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# *Plasma Drug Efflux—A New Approach to Optimization of Drug Infusion for Constant Blood Concentration of Thiopental and Methohexital*

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**Plasma Drug Efflux is a time-varying measure of the rate of loss of drug from the plasma during conditions of constant plasma concentration. Its practical use is to define the parameters required for a programmed infusion to maintain a desired plasma concentration. The method of deriving the Efflux function, which does not depend on conventional pharmacokinetic models, was developed and tested using thiopental and methohexital in a total of 51 unselected surgical patients free of hepatic or renal disease. Throughout a predetermined, known, but arbitrary computer-controlled drug infusion, the rate of which was modified according to patient lean body mass (LBM) and the desired concentration, blood samples were taken and the plasma assayed for either drug by an HPLC method. By dividing the known variable infusion rate at the time of each sampling by the arterial plasma concentration at each time, an estimate of the rate of loss of drug from the plasma at each point, the Plasma Drug Efflux, was obtained. An error correcting iterative process was used with successive groups of patients until the optimum infusion profile was achieved. Only three iteration steps were required to optimize the infusion profile for each drug. The optimized infusion profile for thiopental was $25.35e^{-.145t} + 4.85e^{-.0148t} + 8.8$ ml·min$^{-1}$·kgLBM$^{-1}$, and, for methohexital, $22.21e^{-.092t} + 5.09e^{-.0121t} + 15$ ml·min$^{-1}$·kgLBM$^{-1}$. It was concluded that the process of optimization under clinical conditions resulted in infusion profiles suitable for establishing and maintaining a designated arterial plasma concentration in adult surgical patients for periods up to 3 h. (Key words: Anesthesia: intravenous infusion. Barbiturate: methohexital; thiopental. Pharmacokinetics: theory.)**

THE ABILITY TO ESTABLISH and maintain a constant blood level of a drug permits the anesthesiologist to accurately assess anesthetic requirements in the absence of the rapid fluctuations characteristic of bolus injection. Studies of the relationship between drug concentration and effect are more meaningful if an equilibrium can be established between the concentration in blood and that at the site of drug action.[1] In fact, without the ability to achieve constant, known concentrations of parenterally administered drugs over a reasonable period of time, concepts such as MAC cannot be applied.[2] The need for constant plasma concentrations for pharmacodynamic studies has been strongly reinforced by a report of a definite hysteresis associated with changing fentanyl and alfentanil blood concentrations when assessed by their effect on the EEG during rapid intravenous infusions.[3]

For an intravenous infusion to achieve a constant plasma concentration, a balance must be struck between the rate of administration and the rate of loss of the drug from the circulation to avoid over- or under-dosage during the period of rapid redistribution. It is widely believed that it is necessary to predict pharmacokinetic parameters, such as compartmental or distributional volumes, rate constants, rate of renal excretion, and rate of biotransformation, in order to plan an infusion.[4]

Most investigators have used mathematical models to describe the decay of the plasma concentration over a period of hours or days following the administration of a single dose of the drug to a patient. Using a curve-fitting approach, they have described the decay curve by means of the coefficients (macroconstants) of a polyexponential equation. For each subject, a compartmental model is then constructed to simulate the distribution of drug in the patient.[5] The parameters (microconstants) of compartmental models from a number of patients are then averaged, and infusion profiles are devised for subsequent patients in the expectation that they will behave in accordance with the average compartmental model.

Various infusion schemes have been devised using such parameters, ranging from a simple two-stepped scheme[6] to computer-generated exponential schemes,[7–9] all derived from single-dose, elimination-based pharmacokinetic parameters. Some success in achieving predicted levels of fentanyl,[10] etomidate, and alfentanil[7] has been reported, but a general method of deriving infusion protocols to achieve constant concentrations of drugs over a period of time at their therapeutic concentrations and under clinical conditions has not been reported.

This paper describes an error-correcting iterative approach for establishing and maintaining a desired blood level of an intravenously administered drug which does not rely on the derivation of a pharmacokinetic model. Data are generated under actual surgical conditions in

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unselected patients. The approach demonstrates the utility of the technique in achieving constant blood levels of two barbiturates, thiopental and methohexital, at concentrations appropriate to their use as primary anesthetic agents.

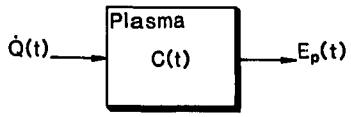


FIG. 1. Relationship between the drug administration function Q(t), the plasma concentration function C(t), and the drug loss function Ep(t).

## Methods and Materials

The process of infusion profile optimization presented here is an iterative approach, new to pharmacokinetics, based on a novel concept: Plasma Drug Efflux. The concept, in its simplest form, states that, if, over some small time interval, the plasma concentration of a drug neither rises nor falls, then the amount of drug delivered into the circulation during that interval must have been equal to the amount of drug lost from the circulation during the interval. Whether this loss is by distribution, biotransformation, excretion, or a combination of these pathways is not important to the concept of Plasma Drug Efflux. Using this approach, the plasma is represented as a single compartment of undetermined volume, as shown in figure 1. The drug is infused into the plasma by a programmed infusion pump at a variable but known rate described by a function Q(t). The resulting arterial plasma concentration is then described by C(t), and the loss of drug from the plasma by a corresponding time-varying function, the Plasma Drug Efflux, Ep(t).

In concept, the time-varying Efflux term is analogous to conventional clearance, and has the same units ($ml \cdot min^{-1} \cdot kg^{-1}$). It describes, at constant drug concentration, the theoretical amount of plasma that is completely cleared of drug per unit of time. In practice, Plasma Drug Efflux represents the sum of the conventional clearance at steady state, and the "net clearance" of drug from the plasma to the various tissues. For any drug that is eliminated from the body and that is distributed from plasma into tissues, the value of Plasma Drug Efflux will be high initially, and will fall to a lower rate in time.

