Interaction of Isoflurane and Nitrous Oxide Combinations Similar for Median Electroencephalographic Frequency and Clinical Anesthesia

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Background: The volatile anesthetic sparing effect of nitrous oxide in clinical studies is less than might be expected from the additivity of minimum alveolar concentration values. Other studies identify nonadditive interactions between isoflurane and nitrous oxide. The aim of this study was to quantify the interaction of isoflurane and nitrous oxide at a constant median electroencephalographic frequency.

Methods: Twenty-five patients were studied during laparotomies. Nitrous oxide was randomly administered in concentrations of 0, 20, 40, 60, and 75 vol%, to ten patients for each nitrous oxide concentration. Isoflurane vaporizer settings were chosen so that the median electroencephalographic frequency was held between 2 and 3 Hz. The relationship between nitrous oxide concentrations and required isoflurane concentrations was examined with the method of isoboles.

Results: Nitrous oxide linearly decreased the isoflurane requirement. Addition of every 10 vol% of nitrous oxide decreases the isoflurane requirement by approximately 0.04 vol%. The total anesthetic requirement of isoflurane and nitrous oxide, expressed in terms of previously reported minimum alveolar concentration values, increased significantly with increasing nitrous oxide concentrations.

Conclusions: The interaction of isoflurane and nitrous oxide in the dose range 0–75 vol% on median electroencephalographic frequency is compatible with additivity. The potency of nitrous oxide as a substitute for isoflurane is less than on a minimum alveolar concentration basis. Maintaining median electroencephalographic frequency more appropriately reflects the clinical usage of isoflurane and nitrous oxide than does maintaining minimum alveolar concentration. (Key words: Anesthetics, gases: nitrous oxide. Anesthetics, volatile: isoflurane. Brain: electroencephalography. Interactions, drug: isoflurane/nitrous oxide. Monitoring: electroencephalography. Potency: anesthetic.)

THE minimum alveolar concentration (MAC) of a single volatile anesthetic[1] necessary to suppress movement to skin incision of 50% of patients, serves as a measure to compare the potencies of inhalational anesthetics. Clinical anesthesia most often uses a combination of nitrous oxide and a volatile agent. Nitrous oxide is well documented to decrease the requirement of volatile anesthetics necessary to suppress the response to skin incision.

It has been shown that the interaction between nitrous oxide and volatile agents such as halothane, enflurane, or isoflurane, is additive in the sense that the linear combination of two MAC fractions of nitrous oxide and the volatile agent totaling 1.0 MAC also suppresses skin incision in 50% of the patients.[2–4] The additivity of MAC supports the "unitary theory of narcosis" that asserts that all anesthetics act in the same way. This theory suggests an identity of action at the molecular level.[5]

Recent studies by Cole *et al.* claimed to have shown a nonlinear contribution to the interaction of nitrous oxide with halothane, enflurane, and isoflurane in rats.[6,7] Chortkoff *et al.* examined the ED_{50} for suppression of learning and the ability to respond appropriately to verbal command using the combination of isoflurane plus 40 vol% nitrous oxide.[8] For both ED_{50}s, a slightly higher value is reported than predicted by assumption of additivity. A study by Yli-Hankala *et al.* showed that the addition of nitrous oxide to isoflurane decreases the frequency and duration of isoflurane-induced burst suppressions in the electroencephalogram (EEG) in a manner indicating a nonadditive interaction.[9]

The type and degree of interaction between two anesthetics also depend on the clinical end point used. Deady *et al.* demonstrated that the ratios of anesthetic

concentration to maintain upright position to response to tail-clamp stimulus and the ratios of anesthetic concentration to maintain upright position to heat applied to the tail differs for the anesthetics nitrous oxide, isoflurane, enflurane, and halothane in mice.[10] Their findings do not support a unitary mechanism of anesthetic action. Instead, righting reflex and response to tail-clamp test or heat test seem to be depressed by different mechanisms.

