Influence of the Concentration Effect on the Uptake of Anesthetic Mixtures: The Second Gas Effect

Robert M. Epstein, M.D., Herbert Rackow, M.D.
Ernest Salanitre, M.D., Gerald L. Wolf, M.D.

The uptake of halothane given in constant concentration (1 per cent) was shown to be more rapid in a mixture with 70 per cent N_2O than in one with 10 per cent N_2O. This demonstrates that the uptake of a gas is influenced by the constituents of the mixture of which it is a component. Changes in the concentration of other components which are sufficient to produce a significant concentration effect will produce alterations of uptake rate of companion gases given in constant concentration ("second gas effect"). This acceleration of uptake was interpreted to be a result of additional inspiratory inflow secondary to the absorption of N_2O at a higher concentration. This absorption produces the concentration effect on the rate of uptake of the N_2O itself, also observed in this study. Second gas effects presumably occur as well for the other gases in the inspiratory mixture, including the usual respiratory gases.

THE TOTAL rate of absorption of an inert gas has long been recognized to depend on a multiplicity of factors which include inspiratory concentration, pulmonary ventilation and perfusion, the perfusion of the components of the systemic circulation, and the various solubilities of the gas in the blood and body tissues.[1] Analysis of the role of each of these is based on the use of some schematic representation of the gas-lung-body system and the one most frequently employed treats the ventilation of the lung as well as all these other factors as constant. In such a model the relative rate of gas uptake, expressed as the fraction of equilibrium concentration reached by the alveolar gas at succeeding time intervals, is independent of the actual concentration inspired.[1]

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Eger has, however, pointed out that the relative rate of gas uptake, as well as its absolute rate, is in fact concentration dependent.[2] This is because absorption of gas creates a potential subatmospheric intrapulmonary pressure which results in augmented tracheal inflow. This inflow adds to the inspiratory ventilation which now is no longer a constant, and results in a more rapid approach to equilibrium. The higher the concentration, the larger the total volume of gas absorbed and therefore the greater the total augmented inflow. For this reason the rate of approach to equilibrium alveolar concentration is accelerated when the inspired concentration is large. This phenomenon has been named the "concentration effect."

Since this effect is ultimately dependent on the magnitude of transfer—by solution—of gas from the alveolus to the blood stream, it will be greater for these gases which are highly blood soluble or which, though less soluble, are given in high concentration. Notably these would include diethyl ether (blood-air partition coefficient $\lambda = 15$, possibly 12) and nitrous oxide (inspiratory concentration $F_I = 0.7 - 0.8$, although $\lambda = 0.47$). The N_2O concentration effect has been confirmed experimentally.[3]

In the case of halothane, chloroform and similar compounds, the anesthetic potency is high and inspiratory percentage concentrations are low. The concentration effect for these compounds given alone is therefore so small that for practical purposes it does not exist. These agents are, however, commonly given with high concentrations of N_2O. Because of this the augmented inspiratory inflow which produces the N_2O concentration effect should in turn augment the inflow and also accelerate the uptake of the low concentration second

component of the inspiratory mixture, such as halothane. We have referred to this acceleration as the "second gas effect." Experimental confirmation of this prediction was obtained.

Methods

Five mongrel dogs weighing 10.5 to 18.0 kg. were anesthetized with pentobarbital, 30 mg./kg., and their tracheas intubated with cuffed endotracheal tubes. Intermittent positive pressure respiration by means of a non-rebreathing valve and a Frumin respirator[4] modified to permit abrupt changes of inspiratory gas composition was begun at 20–22 cycles/minute using air. Apnea and immobility were secured in two studies by intermittent injection of succinylcholine dichloride and in the remainder by gallamine triethiodide.

Gas was sampled from the trachea by a time-phased sampling pump actuated by the respirator. This took approximately a 6 ml. end-tidal sample of each breath and passed it through a sampling train consisting of the 1 ml. gas-sampling loop of a Perkin-Elmer DG 154 gas chromatograph, a Beckman LB-1 N_2O analyzer, a LB-1 CO_2 analyzer, and a Severinghaus CO_2 electrode. The residual volume of the pump was substantially zero, and the lengths and bore of the connecting tubings allowed a 90+ per cent response of the rapid analyzers to a step function input within 3 breaths. This gas was vented to atmosphere. The rapid infrared CO_2 analysis served as a check on the end-tidal character of the sample and on the persistence of apnea but was not otherwise used in calculations.