If the plasma drug concentration is constant, so that the amount of drug in the plasma is not changing, then the instantaneous rate of drug influx to the plasma (the infusion rate) and the instantaneous concentration in the plasma may be used to describe the Efflux (Ep) of drug from the plasma, such that:

$$Ep = \dot{Q}i/Ci, \quad (1)$$

where Ci is the arterial concentration at the $i^{th}$ sampling point, and Qi is the corresponding infusion rate at that same time.

The strict equality described in equation 1 will only occur in a given patient if the infusion profile which produces a constant plasma concentration is used. This, of course, is one of the goals of the method, the other being to achieve a pre-defined concentration. If the concentration during the infusion is falling or rising, then the approximation of equation 2 applies until the shape of the optimum infusion curve is found.

$$Ep \approx \dot{Q}i/Ci \quad (2)$$

The relationship in equation 2 is used to establish infusion profiles in successive groups of patients and, by a process of iteration, to develop the optimized profile needed to describe equation 1.

An explanation of this iterative method is presented in figure 2. Starting with an initial bolus dose D, an infusion of known rate (Q1) is administered to a subject (fig. 2A). During the infusion, arterial blood samples are drawn at various times—1, 2, 3, etc.—and the drug concentrations (Cp) determined (fig. 2B). Estimates of Plasma Drug Efflux (Ep) are then made at each sampling time. The infusing and sampling sequence is repeated in a number of patients, and Efflux estimates are plotted (fig. 2C). A line of best fit is then produced, which provides an estimate of the Plasma Drug Efflux for the group. By forming the continuous product of this curve and the desired concentration (Cd) of the drug, a new infusion profile (Q2) is produced (fig. 2D), which will be closer to the optimum curve than the previous curve shown in figure 2A. The next iteration commences when the new infusion profile (Q2) is administered to a further group of patients, which will result in more optimal concentrations throughout the test period (fig. 2E). New Efflux estimates are obtained by combining the infusion profile (fig. 2D) with the resulting plasma drug concentration data (fig. 2E), and so on until the infusion profile is optimized at the desired concentration (Cd).

It should be noted that the infusion profiles shown in figure 2A and D refer to drug delivery, and must, of course, be scaled on the basis of individual patient size. In view of previous studies,[9,11] we based dosage on calculated lean body mass (LBM) of the patient in preference to total body weight.

While no finite point was defined to initiate the move to the next iteration, statistical tests were performed on each completed iteration to evaluate progress with the method. Two tests were used to describe the distribution of the plasma concentrations about the desired constant concentration. First, a one-way analysis of variance (ANOVA) was performed on the concentration

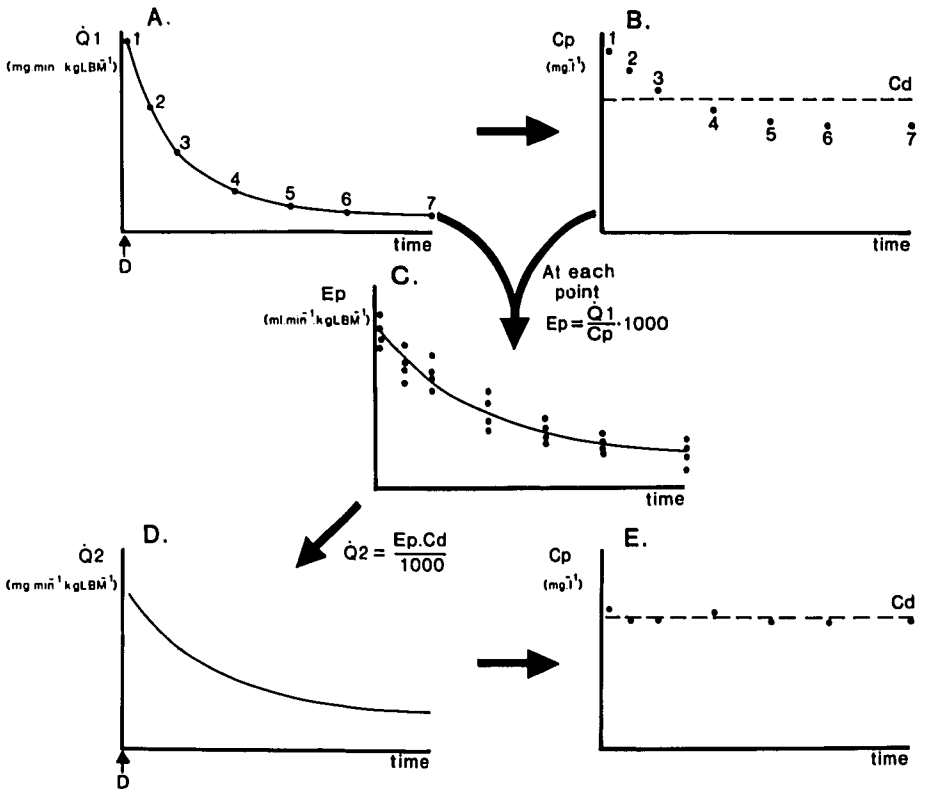


FIG. 2. A graphic explanation of the iterative process for determining Plasma Drug Efflux. Individual data points (1, 2, 3, etc.) from a programmed infusion (*A*) are combined with arterial plasma concentration data (*B*) to calculate estimates of plasma drug Efflux (Ep) at each point in a single patient. Data are combined to produce a best fit estimate in a group of patients (*C*). The profile is used to generate a new infusion (*D*), resulting in an improved concentration-time profile (*E*) at the desired concentration (Cd).