The aim of this study was to quantify the interaction of nitrous oxide and isoflurane while maintaining a constant level of cortical activity as indicated by a median EEG frequency between 2 and 3 Hz during surgery. The rationale for this target range is that earlier work has shown that median EEG frequencies between 2 and 3 Hz are associated with reasonable planes of anesthesia.[11,12] In addition, it has been shown that during anesthesia with isoflurane and 60 vol% nitrous oxide at 1.3 MAC average median EEG frequency was around 2.5 Hz during surgery.[13]

Methods

After approval by the local Ethics Committee, written informed consent was obtained from 25 female patients, ASA physical status 1 or 2, aged 39 ± 8 yr, scheduled for gynecologic laparotomies. Not included were patients with apparent neurologic deficit, hypothyroidism or hyperthyroidism, pregnancy, or patients who had received drugs affecting central neurotransmitter release. Patients received 7.5 mg oral midazolam 2 h before surgery. Anesthesia was induced with 0.5 mg alfentanil and 3 mg/kg thiopental. Vecuronium was administered for neuromuscular block and no anticholinergic agent was used. Once the trachea had been intubated, anesthesia was maintained with isoflurane and nitrous oxide. In addition to nitrous oxide, patients' lungs were ventilated with oxygen and air. End-tidal carbon dioxide tension was monitored and kept constant at 35 mmHg. Blood pressure and heart rate were measured noninvasively with a Dinamap Vital Daten Monitor (Criticon, Tampa, FL) at intervals of 3 min. Esophageal temperature was monitored. After induction of anesthesia, a 60-min waiting period allowed the effects of the induction doses of thiopental and alfentanil to be reduced.

One EEG lead in F_3 and P_3 position (international 10–20 system) (Sirecust 404, Siemens, Erlangen, Germany) was used for on-line signal analysis. The raw signal was filtered between 0.5 and 32 Hz and divided into epochs of 8.192 s duration, which were digitized at a rate of 125 Hz. The median EEG frequency (50% quantile of the power spectrum) and the percentage of activity in the frequency bands 0.5–2, 2–5, 5–8, 8–13, and 13–32 Hz were calculated. A moving average over seven epochs was used for data smoothing. End-tidal isoflurane concentrations were measured by a Normac anesthetic gas analyzer (Datex, Copenhagen, Denmark). For each patient, the analyzer was calibrated without any anesthetic and with a standard concentration of volatile anesthetic. For each EEG epoch, the corresponding end-tidal isoflurane concentration was determined.

The target range for median EEG frequency was chosen as 2–3 Hz. If median EEG frequency was greater than 3 Hz isoflurane vaporizer settings were increased by 20%, if median EEG frequency was lower than 2 Hz isoflurane vaporizer settings were decreased by 20%.

Required isoflurane concentration was defined as the mean end-tidal isoflurane concentration over a period of 15 min. During a period of 15 min, we determined 110 values of end-tidal isoflurane concentration (1 value for each 8.192 s EEG epoch). If the corresponding median EEG frequencies were out of the range of 2–3 Hz these values for measured end-tidal isoflurane concentration were rejected.

The mean of the median EEG frequencies of all 110 epochs was used as an indicator of the adequacy of isoflurane dosage. Deviation from the mean of the target range (2.5 Hz) would indicate too high or too low levels of isoflurane administration.

The standard deviation of the 110 values of end-tidal isoflurane concentrations was used as an indicator of the constancy of end-tidal isoflurane concentrations.

Nitrous oxide was randomly administered in concentrations of 0, 20, 40, 60, and 75 vol%, each concentration was given to ten patients (n = 10 for each concentration), each patient received two different nitrous oxide concentrations. The measurement periods were allocated during surgical stimulation between opening and closure of the peritoneum. A period of 30 min for equilibration of nitrous oxide and isoflurane was allowed after the nitrous oxide change and before a second measurement period.

The hypothesis of additivity between the two anesthetic agents was tested with the method of isoboles.[14] For each concentration of nitrous oxide, we measured the required concentration of isoflurane necessary to maintain the median EEG frequency between 2 and 3 Hz. Additivity is present if all pairs of concentrations

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Table 1. Age, Temperature, Median Electroencephalographic Frequency, Required End-tidal Isoflurane Concentrations, and Total Anesthetic Requirement for Different Nitrous Oxide Concentrations

