A DYNAMIC CONCEPT OF THE DISTRIBUTION OF THIOPENTAL IN THE HUMAN BODY

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THIOPENTAL passes freely through the "blood-brain barrier" and produces almost instantaneously narcosis, the intensity of which depends upon the quantity of drug in the brain.[1] This suggests that the course of thiopental anesthesia depends passively upon a competition between nervous and nonnervous tissues for the barbiturate. According to this view the onset of thiopental anesthesia after intravenous injection of the drug is rapid merely because the rate of cerebral blood flow is rapid and not because the central nervous system has a special affinity for thiopental. Recovery from anesthesia results from uptake of the drug by other tissues which have a high capacity for thiopental but are slowly perfused.

Many of the tissues which take up thiopental are difficult or impossible to obtain from living human beings, and the distribution of thiopental in the body can therefore be measured accurately only at autopsy. In place of direct measurements the quantity of this drug in various areas of the body can be predicted mathematically with surprising accuracy. This approach has the additional virtue of emphasizing the physical processes which cause the redistribution of thiopental in the body after its intravenous injection. The results obtained from a mathematical analysis of these processes are reported below.

In general these results support the idea of competition among body tissues for possession of thiopental. They disagree with previous beliefs in assigning a relatively unimportant role to body fat. While it appears true that adipose tissue ultimately contains most of the thiopental in the body, the rate at which fat abstracts the drug from blood is too slow to make this process clinically important under most conditions. Saturation of the *lean* body tissues with thiopental is probably responsible for the speed with which consciousness is regained after a single intravenous injection of the drug. For this reason the rate at which all these tissues are perfused with blood is important in determining the intensity and duration of narcosis following thiopental injection.

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METHODS

All of the data reported in this paper were secured by mathematical analysis, using conventional methods in some cases and a digital computer in others. Since the validity of such an approach depends entirely upon the correctness of certain necessary assumptions, results obtained mathematically have been compared with direct measurements of thiopental concentration in human tissue obtained during surgical operations. These results, which showed satisfactory agreement, have been published elsewhere[2] and will not be reviewed here.

The previous paper also describes the mathematical theory in detail. In brief, the mathematical analysis makes the following assumptions. It assumes that thiopental injected intravenously is mixed at once in a central blood pool of 1.5 liter volume and distributed immediately to the tissues. It is further assumed that blood or lymph leaving a tissue is in equilibrium with that tissue with respect to its thiopental concentration. It is assumed that neither metabolism nor excretion of the drug occurs during the period considered. Finally, it is assumed that thiopental injection does not alter tissue blood flow.

These assumptions can be represented mathematically as follows:

$$(1) \qquad Q = \sum_{i=1}^{n} \lambda_i M_i C_i$$

$$(2) \qquad \frac{dC_i}{dt} = \frac{F_i}{\lambda_i M_i} (C_A - C_i) \qquad i = 1, 2, \cdots n$$

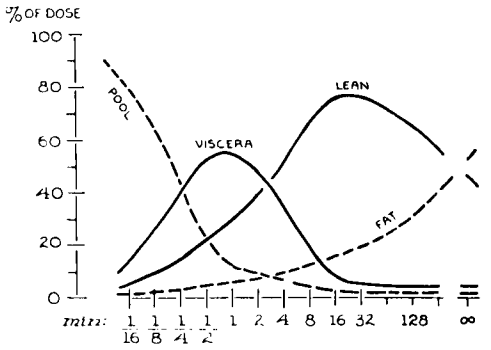

FIG. 1. Distribution of thiopental in different bodily tissues at various times after its intravenous injection. Time scale (in minutes) progresses geometrically. Final values at infinity (∞). Reprinted, by permission, from Price, H. L., and others, Clin. Pharmacol. & Therap. 1: 1960.

C_i equals the concentration of thiopental at any time in blood or lymph leaving any area (i), C_A is the concentration in arterial blood, F is the rate of blood and lymph flow through these areas, M is their mass, λ is the concentration ratio (tissue/blood) of thiopental in these areas at equilibrium, and Q is the dose of thiopental. Since the equations are simultaneous, their solution yields an estimate of the concentration of thiopental in any tissue at any time after its injection. Solutions of these equations and other calculations comprise this paper.*

Although mathematical formulation is needed to permit solution of the equations, their meanings can also be simply stated. Equation 1 says that the quantity of thiopental in the body at any time is the same as the amount injected. The second equation states that the rate at which the quantity of thiopental in any area is changing is equal to the flow rate through the area times the arteriovenous concentration difference.

