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A Simplified Digital Method for Predicting Anesthetic Uptake and Distribution

ALAN L. COWLES, HAROLD H. BORGSTEDT and ALASTAIR J. GILLIES

Departments of Pharmacology and Toxicology and of Anesthesiology, University of Rochester School of Medicine and Dentistry, Rochester, New York 14642, U.S.A.

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Abstract—A simple, yet flexible and accurate method of calculating anesthetic uptake and distribution is presented. The basic program is described with modifications which allow calculations of anesthetic uptake and distribution under a wide variety of biological conditions. Data are included for making predictions of anesthetic uptake and distribution in man and also examples to illustrate some predictions which may be made.

Anesthetic, inhalation Capacitance, anesthetic Compartmental model Computer, digital Concentration effect Conductance, anesthetic Diethyl ether Optimal inspired concentration Second gas effect Uptake and distribution

BECAUSE of the importance of the uptake and distribution of inhalation anesthetics in determining how an anesthetic should be administered, several methods of computing anesthetic uptake and distribution have been devised. Resistor-capacitor and operational amplifier analogs[1–12] have most commonly been used. These are convenient for illustrating anesthetic uptake and distribution in cases where rather simple models are used and where respiration, cardiac output and the distribution of blood flow do not change. Predictions of anesthetic uptake and distribution using more complex models or under changing conditions, however, require complex analog circuits with dozens of multipliers and amplifiers[11,12] or changes in the circuit which are very difficult to make during the course of predictions. The accuracy of electric analogs is further limited by the accuracy of their components, and is also affected by such problems as capacitor leakage, finite gain and amplifier drift.

Because of these difficulties, methods have been devised for predicting anesthetic uptake and distribution using digital computers. They provide greater flexibility coupled with greater accuracy than is available with any of the analog computers. The only method which has appeared in the literature to date is that of EGER.[13] His method uses a bewildering array of equations involving 35 variables, some of which may take on multiple subscripts. This paper presents a simplified method for predicting anesthetic uptake and distribution using digital computers, and gives suitable data for making predictions in man. Despite the simplicity of the method, flexibility and accuracy are not compromised.

THEORY

The mathematical model used to predict the uptake and distribution of inhalation anesthetics is based on the following assumptions:

(1) The partial pressure of a dissolved anesthetic gas is proportional to its concentration in its solvent (Henry's Law).

(2) For purposes of calculation, ventilation can be assumed to be continuous.

(3) The anesthetic contained in alveolar gas, lung tissue and pulmonary capillary blood is in continuous equilibrium.

(4) Circulation time from the lungs to the tissues is insignificant.

(5) Inhalation anesthetics diffuse passively through cells and cell membranes.

(6) Tissues are so finely perfused that venous blood leaving them is in equilibrium with the tissue.

(7) Tissue volumes and rates of blood flow are constant and within normal limits.

(8) With the exceptions of trichloroethylene and methoxyflurane, inhalation anesthetics are not metabolized rapidly enough to significantly affect their uptake and distribution.

(9) Diffusion of anesthetics between tissues and through the skin is not significant.

These assumptions have been discussed in detail by several authors and appear to be reasonable.[1,14–16] Modifications of the basic computer programs which may be used to account for modifications of these assumptions are discussed later.

Calculations of anesthetic uptake are based on a compartmentalized body model. A compartment is considered to be any tissue or group of tissues within which the anesthetic is in continuous equilibrium. An example is a skeletal muscle, in which perfusion is sufficiently uniform so that the anesthetic can be considered to be uniformly distributed. Another example is the alveolar air, lung tissue and arterial blood compartment (hereafter called the "lung-blood" compartment) in which the anesthetic is so rapidly distributed that alveolar air, lung tissue and arterial blood are in continuous equilibrium. Perfusion is nowhere perfectly uniform, and complete and instantaneous equilibrium never actually exists, but, for the purposes of calculation, some grouping into compartments of tissues which are in nearly complete equilibrium is necessary and justified.