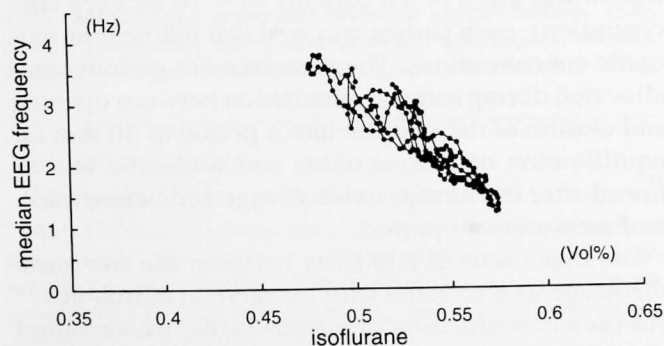| Nitrous Oxide (vol %)	Age (yr)	Temperature (°C)	Median EEG Frequency (Hz)	Mean of Required End-tidal Isoflurane (vol %)	Mean of Standard Deviations of Required End-tidal Isoflurane (vol %)	Total Anesthetic Requirement (MAC)
0	38.4 ± 8.0	35.7 ± 0.6	2.51 ± 0.12	1.06 ± 0.24	0.11	0.92 ± 0.21
20	40.9 ± 9.3	35.7 ± 0.6	2.47 ± 0.08	1.04 ± 0.25	0.07	1.09 ± 0.22
40	37.3 ± 6.4	35.9 ± 0.5	2.45 ± 0.06	0.87 ± 0.27	0.11	1.14 ± 0.23
60	38.0 ± 9.4	35.6 ± 0.7	2.48 ± 0.10	0.77 ± 0.15	0.10	1.24 ± 0.13
75	38.7 ± 9.7	35.7 ± 0.5	2.46 ± 0.07	0.79 ± 0.23	0.10	1.41 ± 0.20

Values are mean ± SD.

of both agents ($C_{isoflurane}$, $C_{nitrous\ oxide}$) that lead to the same effect obey the equation

$$\alpha \times C_{isoflurane} + \beta \times C_{nitrous\ oxide} = 1$$ with suitable coefficients $\alpha > 0$ and $\beta > 0$.

Thus, additive interaction is present if data points lie on a straight line. Deviations from linearity indicate a nonadditive interaction.

Differences in age, temperature, and median EEG frequency in the groups of different nitrous oxide concentrations were tested with analysis of variance. Regression analysis was used to quantify the nature and strength of the relationship between nitrous oxide concentrations and end-tidal isoflurane concentrations, necessary to maintain median EEG frequency between 2 and 3 Hz, and the relationship between blood pressure, heart rate, and nitrous oxide concentrations. Regression analysis was used to determine whether nitrous oxide influenced isoflurane requirement differently at the first and second measurement periods. Statistical significance was assumed at probability levels of ≤ 0.05.

Results

Age and temperature did not differ between the groups receiving the various nitrous oxide concentrations (table 1).

Figure 1 depicts as an example the relationship between isoflurane concentration and median EEG frequency for one subject. The hysteresis between end-tidal isoflurane concentrations and median EEG frequency was eliminated, using the concept of effect compartments.

At a constant median EEG frequency of 2.5 Hz, the nitrous oxide concentrations did not influence the pattern of EEG, as depicted in figure 2. In addition, analysis of variance showed no significant difference in the percentage of activity in the EEG frequency bands between the various nitrous oxide concentrations (table 2).
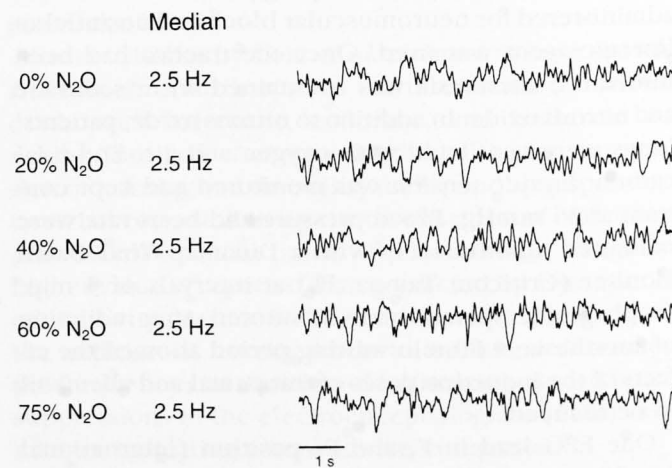

Fig. 1. Relationship between isoflurane concentration and median electroencephalographic frequency after hysteresis elimination for patient 1 receiving 75 vol% nitrous oxide.

