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A Simple Pocket Calculator Approach to Predict Anesthetic Drug Concentrations from Pharmacokinetic Data

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Use of pharmacokinetic concepts to predict anesthetic drug concentrations has not had extensive use in clinical anesthetic practice to date. The multiple exponent equations needed to describe iv drug disposition have required computer capability not practical for the operating room. An algorithm is presented that allows the clinician to use information from the pharmacokinetic literature to improve accuracy of drug dosing in the operating room. Implemented on a pocket calculator, this approach does not involve complex mathematics or lengthy computations and allows the clinician to obtain a continuous prediction of the plasma anesthetic concentration during the course of the anesthetic from iv bolus or continuous infusion of anesthetic drugs. (Key words: Anesthetics, intravenous: drug concentration. Pharmacodynamics. Pharmacokinetics.)

RESEARCH INTO THE pharmacokinetics of iv anesthetics has resulted in detailed information about the rate of disappearance of these drugs from the plasma following administration by bolus injection or continuous infusion. The rate at which the drug leaves the plasma changes over time because of the separate processes of distribution and elimination. This changing rate of drug disappearance can be modeled by expressing the concentration of drug remaining in plasma at any point in time as the sum of several negative exponentials.[1] We suspect that most anesthesiologists do not calculate exponential decay curves during the course of a typical anesthetic. This may explain why intravenous anesthetic drugs are usually administered based on clinical end points, or simple dosing guidelines, and why pharmacokinetic principles are seldom used to help dosing in the operating room.

Accurate intraoperative prediction of the plasma concentration of iv anesthetics using an inexpensive, small calculator might initially allow the clinician to learn about the drug concentration *versus* effect relationship by observing the patient's reaction and the corresponding predicted plasma concentration of the drug. After gaining experience with this relationship, intraoperative prediction of the drug concentration could help dosing the drug in such a way that the desired drug concentration could be maintained. The classical equations describing plasma drug concentration at any point in time following a single bolus or infusion are straightforward and easily programmed into a small calculator. However, multiple dosing is the rule in anesthesia, and a small calculator is rapidly overwhelmed in this situation when using the classical equations.

We describe a method using a programmable pocket calculator to obtain, in the operating room, a continuous prediction in real-time of the plasma concentration of any iv anesthetic for which pharmacokinetic parameters are available. Our equations are simple approximations of the classical pharmacokinetic equations. The method requires programming the pharmacokinetic parameters for each drug into the calculator. During administration of an anesthetic, the anesthesiologist selects the drug from the calculator's memory and then enters each bolus or infusion rate change during the case. The predicted plasma drug concentration is continuously updated by the calculator. Although the displayed value is only a prediction based on published pharmacokinetic parameters,[2–17] the anesthesiologist has a good indication of what range of plasma concentrations can be expected in each patient. This new information, combined with the close observation of clinical signs, should permit the anesthesiologist to administer iv anesthetics with a better understanding of the dose : plasma concentration : effect relationship.

Method

DESCRIPTION

The method can be implemented on many scientific programmable calculators. We used a Hewlett Packard 41 CX, but the algorithm is presented in a general form that can be adapted to other calculators.

The algorithm requires the pharmacokinetic micro-rate constants k_{10}, k_{12}, k_{21}, k_{13}, k_{31}, and V_1, the volume of the central compartment (fig. 1). These parameters for each iv anesthetic can be permanently stored in the calculator's memory and recalled whenever needed. Suggested pharmacokinetic parameters for several commonly used iv drugs are listed in tables 1A and 1B. Most of the drugs listed are described by three-compartment pharmacokinetics, but some of them are described by a two-compartment model. In this case, the micro-rate constants k_{13} and k_{31} have to be set to zero.

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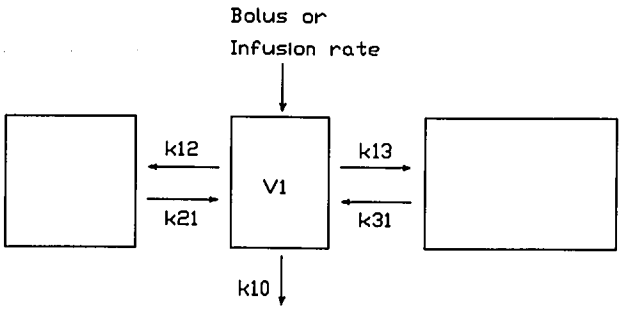

FIG. 1. Three-compartment model with drug administration into and elimination from the central compartment.