time data of the group of patients receiving a given infusion profile. If all the concentration data of all the patients in the group is tabulated into smaller subgroups according to the length of time from the start of infusion until the sample was taken, the one-way ANOVA of concentration against time will disclose the presence of any sub-groups which have mean concentrations differing significantly from the overall mean value of all the data from this group of patients. This occurrence indicates that, at some time, or times, during the infusion, there is a systematic deviation from the overall mean concentration for infusions in the group. If the ANOVA is unable to distinguish any systematic deviation from the overall mean value, then the infusion profile has produced results which are statistically indistinguishable from a constant level. The other criterion to be satisfied in the process is that the constant level must be at the pre-defined concentration, with equal amounts of patient concentration time data scattered above and below this pre-defined level. This is tested by determining 95% confidence intervals of the mean of all the concentration time data in the group, regardless of sampling time. Thus, if the pre-defined level falls within the confidence interval, then the infusion results are approximately equally scattered above and below the desired result. The two tests must be used together, and failure on either test demonstrates that another iteration is necessary. Should the infusion profile satisfy both requirements, it is statistically indistinguishable from the optimum result, and the iterative process may be terminated.

Curve-fitting of "Efflux points" to generate each infusion profile was performed using a program written in our laboratory in the Data Acquisition Operating System, DAOS (Laboratory Software Associates), and running in a Texas Instruments TI 980A minicomputer. The program first uses a curve-stripping technique to produce initial estimates of each parameter of a polyexponential equation. These initial estimates are optimized by the second part of the program by performing a step-wise search of the parameter space from zero to double the initial estimate in each case, for each of the pairs of parameters forming exponential terms. The optimization of the exponential terms is always performed in order of decreasing numerical magnitude of the time-constant in each pair. Minimization of the sum of squared deviation between calculated and observed values is used as the optimization criterion.

Once the equation had been generated for grouped patient data, the resulting infusion profile was trans-

TABLE 1. Infusion Group Characteristics

| Iteration | n | Age (Yr) | Weight (kg) | LBM (kg) | Desired Levels* (mg/l) |
|---|---|---|---|---|---|
| Thiopental 1 | 12 | 59 ± 15 | 70 ± 14 | 55 ± 9 | 10 (×11), 8 |
| 2 | 10 | 53 ± 14 | 78 ± 13 | 55 ± 8 | 10 (×10) |
| 3 | 14 | 53 ± 16 | 71 ± 12 | 54 ± 9 | 10 (×12), 7.5 (×2) |
| Methohexital 1 | 3 | 59 ± 18 | 53 ± 16 | 46 ± 12 | 6 (×2), 4 |
| 1a | 1 | 76 | 81 | 45 | 3 |
| 1b | 1 | 67 | 74 | 60 | 5 |
| 2 | 4 | 61 ± 6 | 57 ± 14 | 47 ± 10 | 5 (×4) |
| 3 | 6 | 58 ± 20 | 62 ± 10 | 48 ± 8 | 5 (×5), 4 |

Mean ± S.D.

* Numbers in parenthesis indicate the number of patients in whom the desired level was sought.

ferred to read-only memory (ROM) and used to control the rate of drug delivery by a programmable syringe pump during the following iteration.

## CLINICAL METHODS

Fifty-one adult patients undergoing a variety of surgical procedures participated in the study, which was approved by the Board of Medical Research of the Royal Melbourne Hospital. Patients gave informed consent after oral explanation of the protocol. Routine preoperative biochemical tests were used to exclude patients with evidence of hepatic or renal dysfunction. The desired constant plasma concentration of the drug in each patient was determined according to the clinical judgement of the attending anesthesiologist, and was usually 10 $mg \cdot l^{-1}$ for thiopental and 5 $mg \cdot l^{-1}$ for methohexital. The lean body mass of each patient was estimated by the method reported by James,[12] using height (Ht in cm), total body weight (TBW in kg), and sex, according to the following equations:

$$LBM(Males) = 1.10 \times TBW - 128 \times (TBW/Ht)^2 \quad (3)$$

$$LBM(Females) = 1.07 \times TBW - 148 \times (TBW/Ht)^2 \quad (4)$$

The grouped patient characteristics are presented in table 1.

Apart from excluding those with hepatic or renal dysfunction, patients were those presenting for elective head and neck, neuro, and cardiac surgery in whom an indwelling radial artery cannula would normally be used. Medications other than the drugs under study were administered according to the clinical judgement of the attending anesthesiologist. As such, the patients received a wide range of adjuvants, including volatile anesthetic agents, narcotic analgesics, nitrous oxide, hypnotics, and muscle relaxants, on the basis of clinical signs and in accordance with current practice. No attempt was made to control the use of other drugs, as it was our aim to produce infusion profiles that would be applicable in the general clinical environment.

Either thiopental or methohexital was administered according to a pattern stored in ROM, using a syringe pump capable of reading successive ROM locations at specific times and scaling the infusion rate according to the patient's LBM and the desired plasma concentration. Calibration of the syringe pump before, during, and after the study demonstrated a relationship of 2.56 $\mu l$ per stepper motor pulse, with a linear range from 0.1–45.0 $ml \cdot h^{-1}$ ($r = 0.996$, $n = 15$).

For thiopental, the initial infusion profile ($ml \cdot min^{-1} \cdot kgLBM^{-1}$) used was:

$$Ep(t) = 62.64e^{-.142t} + 16.76e^{-.0121t} + 3.37 \quad (5)$$

This function was generated by applying equation 1 to infusion rate and thiopental concentration data generated in two previous studies.[9,13] Equation 5 was also used as the initial infusion profile for methohexital because of the paucity of published kinetic data for this drug, recognizing that the Efflux method naturally converges towards the optimized curve irrespective of the starting profile.

