Calculated Kinetics of Distribution of Nitrous Oxide and Methoxyflurane during Intermittent Administration in Obstetrics

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Concentrations of nitrous oxide or methoxyflurane to be expected in the brain with intermittent administration to a woman in labor have been calculated. Moderate cyclic fluctuations in cerebral concentration of nitrous oxide result from intermittent administration on a two-minute cycle. For obstetric analgesia, nitrous oxide should be given about 50 seconds before the anticipated onset of each contraction for a period lasting approximately half the time between onsets of succeeding contractions. When methoxyflurane is administered intermittently, negligible cyclic variation in brain concentration can be expected when the patient is breathing normally. An explicit analytical model for the concentration effect is presented and its features discussed. (Key words: Nitrous oxide; Methoxyflurane; Obstetric analgesia; Computed kinetics; Concentration effect.)

INTERMITTENT ADMINISTRATION of an inhalation anesthetic may be used to produce analgesia in the second stage of labor. The custom of giving the anesthetic "with the pains" is obviously inappropriate; by the time uterine contractions have begun, it is too late to start administering the analgesic. There is an appreciable lag after the onset of administration before an adequate analgesic concentration of the drug in the brain can be expected. In fact, if the patient "breathes with the pains," she experiences analgesia by the end of the contraction, sleeps peacefully between the contractions, and wakes up just in time for the next one. Clearly, the anesthetic must be administered before the contraction is expected to begin. This then leads to the question, how far ahead should one start?

To answer this question a group of women in labor might be studied, but it would be difficult to do so without withholding the analgesic agent from some patients. Furthermore, the degree of variability among patients would be so great that an inordinately large number of patients would have to be studied before values could be measured with a useful degree of accuracy. Therefore, we have tried to answer the question with calculations based on conventional mathematical models describing the uptake and distribution of volatile anesthetics. There is considerable evidence that such mathematical models provide descriptions which are in excellent quantitative agreement with experimental results.

Methods

Calculations were carried out with an analog computer (EAI Model TR 10). Voltage pulses which provided the analog for the intermittent inspired concentrations of the anesthetic agent were obtained from Tektronix series 160 pulse generators. The output of the analog computer was recorded on a Sanborn Model 77011-1 pen recorder modified to have two 10-cm channels. The mathematical models used were based on conventional approaches.[1,2]

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The following equations were used:

(1) Balance equation for lung:

$$\frac{dC_a}{dt} = \frac{\dot{V}_A\lambda C_I - \dot{V}_A C_a - [(C_v - C_a)\dot{Q}/D]\lambda C_I + \dot{Q}\lambda C_v - \dot{Q}\lambda C_a}{V_A + V_B + V_W} \quad (1)$$

Equation 1 may be rearranged into a form more convenient for calculation:

$$\frac{dC_a}{dt} = \frac{\dot{V}_A}{V'_A}\lambda C_I - \frac{\dot{V}_A}{V'_A}C_a + \left(1 - \frac{C_I}{D}\right)\left(\frac{\dot{Q}\lambda}{V'_A}\right)(C_v - C_a) \quad (2)$$

where

$$V'_A = V_A + V_B + V_W \quad (2a)$$

(2) Balance equations for tissues:

$$\frac{d(C_i/\lambda_i)}{dt} = \frac{\dot{Q}_i}{\lambda_i V_i}\left(C_a - \frac{C_i}{\lambda_i}\right) \quad (3)$$

(3) Expression for mixed venous concentration:

$$C_v = \Sigma_i \frac{\dot{Q}_i C_i/\lambda_i}{\dot{Q}} \quad (4)$$

Symbols:

C_a = arterial concentration of anesthetic
V_A = alveolar ventilation as (respiratory rate) times (tidal volume − deadspace).
λ = blood–gas partition coefficient (0.468 for N_2O, 13 for methoxyflurane)
C_I = inspired concentration of anesthetic
D = density of anesthetic gas (1.73 g/l for N_2O, 6.5 g/l for methoxyflurane)
$\dot{Q}$ = cardiac output
C_v = mixed venous concentration of anesthetic
V_A = functional residual capacity + tidal volume
V_B = $\lambda \times$ cardiac output ÷ respiratory rate (see discussion)
V_W = volume of water vapor taken up by inspired gas
$V'_A = V_A + V_B + V_W$
C_i = concentration of anesthetic in i^{th} tissue group. i = 1 to 4 (i = 1 for vessel-rich group, 2 for muscle group, 3 for fat and 4 for vessel-poor group.)
λ_i = tissue–blood partition coefficient
$\dot{Q}_i$ = blood flow to i^{th} tissue group
V_i = volume of i^{th} tissue group

The circuit used is shown in figure 1. Values of the constants used are listed in tables 1 and 2.

