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Quantitation of the Effect of Nitrous Oxide on Rocuronium Infusion Requirements Using Closed-loop Feedback Control

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Background: **Nitrous oxide has a minor effect on the effective dose 50% values of bolus doses of rocuronium. The authors have studied the effect of nitrous oxide on the infusion requirements of rocuronium using closed-loop feedback control of rocuronium infusion.**

Methods: **The authors obtained institutional approval and informed consent to study 70 patients. The patients were given total intravenous anesthesia with propofol and remifentanil by target-controlled infusion and were randomly assigned to one of two groups, one receiving nitrous oxide with 30% oxygen (n = 35) and the other group receiving air with 30% oxygen (n = 35). The possible interaction of rocuronium with nitrous oxide was quantitated by determining the asymptotic steady state rate of infusion of rocuronium necessary to produce a constant 90% neuromuscular block. This was accomplished by applying nonlinear curve fitting to data on the cumulative dose requirement during the initial 90-min period after bolus administration of rocuronium.**

Results: **Patient characteristics and controller performance, *i.e.*, the ability of the controller to maintain the neuromuscular block constant at the set point, did not differ significantly between the groups. The administration of nitrous oxide did not affect rocuronium infusion requirements. The mean steady state rates of infusion were 33.0 ± 9.8 and 36.9 ± 13.2 mg/h in the nitrous oxide–total intravenous anesthesia and air–total intravenous anesthesia groups, respectively.**

Conclusions: **Nitrous oxide does not affect the infusion requirements of rocuronium to a clinically significant degree.**

NEUROMUSCULAR blocking drugs are usually studied during nitrous oxide anesthesia supplemented with opioids and intravenous hypnotics, because volatile anesthetics have been shown to affect the pharmacodynamics of neuromuscular blocking drugs.[1,2] The common belief has been that, unlike volatile anesthetics, nitrous oxide has no effect on the dose–response relation of neuromuscular blocking agents. However, recent studies have shown that after bolus administration of neuromuscular blocking drugs, such as mivacurium and rocuronium, nitrous oxide may actually potentiate their action.[3,4] Although it is important to quantitate the interaction of nitrous oxide with muscle relaxants in connection with their bolus administration, it would clinically also be important to quantitate the possible interaction of nitrous oxide with muscle relaxants during longer-lasting anesthesia in steady state. So far, there seems to be no information on the effect of nitrous oxide on rocuronium infusion requirements. To study this possible interaction, we used a closed-loop feedback control method of administering rocuronium to produce and maintain a relatively constant neuromuscular block of 90%. The interaction between rocuronium and nitrous oxide was measured by determining the asymptotic steady state rate of infusion necessary to produce 90% neuromuscular block with rocuronium.

Materials and Methods

Study Design

We used a randomized study design in parallel groups. On the basis of previous studies,[1] we calculated that 35 patients would be required in each of the two groups to demonstrate a 15% difference in rocuronium infusion requirements at a level of significance of $P = 0.05$ and power of 80%. We obtained approval from the ethics committee of the Hospital District of Southwest Finland (Turku, Finland) and informed written consent to study 70 patients, aged 18–75 yr, with American Society of Anesthesiologists physical status I–III. The patients were scheduled to undergo elective surgery with an estimated duration of at least 90 min. Patients with hepatic, renal, or neurologic diseases; increased intracranial pressure; or a body mass index greater than 32.5 kg/m^2 and patients receiving medication known to affect neuromuscular transmission were excluded from the study.

Premedication consisted of 3.75–7.5 mg oral midazolam 1 h before the induction of anesthesia. All patients were given total intravenous anesthesia (TIVA) with propofol and remifentanil by target-controlled infusion. In addition, the patients were randomly assigned to one of two groups, one receiving air with 30% oxygen (air–TIVA group) and the other group receiving nitrous oxide with 30% oxygen (nitrous oxide–TIVA group) throughout anesthesia. The initial target of propofol was set to 6 μg/ml. After tracheal intubation, the target was decreased to 4 μg/ml, and that level was maintained until the end of surgery. The target of remifentanil was set to 2 ng/ml at induction. Thereafter, the target was adjusted according to clinical needs between 1.5 and 6 ng/ml. If systolic blood pressure was decreased to less than 85 mmHg or mean arterial pressure was decreased to less than 55 mmHg, the target of remifentanil was set to 1.5 ng/ml and patients received, if necessary, a rapid infusion of Ringer's acetate solution and/or 5–10 mg intra-

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venous ephedrine. In hypertensive patients, the trigger for the treatment of hypotension was a 30% decrease in systolic blood pressure. Fresh gas flow was kept at 10 l/min until tracheal intubation. During maintenance of anesthesia, gas flow was 5 l/min and end-tidal nitrous oxide concentration was kept above 65% in patients receiving nitrous oxide.