Thiopental sodium (Pentothal, Abbott) 2.5% or methohexital sodium (Brietal Sodium, Lilly) 1.0% in water for injections BP was administered from a 50-ml syringe. Simultaneously with the commencement of the infusion, a single bolus of the drug under study was administered to induce anesthesia. The size of this bolus was arbitrary, but was generally half of the dose that would normally be administered for induction of anesthesia in a patient of that size (tables 2, 3).

Blood samples (3 ml) were collected from an arterial cannula throughout the infusions, generally at 0, 2, 5, 10, 15, 20, and 30 min after the start of the infusion, and then every 15 min until its termination. Blood was immediately placed in heparinised tubes, cooled on ice, and centrifuged as soon as possible, and the resulting plasma was stored frozen for later analysis.

TABLE 2. Individual Patient Physical, Dosage, and Concentration Characteristics for Thiopental Iteration 3

| Patient Number | Age (Yr) | Height (cm) | Weight (kg) | Sex | LBM (kg) | ASA Class | Infusion Duration (Min) | Desired Level (mg/l) | Bolus Dose (mg) | Total Dose (mg) | Max. Conc. (mg/l) | Min. Conc. (mg/l) | End Inf. Conc. (mg/l) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 73 | 153 | 65 | F | 44 | NA* | 45 | 10 | 90 | 410 | 13.56 | 9.84 | 9.93 |
| 2 | 53 | 171 | 85 | M | 62 | 3 | 45 | 10 | 125 | 575 | 10.73 | 9.80 | 10.28 |
| 3 | 46 | 177 | 80 | M | 62 | 3 | 45 | 10 | 125 | 575 | 13.74 | 10.73 | 13.74 |
| 4 | 23 | 174 | 62 | M | 52 | 2 | 45 | 10 | 100 | 480 | 11.32 | 6.25 | 10.48 |
| 5 | 71 | 173 | 72 | M | 57 | 3 | 45 | 10 | 45 | 460 | 11.22 | 9.99 | 11.22 |
| 6 | 38 | 179 | 100 | M | 70 | 3 | 45 | 10 | 140 | 650 | 9.38 | 8.13 | 9.38 |
| 7 | 42 | 173 | 82 | M | 61 | 1 | 180 | 7.5 | 250 | 1195 | 8.74 | 7.03 | 8.74 |
| 8 | 68 | 159 | 64 | F | 44 | 1 | 180 | 10 | 200 | 1115 | 9.10 | 6.19 | 6.19 |
| 9 | 30 | 164 | 54 | F | 42 | 1 | 180 | 7.5 | 250 | 895 | 9.76 | 8.16 | 9.76 |
| 10 | 48 | 169 | 61 | M | 50 | 3 | 135 | 10 | 300 | 1125 | 13.75 | 10.07 | 13.57 |
| 11 | 52 | 163 | 65 | F | 46 | 1 | 180 | 10 | 200 | 1150 | 8.76 | 6.33 | 6.33 |
| 12 | 69 | 160 | 62 | F | 44 | 3 | 150 | 10 | 90 | 880 | 8.29 | 7.24 | 8.29 |
| 13 | 58 | 180 | 73 | M | 59 | 2 | 195 | 10 | 115 | 1415 | 11.26 | 7.72 | 10.62 |
| 14 | 68 | 180 | 68 | M | 56 | 2 | 195 | 10 | 115 | 1345 | 11.86 | 7.05 | 11.86 |
| Mean (± SD) | | | | | | | | | | | 11.06† (1.91) | 8.28† (1.70) | 10.16† (2.39) |

* Information not available.

† Data from patients 7 and 9 excluded due to differences in desired levels.

## ANALYTICAL METHODS

Plasma thiopental and methohexital concentrations were measured by a high-pressure liquid chromatographic (HPLC) technique. After addition of 100 μl of water to 500 μl aliquots of plasma, 1.25 ml of acetonitrile was added, while vortex mixing, to precipitate plasma proteins. The mixture containing the precipitate was then centrifuged at 1000 g for 10 min, and 10 μl of the supernatant was injected into the HPLC. Chromatographic equipment consisted of a Waters™ Model 510 pump, Waters™ Model 710B autosampler, Waters℠ Model 481 ultraviolet absorbance detector, and a Pye-Unicam AR25 chart recorder. The thiopental assay used a 15 cm × 3.9 mm μBondapak™ $C_{18}$ column and absorbance measurements at 290 nm, whereas the methohexital assay used a 15 cm × 3.9 mm Nova-pak™ $C_{18}$ column and absorbance measurements at 210 nm. The mobile phase was 52.0% methanol, 43.5% distilled water, 4.5% isopropanol, and sufficient o-phosphoric acid and ammonia to achieve a *p*H of 3.5. The flow rate was kept at 1 $ml \cdot min^{-1}$.

A standard curve was prepared on each analysis day to correct for minor variations in detector response. For the standard curves, blank plasma was used, and the distilled water was replaced with 100 μl of standard solution. The linear regression correlation coefficient was >0.9999 for both assays. The within-day coefficient of variation at representative concentrations was 1.01% (n = 6) for thiopental at 12.07 $mg \cdot l^{-1}$ and 3.83% (n = 6) at 3.980 $mg \cdot l^{-1}$ for methohexital.