Fig. 2. Raw electroencephalograms of five typical patients with isoflurane/nitrous oxide anesthesia when median electroencephalographic frequency reached 2.5 Hz.

The mean of all median EEG frequencies from the ten patients of each nitrous oxide group did not differ significantly between the various nitrous oxide concentrations (table 1).

Figure 3 depicts the isobole of required end-tidal isoflurane concentrations to maintain the median EEG frequency between 2 and 3 Hz *versus* the chosen nitrous oxide concentrations. Regression analysis was performed by fitting linear and quadratic models relating isoflurane concentrations to independently chosen nitrous oxide concentrations. Lowest standard error of estimation was found for a linear model. The line of regression was calculated as:

$$C_{isoflurane} = 1.05 \text{ vol\%} - 0.0041 \times C_{nitrous\ oxide} \quad (1)$$

The probability level for dependence of the required isoflurane concentration on nitrous oxide concentration (slope $\neq 0$) is 0.015. The correlation coefficient is -0.93, R-squared is 89.6%, standard error of estimation is 0.05.

No statistically significant differences were observed between the nitrous oxide administrations at the first and second measurement periods.

If the total anesthetic requirement is expressed as the sum of isoflurane and nitrous oxide MAC-fractions (assuming 1.0 MAC of isoflurane to be 1.15 vol% and 1.0 MAC of nitrous oxide to be 1.04 atm absolute) there is a significant increase in the total anesthetic MAC multiples with increasing nitrous oxide concentrations (fig. 4).

No significant difference in systolic blood pressure, diastolic blood pressure, and heart rate between the various nitrous oxide concentrations could be observed (table 2).

Discussion

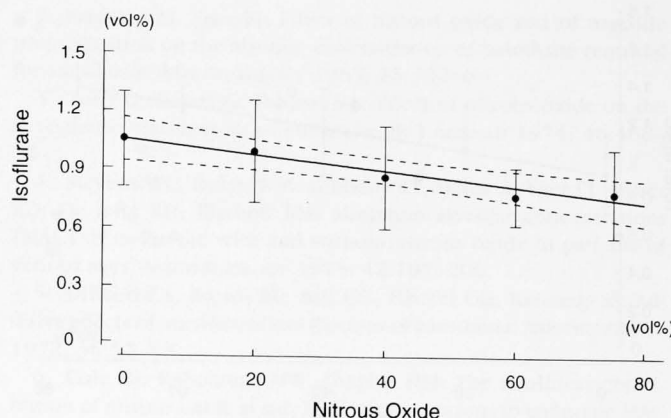The results of this study are limited by the absence of the concentration of nitrous oxide alone, which leads

Fig. 3. Isobole of nitrous oxide concentrations *versus* required end-tidal isoflurane concentrations to maintain median electroencephalographic frequency between 2 and 3 Hz. Data points are mean ± SD. —— Regression line. - - - 95% Confidence limits.

to a median EEG frequency of 2–3 Hz during surgery. Nitrous oxide can be used as the sole anesthetic only in hyperbaric conditions. This is not practicable under clinical conditions. However, this study shows that nitrous oxide in the dose range 0–75 vol% linearly decreases the isoflurane requirement necessary to maintain median EEG frequency between 2 and 3 Hz during surgical operation. This is compatible with an additive type of interaction between nitrous oxide and isoflurane on median EEG frequency.

Cole *et al.* reported deviations from linearity of the interaction between nitrous oxide and halothane, enflurane, or isoflurane on MAC in rats.[6,7] The observed deviations, however, were judged as rather small,[15] so that clinical relevance may be questioned.

