Elimination of Nitrous Oxide Accelerates Elimination of Halothane: Reversed Second Gas Effect

Tadanori Masuda, M.D.,* and Kazuyuki Ikeda, M.D., Ph.D.†

The effect of nitrous oxide on the elimination of halothane was studied in 10 patients ranging in age from 20 to 50 years. After establishing a stable baseline (inspired halothane concentration: 0.85%, end-tidal halothane concentration: 0.75%), halothane administration was stopped and the rate of decrease in alveolar concentration of halothane (FE/FEm, FE: measured end-tidal concentration of halothane; FEm: the end tidal concentration immediately preceding the cessation of halothane administration) was measured continuously. The rate of decrease in FE/FEm was more rapid when nitrous oxide (70%) is discontinued abruptly and replaced by the same concentration of nitrogen (Part 2) than when the nitrous oxide is continued (Part 1). One minute and a half after the cessation of halothane administration, FE/FEm was 0.33 ± 0.05 (mean ± SD) in Part 2 and 0.45 ± 0.04 in Part 1 (P < 0.01). In Part 2, the fall in the alveolar concentration of halothane was accompanied by a decrease in alveolar carbon dioxide from 4.27 ± 0.01% to 4.16 ± 0.01% at 1.5 min and an increase in the mean expired tidal volume from 522 ± 39 ml to 557 ± 29 ml. The authors conclude that the elimination of nitrous oxide accelerates the elimination of halothane both by dilution and by an increased expired ventilation. (Key words: Anesthetics, gases: nitrous oxide. Anesthetics, volatile: halothane. Pharmacokinetics: reversed second gas effect; elimination. Recovery.)

The uptake of a large volume of nitrous oxide during the induction of anesthesia accounts for the concentration and second gas effect. Recovery from anesthesia, nearly all the factors governing the rate of increase in alveolar anesthetic concentration during induction are equally important in determining rate of recovery. The outpouring of a large volume of nitrous oxide can produce what Fink called "diffusion anoxia." Rackow et al. and Frumin et al. reported that the elimination of nitrous oxide washes out and dilutes alveolar carbon dioxide.

The effect of the elimination of nitrous oxide on that of halothane has not been reported. Accordingly, the present study was carried out.

Materials and Methods

The experiments were carried out on 10 healthy patients ranging in age from 20 to 50 years. Informed consent and institutional approval were obtained. In Part 1, the ten patients were studied during the elimination of halothane when the inspired gas was maintained as 70% nitrous oxide and 30% oxygen. In Part 2, the same patients were studied but under the condition that the inspired 70% nitrous oxide was replaced by 70% nitrogen during halothane elimination. All the patients were premedicated with 1 mg/kg hydroxyzine pamoate and 0.5 mg atropine sulfate intramuscularly. Anesthesia was induced with 4 ~ 5 mg/kg thiopental followed by 1 mg/kg succinylcholine for intubation and 70% nitrous oxide in oxygen. This was supplemented for halothane, 0.85% inspired. The patients were given 0.1 mg/kg pancuronium bromide and ventilated with a volume-cycled ventilator to maintain a state of normocapnia at a tidal volume of 10 ml/kg. End-tidal carbon dioxide and halothane were measured using a mass spectrometer (MGA 1100 Medical Gas Analyser, Perkin-Elmer). The expired tidal volume was determined by the electric Wright Flow Transducer. Blood pressure, heart rate, and electrocardiogram were monitored in all cases. Measurements were done during surgical stimulation.

After establishing a stable baseline (inspired halothane concentration: 0.85%, end-tidal halothane concentration: 0.75%), halothane administration was stopped and its elimination was measured for a period of 1.5 min with the inspired gas maintained as 70% nitrous oxide and 30% oxygen (Part 1). Halothane administration then was reinitiated, and again after a stable baseline was obtained, its elimination was measured for 1.5 min when the inspired gas was changed from 70% nitrous oxide and 30% oxygen to 70% nitrogen and 30% oxygen (Part 2).