The greater bulk of the expired gas was passed alternately into one of a pair of 9-liter spirometers for volume measurement on a direct writing kymograph and then collected (during filling of the other 9-liter spirometer) into a 120-liter Tissot spirometer. The dead space of the larger spirometer was washed out with expired gas for approximately 10 minutes prior to each collection period, and CO_2 in the mixed expired gas collected during experimental periods was analyzed by the CO_2 electrode. Total expired volume measurement on the Tissot served as a check on the minute to minute values determined with the small spirometers.

Halothane concentration was determined with the gas chromatograph using a 0.5 meter column of Ucon polyglycol LB 550-X with helium carrier gas at 100° C. and 5 pounds per square inch, employing a hydrogen flame detector and 5 mv. servo-recorder. The height of the symmetrical peak which appeared in approximately 40 seconds was considered linearly proportional to halothane concentration over the range encountered. The validity of this assumption had been previously confirmed.

N_2O concentration was determined by the LB-1 infrared analyzer using two separate N_2O detector units. One of these was a standard 0–100 per cent N_2O detector which was operated in suppressed zero mode over the restricted range from approximately 50 to 75 per cent N_2O. The second was a modified detector unit in which the sample cuvette had been replaced with one of twice the path length.* This detector operated over a full scale range from approximately 0 to 15 per cent N_2O. The output of these analyzers was recorded on a Grass Model 5 polygraph. Both analyzers were found to be free of cross-over effect due to CO_2 or halothane. They were calibrated frequently with N_2O-O_2 mixtures which were standardized both by density determination (Beckman 3A gas density balance) and by oxygen analysis (Beckman Model F-3 Pauling analyzer). Both standardization techniques agreed closely.

During control and calibration periods the animal was respired with air from one of two independent bellows in the plastic dome of the modified Frumin respirator while a second bellows was filled and its own outlet valves and tubing flushed with the inspiratory mixture to be used for uptake. In this way, by switching from one to the other bellows, the animal could be respired throughout the entire study at an unchanged frequency and inflating pressure while permitting abrupt changes of inspiratory mixture at zero time of uptakes.

Inspiratory mixture was sampled from the outlet tubing of the second bellows until repeated analyses indicated a constant value had been reached. A 10 minute control period for total ventilation and flushing of the Tissot with

* Special sample cuvette available from Invengineering, Inc., Belmar, New Jersey.

TABLE 1. N_2O Uptake: The Concentration Effect

Time (minutes)	1		2		3		4		5	
N_2O concentration	70%	10%	70%	10%	70%	10%	70%	10%	70%	10%
Dog 1	0.923	0.845	0.961	0.897	0.973	0.924	0.979	0.943	0.983	0.949
2	0.795	0.775	0.913	0.898	0.940	0.931	0.956	0.944	0.962	0.952
3	0.82*	0.696	0.894	0.800	0.925	0.825	0.945	0.872	0.958	0.872
4	0.895	0.738	0.954	0.831	0.970	0.885	0.978	0.908	0.982	0.918
5	0.849	0.735	0.934	0.864	0.950	0.894	0.962	0.916	0.973	0.928
Mean	0.856	0.758	0.931	0.858	0.952	0.892	0.964	0.917	0.972	0.924
Mean decrease		0.098		0.073		0.060		0.047		0.048
Standard error		0.023		0.018		0.016		0.011		0.015
t		4.26		4.06		3.75		4.27		3.20
P		<0.025		<0.025		<0.025		<0.025		<0.05

* Extrapolated value.

expired air followed, and the stability of the inspiratory mixture was checked late in this period. Uptake of 0.5 per cent halothane in 70 per cent N_2O was then begun using 70 per cent N_2O in O_2 from a gas cylinder passed through a calibrated Fluotec vaporizer. Recording of end-expiratory N_2O concentrations was continuous and chromatographic sampling for halothane was done 30 seconds after starting and subsequently at approximately 1 minute intervals. The CO_2 electrode was periodically isolated from the sample stream and read. After an uptake of 6 to 10 minutes, the Tissot was sealed and the animal returned to air breathing. The mixed expired CO_2 tension in the Tissot was determined in duplicate and recorded.

