during their first passage through the heart and lungs = 250/1.5 = 167 mg/1. However, this is our physiologically based calculation.
- Based on 2-compartment pharmacokinetic data, the initial plasma Thiopental concentration in the V_c of Mrs. Elmore before distribution begins = Dose/V_c = 5/0.128 = 39 mg/1.

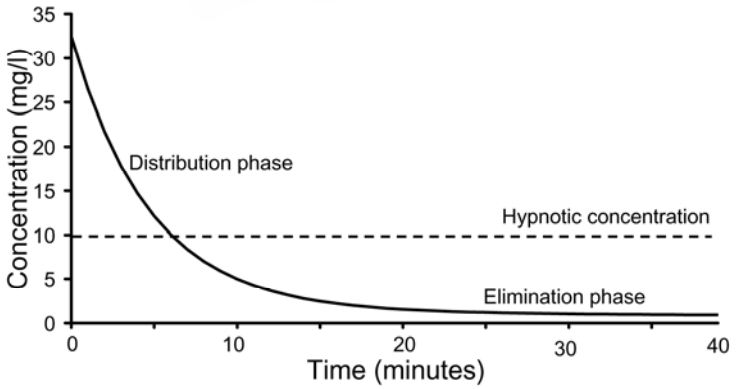

Figure 3.4: Plasma concentration-time curve of a 250 mg dose of Thiopental administered to an average adult. Note the initial rapid decline in plasma concentration due to drug distribution throughout the body, (distribution phase), and the subsequent slower decline of plasma drug concentration due to further distribution of drug within the body, as well as elimination, (elimination phase). The hypnotic concentration is the average plasma Thiopental concentration at which most people awaken.

Gerry continued, "These two initial Thiopental plasma concentrations are quite different. Even so, both initial plasma Thiopental concentrations describe why Mrs. Elmore fell asleep rapidly. But only the physiologically based model really explains the myocardial depression we also observed. Let's continue our exercise."

- Assuming no plasma drug elimination at ten minutes after Thiopental injection, then Mrs. Elmore's plasma Thiopental concentration after complete distribution = Dose/V_d = 5/3.5 = 1.43 mg/1. This is a reasonable assumption be-

cause is evident from the relationship between the distribution and elimination half-lives, that practically no Thiopental will have been eliminated from her plasma before completion of distribution.

- So after complete distribution throughout the volume of distribution, blood Thiopental concentration will have fallen far below that which is needed to cause hypnosis or myocardial depression. Therefore metabolism plays no role in awakening after a single induction dose of Thiopental. Instead, distribution of the drug throughout the body is the reason a person awakens after an induction dose of Thiopental.

Gerry continued. "The following list illustrates this point."

- After one distribution half-life = 3.3 minutes, plasma Thiopental concentration will have fallen from 39 mg/1 to about 20 mg/1.
- After two distribution half-lives = 6.6 minutes, plasma Thiopental concentration will have fallen from 20 mg/1 to about 10 mg/1.
- Accordingly it will take somewhere between two and three distribution half-lives for a person to awaken after such a dose of Thiopental, i.e. somewhere between 6.6 and 10 minutes.
- Figure 3.4 shows the calculated plasma Thiopental concentrations after intravenous bolus administration of 250 mg to an average patient such as Mrs. Elmore. This figure also shows the distribution and elimination phases.

"This is what I mean by insights," said Gerry. "When used in this manner, these parameters provide invaluable insights. This example is a beautiful demonstration of the fact that the mechan-

ism of termination of the hypnotic action of Thiopental is distribution, and not metabolism as popular superstition would have it. Think about it. You can perform this same type of calculation for all anesthetic induction agents and gain similar, or other valuable insights."

"I must admit this is certainly a useful method," was Bobs grudging reply. "I'll try it out on the other induction agents."

"You do that. But there is one last physiological insight I want to leave you with—the relationship of pharmacokinetic volumes to real physiological volumes. You were wondering how the pharmacokinetic volumes of some drugs could be larger than the volume of the body, or the other fluid compartment volumes of the body (Table 3.2). To begin with, there is one important consideration to keep in mind when looking at pharmacokinetic parameters of anesthetic drugs—unless otherwise stated, they are all based upon measurements of plasma drug concentrations. Looked at very simply, a pharmacokinetic volume is measured by administering a known dose of a drug, and then measuring its concentration in the volume into which it is administered. The drug concentration is given by the relationship below."