## Results

Table 1 presents the physical characteristics and the derived LBM relating to each patient group studied. Tables 2 and 3 contain the infusion data and a summary of the concentration results for each patient in the final

TABLE 3. Individual Patient Physical, Dosage, and Concentration Characteristics for Methohexital Iteration 3

| Patient Number | Age (Yr) | Height (cm) | Weight (kg) | Sex | LBM (kg) | ASA Class | Infusion Duration (Min) | Desired Level (mg/l) | Bolus Dose (mg) | Total Dose (mg) | Max. Conc. (mg/l) | Min. Conc. (mg/l) | End Inf. Conc. (mg/l) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 59 | 173 | 72 | M | 57 | 3 | 180 | 5 | 52 | 945 | 5.44 | 4.03 | 5.01 |
| 2 | 69 | 168 | 65 | M | 52 | NA* | 180 | 5 | 52 | 862 | 6.22 | 4.88 | 4.88 |
| 3 | 70 | 147 | 47 | F | 35 | 2 | 75 | 5 | 35 | 283 | 5.94 | 4.28 | 4.28 |
| 4 | 49 | 163 | 59 | M | 48 | 2 | 180 | 5 | 50 | 795 | 5.48 | 3.83 | 3.83 |
| 5 | 23 | 160 | 74 | M | 54 | 1 | 120 | 5 | 54 | 638 | 5.71 | 4.42 | 5.18 |
| 6 | 77 | 163 | 57 | F | 43 | NA* | 135 | 4 | 43 | 448 | 4.32 | 3.17 | 3.17 |
| Mean (±SD) | | | | | | | | | | | 5.76† (0.34) | 4.29† (0.40) | 4.64† (0.56) |

* Information not available.

† Data from patient 6 excluded due to different desired level.

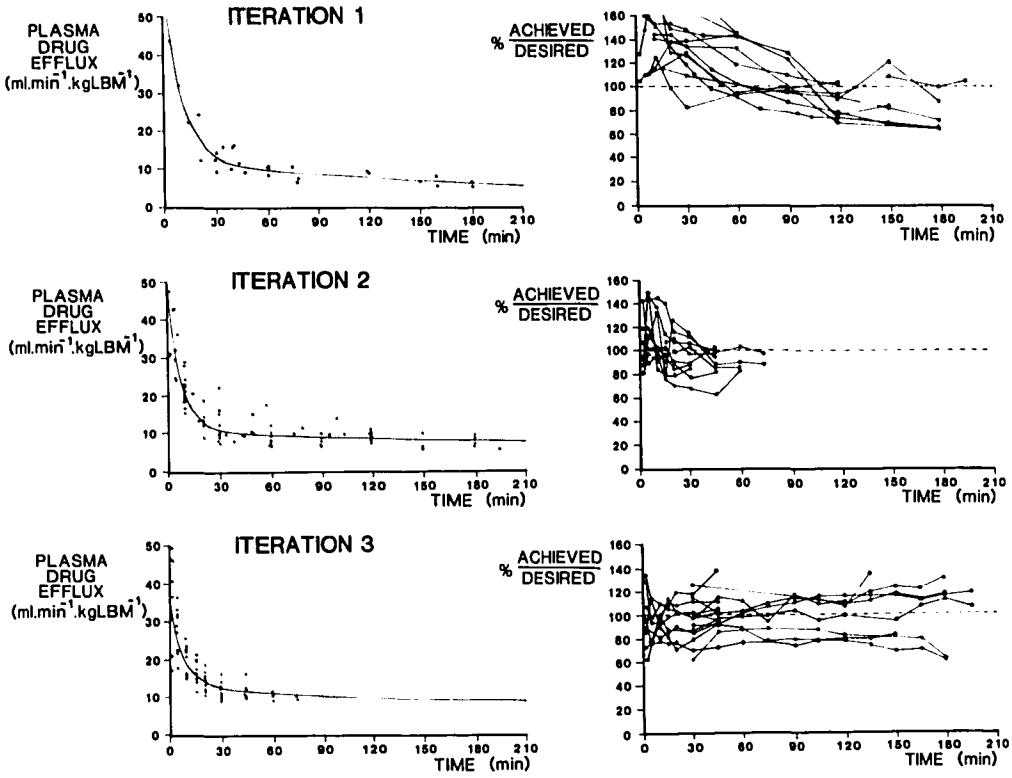


FIG. 3. Infusion optimization procedure for thiopental. Left-hand panels show the infusion profiles for each iteration, together with individual Efflux points used to generate the profile (see Text). Right-hand panels show individual concentration values, interpolated for each patient in the iteration. Efflux points for Iteration 1 are taken from the results of two previous studies.[10,15]

iteration with thiopental and methohexital, respectively.

## THIOPENTAL

A graphical representation of the entire infusion profile optimization procedure for thiopental is presented in figure 3, and consists of three pairs of plots corresponding to the three iterations used. The left-hand panel of each pair shows the infusion profile (solid line) and the Efflux points used to generate it, plotted as a function of time. The right-hand panel shows the arterial plasma thiopental concentration data resulting from the administration of the infusion to a group of patients. These data are plotted as the percentage of the achieved concentration divided by the desired concentration, in order to eliminate minor differences in desired levels between patients (table 1).

The infusion profile for Iteration 1 (fig. 3) resulted in a systematic early over-administration of drug followed by an under-administration. Clearly, this profile was not optimal.

The concentration time data and infusion profile of Iteration 1, when treated by the Plasma Drug Efflux Method, produced the infusion profile of Iteration 2, which had the following equation:

$$Ep(t) = 42.26e^{-.142t} + 4.31e^{-.0085t} + 7 \qquad (6)$$

The corresponding concentration data for the first 60 min were much more evenly distributed around the desired level than for Iteration 1, but analysis of variance indicated that there was a significant degree of skew in this data ($F_{7,61} = 2.71, P < 0.05$), showing that this was still not the optimal profile.