After induction of anesthesia, but before administration of rocuronium, we used a Relaxograph® neuromuscular transmission monitor (Datex, Helsinki, Finland) to obtain control electromyographic values while the patients were still manually ventilated with a facemask by an experienced anesthesiologist. Specifically, the train-of-four sequence was assessed (2-Hz frequency of stimuli, 100-ms pulse width), and the stimulating surface electrodes were placed on the ulnar nerve. Recording electrodes were placed on first dorsal interosseus muscle and index finger.[5] The stimulus output was a rectangular wave with a current of 0–70 mA, and the machine calibrated automatically by searching for optimal signal levels before setting the supramaximal level. A stable baseline calibration signal was awaited before administration of rocuronium, and a second calibration was performed approximately 10 min after induction of anesthesia. The degree of neuromuscular block, assessed every 20 s, was defined as the ratio of the measurement of the first twitch in the train-of-four sequence to the corresponding control value. During recovery of neuromuscular function, the twitch height returned to at least 85% of the control value in all cases. No corrections were made to the values of intraoperatively measured neuromuscular block.

After obtaining a stable calibration signal, tracheal intubation was performed after administration of 0.6 mg/kg rocuronium. We used the ideal body weight (IBW) as defined by Devine's equation for the calculation of the dose of rocuronium.[6] Bolus administration of rocuronium was followed by infusion of rocuronium by a model-driven closed-loop feedback system as described previously.[7] An infusion pump (Fresenius Infusomat CP®; Bad Homburg, Germany) and the Relaxograph® were attached to a Compaq® portable 386 computer (Houston, TX) by means of a serial RS232C interface. The study time was 90 min for all of the patients. Propofol, remifentanil, and rocuronium infusions were continued as long as clinically indicated, but only the initial 90-min period from the administration of the bolus dose of rocuronium was analyzed. Palmar skin temperature was measured and kept above 33°C, and end-tidal carbon dioxide was maintained at 34–40 mm Hg (4.5–5.3%). Depth of anesthesia was monitored using the Bispectral Index.

The desired level of neuromuscular block (*i.e.*, the set point) was set to 90% (the first twitch in the train-of-four sequence = 10% from control). Controller performance was measured by calculating the mean offset from set point and the mean SD from set point during feedback infusion as described previously.[1] The measured values for effect and rate of the infusion were saved on the computer. The possible effect of nitrous oxide on the infusion requirements of rocuronium was quantitated by comparing the asymptotic steady state rates of infusion for 90% block between the groups. To estimate the asymptotic steady state rates of infusion, we used nonlinear curve fitting for the cumulative dose curve of rocuronium during the 90-min study period.[8]:

$$\text{Cumulative dose of rocuronium} = D \cdot \left(1 - e^{-kT}\right) + I_{ss}t,$$

where D is the amount of rocuronium in its apparent distribution volume, k is the relative rate of distribution of rocuronium, I_{ss} is the asymptotic steady state infusion rate of rocuronium, and t is the duration of administration of rocuronium. The asymptotic steady state rates of infusion were given as actual values and per kilogram ideal body weight (I_{ss}/IBW). By the end of surgery, all patients received a neostigmine–glycopyrrolate mixture to reverse neuromuscular block according to our normal routine.

Statistical Analysis

For statistical analysis, we used the Student *t* test and chi-square test. $P < 0.05$ was considered to indicate statistically significant differences between the two groups. All results are given as mean ± SD. For continuous variables, we also calculated 95% confidence intervals of the differences in mean values. All data were analyzed with use of the statistical program Systat for Windows, version 10.2 (Systat Software, Richmond, CA).

Results

Patient characteristics, controller performance, and values for the cumulative dose of rocuronium during the 90-min study period, I_{ss} and I_{ss}/IBW, are shown in table 1. Patient characteristics and controller performance did not differ significantly between the groups. Peripheral skin temperature, end-tidal carbon dioxide, average values for Bispectral Index, and remifentanil consumption were similar in the two groups. Bispectral Index was below 60 at all times in all subjects. Ephedrine was given to 17 and 14 patients in the nitrous oxide–TIVA and air–TIVA groups, respectively. Figure 1 gives an example of the time course of neuromuscular block and the cumulative dose requirements of rocuronium for one representative patient in the nitrous oxide–TIVA group. Although the mean values for the cumulative dose of rocuronium, I_{ss} and I_{ss}/IBW, tended to be 6–10% higher in the air–TIVA group, no statistically significant differences were observed (table 1 and fig. 2).

