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The Rate Of Decline Of Exhaled Concentrations Of Isoflurane With And Without Nitrous Oxide

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Abstract

The purpose of this study was to investigate the presence of a "reverse second gas effect". To achieve this purpose the study investigated the rate of decline of exhaled concentrations of isoflurane with and without nitrous oxide. A total of 60 subjects were studied. The effects of age, weight, gender, and ASA status were also investigated. The study identified that there was no difference in the rate of decline of exhaled concentrations of isoflurane with and without nitrous oxide regardless of age or ASA status. In this sample the variables of gender and weight were found to affect the rate of decline.

It has been shown in prior studies that nitrous oxide facilitates the onset of anesthesia by accelerating the rise of inspired concentrations of an anesthetic gas.(1) Nitrous oxide has been found to also facilitate the emergence from anesthesia by increasing the rate of decline of exhaled concentrations of an anesthetic gas.(4) Since isoflurane is one of the most commonly used anesthetic gases, it was examined for the influence of nitrous oxide and the "reverse second gas effect".

Data analyses identified no significant difference in the elimination of isoflurane whether nitrous oxide was used or not used. Only one weight group, 90 to 125 kg, had a significant difference in elimination duration. Anesthetists should use the results of this study to guide the delivery of anesthesia. Nitrous oxide should not be expected to speed the rate of emergence from general anesthesia.

INTRODUCTION

Anesthesia gases may be used individually or in combination to produce anesthetic effects. Nitrous oxide may be used in combination with other anesthetic gases. When nitrous oxide is used during induction, it increases the rate of anesthesia onset.(1, 2, 3) This phenomena is known as the second gas effect.

Nitrous oxide may also be an adjunct to the elimination of anesthetic gases from the body. It may be theorized that any factor that increases uptake during induction will have the same influence on emergence in the opposite way.(4) Since nitrous oxide speeds the rate of uptake of inhalational gases it should also speed the rate of elimination.(4) This phenomena is known as the “reverse second gas effect”. Minimal research has been done to investigate the rate of decline (duration) of an exhaled anesthetic.(4) The rate of decline is regarded as the measured percent of exhaled gas. The actual existence of the reverse second gas effect is still a question.

Halothane is a less soluble gas, which means that it does not cross membranes easily. Isoflurane is more soluble than halothane. The physical characteristics of isoflurane are more similar to nitrous oxide than the characteristics of halothane. Since it is the solubility of nitrous oxide that allows either phenomena to exist, research should examine if the “reverse second gas effect” exists with the more soluble anesthetic gas.(4) By studying the difference in time to exhale a set concentration of isoflurane with and without the use of nitrous oxide, the existence of this phenomena may be determined.

The anesthesia provider may select from any number of anesthetic gases for surgical patient management. The choice is based on the patient's physical state, length of surgery, and cost of the gas. A method that allows the patient to awaken from general anesthesia more quickly is seen as cost-efficient because it utilizes less surgical time and anesthesia interventions. This study was undertaken to provide data supporting the existence of a reverse second gas effect by using two low cost inhaled gases that may facilitate rapid awakening from anesthesia.

REVIEW OF THE LITERATURE

Anesthetic agents, such as isoflurane, are inhaled and absorbed into the body through the alveoli of the lungs. Blood carries the agent throughout the body with the purpose of saturating muscle tissue and brain tissue. This saturation gives the desired effects of general anesthesia. Equilibrium occurs when the partial pressure of an agent is relatively equal on both sides of the membrane. Once equilibrium is reached it is thought that the agent has saturated the tissue. Saturation of the brain tissue is the goal of anesthesia.(5)

Solubility of every anesthetic agent is indicated by a blood:gas coefficient. The rate of induction can be predicted by looking at the blood:gas coefficient. Induction depends on the concentration of inspired gas (Fi) and the amount taken up into the blood. The difference between these two numbers is the alveolar concentration (Fa), the amount left in the alveoli after absorption. These numbers are expressed as percentages and are important for determining the saturation of the brain tissue. In order for the brain to be saturated, the uptake into the blood must be at a constant state, signifying equilibrium. As the uptake becomes constant, the Fa has risen and equilibrated with the Fi, reflecting that the amount inspired equals the amount retained in the alveoli, and no more agent is being taken up.(6) A photoacoustic spectrometer (PAS) monitor reflects these concentrations.