Iteration 3, generated from the results of Iteration 2, is shown in the lower panel of figure 3. Analysis of variance was unable to detect any significant deviation from a constant level ($F_{15,104} = 0.0931, P > 0.05$). Pooling of the concentration data over the entire sampling period for this iteration revealed that the average of the concentrations achieved in each patient was 99.1% of the desired level, with a 95% confidence interval of this mean of ±3.3%. Hence, as there was no systematic deviation from a constant level or overall bias of the concentration results, the infusion profile used in Iteration 3 is indistinguishable from the optimum result. Therefore, the Plasma Drug Efflux method can be considered to have "homed-in" on the optimum infusion profile for this group of patients over the sampling period of 3 h.

The equation for the Plasma Drug Efflux profile in Iteration 3 was:

$$Ep(t) = 25.35e^{-.145t} + 4.85e^{-.0148t} + 8.8 \qquad (7)$$

This has a value of 9.1 $ml \cdot min.^{-1} \cdot kgLBM^{-1}$ at the end of a 3-h infusion.

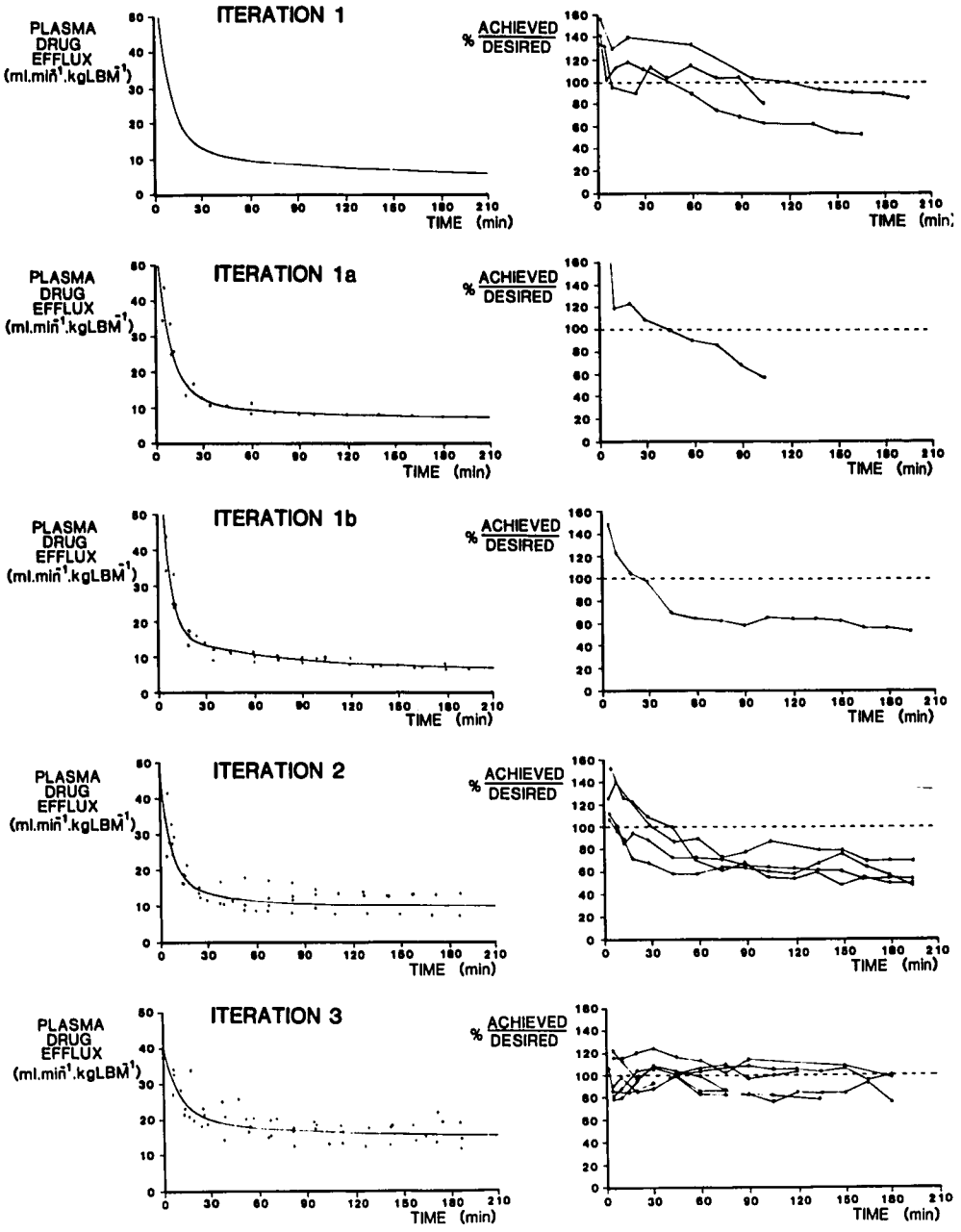


FIG. 4. Infusion profiles, Efflux points, and individual concentration data for successive iterations during the optimization procedure for methohexital (fig. 3). The infusion profile for Iteration 1 is identical to that shown in Iteration 1 for thiopental.

## METHOHEXITAL

The results of the optimization procedure for methohexital are very similar in outline to those of thiopental, and are presented graphically, in the same format, in figure 4. As would be anticipated, the concentration results of Iteration 1 were far from ideal. The profile for Iteration 1a was produced from these results:

$$Ep(t) = 47.53e^{-.112t} + 6.38e^{-.0172t} + 7, \quad (8)$$

and, following this, Iteration 1b:

$$Ep(t) = 84.46e^{-.193t} + 11.07e^{-.0141t} + 6 \quad (9)$$

from the data of the previous two iterations.

