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

B. E. Waud, M.D.,* and D. R. Waud, M.D., D.Phil.†

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 concentra-

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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 7701A pen recorder modified to have two 10-cm channels. The mathematical models used were based on conventional approaches.1,2
The following equations were used:

1) Balance equation for lung:

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

(1)

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

\[
\frac{dC_a}{dt} = \frac{\dot{V}_A}{V_A} \lambda C_I - \frac{V_A}{V_A} C_a + \left(1 - \frac{C_I}{D}\right) \left(\frac{\dot{Q} \lambda}{V_A}\right) (C_v - C_a)
\]

(2)

where

\[V_A = V_A + V_B + V_W\]  

(2a)

2) Balance equations for tissues:

\[
\frac{d(C_v/\lambda_i)}{dt} = \frac{\dot{Q}_i}{\lambda_i V_i} \left(\frac{C_a}{\lambda_i} - \frac{C_i}{\lambda_i}\right)
\]

(3)

3) Expression for mixed venous concentration:

\[C_v = \sum_i \frac{\dot{Q}_i C_i / \lambda_i}{\dot{Q}}\]

(4)

Symbols:

- \(C_a\) = arterial concentration of anesthetic
- \(V_A\) = alveolar ventilation as (respiratory rate) times (tidal volume - deadspace).
- \(\lambda\) = 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. \(i = 1 to 4\) (1 = for vessel-rich group, 2 for muscle group, 3 for fat and 4 for vessel-poor group.)
- \(C_i = concentration of anesthetic in \(i^{th}\) tissue group.
- \(\dot{Q}_i\) = 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 for a "normal" man, and estimated equivalent values for a normal woman. On the basis of a value of 23 per cent 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 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). 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.
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 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 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. The dead-

<table>
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<tr>
<th>Parameter</th>
<th>Units</th>
<th>Vessel-rich Group</th>
<th>Muscle Group</th>
<th>Fat</th>
<th>Vessel-poor Group</th>
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<td>$Q_i$</td>
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<td>Panting</td>
<td>Extreme Panting</td>
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<td></td>
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<td>0.183</td>
<td>0.253</td>
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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 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
First, mark off the interval bd of 46 sec (the length of an average contraction*) 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 concent-

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.

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*Note: The asterisked text in the original document was not transcribed.
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.

Fixation 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. Hyper-ventilation 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” 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 $(1 - C_t/D)$.

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

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

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

(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 $\dot{Q}/V'_A$ (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 $C_t/V_t$ 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 $\dot{Q}_t$ divided not by the anatomic volume $V_t$ but by the effective or virtual volume, $\lambda_t V_t$. It may be noted in passing that a similar scaling may be seen in equation 1, where $\lambda C_t$ becomes the natural unit for inspired concentration, i.e., in equations 1 through 4 all concentrations have been normalized relative to the arterial concentration.
PRACTICAL

The idea that administration of an obstetric analgesia 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
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 onset 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 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. 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 (Ct) and that at equilibrium (C∞) normalized so that the initial difference is unity. Specifically, onset is assumed to follow the equation Ct = C∞(1 − e−kt) and offset to follow Ct = C∞e−kt (where C∞ 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 Ct = C∞e−kt, logCt = logC∞ − kt, this is a linear relation between logCt and t with intercept logC∞ 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).

**Fig. 7.** Simple exponential approximation to concentration fluctuations in the steady state with intermittent administration of nitrous oxide. The rising phase (from minimal concentration Cm to peak concentration Cp) is taken as the segment from Cm to C∞ 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 $C(t) = C_\infty = (C_\infty - C_m)e^{-kt}$ (where C∞ is the initial value). Then the rise is fitted by $C(t) = (C_\infty - C_m)e^{-kt}$ (C∞ becomes Cm), and the fall by $C(t) = C_\infty e^{-kt}$ (C∞ becomes Cm, C∞ = 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. 5B, 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 Pco₂ 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.

References


* An explicit measurement of alveolus-to-brain circulation time is not available, but an estimate can be obtained from the Handbook of Circulation, table 58. 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.

Fig. 5. Calculated values for the difference (Cₚ - Cₘ) between peak and minimal concentrations achieved with intermittent administration of 50 per cent nitrous oxide. Solutions of equation 12 with t₁ + t₂ = 120 sec and k = 0.01/sec. Ordinates are Cₚ - Cₘ as a fraction of the concentration Cₘ that would be reached in the steady state if the nitrous oxide were administered continuously. Abscissa are the durations of the periods of administration in each 120-sec cycle.


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:

$$C(t) - C_m = (C_m - C_a)e^{-kt}$$

during rise of concentration, and

$$C(t) = C_me^{-kt}$$

during washout.

Specifically:

$$C_p - C_m = (C_m - C_a)e^{-kt_1}$$

and

$$C_m = C_pe^{-kt_2}$$

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

$$\frac{C_p}{C_m} = \frac{1 - e^{-kt_1}}{1 - e^{-k(t_1+t_2)}}$$

(10)

and $C_m$ becomes

$$\frac{C_m}{C_p} = \frac{e^{-kt_2} - e^{-k(t_1+t_2)}}{1 - e^{-k(t_1+t_2)}}$$

(11)

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

$$\frac{C_p - C_m}{C_m} = \frac{1 - e^{-kt_1} - e^{-k(t_1+t_2)-k1} + e^{-k(t_1+t_2)}}{1 - e^{-k(t_1+t_2)}}$$

(12)

This may be solved by digital techniques with $t_1$ 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 $C_m$, 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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