Following a washout of 45 to 60 minutes, when the residual halothane in the end-tidal gas had fallen to less than one per cent of inspiratory mixture, the entire procedure was repeated. Control ventilation was again determined and uptake of 0.5 per cent halothane then measured, but this time the diluent gas was 10 per cent N_2O in O_2 and the appropriate infrared analyzer was inserted into the sample train. In two studies, in order to check the stability of the physiological determinants of uptake, a third measurement followed a second washout period. The inspiratory mixture for this check period was again 0.5 per cent halothane in 70 per cent N_2O.

In order not to prejudice the data, the residual halothane prior to uptake of 10 per cent N_2O-halothane was not subtracted from each end-tidal value. This tends to maximize the apparent rate of uptake of the halothane with low concentration N_2O. On the other hand, the residual was subtracted from values obtained during the repetition of uptake of 70 per cent N_2O-halothane. This tends to minimize the rate of uptake and again avoids biasing the result. The residuals were in any event, as stated, small.

Arterial CO_2 tension was determined directly using the CO_2 electrode in two animals as a check on the stability of any alveolar-arterial gradient present.

The relative uptake of each gas, N_2O and halothane, was plotted as a ratio of end-expiratory concentration to mean inspiratory concentration (F_A/F_I) at each experimentally determined point. In order to permit numerical comparisons between successive uptakes at identical time intervals, smoothed curves were drawn through the actual data points, and interpolated values for F_A/F_I read at 0.5, 1, 2, 3, 4 and 5 minutes. This procedure is believed to have introduced no systematic errors.

Alveolar ventilation ($\dot{V}_A$) for each uptake period was computed as $\dot{V}_A = \dot{V}_E \times F_{ECO_2}/F_{ACO_2}$. No study was accepted in which this value varied by more than 200 ml. between uptakes.

TABLE 2. Halothane 0.5 Per Cent Uptake: The Second Gas Effect

Time (minutes)	1		2		3		4		5	
N_2O concentration	70%	10%	70%	10%	70%	10%	70%	10%	70%	10%
Dog 1	0.416	0.374	0.474	0.408	0.500	0.478	0.535	0.492	0.555	0.517
2	0.388	0.344	0.449	0.405	0.489	0.448	0.526	0.484	0.551	0.504
3	0.350	0.305	0.378	0.345	0.398	0.374	0.417	0.397	0.431	0.417
4	0.385	0.298	0.423	0.355	0.453	0.396	0.476	0.421	0.495	0.438
5	0.328	0.282	0.394	0.340	0.427	0.386	0.443	0.423	0.454	0.460
Mean	0.373	0.321	0.424	0.371	0.453	0.416	0.479	0.443	0.497	0.467
Mean decrease		0.052		0.053		0.037		0.036		0.030
Standard error		0.0085		0.0067		0.0063		0.0067		0.013
t		6.12		7.91		5.87		5.37		2.31
P		<0.005		<0.005		<0.005		<0.01		>0.05

One study was discarded because of excessive instability of respiration. It is recognized that the venting of analytical samples to atmosphere introduces a small systematic error into our alveolar ventilation calculations. This error should remain constant among the experimental runs of a single study.

Results

Tables 1 and 2 report the relative uptake values for N_2O and halothane, respectively for each of five studies. The means are plotted in figure 1. The acceleration of the uptake of N_2O in higher concentration is confirmed and the consequent increase in the rate of uptake of halothane is clearly seen. In every one of the five studies, the change is in the predicted direction, and is statistically significant at almost all points when tested with Student's t-test for paired samples.

Table 3 compares the duplicate values in the two studies in which 70 per cent N_2O was used before and after the 10 per cent N_2O. In general the agreement is excellent. An apparently more rapid uptake of halothane in the final run in dog 4 does not correspond to the N_2O data and could be secondary to an inadequately corrected residual from earlier runs. In any event, the slowing of uptake during the inhalation of 10 per cent N_2O was clearly reversed in the final period on 70 per cent N_2O.

