Nitrous oxide produces a non-linear reduction in thiopentone requirements

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Summary
We studied 88 healthy, ASA I patients (aged 20–45 yr), to determine if nitrous oxide affects thiopentone requirements for achieving 50 % probability of no movement in response to verbal commands (CP50). Patients were allocated randomly to one of four nitrous oxide concentration groups (0 %, 20 %, 40 % and 60 %). Patients in each group were also allocated randomly to receive predetermined target plasma concentrations of thiopentone. Computer-controlled continuous infusion was used to maintain the target plasma thiopentone concentration, and this concentration was held constant for 6 min to ensure equilibration. The CP50 value of thiopentone in the absence of nitrous oxide was 14.8 μg ml⁻¹. The reduction in CP50 by nitrous oxide was non-linear, and the interaction coefficient between nitrous oxide and thiopentone was significantly smaller than zero (P = 0.0274), indicating that nitrous oxide antagonized the ability of thiopentone to prevent response to verbal commands. (Br. J. Anaesth. 1996; 77: 265–267)

Key words

General anaesthesia is often performed with a combination of inhalation and i.v. anaesthetics. When nitrous oxide is used in combination with thiopentone alone, intraoperative awareness is sometimes observed [1]. After a single dose of thiopentone, blood concentrations decrease exponentially. However, because of hysteresis between blood and brain concentrations, blood concentration is not a good predictor of brain concentration, and thus bolus administration of thiopentone does not permit its interactions with other drugs to be evaluated accurately. By using a pharmacokinetic model-driven computer-controlled infusion pump, it is possible rapidly to achieve and maintain a constant plasma concentration of thiopentone. Blood concentrations obtained while maintaining the plasma concentration stable can be used to undertake studies on the interactions between nitrous oxide and thiopentone. The aim of this study was to assess accurately the effects of nitrous oxide on the plasma concentration of thiopentone required to achieve a 50 % probability of no movement in response to verbal commands (CP50).

Methods and results
After obtaining the approval of the local Ethics Committee and informed consent, we studied 88 patients of both sexes, ASA I, aged 20–45 yr, undergoing elective surgery. Patients did not receive premedication. An arterial cannula was inserted in the radial artery for blood sampling.

The 88 patients were allocated randomly to one of four groups. Patients in group 1 received no nitrous oxide, while those in groups 2, 3 and 4 received end-tidal concentrations of 20 %, 40 % and 60 %, respectively. Patients in each group were also allocated randomly to receive predetermined target plasma concentrations of thiopentone. Thiopentone was infused using a computer-controlled infusion pump. Pharmacokinetic simulation and infusion algorithms made it possible rapidly to obtain and then maintain the target plasma concentration. The microcomputer was programmed with the thiopentone kinetic parameter set reported by Avram, Krejcie and Henthorn [2].

In group 1, patients breathed 100 % oxygen throughout the study. In groups 2, 3 and 4, nitrous oxide was administered to achieve end-tidal concentrations of 20 %, 40 % and 60 %, respectively. All patients breathed through a face mask connected to a semi-closed anaesthetic circuit. Concentrations of nitrous oxide, carbon dioxide and oxygen were measured continuously using an infrared anaesthetic gas analyser (Capnomac Ultima, Helsinki, Finland).

In groups 2, 3 and 4, nitrous oxide was introduced after the patient had breathed 100 % oxygen for 3 min. In group 1, thiopentone infusion was started 3 min after the start of oxygen, and in groups 2, 3 and 4, thiopentone infusion was started after the specified end-tidal nitrous oxide concentration had been maintained for more than 5 min. Infusion was regulated to maintain the target thiopentone concentration. At 5 min after the start of infusion, blood samples were obtained for measurement of thiopentone concentrations. At 10 min, patients were...
asked to open their eyes and blood samples were obtained. The patient’s response to verbal command was recorded as positive or negative, with slight movement of the eyelids considered a negative response.

Plasma was separated immediately from blood and total plasma thiopentone concentrations were measured as soon as possible, usually within 4 h, using a high pressure liquid chromatographic assay with a sensitivity of 100 ng ml\(^{-1}\). To ensure that stable plasma concentrations of thiopentone was maintained throughout infusion, the 5-min samples were compared with the 10-min samples. The mean concentration of the 5-min and 10-min samples was used for statistical analysis only if the concentration in the 5-min sample was within ±30\% of that in the 10-min sample.