RESULTS AND DISCUSSION

Distribution of thiopental in the human body after a single intravenous injection

Figure 1 indicates the fate of a single dose of thiopental derived from solution of equations 1 and 2 (Methods) using the data of table 1.

The rapidly-perfused viscera (heart, kidney, splanchnic area, and central nervous system) have similar flow rates and affinities for thiopental and have therefore been treated as a unit in this analysis. In figure 1 the quantity of thiopental calculated to be present in the viscera at various times after injection has been compared with that simultaneously present in the central blood pool, the fat, and the poorly-perfused aqueous tissues (muscle, connective tissue, skeleton, and poorly-perfused viscera).

Thiopental added to the central pool is rapidly lost, primarily as the result of uptake by the rapidly-perfused viscera. For example, at one minute after injection these viscera contain 55 per cent of the dose although their combined mass is only 6 per cent of the body weight. This effect is attributable to the high rate of blood flow in these tissues and to the fact that thiopental enters them without hindrance. It is a short step from this finding to the prediction that the narcotic effect of a single intravenous dose of thiopental should reach a maximum roughly one minute after its injection. This prediction is borne out by studies of relative EEG level at intervals after injection of thiopental.[1]

Five minutes after the time of maximal content the viscera contain only half this amount. This results from the uptake of thiopental by lean body tissues. Fat exerts an insignificant effect during this interval.

TABLE 1

CHARACTERISTICS OF HUMAN BODY COMPARTMENTS
(Data from References 3–10)

Area	Blood Flow (ml./minute)	Mass (kg.)	Ratio of Equilibrium Concentrations of Thiopental (Tissue/Blood)
1 Central blood pool	5400	1.5	1.0
2 Central nervous system	800	1.3	1.4
3 Myocardium	250	0.3	1.2
4 Portal circulation	1700	2.5	1.9
5 Renal	1000	0.3	2.0
6 Other aqueous tissue	1400	55.0	1.5
7 Fat	250	10.0	11.0
Total	5400	70.9	2.9

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* We wish to thank M. L. Rockoff, P. J. Kovnat, and J. N. Safer, Computer Center, University of Pennsylvania, for aid in programming these computations.

At thirty minutes after the injection rapidly-perfused viscera contain only 5 per cent of the injected dose, fat 18 per cent, and poorly-perfused aqueous tissues 75 per cent. In other words, the vital organs now have given up 91 per cent of their peak content, or half the total dose, but fat has gained less than one-quarter of this, while the poorly-perfused aqueous tissues have gained more than three-quarters. This is equivalent to saying that depletion of the viscera depends primarily upon competition with the lean body tissues for possession of thiopental. Fat plays a minor role.

Assuming that metabolism and excretion are unimportant, fat will contain 55 to 60 per cent of the injected dose, the lean tissues 35 to 40 per cent, and the well-perfused viscera 4 per cent of the dose at 8–10 hours after injection (when the redistribution of thiopental is essentially complete). This indicates that during the period from ½ to 8 or 10 hours after injection body fat acquires most of the thiopental injected, but it does not acquire the drug from the viscera. These organs have already lost 91 per cent of their peak content in the first half hour after injection. During the interval from 30 minutes to 8 to 10 hours they lose only an additional 2 per cent. Fat acquires thiopental during this period almost entirely from the lean body tissues.

Certain implications of this are clear at once. If body fat is not predominantly responsible for depleting the viscera of thiopental, then the proportion of the body which is fat should not influence the rate of emergence from anesthesia after injection of a single dose of thiopental. This does not mean that obesity will fail to increase the rate at which the viscera are depleted. A primary increase in body mass from *any* cause (*e.g.* addition of muscle) would have nearly the same effect. It is not that fat fails to take up thiopental prior to one-half hour after injection of the drug; it fails to *concentrate* it to an important degree until hours after the drug is given. This follows because fat, although it extracts thiopental almost completely from blood perfusing it, does not receive a sufficient blood supply to make its affinity for the drug apparent during a period as long as 2–3 hours after an injection of the drug.