Most tissue compartments are perfused by blood; the lung-blood compartment is ventilated by air. These fluids (blood and air) have an ability to carry inhalation anesthetic which is dependent on their rates of flow and the solubility of the anesthetic in them. We define the *conductance* of a fluid carrying inhalation anesthetic to be the ability of the fluid to deliver anesthetic agent across a partial pressure gradient. With partial pressure expressed in atmospheres, *conductance* is

$$\text{Cond}_i = \frac{\mathrm{d}V_i}{\mathrm{d}t}\frac{1}{\Delta P_i}. \tag{1}$$

The symbols are defined in Table 1.

Each tissue compartment is able to contain anesthetic at any partial pressure. Its ability is dependent on the volume of the tissue compartment and the solubility of the anesthetic in the tissue. We define the *capacitance* of a tissue compartment to be the ability of the tissue compartment to hold anesthetic at any given partial pressure. With partial pressure expressed in atmospheres, *capacitance* is

$$\text{Cap}_i = \frac{V_i}{P_i}. \tag{2}$$

TABLE 1. SYMBOLS

A	alveolar
art	arterial
bl	blood
C_i	concentration of anesthetic in the ith tissue compartment
Cap_i	capacitance of the ith tissue compartment ($1 \cdot \text{atm}^{-1}$)
Cond_i	conductance to the ith tissue compartment ($1 \cdot \text{atm}^{-1} \cdot \text{min}^{-1}$)
i	ith tissue compartment
j	jth component of the ith tissue compartment
P_i	partial pressure of anesthetic in the ith tissue compartment (atm)
P_o	standard pressure (1.0 atm)
$\dot{Q}_i$	rate of flow of air or blood to the ith tissue compartment ($1 \cdot \text{min}^{-1}$)
lt	lung tissue
t	time (min)
T_0	standard temperature, 273.2°K
T_i	temperature of the ith tissue, normally 310.2°K
ts	tissue
V_i	volume of anesthetic in the ith tissue compartment (1)
Vol_j	volume of the jth component of the ith tissue compartment (1)
Δ	change
λ	blood:gas or tissue:gas partition coefficient

The following symbols are used in the fortran program:

CAP1, CAP2, CAP3, CAP4	capacitances of the 1st–4th tissue compartments ($1 \cdot \text{atm}^{-1}$)
COND1, COND2, COND3, COND4	conductances of the 1st–4th tissue compartments ($1 \cdot \text{atm}^{-1} \cdot \text{min}^{-1}$)
DLT	time interval, delta t (min)
DVDTPT	rate at which anesthetic enters the patient ($1 \cdot \text{min}^{-1}$)
DVDT1, DVDT2, DVDT3, DVDT4	rate at which anesthetic accumulates in compartments 1–4 ($1 \cdot \text{min}^{-1}$)
PINSP	inspired anesthetic partial pressure (atm)
P1, P2, P3, P4	partial pressures of anesthetic in compartments 1–4 (atm)
TME	time (min)

Until these general definitions are converted into biologic terms such as alveolar ventilation, blood flow, tissue volume and anesthetic solubility, they cannot be applied to real problems. This conversion may be accomplished in the following manner: The rate at which anesthetic is brought to the compartment by a fluid is equal to the rate at which the fluid is flowing, multiplied by the difference between the concentration of anesthetic in the fluid entering the tissue and the concentration in the fluid leaving the tissue; this is the Fick Principle

$$\frac{dV_i}{dt} = \dot{Q}_i \Delta C_i. \tag{3}$$

Concentration is expressed as the volume of anesthetic, as a pure gas, at standard temperature and pressure (P_0, T_0) divided by its volume of distribution. It is necessary to convert concentration to partial pressure. This may be done using Henry's Law, which relates the concentration, partial pressure and partition coefficient of the anesthetic. The partition coefficient (λ_i) is the ratio of the concentrations in the fluid and in a gas phase with which it would be in equilibrium.

$$C_i = \frac{P_i \lambda_i T_0}{P_o T_i}. \tag{4}$$

Combining equations (3) and (4) we may convert the concentration gradients to partial pressure gradients:

$$\frac{dV_i}{dt} = \dot{Q}_i \Delta P_i \frac{\lambda_i T_0}{P_0 T_i}. \tag{5}$$

Combining equation (5) with the definition of conductance (equation 1), we may show that the conductance is equal to the rate of flow of the fluid multiplied by its partition coefficient and the factor, T_0/P_0T_i

$$\text{Cond}_i = \dot{Q}_i \lambda_i \frac{T_0}{P_0 T_i}. \tag{6}$$

In the case of blood perfusing a tissue, the conductance is equal to the rate of blood flow multiplied by the blood:gas partition coefficient and the factor, T_0/P_0T_i. In the case of the alveolar gas ventilating the lungs, the conductance is the rate of alveolar ventilation multiplied by the factor, T_0/P_0T_i. The gas:gas partition coefficient is equal to 1.0, by definition.