**STATISTICAL ANALYSIS**

The \(C_{P,50}\) of thiopentone, and its reduction by nitrous oxide, were evaluated using the following multiple independent variable logistic regression model:

\[
P(\text{no response}) = \frac{1}{1 + e^{-X}}
\]

where \(X = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2\)

where \(X_1 = \text{measured plasma concentration of thiopentone}, X_2 = \text{end-tidal nitrous oxide concentration}, \beta_0 = \text{regression intercept constant}, \beta_1 = \text{coefficient for thiopentone}, \beta_2 = \text{coefficient for nitrous oxide}\) and \(\beta_{12} = \text{coefficient for the product of the measured thiopentone and end-tidal nitrous oxide concentrations (interaction coefficient)}\). The likelihood ratio test was applied to determine the independent variables to be removed from the model. \(C_{P,50}\) for a given end-tidal nitrous oxide concentration was determined by setting the probability of no response to 0.5 and solving for thiopentone concentration as a function of the end-tidal nitrous oxide concentrations as follows:

\[
X_1 = \frac{-\beta_0 - \beta_2 X_2}{\beta_1 + \beta_{12} X_2}
\]

Although a total of 88 patients were enrolled in the study, nine patients were excluded from the subsequent analysis because the measured thiopentone concentrations before and after verbal command were not within ±30\%. In addition, one patient was eliminated from the study because of severe excitatory phenomena and vomiting. Thus the results of 78 patients are presented. This group included 48 men and 40 women with a mean age of 36 (range 20–45) yr and mean body weight of 56 (42–78) kg.

The logistic model was fitted to 78 data sets of observed response, measured plasma thiopentone concentration and end-tidal nitrous oxide concentration. The \(C_{P,50}\) of thiopentone in the absence of nitrous oxide was 14.8 μg ml\(^{-1}\). None of the three independent variables was removed from the model by the likelihood ratio test. The interaction coefficient \(\beta_{12}\) was significantly smaller than zero (\(P = 0.0274\)). The reduction in the \(C_{P,50}\) of thiopentone by nitrous oxide is presented in figure 1.

**Comment**

The \(C_{P,50}\) of thiopentone alone was found to be 14.8 μg ml\(^{-1}\). The \(C_{P,50}\) value determined in this study was almost identical to that obtained by Hung and colleagues using a similar technique [3]. The effect of nitrous oxide on the \(C_{P,50}\) of thiopentone has not been documented previously. Nitrous oxide, however, has been shown to reduce the MACawake for isoflurane in a dose-dependent manner, with the MACawake reported as 67 % [4]. Thus, 20 %, 40 % and 60 % nitrous oxide should correspond to MACawake fractions of 0.3, 0.6 and 0.9, respectively. In a previous study, when nitrous oxide was administered together with isoflurane at an end-tidal concentration of 40 %, the MACawake value for the combination of isoflurane and nitrous oxide was 18 (SEM 4)\% greater than the value expected for simple additivity of the two agents [4]. This result indicates that the two anaesthetics are antagonistic with regard to this effect. We found that nitrous oxide reduced the \(C_{P,50}\) in a dose-related manner. The interaction coefficient between thiopentone and nitrous oxide was significantly smaller than zero, indicating that nitrous oxide had a non-linear effect on reducing thiopentone requirements and that thiopentone requirements were greater than would be expected for simple additivity. Nitrous oxide appears to antagonize the ability of thiopentone to prevent responses to verbal commands. This may be caused by the ability of nitrous oxide to stimulate sympathetic activity. Hankala and co-workers found EEG evidence that nitrous oxide opposed the central nervous system depression produced by isoflurane [5]. Although there have been no reports that nitrous oxide reverses the central nervous system depression produced by thiopentone, this may offer a possible explanation for our findings.

In conclusion, nitrous oxide produced a non-linear reduction in thiopentone requirements for
Effect of N₂O on thiopentone requirements

preventing response to verbal commands and the reduction was smaller than would be expected for simple additivity at low concentrations.

References