The minor significance of body fat in controlling the rate of emergence from anesthesia following thiopental injection has been dealt with at length in another publication.[2] We wish to emphasize now the relative importance of the body mass, and therefore of hemodynamic factors, in controlling the quantity of thiopental in the central nervous system. Clearly, unconsciousness results after thiopental injection because the drug enters the brain. It is not as clear that thiopental reaches the brain in high concentration because it has inferior access to other areas which receive less blood per unit time. Our analysis indicates that rapidly-perfused areas receive thiopental early and in high concentration, but lose it later to indifferent tissues (anesthetically speaking) because the latter have far greater mass than the viscera and equal or greater "claim" to the drug (expressed as tissue/blood concentrations at equilibrium). If this is true, as it appears to be, the rate of perfusion of the indifferent body tissues can have more importance than any other factor in determining the duration of narcosis after thiopental injection. This idea, which is new, is explored below.

Role of hemodynamic balance in determining the concentration of thiopental in the central nervous system and in blood

The importance of the poorly-perfused aqueous tissues in controlling the concentration of thiopental in the central nervous system can be illustrated by considering the effects of various situations which affect the circulation. In hemorrhagic shock, for instance, cerebral blood flow is apparently well maintained so long as hypotension is not severe.[11] In contrast, vasoconstriction occurs in the skin, skeletal muscles, splanchnic area, kidneys, and probably even in fat and connective tissue. Cardiac output is reduced and cerebral blood flow represents a higher fraction of the cardiac output than it did previously. It is reasonable to expect the fraction of the dose of thiopental received by the central nervous system of such an individual to be abnormally high and its removal to be slow. Figure 2 illustrates the calculated result of a hemorrhage which reduced the cardiac output by 40 per cent. The normal blood flows have

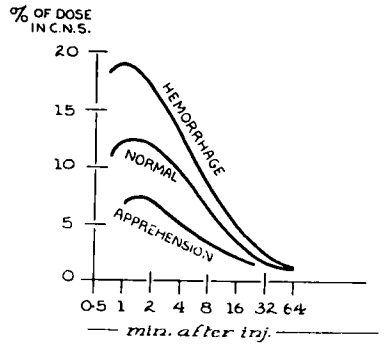

FIG. 2. Percentage of a dose of thiopental estimated to be present in the central nervous system under normal conditions, and in the presence of hemorrhage or apprehension.

been assumed to be reduced equally except in the central nervous system and myocardium, where flow is assumed to be unchanged, and in the kidneys where estimated flow is reduced to 25 per cent of normal. The effect of these changes is to increase the fraction of the dose of thiopental contained within the central nervous system during the first hour after its injection.

Under conditions where blood flow to the aqueous tissues is increased (*e.g.* thyrotoxicosis, apprehension, pregnancy) this effect would be reversed, and a smaller fraction of the injected dose would appear initially in the central nervous system. This is also illustrated in figure 2. These findings offer a rational basis for the clinical impression that after hemorrhage exceptionally small doses of thiopental are effective, while the opposite is true in the presence of apprehension.

It was noted in the previous study that the concentration of thiopental in arterial blood after its intravenous injection was initially lower and later higher than theory predicted.[2] These discrepancies could result from an initially high blood flow rate per unit mass of body (resulting from apprehension) with later reduction below normal (resulting from actions of thiopental).

Redistribution of thiopental following termination of an infusion

The foregoing analysis has dealt only with the fate of thiopental following a single intravenous injection. Since the drug is frequently given by infusion or in repeated small doses this analysis has been expanded to include the rate at which thiopental leaves the central nervous system after termination of thiopental infusions of varying length.

The total capacity of the body for thiopental $(\sum_{i=1}^{i=n} \lambda_i M_i)$ can (table 1) be represented by a quantity of blood approximately equal to three times the body weight. Of this, less than 1 per cent consists of the blood in the central pool, 3–4 per cent comprises the viscera (central nervous system, liver, gut, kidney, heart), 41 per cent the remaining aqueous tissue, and 55 per cent body fat. Before any drug has been given, the dilution capacity of the body is equivalent to that represented by a volume over a hundred times that of the central nervous system. If a single dose of thiopental is given and if none is metabolized, the central nervous system will consequently contain less than 1 per cent of the dose when equilibrium is reached. The results of infusion at a rate which maintains the thiopental concentration in blood at a constant level are different. As infusion continues, more and more tissues approach equilibrium with the thiopental in blood. Since the central nervous system equilibrates rapidly, and thus soon ceases to take up thiopental, the result of continued infusion is that an increasing proportion of the dose accumulates in nonnervous tissues. As a consequence, the capacity of the body to dilute the thiopental present in blood and thus to remove it from the central nervous system is gradually lost.

