An Additional Explanation for the Second Gas Effect:

A Concentrating Effect

Robert K. Stoelting, M.D., and Edmond I. Eger, II, M.D.†*

When an anesthetic such as halothane (second gas) is administered with nitrous oxide (first gas) the rate of rise of alveolar halothane is more rapid than when it is given alone. This "second gas effect" has been attributed to the increased volume of inspired gas which results from the large volume of nitrous oxide taken up. We find that a second explanation, a concentrating effect, is also necessary.

Dogs were equilibrated with ethylene, cyclopropane or halothane as the second gas. Administration of 70 per cent nitrous oxide plus the equilibration concentration of the second gas caused the second gas concentration to rise *above* the inspired concentration, thus precluding the possibility that the second gas effect was due to an increased volume of inspired gas. Only a concentration of the second gas in a smaller volume could explain the increase in second gas concentration. The rise was greatest with the least soluble gas, ethylene and greatest when ventilation was least. At a ventilation which produced a $P_{A_{CO_2}}$ of 80 mm Hg, the alveolar concentration of ethylene reached a peak of 15.6 per cent, that of cyclopropane 10 per cent, and that of halothane 8.3 per cent, above the equilibrium values.

EPSTEIN *et al.*[1] demonstrated that when a constant concentration of halothane was inspired the rise in alveolar concentration was accelerated by concomitant administration of nitrous oxide. This accelerated rise in alveolar halothane was called the "second gas effect." They postulated that uptake of a large volume of nitrous oxide created a potential subatmospheric intrapulmonary pressure which led to an increased tracheal inflow. This increased inspiratory ventilation was felt to be responsible for the second gas effect.

We propose that the second gas effect is only partially explained by an increase in inspiratory ventilation. Concentration of the second gas resulting from uptake of a large volume of nitrous oxide is also necessary to explain this effect. The nitrous oxide uptake increases the proportion of the residual (second) gases.

The following experiments were designed to show that the second gas effect occurs even when increase in inspired ventilation could not raise the alveolar concentration. Under these circumstances, a concentrating effect is the only explanation for the persistent second gas effect.

Methods

Mongrel dogs (15–20 kg) were anesthetized with three inert gases which have different blood/gas partition coefficients (λ).[2] The agents used as the second gases were ethylene ($\lambda = 0.14$, five dogs), cyclopropane ($\lambda = 0.415$, six dogs) and halothane ($\lambda = 2.3$, four dogs) in oxygen. All experiments were performed after total body equilibration with these agents had been attained, as evidenced by equality of the inspired and alveolar concentration, for a minimum of 30 minutes. Equilibration with halothane took place at about 0.5 per cent, with cyclopropane and ethylene 3–5 per cent. Intravenous gallamine and pentobarbital were used to supplement anesthesia when necessary. The trachea of each dog was intubated with a cuffed endotracheal tube and esophageal temperature monitored and maintained at 37 ± 1.5 degrees C. Ventilation was controlled with a volume-limited ventilator to maintain a $P_{A_{CO_2}}$ of 20 mm Hg as measured with a previously-calibrated infrared analyzer. Arterial blood pressure was

* Anesthesia Research Fellow.

† Professor.

Received from the Department of Anesthesia, University of California, San Francisco Medical Center, San Francisco, California. Accepted for publication September 5, 1968. Supported in part by U. S. Public Health Service Grant 5R01 HE07946-05.

monitored continuously via a catheter in the femoral artery. After 30 minutes of stabilization of ventilation, the animal was placed on a second anesthetic system which contained an identical concentration of the second gas under study, plus about 70 per cent nitrous oxide (*i.e.*, 30 per cent O_2 by a Beckman O_2 analyzer). Arterial blood was drawn for blood gas determination, just prior to the addition of nitrous oxide, and again five minutes later. End-tidal (alveolar) gas samples were obtained over the following ten minutes. The experiment was repeated in each dog at a ventilation sufficient to maintain $P_{A_{CO_2}}$ at 40, then 80, mm Hg.

All gas samples were drawn into glycerinized glass syringes previously tested for leaks; the average sample volume was 10 ml. The inspired gas samples were drawn from a Cole adaptor inserted on the inspiratory side of the circle system just distal to the inspiratory valve. Alveolar samples were obtained at end expiration via a narrow-bore nylon tube placed through the endotracheal tube close to the carina. Gas chromatography was used to analyze the gas samples. A 6-inch silica gel column utilizing a flame detector was employed for all three gases. The column temperature for ethylene was 70 C; cyclopropane 100 C; halothane 170 C. Carbon dioxide and nitrous oxide were not detected under these conditions.