Some comment about the derivation of these values is necessary. To get table 1 we proceeded in two stages. We started with the values used by Eger[3] for a "normal" man, and estimated equivalent values for a normal woman. On the basis of a value of 23 per cent[4] for the percentage of fat in a woman, we increased the value for fat from 19 per cent to 23 per cent at the expense of the vessel-poor group, which was reduced from 22 per cent to 18 per cent. Perfusion rates ($\dot{Q}_i/V_i$) for each of the four tissue groups were calculated from Eger's[3] values and applied to the tissue groups of a woman of weight x in whom the sum of the flows through the four tissue groups equalled 4.5 l/min (a value for a normal cardiac output in a woman[5]). The value of weight x required for consistency proved to be 115 pounds, a reasonable value for a normal woman. Thus, the partitioning of the normal woman into 9 per cent vessel-rich group, 50 percent muscle group, 23 per cent fat group, and 18 per cent vessel-poor group has not led to any gross inconsistency.

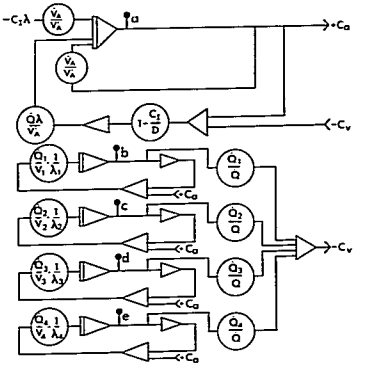

FIG. 1. Circuit used for the analog computation. The circuit consists essentially of three parts. The top three operational amplifiers and associated circuitry deal with the balance equation for the lung (equation 2). The four sets of three operational amplifiers in the lower left represent circuitry for solving the balance equations for the 4 tissue groups (equations 3). Finally, the operational amplifier at the far right computes mixed venous concentration as the appropriate weighted mean of the venous concentrations returning from each of the four tissue groups (equation 4). The voltages corresponding to concentrations of the anesthetic in arterial blood, vessel-rich group, muscle, fat and vessel-poor group are available at the terminals labelled *a* to *e*, respectively.

It was next necessary to estimate the tissue volumes to be expected in a pregnant woman. For this we have used the values for changes measured during pregnancy[5] and superimposed these on the values estimated for a nonpregnant woman. Specifically, breast enlargement was taken to add 430 ml to the vessel-rich group. The fetus, placenta, and uterine enlargement were taken to add 5.39 l to the muscle group. These were added to the muscle group rather than the vessel-rich group because the perfusion rates involved resembled more nearly those for muscle. Fat was increased by 4.4 l and the vessel-poor group increased by 800 ml, the volume of the amniotic fluid.

Finally, various tissue flows had to be estimated. Hytten and Leitch[5] reported increases in various specific vascular beds. These were incorporated into the model. They also reported a change in cardiac output. Increases in flow to areas such as skin and muscle were assigned somewhat arbitrarily to produce a total cardiac output compatible with their measured value. The final results of all these calculations are given in table 1.

Values for respiratory parameters in table 2 were derived as follows. The value for functional residual capacity in a pregnant woman was obtained from Cuggell *et al.*[6] The des-