Table 1. Steady State Rate of Infusion of Rocuronium Controlled by Closed-loop Feedback System to Maintain Neuromuscular Blockade Constant at 90% during Air–TIVA or Nitrous Oxide–TIVA

	Patients					Controller Performance		Time to 10% Recovery of T1 after Initial Bolus, min
Group	n (M/F)	ASA, I/II/III	Age, yr	Weight, kg	Height, cm	Offset from Set Point, %	SD from Set Point, %	
Air–TIVA	35 (23/12)	24/5/6	45.1 ± 14.9	74.6 ± 12.6	173 ± 10	0.3 ± 1.3	2.5 ± 1.3	25 ± 8
Nitrous oxide–TIVA	35 (21/14)	17/14/4	48.9 ± 12.5	73.9 ± 10.9	172 ± 8	0.2 ± 0.9	2.8 ± 1.0	27 ± 8
Mean difference (95% CI)			3.7 (−2.8, 10.3)	−0.7 (−6.4, 4.9)	−0.9 (−5.0, 3.3)	−0.1 (−0.7, 0.4)	0.2 (−0.3, 0.8)	2.4 (−1.5, 6.3)

Values are mean ± SD. There were no statistically significant differences between the groups.

ASA = American Society of Anesthesiologists physical status; CI = confidence interval of the difference in mean values; IBW = ideal body weight; I_{ss} = asymptotic steady state rate of infusion; I_{ss}/IBW = asymptotic steady state rate of infusion per kilogram ideal body weight; T1 = first twitch in the train-of-four sequence; TIVA = total intravenous anesthesia.

Discussion

The model-driven computerized infusion of rocuronium kept the desired degree of muscle relaxation at a reasonably constant level. Accordingly, by investigating the steady state infusion requirements of rocuronium, it was possible to draw conclusions about the possible interaction between rocuronium and nitrous oxide during maintenance of anesthesia. Interestingly, unlike what was observed previously with bolus administration of rocuronium, vecuronium, and mivacurium,[3,4,9] nitrous oxide had no statistically significant effect on rocuronium when given by infusion, although the study was adequately powered to observe as small as a 15% difference in rocuronium infusion requirements at a level of significance of $P = 0.05$ and a power of 80%.

Our study differs from previous studies on the interaction between nitrous oxide and muscle relaxants in several respects. Unlike previous studies, we used a closed-loop feedback control method of administering rocuronium to produce and maintain a relatively constant neuromuscular block of 90%. It was thus feasible to quantitate the possible interaction between rocuronium and nitrous oxide during maintenance of anesthesia with minimal disturbance of the clinical routine. In the only study that has investigated the interaction between rocuronium and nitrous oxide, a 20% decrease of the mean effective dose 50% value (ED_{50}) was observed. However, 95% confidence limits in that study were rather wide, and the evidence for a clinically significant interaction between nitrous oxide and rocuronium was rather weak. The authors calculated ED_{50} for a bolus dose of rocuronium assuming that when the dose–effect relation of rocuronium is described using a log-dose/logit plot, the slope has a constant value of 4.5.[4] Although the real value of the slope was not determined, this methodology provides a robust estimate of the ED_{50}. The estimate for the ED_{50} would increase by approximately 3% at a slope of 3.5 and decrease by 1% at a slope of 5.5. The single-dose technique could have been used to estimate ED_{95}, too, but because such calculations are much more sensitive for having the correct value of the log-dose/logit slope, the values of ED_{95} were not calculated.[4]

Fiset *et al.*[9] studied the effect of nitrous oxide on ED_{50} and ED_{95} values of vecuronium. They found an approximately similar change in the potency of vecuronium as was observed by Kopman *et al.*[4] Nitrous oxide also potentiates the neuromuscular effects of mivacurium, as has been shown recently.[3] However, the duration of nitrous oxide administration before muscle relaxant was only 15 min in these rocuronium and mivacurium studies and 5 min in the vecuronium study. While the interaction between muscle relaxants and volatile anesthetics is clearly a pharmacodynamic one, the mechanism of action of nitrous oxide on neuromuscular blocking drugs is thus far unknown. Volatile anesthetics do not seem to affect the pharmacokinetics of muscle relaxants, and it is generally assumed that nitrous oxide has no effect on the pharmacokinetics of muscle relaxants.[10–14] It has been suggested that nitrous oxide affects the neuromuscular junction itself[3] or by altering delivery of the muscle relaxant to the site of action.[4] It has also been proposed that although the saturation of muscle tissue with nitrous oxide is less than 30% complete after 15 min of nitrous oxide anesthesia, nitrous oxide exerts its action on neuromuscular junction independently of its rate of accumulation in the muscle.[3]