Measurements of ventilation are summarized in table 4. The alveolar ventilation averaged 1.40 liters/minute during the first uptake and 1.44 liters/minute during the second. Thus the uptake rates were slowed despite sub-

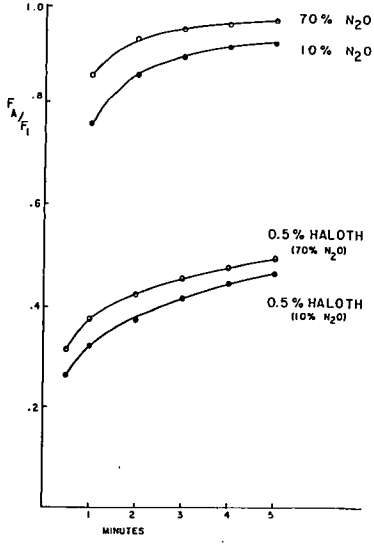

FIG. 1. Relative uptake of N_2O and of halothane plotted as the ratio of the end-tidal to inspired concentrations of each gas. Means of five studies.

TABLE 3. 70 Per Cent N_2O: Repetition of Uptakes

	70% N_2O				0.5% Halothane			
Dog:	4		5		4		5	
Time: 0.5	—	—	—	—	0.360	0.399	0.258	0.258
1.0	0.895	0.899	0.849	0.894	0.385	0.425	0.328	0.328
2.0	0.954	0.948	0.934	0.943	0.423	0.461	0.394	0.388
3.0	0.970	0.962	0.950	0.963	0.453	0.487	0.427	0.420
4.0	0.978	0.974	0.962	0.976	0.476	0.503	0.443	0.442
5.0	0.982	0.981	0.973	0.981	0.495	0.515	0.454	0.456

stantially uniform ventilation. CO_2 output likewise appears reasonably stable within each study.

In order to rule out the possibility of instrumental artifacts the procedures of the study were carried out using a 15 liter steel tank as a "subject." Measurements of ventilation and of halothane uptake were performed. Individual halothane values agreed well regardless of the diluent gas.

Alveolar-arterial CO_2 gradients determined in two animals averaged 4 mm. of mercury and showed no evidence of appreciable variation during the studies.

Discussion

The uptake of the potent anesthetic, halothane, was shown to be accelerated when administered with high concentrations of N_2O. This phenomenon, which we have called the second gas effect, is a general one which we interpret as due entirely to the increased inspiratory inflow produced by the absorption of any soluble gas in significantly large volume from the lung. Once such absorption occurs it will increase the uptake of all components of the inspiratory mixture, including that of the soluble gas itself.

The acceleration of uptake of the soluble gas, greater when it is given in high concentration, was demonstrated by Eger.[3] This is the concentration effect. The acceleration of uptake of all companion gases brought into the lung, *pari passu*, constitutes the second gas effect. Detection of the second gas effect represents a further confirmation of the principles which predict the other. It should be stressed that in our studies no change in halothane inspired concentration is involved, and this is in no way a halothane concentration effect.

Because the second gas effect is a small one the data must be subjected to cautious analysis. Every effort was made in the design of the study to confound its detection. Seventy per cent N_2O was administered first, so that retained halothane prior to the uptake with 10 per cent N_2O would produce apparent acceleration rather than the predicted slowing. For the same reason the residual "blank" value was not subtracted from the values of the second period.

In addition, the possibility existed that apparent slowing of uptake with 10 per cent N_2O was due to a change in the animal. Thus a reduction of alveolar ventilation or an increase in the circulation through the lung can produce apparent slowing of the early phases of uptake.[1] Several bits of evidence make this explanation unlikely. The final uptakes repeated with 70 per cent N_2O in the last two studies closely approximated or exceeded the rate in the initial uptake, despite correction (appropriate in this case) for the "blank." Carbon dioxide removal throughout each individual study (table 4) remained relatively constant, suggesting that neither CO_2 production nor its delivery to the lung were greatly altered. Finally those alterations in ventilation which did occur were, fortuitously, in the direction which might have been expected to speed, not slow, the uptake of the 10 per cent mixture. Nevertheless the predicted change was clearly detected in every study, the uptake of halothane with 70 per cent N_2O proceeding more rapidly than with 10 per cent. For these

TABLE 4. Respiratory data for the two succeeding uptake periods on 70 and 10 per cent N_2O. Stability of the physiologic data suggests that the observed change in rate of gas uptake is not the result of changes in ventilation.