TABLE 1. Cardiovascular Parameters in a Pregnant Woman at Term

Parameter	Units	Vessel-rich Group	Muscle Group	Fat	Vessel-poor Group	Total
$\dot{Q}_i$	l × min^{-1}	3.775	1.117	0.290	0.046	5.228
	l × sec^{-1}	0.0629	0.0186	0.0048	0.0008	0.087
V_i	l	5.043	30.838	17.920	8.483	62.284
$\frac{\dot{Q}_i}{V_i}$	sec^{-1}	0.0125	0.0006	0.00026S	0.00009	
$\frac{\dot{Q}_i}{\dot{Q}}$	—	0.723	0.214	0.055	0.009	
Nitrous oxide λ_i	—	1.06	1.13	2.3	1.0	
$\frac{\dot{Q}_i}{V_i}\cdot\frac{1}{\lambda_i}$	sec^{-1}	0.0118	0.000534	0.000116	0.00009	
Methoxyflurane λ_i		2.0	1.34	63	1.0	
$\frac{\dot{Q}_i}{V_i}\cdot\frac{1}{\lambda_i}$	sec^{-1}	0.00625	0.00044S	0.00000422	0.00009	

TABLE 2. Respiratory Parameters in a Pregnant Woman at Term

Parameter	Units	Normal Respiration	Panting	Extreme Panting
$\dot{V}_A$	liters × sec^{-1}	0.237	0.620	1.24
V_A	liters	2.191	2.658	2.658
V_W	liters	0.054	0.124	0.124
Nitrous oxide				
V_B	liters	0.125	0.123	0.610
V'_A	liters	2.37	2.905	2.843
$\frac{\dot{V}_A}{V'_A}$	sec^{-1}	0.1	0.2134	0.436
$\frac{\dot{Q}_\lambda}{V'_A}$	sec^{-1}	0.0172	0.0140	0.0144
Methoxyflurane				
V_B	liters	3.471	3.406	1.690
V'_A	liters	5.716	6.188	4.472
$\frac{\dot{V}_A}{V'_A}$	sec^{-1}	0.04146	0.100	0.277
$\frac{\dot{Q}_\lambda}{V'_A}$	sec^{-1}	0.198	0.183	0.253

space of 140 ml was obtained from Hytten and Leitch.[5] The remaining values for the pregnant woman during labor were obtained from Crawford and Tunstall,[7] who reported that contractions occurred about every two minutes and lasted an average of 46 seconds during stage II. They observed 15 respirations per contraction, amounting to a respiratory rate of 19.6/min. This value, along with those for deadspace and tidal volume, yields an alveolar ventilation of 0.237 l/sec.

Rate of onset of analgesia can be affected by changes in respiration. It is of interest, therefore, to extend calculations to include the effects that might be expected if the patient were panting. Values for respiratory parameters in a pregnant woman who is panting are not directly available. Cuggell *et al.*[6] give a maximal breathing capacity of 97 l/min for a pregnant woman. We have arbitrarily decided to use approximately half this value to describe the panting patient. Specifically, we chose a tidal volume of 2 l and a respiratory rate of 20/min. Deadspace was not modified, and alveolar ventilation became 620 ml/sec. The increased tidal volume was taken partly at the expense of the functional residual capacity, which was lowered to 660 ml. Finally, we made a few calculations assuming the patient were breathing at twice the rate used for "panting" to get an indication of the limit to be expected with hyperventilation.

The value V_W for the volume of water vapor added to the inspired gas was obtained by taking (47 + 760)/760 times the uncorrected value for the tidal volume where 47 torr is the vapor pressure of water at 37 C.

Nitrous oxide is representative of an anesthetic with low solubility. Trichlorethylene (Trilene) and methoxyflurane (Penthrane), agents with higher solubilities, are also used for obstetric analgesia. Values for the relevant partition coefficients for trichlorethylene are not available. However, enough values for methoxyflurane were available[8] to make possible a reasonable calculation. The values used are given in tables 1 and 2.

Results

The general nature of the phase relationships involved can be seen in figure 2, a tracing of the concentration of nitrous oxide in the vessel-rich group when the anesthetic is administered in an inspired concentration of 50 per cent for 60 sec every 120 sec. Elevation of the signal tracing indicates the periods when the inspired concentration was 50 per

