Laboratory Report

The Concentration Effect Can Be Mimicked by a Decrease in Blood Solubility

Edmond I. Eger, II, M.D.,* Raymond A. Smith, Ph.D.,† Donald D. Koblin, Ph.D.†

The concentration effect defines the impact of the inspired anesthetic concentration on the rate at which the alveolar concentration rises towards the inspired concentration.1,2 At low inspired concentrations, the alveolar level reflects a balance between ventilatory input and uptake (e.g., when three fourths of the anesthetic inspired is taken up, then the alveolar concentration is one fourth of that inspired). At higher inspired concentrations, uptake has less influence, and at 100 per cent inspired concentration, uptake into blood no longer influences the rate at which the alveolar concentration rises. That is, at 100 per cent, the rate of rise is solely determined by the washin rate of the lungs. The existence of the concentration effect and its quantitation have been described by computer simulation3 and by experiments in animals4 and man.1

The description by computer simulation must take into account both the concentration of residual gas in the lungs that results from uptake of a large volume of anesthetic and the increase in input (inspired) ventilation that must accompany such uptake. These requirements prevent simulation by an analog computer and generally impose a need for a digital solution. Furthermore, the concepts involved appear to be difficult for many anesthetists to assimilate. We believe these problems may be solved by a new approach. The problem is to describe the influence of the inspired concentration on the rate of rise of the alveolar concentration without having to consider either the concentration of residual gas secondary to uptake or the concomitant increase in input ventilation.

As noted above, an increase in the inspired concentration accelerates the rate of rise of the alveolar concentration. A similar acceleration would be accomplished by a decrease in blood solubility. We shall demonstrate that the effect of the inspired concentration on the rate at which the alveolar concentration rises can be quantitatively described in terms of an apparent blood solubility. This apparent solubility is related both to the actual blood solubility and to the inspired concentration. The appeal of the relationship lies in its surprising simplicity.

The First Breath

The following proof demonstrates the relationships that exist for the first breath of anesthetic. Case A of figure 1 indicates the sequence that in fact occurs when anesthetic is taken up from alveoli into blood and is replaced by fresh inspired gas. Case B indicates how this would be mimicked by a hypothetical agent of solubility λ′, which differs from that of the real agent (λ) in A. The difference results in an identical change in the alveolar anesthetic concentration without (in Case B) concomitant volume changes due to uptake. Vλ′ is the volume of blood brought to the alveoli during one respiratory cycle. Vλ instantaneously equilibrates with the anesthetic brought into the lungs during that period. Vλ is the functional residual capacity and Vλ′ is the tidal volume. In Case A the volume of anesthetic taken up by the blood during the first respiratory cycle is replaced by Vλ′ (i.e., Vλ′ equals the volume taken up), thus sustaining the volume of gas to be expired. That is, Vλ′ increases the ventilation going into the lungs by an amount sufficient to maintain a constant expired ventilation. The inspired anesthetic concentration, Fλ′, is decreased to Fλ′ by dilution in the gas phase and by transfer to blood as defined by λ. In Case B the components have the same meaning and are numerically equal to those in A except that the absolute volume of gas taken up does not decrease the volume of gas remaining in the lungs. That is, in Case B there is no volume of gas drawn into the lungs to replace uptake and there is no decrease in lung volume due to uptake. As noted above, the equality of Fλ′ in Cases A and B is explained by λ′, the partition coefficient for B, which differs from λ (as we shall prove) as a function of Fλ′.
By definition:

$$\lambda = \frac{\text{anesthetic blood concentration}}{\text{anesthetic gas concentration}} = \frac{V_U}{V_B} \cdot \frac{1}{F_A} \quad (1)$$

or

$$\lambda = \frac{F_AV_T + F_UV_U - F_A(V_A + V_T)}{V_BF_A} \quad (2)$$

and

$$\lambda' = \frac{F_AV_T - F_A(V_A + V_T)}{V_BF_A} = \frac{F_AV_T + F_UV_U - F_A(V_A + V_T)}{V_BF_A} - \frac{F_UV_U}{V_BF_A} \quad (3)$$

Substituting (1) and (2) into (3):

$$\lambda' = \lambda - F_A\lambda = \lambda(1 - F_1) \quad (4)$$

Equation 4 says that the alveolar rate of rise of agent X with a blood/gas partition coefficient equal to \( \lambda \) will be slowest (i.e., the \( F_A/F_1 \) ratio increase is slowest) when \( F_1 \) is very low (less than a few per cent), because then \( 1 - F_1 \) approximately equals 1 and thus \( \lambda' = \lambda \). As \( F_1 \) becomes larger, the apparent solubility \( \lambda' \) decreases and accordingly allows a more rapid increase in \( F_A/F_1 \). When \( F_1 \) for agent X is 50 per cent, then the effective solubility becomes half of the true solubility \( \lambda \). When \( F_1 \) is 100 per cent, then \( \lambda' \) becomes zero and the rate of washin is determined solely by alveolar ventilation and the functional residual capacity.

**Breath N**

The preceding example describes the relationships for the first breath. With succeeding breaths we cannot assume that no anesthetic exists in \( V_B \) or \( V_A \) prior to inspiration. As we shall demonstrate, such an assumption is not necessary to the conclusion reached in equation 4.