Conversion of the definition of capacitance into biologic terms is accomplished in the following manner: The volume of anesthetic contained in the compartment is equal to the sum of the volumes of anesthetic contained in each of its components. The components (j) are numbered 1, 2, 3, . . . , n.

$$V_i = \sum_{j=1}^{n} V_j. \tag{7}$$

The volume of anesthetic contained in any component is equal to the product of the volume of the component and the concentration of anesthetic in that component

$$V_j = \text{Vol}_i C_j. \tag{8}$$

Combining equations (7) and (8) we obtain

$$V_i = \sum_{j=1}^{n} \text{Vol}_j C_j. \tag{9}$$

Changing concentration to partial pressure using Henry's Law (equation 4) we obtain

$$V_i = \frac{T_0}{P_0 T_i} \sum_{j=1}^{n} \text{Vol}_j P_j \lambda_j. \tag{10}$$

The components of a tissue compartment are in equilibrium with each other, by definition. Therefore, their partial pressures must be equal

$$P_i = P_{j, j=1,n}. \tag{11}$$

Combining equations (10) and (11), we obtain:

$$V_i = \frac{P_i T_0}{P_0 T_i} \sum_{j=1}^{n} \text{Vol}_j \lambda_j. \tag{12}$$

Using the definition of capacitance (equation 2) we may show that the capacitance of a tissue compartment is equal to the sum of the products of the volumes of its components and their respective partition coefficients, multiplied by T_0/P_0T_i

$$\text{Cap}_i = \frac{T_0}{P_0\,T_i}\sum_{j=1}^{n}\text{Vol}_j\,\lambda_j. \tag{13}$$

KETY[14] has shown that most tissues are so finely perfused that they can be considered to be in equilibrium with their venous blood. Therefore the venous blood contained within a tissue compartment must be considered to be a part of that tissue compartment. For a single tissue compartment, other than the lung-blood compartment, the capacitance is

$$\text{Cap}_t = \frac{T_0}{P_0\,T_i}(\text{Vol}_{ts}\,\lambda_{ts} + \text{Vol}_{bl}\,\lambda_{bl}). \tag{14}$$

Alveolar air, lung tissue and arterial blood are also in equilibrium. For the lung-blood compartment, the capacitance is

$$\text{Cap}_{L-bl} = \frac{T_0}{P_0\,T_i}(\text{Vol}_A + \text{Vol}_{lt}\,\lambda_{lt} + \text{Vol}_{art}\,\lambda_{bl}). \tag{15}$$

These equations are sufficient for the prediction of anesthetic uptake and distribution.

Tissues having the same conductance:capacitance ratio will always be in equilibrium with each other, and can be grouped in the same tissue compartment. Because of the practical difficulties involved in having a large number of tissue compartments, most authors have used four. MAPLESON[1] has provided convincing evidence for the grouping of tissues into three compartments, in addition to the lung-blood compartment, as follows: (1) a *visceral* compartment, consisting of adrenals, kidneys, thyroid, heart, brain, spinal cord, splanchnic tissue, red marrow, small visceral organs and tissues; (2) a *lean tissue* compartment, consisting of skin, subcutaneous tissue, muscle and bladder; and (3) a *fatty tissue* compartment, consisting of yellow marrow and fat. Some authors add a non-perfused compartment, consisting of skeleton, gastrointestinal fill and teeth, but because these tissues do not take up anesthetic appreciably, they do not affect the calculations.

DATA FOR PROGRAMMING THE COMPUTER

Partition coefficients for the inhalation anesthetics have been summarized by several authors.[14,16–19] Partition coefficients for common inhalation anesthetics are given in Table 2, grouped according to the compartments defined above.