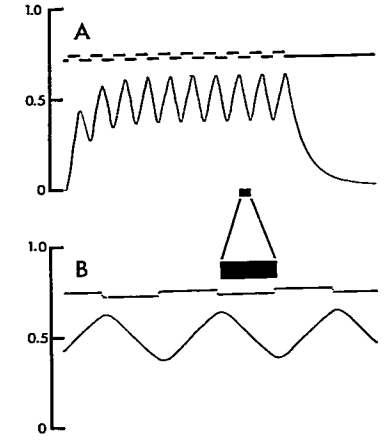

FIG. 2. Computed concentrations of nitrous oxide in the vessel-rich group. *Ordinates:* concentration as fraction of value that would obtain if equilibrium were reached (0.0111 *M* when inspired concentration is 50 per cent). *Abscissae:* time, horizontal black bar represents 60 sec. The time scale is expanded fivefold in panel *B*, where the longer black bar also represents 60 sec. Panel *A* shows the approach to steady state for the first ten cycles, followed by washout. Initially, the concentration in the vessel-rich group is zero. When nitrous oxide is administered for the first 60-sec period, the concentration rises rapidly, then falls as the patient returns to breathing room air. With the next cycle of administration of nitrous oxide, the concentration rises again and reaches a somewhat higher peak, and by about the 4th cycle, the steady state is reached. With the return to room air after the 10th period of administration, the concentration falls monotonically to zero. The concentration in the vessel-rich group clearly lags in time behind the administered concentration, but this can be seen more clearly in panel *B*, where the values obtained in the steady state are presented on a faster time base. In each panel an upward deflection of the upper tracing indicates the periods during which nitrous oxide was administered for the first 60 sec of each 120-sec cycle.

cent. The expected phase lag is clearly visible. In each cycle, concentration in the brain reaches peak values about a minute after administration starts.

To achieve maximal analgesia during the contraction, administration should be timed so that the highest concentrations are achieved during the period of the contraction. This can be shown geometrically, as in figure 3. First, mark off the interval bd of 46 sec (the length of an average contraction[7]) and locate this interval on the concentration curve so that highest levels occur between b and d, as indicated in the figure. Then ab indicates how much the onset of administration of the nitrous oxide should precede the anticipated onset of the contraction. The time is about 45 sec in figure 3. Clearly, the practicing anesthesiologist cannot make such an explicit calculation of the exact time relations to use. However, a schema such as that depicted in figure 3 can still be in the back of his mind.

This value for the time lag implies that one should administer nitrous oxide about 45 sec before the contraction is anticipated. However, one might ask how sensitive this value is to changes in duration of period of administration, inspired concentration, respiratory rate and tidal volume. Figure 4 shows calculations for situations in which 50 per cent nitrous oxide is given for periods varying from 30 to 90 sec in each two-minute interval. The shorter the period of administration, the shorter the interval between beginning of administration and the time when concentrations in the brain will be highest. Calculations to illustrate the effects of different concentrations of nitrous oxide have not been illustrated because changing the concentration was found to have a negligible effect on the phase relationships. For example, when the nitrous oxide is given for 60 sec the peak concentra-

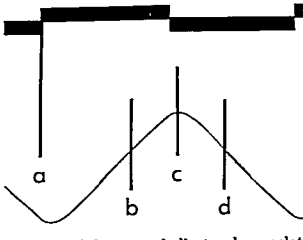

FIG. 3. Scheme to indicate phase relationships relevant to the administration of nitrous oxide to a woman in labor. Tracings as in figure 2, panel *B*. The point *c* indicates the peak of the concentration curve. Interval *bd* indicates where the contraction should occur. Interval *ab* indicates the appropriate amount of time that onset of administration should precede anticipated onset of contraction.