The reason for the disagreement between our study using continuous infusion and previous studies using bolus administration of muscle relaxants[3,4,9] is not quite clear. The duration of the exposure to nitrous oxide could have an effect, but there is no conclusive evidence supporting this hypothesis. The more likely explanation is that nitrous oxide has only a minor effect, if any, on the neuromuscular action of rocuronium. While looking at the scattergram of the individual I_{ss} values in the current study (fig. 2), it is plausible to conclude that the

Table 1. Continued

Cumulative Dose of Rocuronium/ IBW, mg/kg	Steady State Rate of Infusion of Rocuronium	
	I_{ss}, mg/h	I_{ss}/IBW, mg · kg^{-1} · h^{-1}
1.29 ± 0.29	36.9 ± 13.2	0.55 ± 0.17
1.21 ± 0.24	33.0 ± 9.8	0.50 ± 0.14
−0.08 (−0.20, 0.05)	−3.9 (−9.4, 1.7)	−0.05 (−0.12, 0.03)

effect of nitrous oxide on rocuronium pharmacodynamics is negligible and has no clinical significance. The same information is delivered also by the 95% confidence intervals of the differences in mean I_{ss} and I_{ss}/IBW values. For example, even if the I_{ss}/IBW in patients anesthetized with nitrous oxide were 0.12 mg · kg^{-1} · h^{-1} less than in patients anesthetized with TIVA, this change could be regarded as clinically insignificant (a decrease of 0.12 mg · kg^{-1} · h^{-1} of I_{ss}/IBW is the maximum decrease in I_{ss}/IBW obtained by calculation of the 95% confidence interval). The study of Kopman *et al.*[4] did not report the 95% confidence intervals of the differences in mean ED_{50} values, but the scattergram demonstrates the minor effect of nitrous oxide on ED_{50}.

We conclude that nitrous oxide does not affect the infusion requirements of rocuronium to a clinically significant degree. This occurrence means that the recent recommendation[15] of using preferably intravenous anesthesia in pharmacodynamic phase I and II studies of neuromuscular blocking agents may have to be reconsidered.

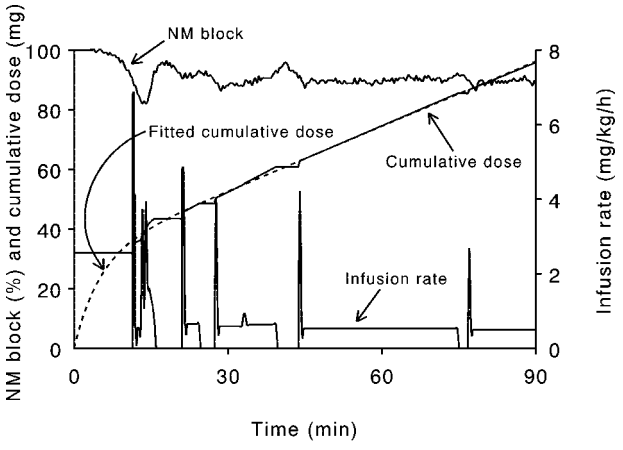

Fig. 1. Data for one representative patient in the nitrous oxide–total intravenous anesthesia group showing the rate of infusion (I_{ss}) necessary to produce a constant 90% neuromuscular (NM) block by closed-loop infusion of rocuronium, the corresponding cumulative dose requirements of rocuronium, the fitted cumulative dose requirements, and the measured NM block.

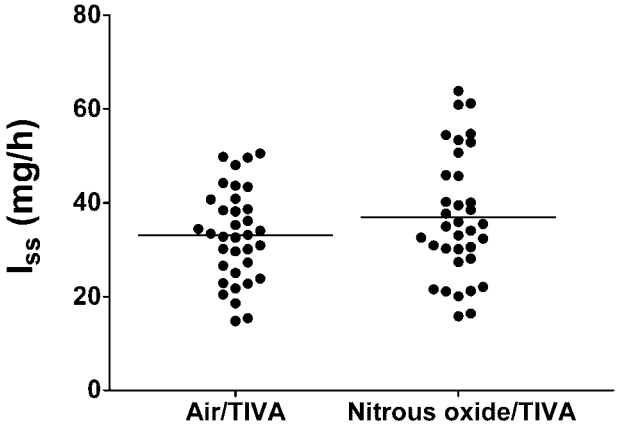

Fig. 2. Scattergram of the individual values of the rate of infusion (I_{ss}) necessary to produce a constant 90% neuromuscular block during total intravenous anesthesia with air (air–TIVA) and nitrous oxide (nitrous oxide–TIVA). The *horizontal line* represents the mean value in each group. Rocuronium was administered by model-driven closed-loop infusion.

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