Iteration 2 was performed using the data from Iterations 1, 1a, and 1b combined, and may be considered to be the true second iteration step with an equation of:

$$Ep(t) = 30.27e^{-.158t} + 9.00e^{-.032t} + 10 \quad (10)$$

Analysis of variance indicated the presence of significant deviation from a constant level ($F_{14,28} = 5.11$, $P < 0.05$), which is evident from a visual inspection of the data.

Analysis of variance on the concentration data of Iteration 3, using the infusion profile derived from Iteration 2, indicated no significant deviation from a constant level ($F_{13,49} = 0.628$, $P > 0.05$). Pooling of the

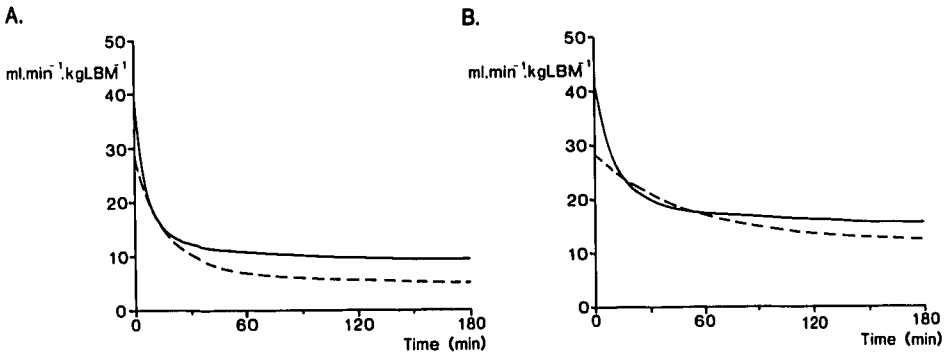


FIG. 5. *A.* Graphical comparison of the infusion profile for thiopental in the final iteration in this study (—) with the infusion profile used in our previous study using a standard compartmental model and coefficients averaged from published kinetic data[9] (---). *B.* Graphical comparison of the infusion profile for methohexital in the final iteration of this study (—) with a theoretical infusion profile generated using a compartmental model and based on the only suitable published kinetic data available (---).[14]

concentration data over the entire sampling period for this iteration revealed that the average of the concentrations achieved in each patient was 97.9% of the desired level, with a 95% confidence interval of this mean of ±3.1%. The infusion profile of Iteration 3 can thus be considered to be indistinguishable from the optimum result for methohexital.

The equation for the Plasma Drug Efflux profile for Iteration 3 was:

$$Ep(t) = 22.21e^{-.092t} + 5.09e^{-.0121t} + 15 \quad (11)$$

This has a value of 15.6 ml · min$^{-1}$ · kgLBM$^{-1}$ at the end of a 3-h infusion.

## Discussion

The results of the Plasma Drug Efflux method for both thiopental and methohexital indicate that the technique is a powerful tool for the generation of optimal infusion profiles. The performance of the task in only three iterations for each drug and, particularly, the need for only nine patients for the methohexital optimization, despite the use of an early thiopental profile for Iteration 1, emphasize the economical nature of the method.

The choice of polyexponential equations to describe the Efflux function was based on the availability of curve fitting routines, and does not imply dependence on an exponential model. In the context of this study, only the shape of the profile is important, and not the number or values of the coefficients. If a polynomial equation had been employed for curve fitting, this would have permitted automatic correction, up or down, if needed. While the Efflux method would permit such correction, it appears that a general approach was not required for either thiopental or methohexital.

The use of different bolus doses at the start of each infusion appeared to have little effect on the resulting profile, but this would be expected from the well-known rapid distributive properties of both thiopental and methohexital. For other drugs with smaller volumes of distribution, such as alfentanil, much closer attention would need to be paid to the control of bolus size.

The use of calculated lean body mass (LBM) to individualize dosage was based on our success with the use of LBM in unselected surgical patients when $ED_{50}$ values were determined for a variety of anesthetic induction agents, including thiopental and methohexital.[11] We were not able to formally compare various possible methods of measuring patient size in this study, but we feel that LBM is a more useful predictor of dose requirements for the barbiturates than total body weight.

Achieved concentrations in the final iteration for each drug in general remained within the range of ±20% of the desired concentration for each drug throughout the infusion period (figs. 3, 4). We feel that this is acceptable in a quite heterogeneous group of patients (tables 2, 3). Again, a formal comparison was not made with the results of other studies, due to the limited amount of comparable infusion data available. It can be said, however, that, if variations in drug distribution and elimination occur during the infusion and they are reproduced in successive patients, the Efflux method will account for them. On the other hand, if individual patients vary, due to either hepatic or renal disease, for example, departures from expected levels may occur whether the Efflux method or single-bolus elimination-based profiles are used to generate infusion profiles.

Figure 5A presents a graphical comparison of the infusion profile used for thiopental in the final iteration in this study (solid line) with the infusion profile used in our previous study, using a standard compartmental model and coefficients averaged from published elimination based kinetic data (broken line).[9] Figure 5B presents a comparison of the final infusion profile for methohexital (solid line) with a theoretical infusion profile generated from a compartmental model based on the only suitable kinetic data available (broken line).[14] When considered over the 3-h study period, it can be seen, in the case of thiopental, that a departure com-

mences at 15 min, and that, at 1 h, the Efflux function is 50%, and, at 3 h, 100%, greater than the elimination-based profile. While a point-by-point comparison has not been undertaken, previous infusions derived from elimination-based kinetic data produced mean concentrations of 74.5 ± 16.0% of the desired levels at the end of 2 h.[9] This is significantly different from the present infusion results of Iteration 3 for thiopental (table 2), where the mean concentration after 2 h was 96.0 ± 14.9% of the desired level in 14 patients ($t_{11} = 9.56$, $P < 0.05$).