Concentration = Dose / Volume

Gerry continued, "Now in the case of measurements performed for pharmacokinetic purposes, we know the drug dose, and we can measure the drug concentration. This means that the unknown pharmacokinetic volume is given by the following relationship."

Volume = Dose / Concentration

"Are you following me so far Bob?" asked Gerry.

"Yes, even though you seem to be taking your time about it."

"First crawl then walk young man. Now, here it comes. Into which fluid do we administer anesthetic drugs, and in which fluid do we measure drug concentration?"

"We administer drugs intravenously, meaning we administer them into blood. As regards drug concentrations, you've repeatedly told me that all pharmacokinetic drug concentrations are plasma drug concentrations. So the drug concentrations measured for pharmacokinetic purposes are plasma drug concentrations," replied Bob.

Table 3.2

Volumes of different body compartments in "average" adults

Fluid compartment	**Men (l/kg)**	**Women (l/kg)**
Total Body Water	0.55	0.50
Extracellular Fluid Volume	0.25	0.20
Interstitial Fluid Volume	0.175	0.13
Blood Volume	0.075	0.07
Plasma Volume	0.045	0.04

"Very good Bob. You've learned that lesson well. And there you have the reason for these sometimes improbably large pharmacokinetic volumes. For example, if a drug is enormously fat soluble, and practically insoluble in something as watery as plasma, then most of it will be dissolved in adipose tissue and cell membranes, and these things are not in the plasma. In this situation, the measured plasma drug concentration would be much lower than you would expect if the drug were present only in the plasma. The same is also true for highly protein bound drugs. Such drugs not only bind to plasma proteins, but also bind to

proteins outside the plasma, which means that the measured plasma drug concentration is much lower than you would expect if the drug were only present in the plasma. I could go on and on with more examples, but the physiological volumes shown in Table 3.2 give an idea of the relationship of various pharmacokinetic volumes of drugs listed in the appendix to known body fluid compartment sizes. When combined with known physicochemical properties of drugs, this table also gives some insights into the reasons why pharmacokinetic volumes such as V_c and V_d are different to these physiological volumes. Here is also a short list of some physicochemical considerations."

- Fat-soluble drugs diffuse readily through phospholipid cell membranes into, and out of cells. This means they rapidly diffuse into erythrocytes, and diffuse rapidly through capillary endothelial cells into extravascular fluids and cells. Accordingly, such drugs have a reasonably rapid onset of action, as well as a V_c and a V_d very much larger than the plasma volume. Examples of such drugs are Thiopental and Propofol.
- Highly ionized, or fat-insoluble drugs cannot dissolve in phospholipid cell membranes, and because of this they cannot pass through cell membranes to enter into cells. This means they can only diffuse out of capillaries through transcapillary pores, as well as through the interstices between capillary endothelial cells, a fact slowing their passage into extravascular tissues. This explains why such drugs have a slower onset of action than fat-soluble drugs, and also explains why they have a V_c and a V_d not much larger than the extracellular fluid volume. Examples of such drugs are the highly ionized muscle relaxant drugs.

- Highly protein bound drugs have a V_c and V_d which is larger than the plasma volume, because they not only bind to plasma proteins, but also bind to proteins outside the plasma volume. Examples of such drugs are the opiates.

"This should make the relationship between pharmacokinetic volumes and physicochemical properties of drugs a little clearer. In the meantime, I do believe Bert would also like a cup of coffee. So it's back to the hell of the Crippen operating theater for you. I can't image he's finished yet. Give Hawley my regards, and thank him for his advice to leave the operating theater. I'm going to drink another cup of coffee."

Bob understood the lesson had come to an abrupt end. Feeling somewhat dazed with this information overload, he slowly stood up and shuffled back to the operating theater wondering why he always seemed to get this particular operating list.

Gerry's Real World Guide to Pharmacokinetics & Other Things teaches the basic elements of pharmacokinetics of anesthetic drugs in the form of conversations between a curmudgeonly older anesthesiologist and an anesthesia resident as they administer anesthesia.

Gerry's Real World Guide to Pharmacokinetics & Other Things