		Alveolar ventilation		Mean end-tidal P_{CO_2}		CO_2 excretion	
		liters/minute		mm. Hg.		ml./kg./minute	
N_2O concentration:		70%	10%	70%	10%	70%	10%
Dog	Weight (kg)						
1	18.0	2.3	2.3	32	32	5.7	5.7
2	13.7	1.7	1.8	37	35	6.4	6.5
3	11.8	1.2	1.1	34	33	4.9	4.3
4	10.9	1.1	1.2	32	34	4.5	5.2
5	10.5	0.7	0.8	33	28	3.1	3.0
Mean		1.40	1.44	33.6	32.4	4.92	4.94

reasons we believe the system was successful in detecting the second gas effect.

In order to facilitate further discussion we shall define the ratio of the fraction of equilibrium obtained at a given time with the higher concentration inspiratory mixture (*e.g.*, 70 per cent N_2O) to that reached in the same time interval with a lower concentration inspiratory mixture (*e.g.*, 10 per cent N_2O) as the "augmentation ratio." In the absence of a concentration effect this ratio would be always 1.0, but in the real case it has a limiting value of 1.0 at zero time and at equilibrium (infinite) time but is greater than 1.0 between.

It is not possible to compare our results directly with those of Eger[3] as his high concentration of nitrous oxide was 85 per cent. We interpolated the data in his figure 3 to yield estimates of the time course of uptake of 70 per cent N_2O. Several techniques of interpolation yielded substantially identical conclusions. The augmentation ratio with "70 per cent" N_2O in his studies was then compared to that calculated for our own data. Table 5 gives these ratios at each minute. Although our studies agree with Eger's as to the magnitude of the concentration effect in increasing the uptake rate for N_2O, the maximum effect seems to be reached and passed somewhat more rapidly in our work. Variation in ventilation and cardiac output and especially in their ratio may account for the difference. Recent theoretical analysis of this problem by Perl,[5] who extended the usual compartment model equations to allow variable inspiratory ventilation rates and gas concentrations, does in fact suggest that the N_2O concentration effect should reach a maximum within one minute and then taper off quickly. The additional volume of gas absorbed due to the concentration effect will in fact be limited if the augmentation ratio does fall quickly to near unity. Averaging in table 5 suggests the possible range of augmented N_2O absorption: approximately 8 to 14 per cent additional gas—either N_2O or halothane—absorbed over the first 5 minutes. Our data favor the lower figure, but the difference is admittedly small in the face of methodologic uncertainties.

Since the concentration and second gas effects are predicated on an increase in inspiratory ventilation secondary to absorption of soluble gas into the blood stream, it should be possible during the period of rapid uptake to show a transient increase in inspiratory ventilation and an excess of this over expiratory ventilation. Unfortunately our system of respira-

TABLE 5. Augmentation Ratios

Time	N_2O	Halothane	$N_2O_{(Eger)}$
0.5	—	1.19	—
1.0	1.13	1.16	1.14
2.0	1.09	1.14	1.14
3.0	1.07	1.09	1.16
4.0	1.05	1.08	1.13
5.0	1.05	1.06	1.10

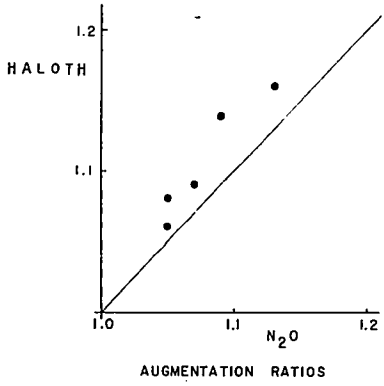

FIG. 2. Augmentation of the uptake of halothane (second gas effect) compared to that of N_2O (concentration effect). For details see text.

tion did not permit such measurements to be made. Similar inspired-expired volume differences have been reported in connection with a related problem by Fink.[6]

The absorption which produces the concentration effect presumably continues during expiration as well. In this case it should be observed as a transient decrease of expired minute volume occurring during the period of rapid uptake of the higher concentration of N_2O. The 9-liter spirometer kymograph records were inspected for evidence of this change, but it was not found. We believe this to be the result of two factors. One is the basically small magnitude of the expected change compared to the sensitivity of our detecting instrument (1 mm. = 20 ml.) and the other is the relatively high dead-space ratio in the dog which makes it more difficult to detect alveolar changes in records of total ventilation.