Tissue volumes may vary widely with varying body weight and habitus. For simplicity, we use the tissue volumes of the 70 kg "standard man" of the International Commission on Radiological Protection[20] and make alterations for individuals whose weight and habitus do not conform reasonably to that of a normal 70 kg man. Tissue weights given in Table 3 are grouped into the compartments defined above.

Rates of blood flow and volumes of venous blood in equilibrium with the tissues are given in Table 3 for a resting, supine man.[21] Alterations should be made for individuals whose cardiac output or distribution of blood flow is abnormal.

TABLE 2. PARTITION COEFFICIENTS FOR COMMONLY USED INHALATION ANESTHETICS FOR FOUR TISSUE COMPARTMENTS AT 37–38°C

	Lung-blood	Viscera	Lean	Fat	Ref.
Nitrous oxide	0.463	0.463*	0.463*	1.03†	24–27
Cyclopropane	0.429	0.429*	0.429*	11.12	28, 29
Halothane	2.3	6.0‡	8.0	138.0	30
Diethyl ether	12.1	12.1*	12.1*	44.1†	31–33

*Assuming the tissue:blood partition coefficient is 1.0.
†Estimate based on evidence that fatty tissue is composed of about 60 per cent lipid and 40 per cent water, using water:gas and oil:gas partition coefficients.[11]
‡Partition coefficient of brain and liver.

TABLE 3. COMPARTMENTAL VOLUMES AND RATES OF BLOOD FLOW *for a standard* 70.0 kg MAN

Compartment	Volume (l.)	Volume of blood in equilibrium (l.)	Rate of blood flow (l/min)
Lung air, lung tissue	2.68*		
and arterial blood	1.00†	1.40‡	6.30
Viscera	8.83	3.20	5.03
Lean	36.25	0.63	0.99
Fat	11.50	0.18	0.28
Non-perfused	7.02	0.0	0.0

*Lung air.
†Lung tissue.
‡Arterial blood.

A rate of alveolar ventilation of 4.0 l./min has been used by several investigators and appears to be reasonable.[22]

PROGRAMS AND RESULTS

The uptake and distribution of inhalation anesthetics may be calculated over short time intervals using equations (1) and (2), rearranged, with conductances and capacitances calculated according to equations (6), (14) and (15). The course of anesthesia is divided into such short time intervals (0.1–0.01 min) that during each interval the partial pressures of anesthetic in each tissue compartment may be considered to be constant. For each time interval, the rate of flow of anesthetic is computed for each tissue compartment. The partial pressure changes in each compartment are calculated and added to the partial pressures of anesthetic in the compartments at the beginning of the time interval. These partial pressures are then used in calculating the rates of flow of anesthetics and partial pressure changes in the subsequent time interval. This process is repeated until predictions have been made for the whole course of anesthesia. If there is a change in the conditions of anesthesia, the appropriate values may be changed between any two time intervals.

Time intervals must be short enough so that the partial pressures of anesthetic remain essentially constant during the time interval. Intervals of 0.1 or 0.01 min are sufficiently

short that division of the course of anesthesia into smaller intervals does not change the computed results.

A program written in Fortran IV for the calculation of anesthetic uptake and distribution is shown in Fig. 1. The four-compartment model, as previously defined, is used. Statements which set the value of constants and provide for writing out the computed results vary according to the convenience of the programmer and are not shown. The use of very short time intervals requires that calculations of partial pressures (P1, P2, P3 and P4) be of high precision.

```
      DOUBLE PRECISION P1,P2,P3,P4
    1 DO 2 N = 1,10000
      DVDTPT = (PINSP-P1)*COND1
      DVDT2 = (P1-P2)*COND2
      DVDT3 = (P1-P3)*COND3
      DVDT4 = (P1-P4)*COND4
      DVDT1 = DVDTPT-DVDT2-DVDT3-DVDT4
      P1 = P1 + DVDT1*DLT/CAP1
      P2 = P2 + DVDT2*DLT/CAP2
      P3 = P3 + DVDT3*DLT/CAP3
      P4 = P4 + DVDT4*DLT/CAP4
      TME = N*DLT
      WRITE(6,10)PINSP,TME,P1,P2,P3,P4
    2 CONTINUE
```

FIG. 1. Fortran IV program for the calculation of anesthetic uptake and distribution. Statements which set the value of constants and print computed results are not shown. Modifications for more complex situations are given in the text.