PAS displays the Fi and Fa in terms of inspired and expired (end-tidal) concentrations, respectfully. End-tidal concentrations are monitored to indicate the level of arterial partial pressure which also represents the partial pressure in the brain.(7, 8) Once the displayed inspired and end-tidal concentrations equal each other, the agent has reached equilibrium and has saturated the brain tissue. One known gas that causes a more rapid rate of equilibrium is nitrous oxide.(3, 6)

Nitrous oxide causes what is known as the second gas effect. As nitrous oxide is additionally inspired along with the anesthetic agent, the Fa/Fi ratio will quickly rise to near one.(1) In addition, nitrous oxide is more soluble than other gases, which allows it to cross into the tissues more rapidly.(6) Nitrous oxide is taken up into the blood more readily than other gases. This leaves a higher concentration of the second gas in the alveoli, causing a concentration gradient between the alveoli and blood.(3) The higher the gradient, the more quickly the gas crosses into the blood, despite a low solubility. Any anesthetic agent inspired along with nitrous oxide will reach equilibrium more quickly than it would have been if inspired alone.(3, 8)

Once an equilibrium is reached and the concentration of inspired nitrous oxide remains the same, the gradient is almost insignificant. If nitrous oxide is kept at a constant influx, then the uptake or elimination of anesthetic gases is dependent on the gas's solubility. A gradient does not exist to force the gas molecules across the membrane. In other words, as nitrous oxide is kept constant, the second gas effect does not occur. The second gas effect will occur if the influx or elimination of nitrous oxide is changing.

Induction is a function of Fi and the degree of uptake. As a result a higher Fi and higher degree of uptake would cause a more rapid rate of increase of Fa. Any factor that influences the rate of uptake should influence the rate of elimination. (5, 6) Nitrous oxide has been suggested as a factor that will speed the rate of uptake, therefore, it should also speed the rate of elimination. Rate of emergence from anesthesia may be prolonged by two factors: duration of exposure to anesthesia and a lesser degree of alveolar ventilation. (9, 2, 3)

The achievement and maintenance of minimum alveolar concentration (MAC) is important for adequate anesthesia levels in the patient undergoing surgery. The MAC of isoflurane is lower when nitrous oxide is used.(10) The MAC for isoflurane alone ranges from 1.05 +/- 0.05 to 1.28 +/- 0.01, and the MAC for isoflurane with nitrous oxide ranges from 0.37 +/- 0.04 to 0.56 +/- 0.07.

When nitrous oxide is used in combination with isoflurane, the amount of isoflurane necessary for adequate anesthesia (MAC) is reduced.(10, 11, 12) Isoflurane is eliminated mostly by the lungs and less than 1% is metabolized in the liver. For this reason isoflurane is dependent on alveolar ventilation for elimination from the body.(6)

Currently, nitrous oxide is used as a support to anesthesia rather than being the sole anesthetic.(13) The second gas effect, also known as the concentration effect, is a result of the low solubility of nitrous oxide, and the concentrating effect in the alveoli.

Many studies have looked at the significance of the second gas effect during induction.(1, 2, 3) Only one study was found that looked at this effect during emergence from anesthesia and it utilized the anesthetic agent halothane.(4) Researchers found that a gas of lower solubility, such as nitrous oxide, speeds the rate of decline of exhaled gases and named this phenomena “reverse second gas effect”.(4)

PURPOSE OF THE STUDY

The purpose of this study was to investigate the presence of a “reverse second gas effect”. To achieve this purpose the study described the rate of decline of exhaled concentrations of isoflurane with and without nitrous oxide. Selected variables (with or without nitrous oxide, age, weight, gender, American Society of Anesthesiologists (ASA status) were investigated for their effect on the rate of decline of exhaled concentrations of isoflurane.

HYPOTHESIS

The hypothesis of this study stated that the use of nitrous oxide will increase the rate of decline in exhaled concentrations of isoflurane regardless of age, weight, gender, or ASA status.

METHODOLOGY

This quasi-experimental study utilized 60 subjects undergoing general anesthesia. Human subject protocols were adhered to. Patients were selected on the day of their surgery following medical record review for exclusion criteria. The subjects were over 18 years of age; ASA status I, II, or III; and undergoing general anesthesia via endotracheal intubation for respiratory management.