The elimination rate of halothane was determined by the rate of change in the ratio FE/FEm where FE is the

<table>
<thead>
<tr>
<th>Time Interval on Recovery from Halothane</th>
<th>Table 1: Average FE/FEm Ratios and Standard Deviations at Each Time Interval on Recovery from Halothane</th>
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</thead>
<tbody>
<tr>
<td>Seconds</td>
<td>Part 1 (Nitrous Oxide)</td>
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<tr>
<td>---------</td>
<td>------------------------</td>
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<tr>
<td>12</td>
<td>0.76 ± 0.03</td>
</tr>
<tr>
<td>24</td>
<td>0.65 ± 0.04</td>
</tr>
<tr>
<td>36</td>
<td>0.59 ± 0.05</td>
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<tr>
<td>48</td>
<td>0.55 ± 0.04</td>
</tr>
<tr>
<td>60</td>
<td>0.51 ± 0.04</td>
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<tr>
<td>90</td>
<td>0.45 ± 0.04</td>
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* P < 0.01.

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Received from the Department of Anesthesiology, Hamamatsu University School of Medicine, 5600 Handa-cho, Hamamatsu, 431-31, Japan. Accepted for publication November 28, 1983.
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TABLE 2. Effects of the Elimination of Nitrous Oxide on the End-tidal Carbon Dioxide and the Expired 'Tidal Volume when Nitrous Oxide (70%) Is Discontinued Abruptly and Replaced by the Same Concentration of Nitrogen (Part 2) (Mean ± SD)

<table>
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<tr>
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<th>Stable Baseline</th>
<th>1.5 min after the Cessation of Halothane</th>
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<tr>
<td>End-tidal carbon dioxide (%)</td>
<td>4.27 ± 0.01</td>
<td>4.16 ± 0.01*</td>
</tr>
<tr>
<td>Mean expired tidal volume (ml)</td>
<td>522 ± 39</td>
<td>557 ± 29†</td>
</tr>
</tbody>
</table>

* P < 0.01.
† The mean expired tidal volume during 1.5 min after the cessation of halothane.

measured end-tidal concentration of halothane after the cessation of its administration and FEₕ is the end-tidal concentration immediately preceding the cessation of halothane administration. Analysis of the data was carried out by Student’s paired t test.

**Results**

Table 1 shows the mean FE/FE₀ ratios at each time interval after cessation of halothane administration while breathing either 70% nitrous oxide (Part 1) or 70% nitrogen (Part 2) in oxygen. The rate of decrease in the alveolar concentration of halothane was significantly more rapid while breathing nitrogen. At all time intervals after cessation of halothane administration the FE/FE₀ was significantly less.

Table 2 gives the mean figures for the expired tidal volume and end-tidal carbon dioxide in Part 2. The mean tidal volume of expiration was increased from 522 ± 39 ml to 557 ± 29 ml. End-tidal carbon dioxide gradually decreased from 4.27 ± 0.01% to 4.16 ± 0.01% at 1.5 min.

Blood pressure and heart rate did not change during the course of this study.

**Discussion**

During recovery from halothane–nitrous oxide anesthesia, the alveoli soon become filled with a mixture of nitrogen, oxygen, carbon dioxide, halothane, nitrous oxide, and water vapor. Nitrous oxide is about 34 times more soluble than nitrogen and, therefore, the blood can carry much more nitrous oxide than nitrogen. Shaffer et al.² found that the rate of nitrous oxide elimination was greatest during the first 3 min and the peak outflow occurred in the first minute. The result of this outflow is that, temporarily, the volume of expiration exceeds that of inspiration so that an increased volume of halothane can be removed from alveoli.

Nearly all the factors governing the rate at which the alveolar anesthetic concentration increases during induction are applicable to the rate of recovery. A reduced cardiac output or increased ventilation allows for a more rapid decrease in alveolar anesthetic concentration. In our study, though the measurements were done during surgical stimulation, blood pressure and heart rate did not change during the course of this study and ventilation was unchanged.

Differences in the rate of recovery depends in part on the duration of anesthesia. Stoelting et al.⁹ have found that a longer duration of anesthetic slows the rate of decrease in alveolar concentration. The duration of anesthesia for Part 2 of our study was longer than for Part 1. This should have decreased the rate of halothane elimination such that the magnitude of the nitrous oxide effect must be even greater than that observed.

We conclude that the elimination of nitrous oxide accelerates that of halothane by diluting the alveolar concentration of halothane and increasing the expired volume. We have termed this phenomenon the "reversed second gas effect."

**References**