In the case of methohexital, the only study providing the kinetic data required to generate an elimination-based infusion is presented by Breimer.[14] Considerable disparity exists, both early and late between the elimination-based and the Efflux-based curves (fig. 5). No infusion data have been published to permit a comparison with the Efflux method.

With regard to the ultimate drug elimination rate, it is likely, in the case of thiopental, that equilibrium was not reached within the 3-h study period. The plasma drug Efflux, at 3 h of 9.1 $ml \cdot min^{-1} \cdot kgLBM^{-1}$, is markedly different from previously reported clearances of 4.3, 2.6, and 3.2 $ml \cdot min^{-1} \cdot kg^{-1}$.[15–17] Whether the full explanation of the disparity is a failure to approach steady state after 3 h, or it is the result of an actual increase in clearance at the therapeutic concentration (10 $mg \cdot l^{-1}$), as opposed to those encountered during the late phase of elimination (0.01–0.05 $mg \cdot l^{-1}$), is not clear. Failure to reach equilibrium is a probable explanation for a drug with extensive distribution, such as thiopental. A disparity by a factor in excess of two is massive, however. Non-linear kinetics have been demonstrated for thiopental at concentrations above 20 mg/l,[18,19] where a clearance under infusion conditions of 2 $ml \cdot min^{-1} \cdot kg^{-1}$ has been reported,[18] but, at 10 $mg \cdot l^{-1}$, this is unlikely. The possibility of altered clearance at therapeutic levels remains, and has been discussed recently.[20] It is clear that the matter can only be resolved by studying much longer infusions in order to calculate clearance under true steady-state conditions.

In the case of methohexital, shown in figure 4, a plasma drug Efflux of 15.6 $ml \cdot min^{-1} \cdot kgLBM^{-1}$ compares somewhat better with clearance estimates of 10.9 and 12.1 $ml \cdot min^{-1} \cdot kg^{-1}$ reported from two single-dose studies.[14,21] The results suggest that equilibration is more closely approached with methohexital than with thiopental after 3 h, although the use of kinetic data based on total body weight in contrast to our data based on LBM makes comparison difficult.

As indicated previously, the results of this study only define infusion profiles for the 3 h studied. Longer infusions would be required to determine the continuation of either profile. In the absence of such studies, it could be said that predictions from a conventional single dose model would be more valid. It must be appreciated, however, that even with a single-dose model, the predictions of clearance relate to the accuracy of definition of the terminal elimination phase. This requires at least three well-spaced data points, and accuracy may be compromised by limitations in resolution of the analytical methods used. This is clear when comparing a study of thiopental elimination kinetics, where measurements were made to a plasma concentration in the vicinity of 100 $ng \cdot ml^{-1}$,[15] in which an elimination half-life of 5.14 h was reported, with one where measurements were made below 10 $ng \cdot ml^{-1}$,[16] in which an elimination half-life of 11.5 h was reported.

Methods of generation of infusions in patients using the profiles described in this study and in the various references cited rely on the availability of equipment to deliver drugs at variable rates, according to a predetermined profile. Equipment to achieve this is not generally available, although an appropriate device has been described.‡ External control of existing infusion pumps is possible,[22]§ but reliability, safety, and the compliance of computers with electrical leakage standards limit this approach in the operating theatre environment. The only other method available is to break a continuous infusion profile into a number of steps and to manually adjust the delivery rate of a conventional infusion pump. We have found this to be a workable compromise, either generating a time *versus* rate table prior to the infusion, or by programming a hand-held computer to display, in real time, the required delivery rate, elapsed time, and accumulated dose.[9]

In the event of patient variability or varying surgical stimulus, the programmed delivery rate may be altered once the infusion has commenced. Minor increases, together with a small added bolus, or decreases with a short pause in delivery would normally suffice in the case of thiopental or methohexital. Major adjustments would require, in theory, complete revision of the infusion profile. It should be appreciated, though, that such manipulations during standard general anesthesia are accomplished on a daily basis by anesthesiologists with the delivery of the volatile anaesthetic agents.

Finally, it should be stated that no attempt was made in this study to quantitate the clinical effects of either drug under infusion conditions. Concentrations in the vicinity of 10 $mg \cdot l^{-1}$ of thiopental were chosen by at-

‡ Crankshaw DP, Boyd MD: Open-loop control of drug infusion. European Patent Office, Bulletin 85/51, Application 0164904, December 18, 1985

§ Kenny GNC, Rennie R, Toal F, Reid JA: Computer control of an Imed 929 infusion pump. Journal of Medical Engineering and Technology 5:227, 1985

tending anesthesiologists on the basis of experience gained during a previous study.[9] The concentration of 5 $mg \cdot l^{-1}$ for methohexital, chosen on the basis of its potency being roughly twice that of thiopental, was also found to be satisfactory in most instances. Major departures in achieved levels or in drug requirements may well occur in differing situations[13,23] but such departures would apply equally to Efflux-based or elimination-based profiles. Variation in drug requirements should, in most cases, be anticipated by a trained anesthesiologist. It should also be appreciated when considering the safety of infusions that the levels of both thiopental and methohexital used in this study are approximately one-tenth of peak levels commonly achieved with bolus induction doses. No attempt was made to study depth of anesthesia, effects on the cardiovascular system, departures of the profile at higher or lower plasma concentrations, the effects of organ dysfunction, such as liver or kidney failure, or the effects of severe physiological disturbance, such as massive blood loss. Each would require separate study.

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