The symbols used to describe the events occurring in the \( N \)th breath (fig. 2) are for the most part identical to those used in figure 1. For Case C the volume of blood \( (V_B) \) brought to the lungs in one respiratory cycle contains anesthetic at a fractional concentration, \( F_B \). This is to be brought into equilibrium with the anesthetic in the gas phase. As in figure 1 (Case A), the gas phase consists of three parts. The functional residual capacity \( (V_A) \) contains the anesthetic that remains after the previous equilibration and has a concentration of \( F_A0 \). The tidal volume, \( V_T \), contains inspired anesthetic at concentration \( F_i \). As anesthetic is absorbed in the course of equilibration, the absorbed anesthetic is replaced (i.e., the gas volume in the lung is not permitted to shrink) by a volume \( (V_B) \) that exactly equals the anesthetic volume taken up. Since \( V_B \) is inspired gas, it has an anesthetic concentration of \( F_i \). After equilibration, the anesthetic concentration in the gas phase \( (V_A + V_T) \) will equal \( F_A0 \). The distribution of anesthetic must satisfy the blood/gas partition coefficient, \( \lambda \).

Case D describes the assumptions used to estimate the apparent blood/gas partition coefficient \( \lambda' \) when, as with Case B, it is assumed that the gas volume diminution imposed by uptake is insignificant and therefore \( V_B0 \) approaches zero. \( V_B \), \( V_A \), \( V_T \), \( F_A0 \), \( F_i \) and \( F_A0 \) have the same definition and absolute values as in Case C. However, \( F_B' \), the concentration of anesthetic in \( V_B \), differs from \( F_B \) as defined by \( \lambda' \). Since the alveolar concentrations of anesthetic in Cases C and D are equal at all identical points in time then

$$\frac{F_B'}{\lambda} = \frac{F_B}{\lambda'}$$

and

$$F_B' = F_B\lambda'/'\lambda \quad (5)$$

In Case C, upon equilibration, the sum of anesthetic initially contained in all of the gas phase minus
Fig. 5. As predicted by equation 11, an inspired nitrous oxide concentration of 75 per cent produces an alveolar rate of rise (as a function of the alveolar/inspired concentration ratio, $F_A/F_I$) that is slightly more rapid than that found with 1 per cent ethylene. The remaining nitrous oxide curves indicate the range of potential rates of rise with nitrous oxide at various inspired concentrations.

that transferred to blood equals the amount remaining in the residual gas phase:

$$F_A V_{un} + F_I V_T + F_{AO} V_A - V_{un} = F_{An} (V_A + V_T)$$

Solving for $V_{un}$:

$$V_{un} = \frac{F_I V_T + F_{AO} V_A - F_{An} (V_A + V_T)}{1 - F_I} \quad (6)$$

After equilibration the concentration of gas in blood must be $(F_B V_B + V_{un})/V_B$. By definition:

$$\lambda = \frac{F_B V_B + V_{un}}{F_{An} V_B} \quad (7)$$

Substituting (6) into (7) for $V_{un}$ and simplifying:

$$\lambda = \frac{F_B V_B (1 - F_I) + F_I V_T + F_{AO} V_A - F_{An} (V_A + V_T)}{F_{An} V_B (1 - F_I)} \quad (8)$$

A similar description applies to $\lambda'$ (Case D). The volume of anesthetic transferred to blood equals the total volume of anesthetic in the lungs before equilibration $(F_V V_T + F_{AO} V_A)$ minus the volume left in the lungs after equilibration $(F_{An} V_A + F_{An} V_T)$. Substituting these values into the definition for the blood/gas partition coefficient gives:

$$\lambda' = \frac{F_B' V_B + F_I V_T + F_{AO} V_A - F_{An} (V_A + V_T)}{F_{An} V_B}$$

Substituting for $F_B' = F_B/\lambda$ from equation 5:

$$\lambda' = \frac{(F_B'/\lambda) V_B + F_I V_T + F_{AO} V_A - F_{An} (V_A + V_T)}{F_{An} V_B}$$

Solving for $\lambda'$ and rearranging:

$$\frac{\lambda'}{\lambda} (\lambda F_{An} V_B - F_B V_B) = F_I V_T + F_{AO} V_A - F_{An} (V_A + V_T) \quad (9)$$

Rearranging equation 8:

$$(1 - F_I) (\lambda F_{An} V_B - F_B V_B) = F_I V_T + F_{AO} V_A - F_{An} (V_A + V_T) \quad (10)$$

Since the right sides of equations 9 and 10 are identical, the left sides may be equated. Solving for $\lambda'$ gives:

$$\lambda' = \lambda (1 - F_I) \quad (11)$$

which is identical to equation 4.

Discussion

Equation 11 provides a new quantitative way of looking at the concentration effect. The equation says that the apparent solubility of an agent decreases in proportion to the inspired concentration. Note that the apparent solubility applies only to the rate of rise of the alveolar anesthetic concentration—it has nothing to do with the actual volumes of anesthetic taken up. But it is the rising alveolar anesthetic concentration that is crucial to the development of the anesthetic state. The anesthetic partial pressure in all tissues of the body must approach the alveolar anesthetic partial pressure, which thereby assumes a key role in determining the level of anesthesia.

The application of equation 11 may be illustrated with the following example. The blood/gas partition coefficient for nitrous oxide is 0.47. When given at a 75 per cent inspired concentration, the apparent coefficient becomes 0.47 (1 - 0.75) or 0.12. That is, the rate of rise of alveolar nitrous oxide towards the inspired concentration now becomes as rapid as the rate obtained with an anesthetic having a blood/gas partition coefficient of 0.12. Thus, at a 75 per cent inspired concentration, the rate of rise of alveolar nitrous oxide should be slightly faster than that seen with 1 per cent ethylene (blood/gas partition coefficient 0.14). Simulation data obtained previously confirm this prediction (fig. 3). Equation 11 is useful to investigators who wish to simulate anesthetic uptake because it allows the application of an analog computer solution to problems incorporating the concentration effect.

References