Results

Figure 1 illustrates the effect of solubility on the magnitude of the second gas effect, for the three gases studied, when $P_{A_{CO_2}}$ equalled 80 mm Hg. The average per cent rise in the alveolar concentration of the second gas above that inspired after equilibrium and following the addition of 70 per cent nitrous oxide is plotted against time. The introduction of nitrous oxide after prior equilibration produced rises in the alveolar concentrations of all gases. The least soluble gas, ethylene, showed a maximum increase in the alveolar concentration of 15.6 per cent; the intermediate gas, cyclopropane, showed a maximum increase of 10 per cent; the smallest change, 8.3 per cent, was seen with the most soluble gas, halothane.

Figure 2 shows the effect of ventilation on the magnitude of the second gas effect. In all instances the greatest effect (greatest rise in alveolar second gas) was seen at the lowest alveolar ventilation ($P_{A_{CO_2}}$ 80 mm Hg) and decreased as the alveolar ventilation increased. With ethylene the maximum increase in alveolar concentration was 15.6 per cent at a $P_{A_{CO_2}}$ of 80 mm Hg, after 90 seconds. At a $P_{A_{CO_2}}$ of 40 mm Hg the maximum increase was 13.1 per cent after 60 seconds, while at a $P_{A_{CO_2}}$ of 20 mm Hg the maximum increase was 9.1 per cent after 30 seconds. With the less soluble agent, cyclopropane, the maximum increase of

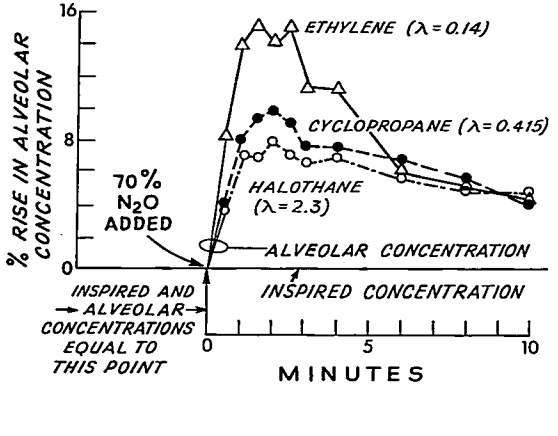

FIG. 1. Effects of solubility on the magnitudes of the second gas effects for the three gases studied when $P_{A_{CO_2}}$ equalled 80 mm Hg. Average per cent rise in the alveolar concentration of the second gas above that inspired after equilibrium and following the addition of 70 per cent nitrous oxide is plotted against time. The inspired concentration was held constant after the introduction of nitrous oxide.

10 per cent was seen after 120 seconds at a PA_{CO_2} of 80 mm Hg. With increasing alveolar ventilation the maximum increase in alveolar concentration was less, and occurred at an earlier time, corresponding to the predicted maximum uptake of nitrous oxide. The most soluble agent studied, halothane, followed the same pattern, showing a maximum increase in the alveolar concentration of 8.3 per cent after 120 seconds at a PA_{CO_2} of 80 mm Hg. The absolute separation with different alveolar ventilations was less than that seen with ethylene or cyclopropane.

Table 1 gives the averages and standard errors of the means for these data. Several peak heights (*i.e.*, maximum increases in alveolar concentration) were significantly different. At all ventilations peak ethylene was greater than peak cyclopropane (PA_{CO_2} 20 mm Hg, $P < 0.05$; 40 mm Hg, $P < 0.01$; 80 mm Hg, $P < 0.05$). Peak ethylene also exceeded peak halothane at all ventilations, and was statistically different at 40 mm Hg ($P < 0.01$) and 80 mm Hg ($P < 0.05$). At a PA_{CO_2} of 20 mm Hg, peak halothane exceeded peak cyclopropane ($P < 0.01$). This difference at 20 mm Hg cannot be explained on the basis of our other findings, because the second gas effect was greatest for the least soluble gas on all other occasions. The differences in peak heights for ethylene became significantly higher as ventilation decreased (PA_{CO_2} 20 mm Hg *vs.* 40 mm Hg, $P < 0.01$; 20 mm Hg *vs.* 80 mm Hg, $P < 0.01$). Cyclopropane peak heights were also significantly elevated as ventilation decreased (20 *vs.* 40, $P < 0.01$; 40 *vs.* 80, $P < 0.05$; 20 *vs.* 80, $P < 0.01$). In no other comparisons did we find significant differences.

Figure 3 represents a hypothetical lung to illustrate the two proposed mechanisms in the production of the second gas effect.