Some of the possible modifications to take into account changes in the patient or conditions of anesthesia and to account for more complex situations in anesthesia are listed below. Compartmental concentrations predicted for a course of diethyl ether anesthesia using these methods are shown in Table 4.

(1) Changes in alveolar ventilation, cardiac output and tissue perfusion: the conductances are recalculated using equation (6). An increase in the rate of alveolar ventilation may greatly increase the rate of uptake of anesthetics. Changes in cardiac output usually have smaller effects (Table 4).

(2) Warming of the inspired gas: the partial pressure of the anesthetic remains constant. The molar concentration decreases in proportion to the rise in absolute temperature.

(3) Humidification of the inspired gas: the partial pressure of the humidified inspired gas (PHI) can be calculated using the statement

$$\text{PHI} = \text{PINSP}*(\text{PAMB}/(\text{PAMB} + \text{DPH2O}))$$

where PAMB is the ambient pressure and DPH2O is the change in the partial pressure of water vapor in the gas mixture. The partial pressure of humidified inspired gas is then used to calculate the rate of gas uptake by the patient (DVDTPT)

$$\text{DVDTPT} = (\text{PHI}-\text{P1})*\text{COND1}.$$

A decrease in the calculated partial pressure results for all tissues (Table 4).

(4) The concentration effect: When an inhalation anesthetic enters the lung tissue and arterial blood in large quantity over a short time it is replaced by more inspired gas mixture, essentially increasing the rate of alveolar ventilation. Under these conditions the conductance to the lung-blood compartment is the sum of that given by equation (6) and the current rate of gas uptake by the patient (DVDTPT)

$$\text{COND1} = \text{ALVNT*TO/(TI*PO)} + \text{DVDTPT}.$$

A slightly increased rate of anesthetic uptake results (Table 4).

TABLE 4. COMPARTMENTAL CONCENTRATIONS OF DIETHYL ETHER AFTER 10.0 MIN OF ANESTHESIA CALCULATED BY METHODS DESCRIBED IN THE TEXT

	Inspired gas	Alveolar gas	Arterial blood	Viscera	Lean	Fat	Central venous
Normal	12.0	1.73	1.73	1.48	0.28	0.08	1.23
$\uparrow V_A$	12.0	3.11	3.11	2.69	0.51	0.14	2.23
$\downarrow C.O.$	12.0	2.24	2.24	1.59	0.20	0.05	1.30
Humidification of inspired gas	12.0	1.63	1.63	1.39	0.26	0.08	1.16
Concentration effect	12.0	1.91	1.91	1.64	0.31	0.08	1.36
Second gas effect (with 70% N_2O)	12.0	2.18	2.18	1.92	0.38	0.10	1.60
Pulmonary shunt (10%)	12.0	1.78	1.72	1.47	0.28	0.08	1.22
Metabolism (5% per hour)	12.0	1.72	1.72	1.47	0.28	0.08	1.22
Anesthesia circle system uptake*	9.6	1.24	1.24	1.01	0.17	0.05	0.84

Abbreviations: $\uparrow V_A$ = twice normal rate of alveolar ventilation; $\downarrow C.O.$ = one-half normal rate of cardiac output.

*Closed circle system of 5.0 l. initial volume with 0.3 l./min inflowing diethyl ether.

(5) The second gas effect: When two anesthetics are administered simultaneously, both may effectively increase the rate of alveolar ventilation in the manner shown above; this is called the second gas effect. Because the two anesthetics are simultaneously involved, their rates of uptake (DVDTA and DVDTB) are calculated simultaneously and COND1 (equation 6) is increased by their sum

$$\text{COND1} = \text{ALVNT*TO/(TI*PO)} + \text{DVDTA} + \text{DVDTB}.$$

An increase in the rate of anesthetic uptake results (Table 4).