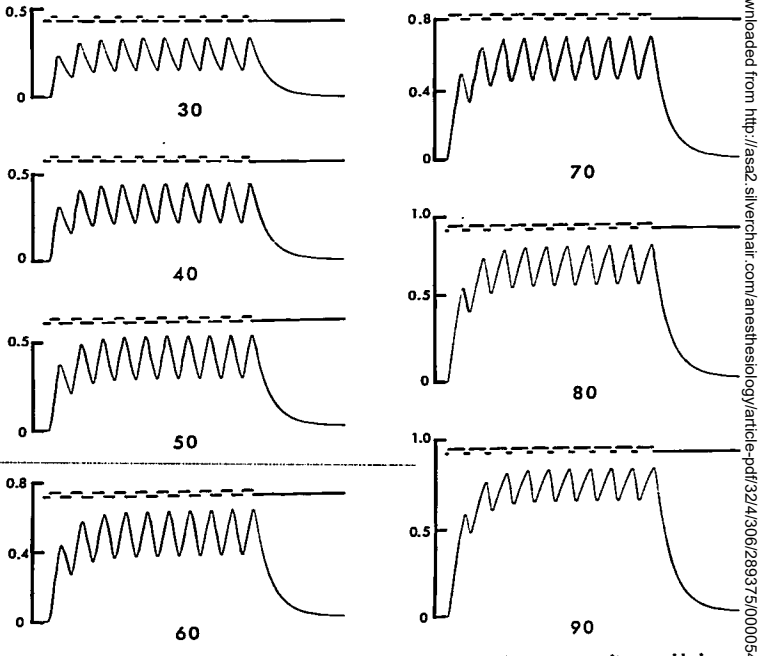

FIG. 4. Effect of varying the duration of the administration of 50 per cent nitrous oxide in each cycle. Tracings as in figure 2A. 120-sec cycle. Normal respiration. Nitrous oxide was administered for 30, 40, 50, 60, 70, 80 and 90 sec of each 120 sec. The nitrous oxide concentration was 50 per cent. With increasing duration of the period of administration, the concentration in the vessel-rich group lags farther behind the onset of administration. The difference between the highest and lowest concentrations achieved in a steady state is least at the high and low durations of administration and rises to its highest values in between.

tion in the vessel-rich group occurs about 60 sec after the beginning of administration at both inspired concentrations. An increase in the inspired concentration was found to produce a slight increase in the difference between the peak and minimal relative concentrations achieved in the quasi-steady state reached with a few cycles of administration.

Finally, when the effect of ventilation was examined, it was found that, as expected, increased ventilation increases the difference between the peak and minimal relative concentrations achieved in the steady state. The effect was greater when the anesthetic was given for 60 sec of the 120-sec cycle than for 30 or 90 sec. Again as expected, concentrations achieved were higher with increased ventilation, but the effect is not pronounced. Increased ventilation produced no appreciable change in phase relationships.

Figure 5 shows representative results with methoxyflurane. The phase lag seems similar to that seen with nitrous oxide. The most striking feature of methoxyflurane is the decrease in difference between peak and minimal concentrations achieved in each cycle. Hyperventilation produces a greater percentage increase than that seen with nitrous oxide.

Discussion

Theoretical

Several features of the balance equations merit comment. First, the form of the term expressing the "concentration effect"[3] is of interest.

When an anesthetic crosses the alveolar membrane to dissolve in the blood, the alveolus is refilled by gas that flows in from the mixture being administered. An increase in the effective $\dot{V}_A$ results. The magnitude of this effect will be proportional to the rate at which the anesthetic becomes dissolved in the blood, *i.e.*, to $-(C_v - C_a)\dot{Q}$. This rate of change of *amount* of anesthetic taken up can be converted into a rate of change of an equivalent gaseous *volume* by dividing by the density, D. The resulting rate of change of volume is added in the third term of the numerator in equation 1. Equation 1 can be rearranged, however, to the form in equation 2, by collecting terms in $(C_v - C_a)$. In this form the concentration effect appears as the second element in the expression $(1 - C_I/D)$.

This form is particularly interesting. First, it indicates a natural unit for inspired concentration; it is most meaningful to express C_I relative to D. Inspired concentration, then, is measured on a scale of C_I/D running from 0 to 1. An inspired concentration of 50 per cent would correspond to a value of C_I/D of 0.5.

If C_I is much less than D, *i.e.*, the agent is used at a low concentration, the expression $(1 - C_I/D)$ becomes unity; that is, there is no concentration effect. If the agent is used at 100 per cent, the term C_I/D becomes 1, the term in brackets becomes zero, and the last term in equation 2 vanishes to give the special case:

$$\frac{dC_a}{dt} = \frac{\dot{V}_A}{V'_A}\lambda C_I - \frac{\dot{V}_A}{V'_A}C_a = \frac{\dot{V}_A}{V'_A}(\lambda C_I - C_a) \quad (5)$$

