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Continuous Intravenous Infusion of Rocuronium (ORG 9426) in Patients Receiving Balanced, Enflurane, or Isoflurane Anesthesia

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Background: **Rocuronium (ORG 9426) is a new nondepolarizing neuromuscular blocking agent with a rapid onset and an intermediate duration of action. This study obtains the infusion requirements of rocuronium in 30 patients in whom anesthesia was maintained with barbiturate-nitrous oxide-opioid, nitrous oxide and enflurane, or nitrous oxide and isoflurane.**

Methods: **For all 30 patients, anesthesia was induced with intravenous thiopental and fentanyl, followed by 0.45 mg/kg rocuronium. Patients were randomly allocated to receive either: 1) nitrous oxide in 40% oxygen supplemented with fentanyl, thiopental, and droperidol (balanced anesthesia), 2) 1.25 MAC enflurane-nitrous oxide, or 3) 1.25 MAC isoflurane-nitrous oxide. Once blockade had recovered to 95% depression of twitch height, muscle relaxation was maintained by continuous infusion of rocuronium, adjusted to maintain mechanical twitch response at 95% depression.**

Results: **At 90 and 120 min, the enflurane and isoflurane groups had lower infusion requirements than those receiving barbiturate-nitrous oxide-opioid anesthesia ($P < 0.02$), but these did not differ significantly between the two volatile agents. Final infusion requirements (mean ± SD) were 9.8 ± 3.7, 5.9 ± 3.1, and 6.1 ± 2.7 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for the groups receiving barbiturate-nitrous oxide-opioid, enflurane, and isoflurane anesthesia, respectively. Spontaneous recovery began soon after termination of the infusion; in all patients, twitch tension equaled 10% of control within 5 min.**

Conclusions: **The infusion requirements to maintain 95% twitch depression approximated 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ during barbiturate-nitrous oxide-opioid anesthesia. These requirements were reduced by 40% during anesthesia involving enflurane or isoflurane. (Key words: Neuromuscular relaxants: ORG 9426; rocuronium.)**

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§ Nagashima H, Nguyen HD, Kinsey A, Rosa M, Hollinger I, Goldiner PL, Foldes FF: The human dose response of ORG 9426 (abstr). ANESTHESIOLOGY 71:A773, 1989.

BECAUSE previous reports of rocuronium usage indicated that it was a nondepolarizing blocking agent with rapid onset and intermediate duration, clinicians are likely to administer it by continuous infusion. The infusion requirements for rocuronium during maintenance with different anesthetic agents have not been determined. In this study, once neuromuscular blockade was obtained with a single dose of 0.45 mg/kg rocuronium, its infusion requirements were recorded during 2 h of either barbiturate-nitrous oxide-opioid, nitrous oxide-enflurane, or nitrous oxide-isoflurane anesthesia. Enflurane and isoflurane might be expected to potentiate this nondepolarizing relaxant, both in terms of its peak effect and for continued surgical relaxation.[1]

Methods

The 30 patients who gave their informed consent to the institutionally approved study were scheduled for elective surgery to last more than 2 h, usually for orthopedic surgery of the lower limb. These were men or women between 18 and 70 yr old, ASA physical status 1 or 2. Excluded were patients of child-bearing potential; those whose weight deviated more than 30% from their ideal body weight; those with known renal, hepatic, metabolic, or neuromuscular disorders; and those receiving antihistamines or drugs known to modify the action of neuromuscular blocking agents.

The patients enrolled in this open-label study were randomly assigned to one of three anesthetic groups just before induction of anesthesia. Anesthesia was induced with intravenous thiopental and fentanyl, with further doses added as required. After adequate anesthesia and baseline measurements of neuromuscular blockade had been established, 0.45 mg/kg rocuronium was administered. Early studies had suggested that this was 1.5 times the ED_{95}.§

The intensity of neuromuscular blockade was assessed by measuring the force of thumb adduction in response

to supramaximal train-of-four stimulation of the ulnar nerve at the wrist, 2 s of 2 Hz, applied with 10 s between trains. The force of isometric contractions of the splinted thumb of an immobilized upper limb was recorded from a linear force transducer applied at a right angle to the vector of maximal response. Twitch depression was calculated from the chart recording as the ratio of depression of the first response of the train compared with its baseline control tension. Rocuronium was administered once the baseline had remained steady for 1 min.

Following tracheal intubation, the first group received 50% nitrous oxide in oxygen, supplemented with doses of 50–150 μg fentanyl, 50–100 mg thiopental, and 5–10 mg droperidol, as indicated clinically. The second and third groups received 50% nitrous oxide in oxygen plus either enflurane or isoflurane, commencing with 1.5–2%, adjusted later to a combined nitrous oxide-volatile agent end-tidal concentrations between 1.24 and 1.27 MAC. These anesthetic concentrations were maintained until twitch tension recovered to 10% depression for all but 2 of the 30 patients.

When blockade induced by the bolus dose had recovered to 5% of control, a continuous infusion of rocuronium diluted in 0.25 mg/ml normal saline was commenced at a rate of 7 $\mu g \cdot kg^{-1} \cdot min^{-1}$. For the next 2 h, the infusion rate was adjusted, attempting to maintain responses between 90% and 99% twitch depression. Spontaneous recovery was observed until conclusion of surgery ended the study or until recovery was complete; residual blockade was reversed with atropine and edrophonium. The infusion rates and blockade intensities at 30, 60, 90, and 120 min during the infusion were compared, and the times taken to achieve 10%, 25%, 75%, and 90% blockade were used as indices of recovery from rocuronium-induced neuromuscular blockade.