Discussion

Figures 1 and 2 demonstrate that a second gas effect occurs after total body equilibration. These results cannot be explained by an increase in the inspired ventilation. Following equilibration the concentration of the second gas entering the lung is less than the concentration developed within the lung and, therefore, if anything, would oppose the effect seen. Instead, we propose that the second gas is concentrated in the alveoli by the reduction in alveolar gas volume resulting from nitrous oxide uptake. Figure 3*A* is a diagrammatic illustration of how the second gas is concentrated in the lungs following the uptake of nitrous oxide. A hypothetical lung initially contains 80 per cent nitrous oxide, 19 per cent oxygen and 1 per cent second gas. If half the nitrous oxide is taken up (40 parts) the remaining second gas now represents 1.7 per cent (one part in 60) of the total gas volume, while before it represented only 1 per cent (one part in 100). Consequently, the second gas has been concentrated in a smaller gas volume following nitrous oxide uptake, and its alveolar concentration increases.

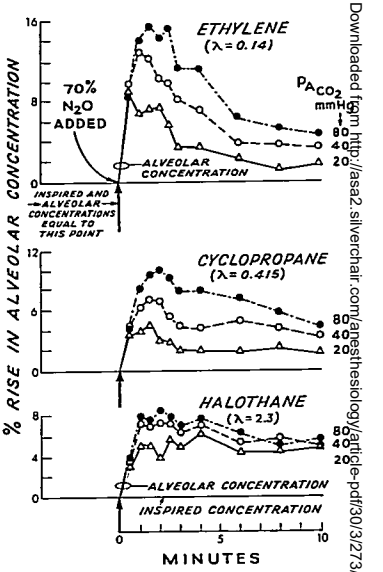

FIG. 2. The effect of ventilation on the magnitude of the second gas effect for each of the three "second gases." The average per cent rise in the alveolar concentration of the second gas above that inspired after equilibrium and following the addition of 70 per cent nitrous oxide is plotted against time.

TABLE 1. Average Percentage Increases in Alveolar Concentration of the Second Gas Above That Inspired after Equilibrium and Following the Addition of Nitrous Oxide†

Time (mins)	P_{ACO_2} = 20 mm Hg						P_{ACO_2} = 40 mm Hg						P_{ACO_2} = 80 mm Hg					
	Ethylene		Cyclopropane		Halothane		Ethylene		Cyclopropane		Halothane		Ethylene		Cyclopropane		Halothane	
	Avg.	SE	Avg.	SE	Avg.	SE	Avg.	SE	Avg.	SE	Avg.	SE	Avg.	SE	Avg.	SE	Avg.	SE
0.5	0.1*	1.1	3.5	0.5	2.8	0.7	10.0	2.0	4.4	0.6	3.2	0.7	8.5	2.8	4.2	0.6	3.8	0.8
1	6.0	1.2	3.0	0.6	5.1	1.2	13.1*	1.0	6.4	0.8	7.2*	0.4	14.2	1.5	8.1	1.1	7.6	1.4
1.5	7.4	0.7	4.0*	0.4	5.1	0.9	12.4	1.5	7.2*	0.8	6.9	0.7	15.0*	1.5	9.6	1.1	7.2	0.9
2	7.5	0.9	3.1	0.5	3.8	0.6	10.4	0.9	7.0	1.3	7.2	0.8	14.4	2.4	10.0*	0.9	8.3*	0.8
2.5	5.8	1.0	2.9	0.6	5.9	0.2	10.0	1.2	5.4	1.1	7.2	0.6	15.5	2.5	9.3	1.2	7.4	1.2
3	3.6	0.9	2.1	0.5	4.9	0.9	8.4	1.1	4.5	1.5	6.1	1.1	11.6	3.2	7.9	1.2	6.9	1.5
4	3.7	0.6	2.1	0.8	6.3*	0.2	7.4	1.2	4.2	0.9	6.0	1.3	11.7	3.4	8.0	0.4	7.7	0.9
6	2.3	0.9	1.9	0.9	4.5	0.8	4.0	1.1	5.0	1.0	5.4	1.1	6.5	3.4	7.2	0.7	6.2	0.7
8	1.2	0.5	2.3	0.9	4.5	0.7	3.0	1.2	4.2	1.4	5.7	0.8	5.0	2.7	5.8	1.2	5.4	1.0
10	1.8	0.7	1.8	0.1	5.0	0.4	3.5	1.8	3.6	1.5	4.9	0.6	4.7	2.5	4.1	1.6	5.4	1.1

† Shown for each agent at three different ventilations. SE is standard error of the mean. Peak values are denoted by asterisks.

The increased ventilatory inflow which replaces the nitrous oxide lost by uptake can only reduce the rise in the second gas concentration, since the inspired second gas concentration is lower than that in the alveoli. This is shown in Figure 3B, where replacement of the 40 parts of nitrous oxide by the inspired mixture containing 1 per cent second gas reduces the second gas concentration from 1.5 per cent to 1.4 per cent. Thus, the increased inspiratory ventilation secondary to nitrous oxide uptake dilutes the previously-concentrated second gas and diminishes the magnitude of the second gas effect.