Isoboles do not always consistently exhibit one type of interaction throughout their course.[14] Therefore, we cannot conclude that the type of interaction will remain

Table 2. Hemodynamic Parameters and Electroencephalographic Frequency Bands for Different Nitrous Oxide Concentrations

Nitrous Oxide (vol %)	BP_sys (mmHg)	BP_dia (mmHg)	HR (min⁻¹)	δ_1 0.5–2 Hz (%)	δ_2 2–5 Hz (%)	θ 5–8 Hz (%)	α 8–13 Hz (%)	β 13–32 Hz (%)
0	112 ± 4	66 ± 8	80 ± 15	47.1 ± 2.1	14.8 ± 2.7	13.7 ± 3.6	8.6 ± 4.7	1.9 ± 0.7
20	113 ± 14	69 ± 13	80 ± 11	46.9 ± 2.7	15.6 ± 3.4	13.0 ± 2.5	7.9 ± 4.3	2.2 ± 0.9
40	112 ± 15	73 ± 15	72 ± 8	46.8 ± 3.9	15.1 ± 4.2	12.0 ± 3.7	9.4 ± 4.7	3.0 ± 1.7
60	112 ± 11	69 ± 11	77 ± 12	46.4 ± 3.1	16.8 ± 3.4	11.4 ± 3.8	6.8 ± 3.1	3.2 ± 1.0
75	114 ± 15	71 ± 13	76 ± 15	46.6 ± 2.5	18.3 ± 3.7	10.8 ± 5.0	4.8 ± 2.1	3.1 ± 1.6

Values are mean ± SD.

BP_sys = systolic blood pressure; BP_dia = diastolic blood pressure; HR = heart rate.
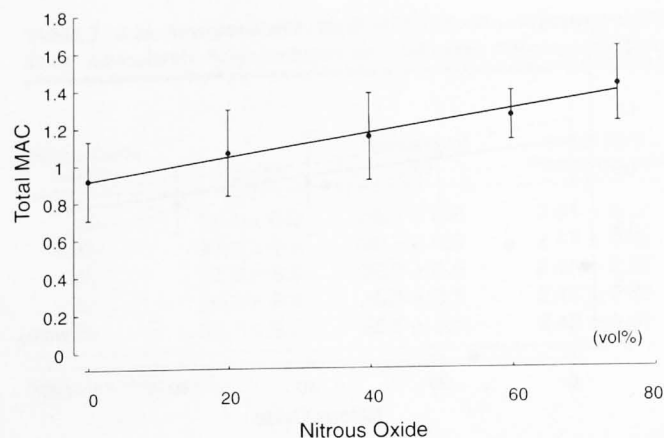
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Fig. 4. Sum of fractional minimum alveolar concentration contributions (total minimum alveolar concentration) of nitrous oxide concentrations and required isoflurane concentrations to maintain median electroencephalographic frequency between 2 and 3 Hz. Data points are mean ± SD. —— Regression line.

additive at higher partial pressures of nitrous oxide then corresponding to 75 vol%.

The slope of isoboles can be used as an indicator of the potency of nitrous oxide to decrease the requirement of isoflurane. The potency of nitrous oxide to decrease the requirement of isoflurane necessary to keep median EEG frequency between 2 and 3 Hz is less than the potency of nitrous oxide to decrease the requirement of isoflurane necessary to suppress movement to skin incision in 50% of patients (MAC). Using equation (1), we can estimate that the addition of every 10 vol% of nitrous oxide decreases the isoflurane requirement as defined by the EEG criterion by approximately 0.04 vol%, while, in terms of MAC, each 10% of nitrous oxide decreases the isoflurane requirement by approximately 0.11 vol% (assuming additive interaction and MAC isoflurane, 1.15 vol%,[4] and MAC nitrous oxide, 1.04 atm absolute[16]; fig. 5).

We cannot exclude the possibility that our results are perturbed by acute tolerance by using subsequent measurement periods for each patient.[17-20] However, using regression analysis we could not identify an influence of nitrous oxide at the different measurement periods.

Other recent studies can be used to estimate the interaction of isoflurane and nitrous oxide when the level of clinical judgment or memory functions are considered (fig. 5). Eger et al. compared isoflurane anesthesia with and without 60% nitrous oxide for several kinds of surgeries.[21] Without nitrous oxide, the attending anesthesiologist determined an average end-tidal concentration of 0.85 vol% isoflurane to be necessary for clinical anesthesia; 60 vol% nitrous oxide allowed a reduction of isoflurane to 0.64 vol%. Assuming a linear relationship, every 10% of nitrous oxide reduces the isoflurane requirement by 0.035 vol%. Eger et al. used lower levels of isoflurane than in our study. This could be explained by the coadministration of 0.23 mg fentanyl, which was not used in our study. In another study, Dwyer et al. determined the dose of isoflurane and nitrous oxide that suppressed memory by 50% (ED_{50}).[22] The ED_{50} was 0.2 MAC for isoflurane and 0.5 MAC for nitrous oxide. Assuming linear dependence, every 10 vol% of nitrous oxide decreases the isoflurane requirement by 0.045 vol%.