(6) Calculation of the optimal inspired partial pressure: A regulatory feedback mechanism is used. During each time interval, the partial pressure inspired (PINSP) is set equal to the desired partial pressure (DSP) plus the product of the control factor (CF) and the difference between the desired partial pressure and the actual partial pressure (P2) of anesthetic in the brain (visceral compartment)

$$\text{PINSP} = \text{DSP} + \text{CF*(DSP–P2)}.$$

The inspired partial pressure must be kept between zero and a maximum safe partial pressure set by the programmer. Control factors are empirically determined to provide rapid attainment of the desired partial pressure without excessive oscillations. Using a desired partial pressure of 3.0 per cent of an atmosphere, a maximum safe partial pressure of 12.0 per cent, and a control factor of 120, optimal inspired concentrations of diethyl ether were found to be: 12 per cent from 0 to 35 min, 8 per cent from 35 to 63 min, 6 per cent from 63 to 92 min, 5 per cent from 92 to 130 min, and 4 per cent thereafter.

(7) Calculation of the central venous partial pressure: this partial pressure is the flow-weighted average of the partial pressures in the venous blood leaving the tissue compartments

$$PCV = (P2*COND2 + P3*COND3 + P4*COND4)/(COND2 + COND3 + COND4).$$

The central venous partial pressure is normally between those of viscera and lean tissue (Table 4).

(8) Pulmonary shunting: the partial pressure of anesthetic in the arterial blood (PART) is equal to the product of the alveolar partial pressure (PALV) and the fraction of the cardiac output which perfuses the alveoli (1.00–SHUNT) plus the product of the partial pressure of anesthetic in the central venous blood (PCV) and the fraction of blood which does not perfuse ventilated alveoli (SHUNT)

$$PART = PALV*(1.00-SHUNT) + PCV*SHUNT.$$

The arterial partial pressure (PART) is used to calculate flow to the viscera, lean tissue, and fatty tissue compartments. Pulmonary shunting usually produces a small alveolar-arterial partial pressure gradient (Table 4).

(9) Metabolism of the anesthetic: Each time interval, the partial pressures of the anesthetic in the tissue compartments are reduced in proportion to the fraction of anesthetic assumed to be metabolized in that compartment (FMET) during a time interval

$$P = P*(1.00-FMET).$$

Rates of metabolism for most anesthetics are so low that there is little or no effect on their uptake and distribution (Table 4).

(10) Uptake of anesthetic by an anesthesia circle system: A separate compartment is added to represent the circle system. Its mathematical description depends on the exact configuration of the circle system used. Anesthetic uptake by the patient is delayed by the uptake of anesthetic by the circle system (Table 4).

DISCUSSION

The validity of this method of predicting anesthetic uptake and distribution has been demonstrated by investigations in which whole body uptake and inspired gas, alveolar gas, arterial blood, brain, muscle and central venous blood concentrations have been measured. The most direct biological confirmation comes from an investigation in which ethylene, cyclopropane, halothane and diethyl ether were administered to large dogs.[16,23] The concentrations of these anesthetics were measured in alveolar air, arterial blood, brain, muscle and central venous blood. Good agreement ($\pm$11.4 per cent) was found between predicted and actual concentrations of anesthetics.[16,23] Excellent agreement has also been found between observed and predicted rates of whole body uptake of nitrous oxide, cyclopropane, halothane and diethyl ether in man.[1,13] The model therefore appears to be sufficiently accurate to be used for the prediction of anesthetic uptake and distribution in clinical situations.

Digital computers are beginning to be applied to the monitoring of blood pressure, pulse, respiration and the electrocardiogram during anesthesia. Calculation of the uptake and distribution of anesthetics with prediction of the optimal inspired concentration may also play an important part in the development of semi-automated or fully-automated control of anesthesia.

SUMMARY

Anesthetic uptake and distribution may be calculated using a four-compartment body model and knowledge of the physical characteristics of the anesthetic agent and the patient. Calculations may be made using analog or digital computers. Of the two, digital computers offer greater flexibility, accuracy and ease of calculation. This paper presents a simplified digital method for the prediction of anesthetic uptake and distribution which does not compromise flexibility or accuracy. Simple modifications of the basic program are included, which allow predictions for a wide variety of conditions. Because calculations based on these methods have been shown experimentally to be reasonably accurate, digital computers may be useful for prediction of anesthetic uptake and distribution during surgery.

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