The clinician must carefully chose the most representative pharmacokinetic data set for each patient. For instance, a pharmacokinetic data set obtained from a group of young healthy women undergoing a short gynecologic procedure may not produce a reliable drug concentration prediction if applied to an elderly sick patient.

The program is started prior to administering the drug. At this time, the calculator displays "0," indicating that there is no drug in the patient's plasma. During the course of the anesthetic, whenever a bolus is injected, the user presses the "bolus" key. The calculator will then request the amount of the bolus, which is entered. Whenever an infusion is started, stopped, or the infusion rate is changed, the user presses a "new rate" key. The calculator then requests the new infusion rate (which is "0" if the infusion is terminated). The number of bolus doses or changes of infusion rate that the program can accommodate is unlimited and has no influence on the time required to compute the plasma concentrations. Every 10 s the calculator updates its internal pharmacokinetic model and displays the actual time elapsed since beginning the anesthesia and the predicted concentration of the anesthetic. If the calculator has no clock, a 10-s interval can be obtained by repeating a dummy loop that keeps the computer busy during a 10-s period of time. Also, it has to be noted that an interval greater than 10 s may result if longer periods are taken for entering bolus and rate changes on the keyboard, resulting in wrong predictions of concentrations.

The equations and algorithm to implement the proposed method are detailed in the Appendix.

EXAMPLE

Table 2 presents an alfentanil dosing regimen administered to a surgical patient (55-kg, 51-yr-old woman from reference 18). The predicted concentrations calculated on a microcomputer using the exact analytical solution[18] to the three-compartment model are compared with the predicted concentrations obtained on a pocket calculator using the simple approximations described above. The pharmacokinetic parameters are those of Maitre *et al.*[6] (table 1). Although the pocket calculator would display the prediction of the actual plasma concentration every 10 s, table 2 shows only the values of the prediction corresponding to the time where blood was actually withdrawn and assayed for alfentanil concentration. It can be seen that the approximate method gives results very close to those obtained with the more complex exact method. Table 2 also allows the individuals who may use this algorithm on their calculator to check their program and make sure that they have made no major mistakes in implementing the algorithm.

Discussion

This method of predicting plasma anesthetic drug concentration is based on a pharmacokinetic model of drug distribution and elimination. The clinician using such a program has to recognize that the patient's plasma drug concentration will never agree precisely with the concentration predicted by these calculations. An individual pa-

TABLE 1A. Pharmacokinetic Parameters

	Thiopental[8]	Ketamine[12]	Midazolam[11]	Etomidate[16]
V_1	0.079 1/kg*	0.063 1/kg*	0.51 1/kg*	0.090 1/kg*
k_{10}	0.039/min	0.438/min	0.015/min	0.203/min
k_{12}				
Age < 35	0.48/min	0.592/min	0.0139/min	0.283/min
Age > 35	0.48 − [0.0029 · (age − 35)]			
k_{21}	0.079/min	0.247/min	0.0135/min	0.105/min
k_{13}	0.107/min	0.590/min	0†	0.209/min
k_{31}	0.0039/min	0.0146/min	0	0.0043/min
Bolus units	mg	mg	mg	mg
Infusion rate	mg/min	mg/min	mg/min	mg/min
Concentration	μg/ml	μg/ml	μg/ml	μg/ml
Population	Age 20–80 ASA physical status 1–3	Young, healthy men volunteers	Young men ASA physical status 1–2	Men, age 22–82 ASA physical status 1–2

* Must be multiplied by patient's weight to derive V_1 prior to calculation.

† Two-compartment model.