The differences in the potency of nitrous oxide to substitute isoflurane confirm the results of previous studies: the relative potencies of inhaled anesthetic agents depend on the end point measured.[10,23,24] These studies do not support the hypothesis that both anesthetics act in the same way. One possible explanation is that these anesthetics act at different anatomic sites. Whereas the EEG is known to represent the electrical activity of cortical structures, more recent studies suggest that MAC is a test of anesthetic potency that evaluates depression of a spinal reflex. Rampil et al. demonstrated that, with regard to MAC, the anesthetic potency of isoflurane is independent of forebrain structures of the rat.[25] They concluded that surgical
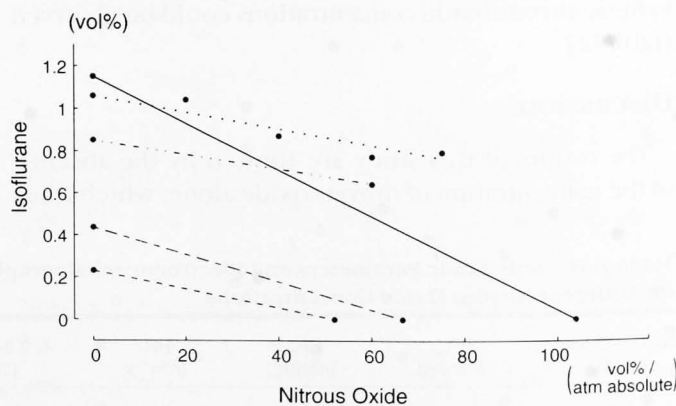

Fig. 5. Comparison of different studies used to estimate the interaction of isoflurane and nitrous oxide. - - - ED_{50} for suppression of learning, Dwyer et al.[22] — — Minimum alveolar concentration-awake, Dwyer et al.[22] · · · - - Clinical signs, Eger et al.[21] —— Minimum alveolar concentration, Stevens et al.,[4] Hornbein et al.[16] · · · · Median electroencephalographic frequency 2–3 Hz (this study). Every point (•) represents the mean of a measurement.

unresponsiveness appears to be supported and may be determined by subcortical structures. In another study, Rampil demonstrated that acute spinal transection at T1 in rats does not change MAC.‡ Antigonini *et al.* measured MAC in goats and found a large increase in isoflurane requirement (from 1.2 vol% up to 2.9 vol%) when the brain was preferentially anesthetized.[26] They conclude, that subcortical structures modulate movement in response to painful stimuli during general anesthesia.

Quantitative EEG measurement during anesthesia with isoflurane and nitrous oxide at 1.3 and 1.5 MAC showed dose-related dependence.[13] However, comparison of EEG and movement response to noxious stimulation showed no correlation.[27] One conclusion could be that EEG effects and movement response to noxious stimulation are to be regarded as components of anesthesia that result from separate pharmacologic actions.

The potency of nitrous oxide as a substitute for isoflurane for clinical anesthesia in the study of Eger *et al.*[21] is approximately equal to the potency found in this study. This suggests that the use of EEG median frequency better reflects what an attending anesthesiologist considers as clinically appropriate anesthesia, than does the addition of MAC fractions of both agents.

In spite of its analgesic properties,[28] nitrous oxide is known to have only weak anesthetic potency. Due to its high MAC value, it cannot be used effectively as a sole anesthetic at normal atmospheric pressure. This study of its interaction with isoflurane on the EEG indicates that the potency of nitrous oxide as a substitute for isoflurane is less than might be expected from its MAC value. Thus, it might be asked whether nitrous oxide is an essential anesthetic component for inhalational anesthesia with isoflurane.

In conclusion, this study has shown that nitrous oxide in the dose range of 0–75 vol% linearly decreases the requirement of isoflurane needed to maintain median EEG frequency between 2 and 3 Hz. The degree of interaction for this endpoint is, however, less than anticipated from MAC studies, but seems to more appropriately reflect the clinical usage of both drugs.

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