Figure 3 shows this graphically, using the data of table 1, and the equation (3): $C_i = \lambda_i C_A (1 - e^{-kt})$ to estimate the tissue content of thiopental at various times after beginning the infusion. This equation is derived from the assumptions detailed in the methods, with the additional assumption that the thiopental concentration in arterial blood remains constant during the period of infusion. C_i again represents the concentration of thiopental in blood leaving any particular tissue, C_A is that in arterial blood, e is the Napierian base (2.718), k is equal to blood flow per unit time divided by the tissue mass times the tissue affinity for thiopental $(F_i/M_i\lambda_i)$, and t is time in minutes. The conditions calculated

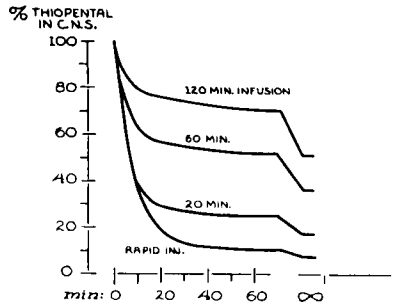

FIG. 3. Calculated rates at which the central nervous system can give up thiopental at the end of intravenous infusions of varying length. Data for the first hour after discontinuing infusion and at infinite time.

to result from infusions of varying length have been substituted into equations 1 and 2. Solutions of these functions now describe the result of terminating the infusion. Figure 3 shows the rate of depletion of the central nervous system after termination of infusions lasting 120, 60, 20, and 0 (single injection) minutes. The central nervous system concentration of thiopental at the instant of discontinuing the infusion has been set equal to 100 per cent. The figure suggests that thiopental is "short-acting" only after anesthesia of brief duration. After anesthesia lasting more than one or two hours, the rate at which the central nervous system can be depleted of thiopental by virtue of its redistribution to nonnervous tissue is so slow that the recovery of consciousness must depend upon other causes. Other causes could include metabolism or excretion of the drug and the rapid development of tolerance to its actions.[12] If metabolism and excretion are as unimportant as has been claimed, the body mechanisms which confer tolerance to the drug are of considerable interest and importance.

SUMMARY AND CONCLUSIONS

A mathematical analysis of the kinetics of thiopental redistribution in the human body has been presented. This method has been validated by the direct measurement of thiopental concentration in human tissue.

The indicated sequence of events after intravenous injection of a single dose of thiopental follows. Within one minute after injection the blood has given up ninety per cent of the dose, principally to the central nervous system, heart, liver, and other rapidly-perfused viscera. During the ensuing half hour these viscera are in turn depleted of the drug as the result of further redistribution. Of the thiopental given up by rapidly perfused viscera, the other aqueous tissues of the body acquire nearly 80 per cent. The remainder enters fat. The rate at which the central nervous system loses thiopental therefore depends predominantly on the rate at which the poorly-perfused aqueous tissues of the body gain it. This in turn depends on the rate at which the body is perfused with blood. Fat is so slowly perfused that it cannot begin to concentrate thiopental to an important degree until after the central nervous system has already lost over 90 per cent of its peak content.

After an intravenous infusion of thiopental lasting over an hour, in contrast, the lean body tissues are saturated with thiopental and cannot aid in depleting the central nervous system of the drug after the infusion is discontinued. Sufficient dilution capacity remains in the fat to deplete the central nervous system by about 50 per cent. This process is not complete until eight hours after discontinuing the infusion. For these reasons rapid emergence from thiopental anesthesia is unlikely after an infusion of long duration and the fact that consciousness is ever regained indicates that other causes beside fat uptake are important in limiting the duration of anesthesia under these conditions.

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ENERGY EXPENDITURE Indirect calorimetry was used to measure the energy output of 11 doctors, 4 nurses and one attendant during 22 operations. Energy expenditure for most tasks fell in a range of light to moderate work, requiring less than 2.5 calories per minute. The energy expenditure for circulating nurses and surgeons doing orthopedic procedures fell into the class of hard work requiring more than 2.5 calories per minute. (*Levey, S., and others: Energy Expenditure of Surgeons, Nurses and Anesthesiologists During Operative Procedures, Surgery 46: 529 (Sept.) 1959.*)

INFECTION PREVENTION Operating room scrub suits should not be worn in other parts of the hospital if the wearer plans to re-enter the operating suite. Conductive shoes should not be worn outside the operating suite and must be kept scrupulously clean if they are not to become breeding places for bacteria. (*Ginsberg, F.: Precise Procedures Area Must to Combat Infection Problems, Mod. Hosp. 93: 106 (July) 1959.*)