TABLE 1B. Pharmacokinetic Parameters

	Propofol[17]	Fentanyl[8]	Sufentanil[7]	Alfentanil[6]
V_1	0.350 1/kg*	2.70 + 0.059 · wght (kg)	0.164 1/kg*	Male: 0.111 1/kg* Female: 0.127 1/kg*
k_{10}	0.086/min	0.0815/min	0.089/min	Age < 40: 0.356/V_1 Age > 40: (0.356 − [0.0027 · (age − 40)])/V_1
k_{12}	0.060/min	0.472/min	0.350/min	0.104/min
k_{21}	0.105/min	0.102/min	0.161/min	0.0673/min
k_{13}	0†	0.226/min	0.077/min	0.017/min
k_{31}	0	0.0061/min	0.010/min	age < 40: 0.0126/min age > 40: 0.0126 − [0.000113 · (age − 40)]
Bolus units	mg	μg	μg	μg
Infusion rate	mg/min	μg/min	μg/min	μg/min
Concentration	μg/ml	ng/ml	ng/ml	ng/ml
Population	Age 30–60 ASA physical status 1–3	Age 45–65 ASA physical status 1–4	Age 22–64 ASA physical status 1–2	Age 19–91 ASA physical status 1–2

* Must be multiplied by patient's weight to derive V_1 prior to calculation.

† Two-compartment model.

tient's pharmacokinetic parameters will differ from other patients' parameters because of differences in patient physiology and disease state. Also, the pharmacokinetic model assumed here (the three-compartment model) assumes that the processes of distribution and clearance are first order processes that do not change over time (*i.e.*, the rate constants never change). Clearly, there are changes in cardiac output, hepatic and renal perfusion, and tissue blood flow during anesthesia that affect distribution and elimination kinetics over time. A simple pharmacokinetic model, such as used here, cannot account for such changes. Even if the plasma concentration could be precisely known, patients will vary in their requirement for iv drugs because of differences in intensity of noxious stimuli and patient response to the anesthetic drugs. Ausems *et al.*[19,20] have described the range of alfentanil concentration necessary for different phases of surgery, Hug has published similar information for fentanyl,[21] and Becker for thiopental.[22]

However, the pharmacokinetic variability and pharmacodynamic variability do not mean that intraoperative prediction of the plasma drug concentration is totally useless. For alfentanil, the prediction error (*i.e.*, the difference between the concentration predicted by the equations and the measured concentration) averages ±25%,[23] although it can be much higher in some patients. However, the

TABLE 2. Administration Scheme for Alfentanil, the Resulting Measured Plasma Concentrations in a Representative Patient (55 kg, 51-yr-old woman), and the Concentrations Predicted Using Two Different Methods

Time (min)	Infusion Rate (μg/min)	Bolus (μg)	Measured Concentration (μg/l)	Concentration Predicted Using the Exact Method (μg/l)	Concentration Predicted Using Euler's Method (μg/l)
0	46.6	8250	—	1175	1176
2	46.6	0	709	868	861
5	46.6	0	568	592	582
15	46.6	0	418	300	296
16	46.6	0	—	291	287
16	68.3	400	—	348	344
18	68.3	0	367	323	321
21	68.3	0	363	298	296
30	46.6	0	287	266	265
45	23.6	0	269	224	224
60	23.6	0	197	181	181
80	23.6	0	177	152	152
80	46.6	800	—	266	266
82	46.6	0	305	238	235
85.5	46.6	0	242	216	214
97	46.6	0	224	181	181
100	23.6	0	—	178	178
111	23.6	0	189	153	153
119	Stop	0	182	144	144
129		0	147	117	117
131		0	145	113	113

time course of the predicted concentrations almost always parallels the measured concentrations, and when a significant prediction error is present, the percent deviation remains fairly constant over the entire anesthetic duration.[19] Thus, even though the predicted concentration will be incorrect, the shape of the predicted concentration curve over time will be correct, and this provides valuable information. It also has to be stressed that the clinician must chose a pharmacokinetic data set that is representative for the patient. Indeed, pharmacokinetic parameters are often obtained from young and healthy patients. They may therefore not be representative for older or sick patients and may lead to a higher drug concentration than expected (*i.e.*, overdosage).

To date, clinicians have rarely applied pharmacokinetic concepts to iv anesthesia. This method should allow the clinician to use information from the pharmacokinetic literature to improve accuracy of drug dosing in the operating room. The method presented does not involve complex mathematics or lengthy computations. The simple equations and algorithm presented allow the clinician to obtain, with the help of a pocket calculator, a continuous prediction of the plasma anesthetic concentration over the course of the anesthetic. We anticipate that most clinicians will find a continuous prediction of the plasma concentration of iv anesthetics a valuable addition to, but not a replacement for, the clinical signs now used as a basis for administration of iv anesthetics.