At first, the form of this equation may seem surprising. As some of the nitrous oxide is absorbed, when 100 per cent nitrous oxide is administered, more pure nitrous oxide would be sucked into the lungs, and one might imagine that the whole process would go to completion very rapidly. In other words, respiration would not be rate-limiting, so respiratory parameters might not be expected in equation 5. However, equation 5 indicates that the rate constant $(\dot{V}_A/V'_A)$ will depend on the rate of ventilation and not on the circulatory parameter $\dot{Q}\lambda/V'_A$ (the measure of pulmonary perfusion in equation 2). The apparent inconsistency can be reconciled by focussing not on the nitrous oxide but on the air in the lungs as one switches from room air to 100 per cent nitrous oxide. The limiting factor now becomes not the rate at which nitrous oxide enters the lungs but the rate at which room air is washed out of the lungs. For it is not until all the air has been removed from the respiratory tract that equilibration with 100 per cent nitrous oxide can occur. The rate at which this air can be removed, of course, will depend directly on respiratory parameters.

The next term of interest in the balance equations is the term V_B in the denominator of equation 1. When the anesthetic is drawn into the alveoli, it is distributed not only in the alveolar volume V_A but also in the blood which happens to be in the lung. The appropriate blood volume to be considered here is the amount of blood that comes into the lung in the period of one breath. In other words, the cardiac output divided by the respiratory rate.

The form of equations 3 deserves comment. The equation is set up in terms of C_i/λ_i for convenience in scaling of the analog computer. However, this form also emphasizes that normalization on the basis of the blood-tissue solubility coefficient has a natural mathematical basis. Furthermore, the equations in the form 3 emphasize the natural form of the perfusion rate constant as the tissue blood flow $\dot{Q}_i$ divided not by the anatomic volume V_i but by the effective or virtual volume, $\lambda_i V_i$. It may be noted in passing that a similar scaling may be seen in equation 1, where λC_I becomes the natural unit for inspired concentration, *i.e.*, in equations 1 through 4 all concentrations have been normalized relative to the arterial concentration.

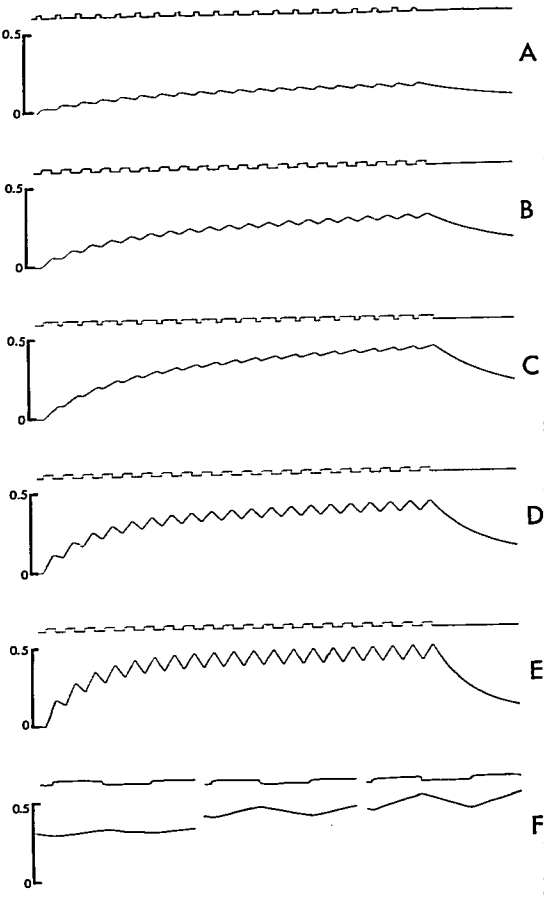

FIG. 5. Concentrations achieved with methoxyflurane. Tracings analogous to those in figure 2A. Panels *A*, *B* and *C*, normal respiration. Methoxyflurane was administered for 30, 60 and 90 sec of each 120-sec cycle. Panels *B*, *D* and *E*, administration for 60 sec of each 120-sec cycle, normal respiration, "panting" and maximal respiratory effort, respectively. In panel *F* are samples of panels *A*, *B* and *C* on a 5 fold-expanded time scale.

PRACTICAL

The idea that administration of an obstetric analgesic should precede the pain is not profound (although it is difficult to find it stated explicitly in textbooks). The point of the present paper is not to show that a lag is involved, nor that cerebral concentrations of methoxyflurane cannot be made to fluctuate as much as those of nitrous oxide—so much is clear intuitively—but rather to estimate the magnitudes of the phase lag and the fluctuations in concentration.