It is well known[1, 7] that the uptake of an inert gas is more affected by alterations of ventilation when it is a highly soluble agent than when it is relatively insoluble. For this reason it might be anticipated that a change in the inspiratory ventilation resulting from the concentration effect would produce a greater increase in the rate of uptake of halothane ($\lambda = 2.3$) than of N_2O ($\lambda = 0.47$). Table 5 and figure 2 suggest that this may be so, although the augmentation ratios of halothane are not sufficiently greater than those of N_2O to be compelling. Further theoretical analysis of this multiple gas problem, extending and generalizing the approach of Perl,[5] would help to clarify this relationship. Such an extension has not yet been attempted.

The relationship of this study to another phenomenon accompanying N_2O transport deserves comment. Rackow, Frumin and Salanitre,[8] in their discussion of the alveolar dilution phenomenon produced during N_2O excretion, pointed out that the reverse phenomenon must occur during N_2O uptake. In their scheme, the absorption of N_2O was expected to increase the alveolar oxygen concentration by removal of the more soluble N_2O from the alveoli with the consequent inflowing of additional oxygen-containing gas. This, in fact, constitutes a second gas effect for oxygen.

Heller and Watson[9] have presented data which support this contention. They measured arterial P_{O_2} polarographically in two dogs during changeover from air to 21 per cent oxygen-79 per cent N_2O and found a small and transient increase in P_{O_2}. Unfortunately their control value in each case was quite low (70–75 mm. of mercury) and represented only a single determination. In addition, after arriving at an early maximum, the arterial P_{O_2} during the period of anesthesia fell but did not return to the control level. Other interpretations of their data, such as changes in the physiological shunt fraction of the cardiac output, are conceivable.

Experimental verification of two concepts which do depend on variable inspiratory ventilation during uptake has, however, been provided by the work on the concentration[3] and second gas effects. This confirmation of the premise of the "alveolar hyperoxygenation" concept of Rackow *et al.*[8] in turn makes the validity of their conclusion seem quite certain.

Summary

The uptake of halothane has been shown to proceed more rapidly when given with nitrous oxide in high rather than low concentrations, despite no change in the inspiratory

concentration of the halothane. This increase in rate of uptake has been termed the "second gas effect" because it is due to an already observed increase in the relative rate of uptake of the first gas, nitrous oxide, with increasing concentration—the "concentration effect." The extent of both effects is small, but the data suggest that at constant inspiratory halothane concentrations perhaps 10 per cent additional halothane may be absorbed over the first five minutes when it is given with clinically effective nitrous oxide concentrations. The effect becomes progressively smaller over longer intervals of time.

The second gas effect, although measured with this combination of anesthetic gases, is a general phenomenon which applies to all components of an inspiratory gas mixture whenever one of the components is sufficiently soluble and in concentration high enough to produce a concentration effect.

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EPIDURAL ANESTHESIA Cervical epidural anesthesia has been used for 24 months for carotid endarterectomy as well as for other surgical procedures on the neck, upper thorax and shoulders without the occurrence of complications attributable to the anesthetic method. The patients are lightly premedicated and the needle is inserted into the epidural space between the sixth and seventh cervical vertebrae. A polyethylene catheter is introduced into the epidural space and the patient placed supine. Eight to 10 ml. of 2 per cent lidocaine with 1 to 100,000 epinephrine is injected. This will provide anesthesia from the second cervical vertebra to the second or fourth thoracic vertebra. Neither diaphragmatic paralysis nor bradycardia has been noted. No evidences of anesthetization of the midbrain or of the cranial nerves have been noted. Presence of abnormal clotting mechanisms is a contraindication to this form of anesthesia. *(Green, C. D.: Cervical Epidural Anesthesia for Carotid Endarterectomy, Surg. Gynec. Obstet. 117: 366 (Sept.) 1963.)*