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Appendix

Equations

Compartmental models (fig. 1) are often used to describe the behavior of iv anesthetics. The first (or central) compartment is defined as the compartment from which the drug is sampled, *i.e.*, the blood or plasma. The drug leaves the central compartment through elimination (usually *via* the liver or kidneys) and through distribution of other tissues.

If we consider only the transfer of drug from one compartment to an adjacent compartment, the rate of drug transfer equals the amount of drug in the source compartment times a rate constant, k, to which we append a subscript indicating which compartment is involved. Of course, drug is transferring in the opposite direction as well at a rate that equals the amount in the adjacent compartment times a different rate constant. The net rate of change in drug concentration in a compartment is the

rate at which the drug is entering the compartment, less the rate at which the drug is leaving the compartment.

The rate of change in each compartment for a three-compartment model can be described with the following differential equations:

$$dA_1/dt = k_{21}A_2 + k_{31}A_3 - (k_{10} + k_{12} + k_{13}) \cdot A_1 \quad (1)$$

$$dA_2/dt = k_{12}A_1 - k_{21}A_2 \quad (2)$$

$$dA_3/dt = k_{13}A_1 - k_{31}A_3 \quad (3)$$

where A_1, A_2, and A_3 are the amount of drug in compartments 1, 2, and 3, respectively. These equations cannot be used directly by a calculator, because dt is an infinitely small time interval. However, we can approximate these equations by substituting Δt for dt, and assigning a small time interval, (*e.g.*, 10 s), to Δt. We can thus approximate the change in drug concentration in each compartment with the following simple equations:

$$\Delta A_1 = [k_{21}A_2 + k_{31}A_3 - (k_{10} + k_{12} + k_{13})A_1] \cdot \Delta t \quad (4)$$

$$\Delta A_2 = (k_{12}A_1 - k_{21}A_2) \cdot \Delta t \quad (5)$$

$$\Delta A_3 = (k_{13}A_1 - k_{31}A_3) \cdot \Delta t \quad (6)$$

Equation 4 calculates the approximate change in the amount of drug in the central compartment over time interval Δt, given the amount of drug in each compartment at the beginning of the time interval. Equation 4 can be easily modified to account for a bolus injection (amount = B) and a continuous infusion (rate = R) of drug to the central compartment:

$$\Delta A_1 = [k_{21}A_2 + k_{31}A_3 - (k_{10} + k_{12} + k_{13})A_1 + R] \cdot \Delta t + B \quad (7)$$

The accuracy of the approximation increases as smaller values for Δt are chosen. For opioids and hypnotic drugs used during anesthesia, a Δt of 10 s results in a maximum error of approximately 5% that occurs within the first 2 min following a bolus injection. The error rapidly decreases to less than 1% during continuous infusions. This technique of solving differential equations by substituting a small Δt for dt was proposed more than 200 yr ago by a Swiss mathematician, L. Euler (1707–1783) and is referred to as "Euler's numerical integration technique."

Algorithm

Start. Get the pharmacokinetic parameters, initialize the amounts in each compartment, and the variables for a bolus and a continuous infusion:

Assign V_1, k_{10}, k_{12}, k_{21}, k_{13}, and k_{31}

A_1, A_2, A_3, B, R = 0

Loop.

1) Check keyboard:
   a. If the "bolus" key is pressed, request the bolus amount and store it in variable B.
   b. If the "new infusion rate" key is pressed, request the new rate and store it in variable R.
   c. If the "end program" key is pressed, terminate the program.
2) Check the current time. If it is 10 s after the last update:
   a. Calculate ΔA_1, ΔA_2, and ΔA_3 using equations 7, 5, and 6, respectively.
   b. Calculate the current amounts in compartments A_1, A_2, and A_3 as follows:
      current A_1 = prior A_1 + ΔA_1
      current A_2 = prior A_2 + ΔA_2
      current A_3 = prior A_3 + ΔA_3
   c. Calculate and display the current plasma anesthetic concentration:
      current concentration = current A_1/V_1
   d. Reset bolus amount (so it is not added at each update):
      B = 0
3) Continue loop.