In the results, concentrations have been expressed relative to the concentration that would be achieved at a steady state if the

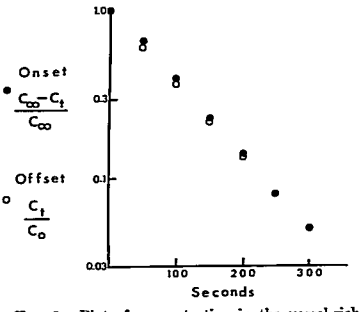

FIG. 6. Plot of concentration in the vessel-rich group against time when nitrous oxide is administered continuously (●) and then washed out (○). Ordinates are the differences between concentration at time t (C_t) and that at equilibrium (C_∞) normalized so that the initial difference is unity. Specifically, onset is assumed to follow the equation $C_t = C_\infty(1 - e^{-kt})$ and offset to follow $C_t = C_o e^{-kt}$ (where C_o is the initial concentration). If these equations are obeyed, then the semilogarithmic plots in the figure should be linear with a slope of $-k$. (For example, if $C_t = C_o e^{-kt}$, $\log C_t = \log C_o - kt$, this is a linear relation between $\log C_t$ and t with intercept $\log C_o$ and slope $-k$). The values plotted were obtained from tracings of calculated concentration changes for onset and offset (such as the falling curve at the right end of fig. 2A).

anesthetic were given continuously. The concentration effect does not produce a great difference in the shapes of the curves at 50 percent and 100 per cent nitrous oxide, and presumably this applies to concentrations between. For the problem at hand, the particular concentration that gives the desired degree of analgesia need not be considered precisely. In practice, an effective inspired concentration would be chosen on the basis of past experience and the results of the present paper would be used to achieve optimal timing.

The difference between the peak achieved with administration and the minimum reached between periods of administration is of interest. The greater this difference, the easier it will be to have the patient comfortable during the contractions, but conscious between them. Figure 4 indicates that the difference between peak and minimum is greatest somewhere between the extremes of very brief and very long periods of administration. (This relationship is examined further in the appendix.)

Note that there is no reason to restrict the duration of the period of administration to values that match the duration of the contraction. On the other hand, anesthetic administration must be repeated at intervals equal to the time between onsets of successive contractions to stay in phase with the latter. Therefore, a rational schedule for the administration of nitrous oxide for obstetric analgesia would be to give the anesthetic for periods equal to approximately half the time between the onsets of two successive contractions. These periods of administration should be timed to start about 45 sec before the anticipated onset of the next contractions.

The computer model does not include delays due to circulation time. In the usual[1] computations of concentrations resulting from reasonably prolonged periods of administration, neglect of circulation time has led to results consistent with those observed experimentally. However, with intermittent administration, in particular when phase lags are of interest, circulation time should be considered.

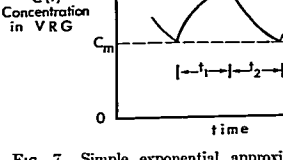

FIG. 7. Simple exponential approximation to concentration fluctuations in the steady state with intermittent administration of nitrous oxide. The rising phase (from minimal concentration C_m to peak concentration C_p) is taken as the segment from C_m to C_p of an exponential rise from zero concentration to the equilibrium value C_∞. Similarly, the falling phase may be taken as a segment from an exponential-falling curve. The appropriate general exponential curve may be written $C(t) - C_\infty = (C_o - C_\infty)e^{-kt}$ (where C_o is the initial value). Then the rise is fitted by $C(t) - C_\infty = (C_m - C_\infty)e^{-kt}$ (C_o becomes C_m), and the fall by $C(t) = C_p e^{-kt}$ (C_o becomes C_p, $C_\infty = 0$).

In the present calculations, the lung-to-brain circulation time should be added to the value of 45 sec given at the end of the previous paragraph; this circulation time is about 6 sec.* This adjustment to the value of 45 sec is probably within the limits of accuracy of that estimate, but a corrected value of about 50 sec seems a reasonable final value to use.