In contrast to our study, Epstein's work was done before body equilibration with halothane had been achieved. Under these circumstances, we predict that both an increase in inspiratory ventilation and the concentrating effect play roles in the production of the second gas effect. The increased inspiratory inflow becomes more important as the difference between inspired and alveolar concentrations increases. Thus, with a very soluble agent such as methoxyflurane, the inspiratory ventilation is most important and the concentrating effect plays a small part. Conversely, the concentrating effect is most important with a poorly-soluble agent such as cyclopropane. With zero equilibration (at induction) increased inspiratory ventilation is more important than the concentrating effect with highly-soluble anesthetics and less important with poorly-soluble anesthetics. As equilibration of the second gas is neared, regardless of solubility, the increased inspiratory ventilation exerts less influence. When equilibrium is achieved (as in our studies) the concentrating effect becomes the only factor in the production of the second gas effect, and the inflow ventilation opposes the increase in the alveolar concentration of the second gas (fig. 3B).

The difference in the magnitudes of the second gas effects seen with the three gases (fig. 1) may be explained as follows. Following the addition of nitrous oxide and the production of the second gas effect, the partial pressure of the second gas in the alveoli is increased above that in the returning venous blood. As a result, there is uptake into the blood, and the alveolar concentration falls to-

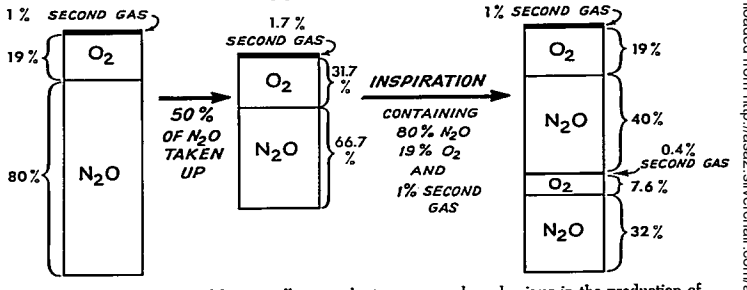

FIG. 3. A hypothetical lung, to illustrate the two proposed mechanisms in the production of the second gas effect. Part *A* is a diagrammatic illustration of how the second gas is concentrated in the lungs following the uptake of nitrous oxide. The hypothetical lung initially contains 80 per cent nitrous oxide, 19 per cent oxygen and 1 per cent second gas. If half the nitrous oxide is taken up, the remaining second gas now represents 1.7 per cent (one part in 60) of the total gas volume, while before it represented only 1 per cent (one part in 100). Consequently, the second gas has been concentrated in a smaller gas volume and its alveolar concentration increases. Part *B* illustrates the effect of increased inspiratory ventilation on the concentrating effect. The inflowing gas contains the same proportions of nitrous oxide, oxygen and second gas which were originally present. Though the absolute amount of second gas is increased (one part to 1.4 parts) it represents a smaller proportion of the total gas volume, and its alveolar concentration falls from one part in 60 (1.7 per cent) to 1.4 parts in 100 (1.4 per cent). Therefore, the increased inspiratory ventilation dilutes the previously-concentrated second gas and diminishes the magnitude of the second gas effect.

ward the equilibrium value, tending to diminish the magnitude of the second gas effect. Uptake is greatest for the most soluble agent, halothane, and, consequently, the second gas effect is smallest. The least soluble gas, ethylene, has the smallest uptake, and the second gas effect is therefore largest. Cyclopropane has a solubility intermediate between ethylene and halothane, and the magnitude of the second gas effect is between those observed for the other two gases.

The inverse relationship between the magnitude of the second gas effect and the alveolar ventilation (fig. 2) can be explained as follows. The uptake of nitrous oxide is relatively unaffected by the differences in ventilation. Thus, the reduction in gas volume produced by this uptake is proportionately less and less as ventilation is increased, since uptake represents a smaller and smaller fraction of the total volume of gases entering the alveoli. At infinite ventilation no second gas effect would be seen.

The halothane (Fluothane) for this study was donated by Ayerst Laboratories.

References

1. Epstein, R. M., Rackow, H., Salanitre, E., and Wolf, G. L.: Influence of the concentration effect on the uptake of anesthetic mixtures: The second gas effect, ANESTHESIOLOGY 25: 364, 1964.
2. Eger, E. I., II, and Larson, C. P.: Anesthetic solubility in blood and tissues: Values and significance. Brit. J. Anaesth. 36: 140, 1964.