Patients participating in the study were prepared for surgery in the same manner that all patients were prepared. Patient charts were flagged to alert the assigned anesthesia providers that the patient was part of a study. The researcher did not provide or plan the anesthetic care for any of the participating patients.

The non-research anesthetist induced all participants with standard intravenous induction medications. Induction and emergence were managed based on accepted standards of anesthesia care for the particular surgical procedure and patient needs. Only 90 seconds of the maintenance period varied for study participants.

Thirty minutes before the end of the surgery, based on an estimated surgical time, the researcher initiated the study protocol. Subjects were divided into two groups for comparison purposes. In order to accomplish this, one flash card was removed from a manila envelope, which contained 60 flash cards. Thirty flash cards were labeled “technique 1” and thirty were labeled “technique 2”. After removal, the card was not returned to the envelope. Appropriate data were recorded on the data collection sheet.

For technique 1, the photoacoustic spectrometer (PAS) monitor indicated an exhaled concentration of 1.0% isoflurane, with nitrous oxide at 70% (2 liter flow) and oxygen at 30% (1 liter flow). Next, the isoflurane was discontinued until the exhaled concentration reached 0.7%. This rate of decline, measured in seconds, was recorded on a data sheet.

For technique 2, the PAS monitor indicated 1% exhaled concentration of isoflurane, with nitrous oxide at 70% (2 liter flow) and oxygen at 30% (1 liter flow). Next, the isoflurane and nitrous oxide were discontinued, simultaneously. At the same time, the liter of flow for oxygen was changed from 1 liter to 3 liters to compensate for the loss of liters of nitrous oxide flow. The rate of decline, measured in seconds, was recorded on a data sheet.

The researcher then used the same stopwatch for all subjects. Constant alveolar ventilation was indicated by maintaining the end-tidal carbon dioxide (ETCO2) at 35% for all patients. The study ended at the time when the PAS indicated 0.7% isoflurane.

The patient continued to emerge from anesthesia and was extubated according to standards of care for all patients. The study in no-way hindered the patient from receiving adequate and safe anesthesia. Both techniques used are currently used for general anesthesia, and are accepted by the ASA.

The participants in the study received the same standards of care for all patients at the research site. No aspect of anesthetic care was withheld from the participants. All information obtained from the patient and their chart remained confidential.

RESULTS

Two techniques were used during the experiment. Technique 1 (N=30) was the elimination of isoflurane without nitrous oxide. Technique 2 (N=30) was the elimination of isoflurane simultaneously with nitrous oxide. A total of 60 subjects were studied.

Statistical analyses were done to determine if a difference existed for the independent variables based on technique. An independent group t-test was used to identify if any differences existed between the two techniques based on age. Chi-square was used to identify if there were differences between the two technique groups based on gender. Mann-Whitney U was used to identify if there was a difference between the two technique groups based on ASA status. Groups were established for Analysis of Variance (ANOVA) for age in years (yr.) and weight in kilograms (kg) to determine the influences of age and weight on duration of elimination.

The mean age for the total sample (N = 60) was 44.67 (SD = 15.6). The mean weight for the total sample was 81.22 (SD = 17.85). There were more males (N=34; 56.7%) than females (N=26; 43.3%) in the total sample.

The number of males and females were compared for each Technique group. Technique 1 group had more females than males (N = 17, 65.4%; N = 13, 38.2% respectively). Technique 2 group had more males than females (N = 21, 61.8%; N = 9, 34.6% respectively). These two groups were found to be statistically different.

The age, weight, ASA status, and duration were compared for each technique group (Table I). The mean weight and age for the males were slightly higher than for females. There was no statistically significant difference found between the two technique groups for these variables.

Figure 1

Table 1: Descriptives of Age, Weight, ASA Status, and Duration for Technique

Variables	Mean	SD	Min	Max
Age				
Technique 1	47.2	15.8	19	86
Technique 2	42.13	15.23	19	79
Weight				
Technique 1	78.17	17.5	50	117
Technique 2	84.27	17.9	50	125
ASA status				
Technique 1	1.97	.67	1	3
Technique 2	2.1	.71	1	3
Duration				
Technique 1	33.53	5.72	25	50
Technique 2	36.2	5.33	20	46

The starting and ending end-tidal isoflurane (ETiso), oxygen (ETO2), and carbon dioxide (ETCO2) were similar in each technique group (Table II). Nitrous oxide (ETN2O) was different in the two techniques due to technique design.