As might be expected from the slow action of methoxyflurane, the fluctuations in concentration with intermittent administration are much smaller than those seen with nitrous oxide. In fact, at normal levels of respiration there is, for all practical purposes, no fluctuation. Thus, when methoxyflurane is used, the anesthesia cannot be expected to decrease appreciably in depth between contractions. Phase lags appear similar to those seen with nitrous oxide, but there is little point in considering them in the face of negligible cyclic variation in concentrations achieved. Hyperventilation does increase the difference between peak and minimal concentrations (figs. 5*B*, *D* and *E*), but not to a degree that would be of much use in practice.

In addition to accelerating the rate of uptake of an anesthetic, hyperventilation can decrease arterial P_{CO_2} and, therefore, cerebral circulation. The brain, however, is so well perfused that the rate of equilibration is limited more by ventilation than by physiologic changes in cerebral blood flow. This secondary effect of hyperventilation has been considered small relative to variation between patients and has been neglected in the calculations.

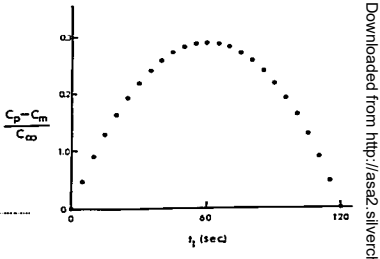

FIG. 5. Calculated values for the difference ($C_p - C_m$) between peak and minimal concentrations achieved with intermittent administration of 50 per cent nitrous oxide. Solutions of equation 12 with $t_1 + t_2 = 120$ sec and $k = 0.01$/sec. Ordinates are $C_p - C_m$ as a fraction of the concentration C_∞ that would be reached in the steady state if the nitrous oxide were administered continuously. Abscissae are the durations of the periods of administration in each 120-sec. cycle.

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* An explicit measurement of alveolus-to-brain circulation time is not available, but an estimate can be obtained from the Handbook of Circulation,[9] table 5S. Arm-to-brain circulation time is given as 13 sec (thiopental). Arm-to-right atrium and arm-to-left ventricle circulation times are given as 6.4 sec and 8 sec, respectively. So arm-to-lung circulation time will be about 7 sec. This leaves 6 sec for the lung-to-brain time.

APPENDIX

In figure 4, the difference between the peak concentration achieved with administration of nitrous oxide and the minimal concentration reached between periods of administration is a function of the duration of the period of administration. This relationship can be examined in more detail. The shape of the tracings suggests that a simple ex-

ponential approximation might be quite close (even though the process is not basically a single exponential). Furthermore, the rate constants for onset and offset might be expected to be the same. Figure 6 shows a semilogarithmic plot which supports both the above expectations. Onset and offset are both exponential. The rate constants obtained from the slope are both 0.01/sec. Thus, the situation in the steady state of figure 4 can be approximated well with the model in figure 7 in which:

$$C(t) - C_\infty = (C_m - C_\infty)e^{-kt} \quad (6)$$

during rise of concentration, and

$$C(t) = C_p e^{-kt} \quad (7)$$

during washout.

Specifically:

$$C_p - C_\infty = (C_m - C_\infty)e^{-kt_1} \quad (8)$$

and

$$C_m = C_p e^{-kt_2} \quad (9)$$

Substitution of (9) into (8) with rearrangement yields

$$\frac{C_p}{C_\infty} = \frac{1 - e^{-kt_1}}{1 - e^{-k(t_1+t_2)}} \quad (10)$$

and C_m becomes

$$\frac{C_m}{C_\infty} = \frac{e^{-kt_2} - e^{-k(t_1+t_2)}}{1 - e^{-k(t_1+t_2)}} \quad (11)$$

Thus, an expression for $C_p - C_m$, the difference we seek, becomes

$$\frac{C_p - C_m}{C_\infty} = \frac{1 - e^{-kt_1} - e^{-k[(t_1+t_2)-t_1]} + e^{-k(t_1+t_2)}}{1 - e^{-k(t_1+t_2)}} \quad (12)$$

This may be solved by digital techniques with t_2 as the independent variable, $t_1 + t_2 = 120$ sec and $k = 0.01$/sec. The results are given in figure 8. The optimal size for t_1 is 60 sec (as may be confirmed by differentiation). The largest peak–minimum difference is 0.29 C_∞, and values of this order may be obtained with t_1 between about 40 to 80 sec in a 2-min cycle.

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