Figure 2

Table 2: Descriptives of Mean End-Tidal Percents of All Gases for Techniques

Variables	Mean	SD	Min	Max
ETiso start				
Technique 1	1.0	0.0	1	1
Technique 2	1.0	0.0	1	1
ETiso end				
Technique 1	0.7	0.0	0.7	0.7
Technique 2	0.7	0.0	0.7	0.7
ETN_2O start				
Technique 1	68.63	2.11	60	72
Technique 2	68.07	1.86	64	72
ETN_2O end				
Technique 1	69.0	2.39	61	74
Technique 2	36.23	7.99	18	55
ETO_2start				
Technique 1	32.03	2.03	29	36
Technique 2	31.43	2.3	27	35
ETO_2 end				
Technique 1	31.97	1.88	28	36
Technique 2	61.9	7.48	46	77
$ETCO_2$start				
Technique 1	34.2	1.24	31	37
Technique 2	34.2	.85	32	36
$ETCO_2$ end				
Technique 1	34.2	1.24	31	37
Technique 2	34.23	.86	32	36

There was no significant difference found to exist between the two technique groups. Statistical analysis was done to determine if a difference existed for the independent variables based on technique.

The hypothesis of this study was that the use of nitrous oxide would increase the rate of decline of exhaled concentrations of isoflurane regardless of age, weight, gender, or ASA status. The rate of decline of exhaled concentrations of isoflurane (duration) for each technique group was similar. The mean rate of decline for Technique 1 was 33.53 (SD = 5.72) and the mean rate of decline for Technique 2 was 36.2 (SD = 5.33). The durations were compared by an independent group t-test. The independent group t-tests identified that there was no significant difference in the duration for each technique group ($t=0.933$, $p=0.067$, $df=58$).

In order to verify that the samples in each technique were homogenous, the independent variables were examined. An independent group t-test was run for the age variable. This test identified no significant difference in the sample for each technique in regards to age (t= 1.26, p= 0.211, df= 58). A Mann-Whitley U was run for the ASA status variable. This test identified no significant difference

in the sample for each technique in regards to ASA status (p=0.448).Chi-square was run for the gender variable. This test identified a significant difference in the sample for each technique in regards to gender (p= 0.037). Fishers exact test revealed a one-tailed p = 0.034.

For statistical analysis, the age and weight data was categorized into three groups (1, 2, and 3) for an ANOVA to determine an influence on the duration for each technique. The results of the ANOVA were insignificant for all age categories. The ANOVA for the weight categories had one significant result (weight group 2; 70 - 89 kg) (Table III).

Figure 3

Table 3: ANOVA Analysis for Age and Weight Categories

		F	
Variables	df	F ratio	Fcv
Age group 1 (19 - 35 yr)	19	0.676	0.421
Age group 2 (36 - 49 yr)	18	4.211	0.056
Age group 3 (50 - 86 yr)	20	0.579	0.456
Wt. group 1 (50 - 69 kg)	17	1.579	0.227
Wt. group 2 (70 - 89 kg)	21	5.057	0.036*
Wt. group 3 (90-125 kg)	19	1.096	0.309

Note. * = p<0.05. cv = critical value

The hypothesis that nitrous oxide would increase the rate of decline of exhaled concentrations of isoflurane regardless of age, weight, gender, or ASA status was rejected. Two independent variables were found to have a significant influence on the duration. Category 2 weight (70 - 89 kg), and gender had a significant result.

CONCLUSIONS

This study identified that there is no significant difference in the rate of decline of exhaled concentrations of isoflurane with or without nitrous oxide regardless of age, gender or ASA status. No significant difference was found in the use or non-use of nitrous oxide. This finding identifies that the "reverse second gas effect" does not exist when nitrous oxide is used with isoflurane. The two independent variables resulting in statistical significance were the weight group 2 (70 - 89 kg) and gender. A possible explanation of the significant result for weight category 2 is that there are slightly more subjects in group 2 compared to groups 1 and 3. For the variable of gender, the significant result may be due to the fact that there are more females in technique group 1, whereas there are more males in technique group 2.

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