These interval data were analyzed with an SPSS package (Chicago, IL), using multivariate analysis of variance, with repeated measures across time for within-group comparison of the infusion rates and twitch responses. *Post hoc* between-group testing was performed with Scheffe's test. Statistical significance was accepted when $P < 0.05$.

Table 1. Clinical Details of the 30 Patients

Anesthesia	Balanced*	Enflurane	Isoflurane
Sex (M/F)	9/1	7/3	7/3
Age (yr)	42 (14)	49 (16)	47 (19)
Height (cm)	175 (11)	174 (11)	175 (9)
Weight (kg)	77 (17)	73 (13)	78 (15)

Values are mean ± SD.

* Barbiturate-nitrous oxide-opioid anesthesia.

Table 2. Details during Rocuronium Infusion, 30-minute Intervals

Anesthesia	Balanced	Enflurane	Isoflurane
Rates ($\mu g \cdot kg^{-1} \cdot min^{-1}$)			
At 30 min	12.4 ± 2.5	9.5 ± 4.1	8.5 ± 5.5
At 60 min	10.9 ± 3.6	7.5 ± 3.7	6.5 ± 2.5
At 90 min*	10.4 ± 3.8	6.7 ± 3.2	6.1 ± 2.4
At 120 min*	9.8 ± 3.7	5.9 ± 3.1	6.1 ± 2.7
Twitch tension (% of control)			
At 30 min	18 ± 13	13 ± 13	10 ± 7
At 60 min	9 ± 6	6 ± 2	6 ± 2
At 90 min	6 ± 4	5 ± 2	6 ± 2
At 120 min	5 ± 1	6 ± 2	5 ± 2

Values are means ± SD.

* Enflurane and isoflurane groups differ from barbiturate-nitrous oxide-opioid ($P < 0.02$).

Results

Clinical details of the patients are shown in table 1. Maximal blockade (mean ± SD) was 95 ± 5%, observed 3.3 ± 1.2 min following rapid intravenous administration of the initial dose of 0.45 mg/kg rocuronium. This included three patients in whom the adductor pollicis twitch responses were completely ablated. The infusion rates required to maintain approximately 95% twitch depression are shown in table 2. By the end of the 2-h infusion, the twitch responses were nearly the desired blockade intensity. Infusion rates were greater during the first hour, showing a statistically significant reduction with time. Spontaneous recovery continued after initiating the infusion, and in 12 patients, the desired intensity of blockade was not achieved in the first 30 min. By 90 min, all patients had reached a plateau in requirements and were in the desired range of 90–99% twitch depression, and the end-tidal concentrations of the inhalation agents were stable. At 90 and 120 min, the enflurane and isoflurane groups had a lower infusion requirement than those receiving barbiturate-nitrous oxide-opioid anesthesia ($P < 0.02$). The mean infusion rates for the two volatile agents did not differ significantly; target blockade intensity was achieved with fewer adjustments in the infusion rate in the presence of the volatile agents.

Spontaneous recovery from rocuronium-induced blockade began a few minutes after termination of its infusion (table 3). There was no difference detected

Table 3. Spontaneous Recovery of the Twitch Response after Infusion of Rocuronium in 30 Patients

Anesthesia	Balanced	Enflurane	Isoflurane
Minutes to achieve			
10% of control	6 ± 3	4 ± 2	8 ± 5
25%	13 ± 4	11 ± 3	18 ± 7
50%	22 ± 8	22 ± 9	34 ± 16
75%	32 ± 9	36 ± 19	50 ± 25†
90%	46 ± 19	71 ± 11*	75 ± 40‡
25–75% interval	20 ± 6	25 ± 18	33 ± 22†

Values are mean ± SD. Due to completion of surgery: *n = 9; †n = 8; ‡n = 6.

between the groups during recovery from blockade, but there was extensive interindividual variation within groups. Completion of surgery mandated reversal of blockade prior to full spontaneous recovery in two patients. Reversal was achieved rapidly with responses at less than 25% twitch depression in these two patients, both in the isoflurane group. At completion of surgery, the train-of-four ratio was less than 0.75 in seven subjects (table 3); in these patients, edrophonium produced rapid reversal of the residual blockade.

Discussion

When rocuronium was administered by continuous infusion during barbiturate-nitrous oxide-opioid anesthesia, rocuronium requirements averaged approximately 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (table 2). Requirements decreased slightly with time, due to both the protocol precondition that the infusion not be commenced until twitch responses recovered to 95% depression of the control tension and the progression toward steady state. The infusion requirements of its analog, vecuronium, during barbiturate-nitrous oxide-opioid anesthesia average 1–1.7 $\mu g \cdot kg^{-1} \cdot min^{-1}$,[2] reduced by as much as 70% in the presence of isoflurane and enflurane.[3] In our study, infusion requirements during barbiturate-nitrous oxide-opioid anesthesia were eight times greater than those expected for vecuronium, and the reductions in the presence of isoflurane and enflurane were 38% and 40%, respectively (table 2).

The time course of blockade with spontaneous recovery after either single-dose or infusion of rocuronium is also important. Following a single dose of rocuronium, the interval between 25% and 75% paralysis is dose-dependent. Doses of 0.3–0.35 mg/kg had recovery indices that averaged 8 min[4–6,‖]; larger doses usually exceeded this interval.[4,7] A dose of 0.6 mg/kg gave average recovery indices of 11–24 min,[6,8–11] similar to that of 20 min obtained with a dose of 1 mg/kg.[7] The recovery index for patients anesthetized with barbiturate-nitrous oxide-opioid anesthesia (table 3) averaged 20 min. It was not significantly different in the presence of the volatile agents. The recovery index after a 2-h infusion of vecuronium during barbiturate-nitrous oxide-opioid anesthesia was 26 min.

In summary, rocuronium is likely to be used by the clinician for its rapidity of onset. Its infusion requirements during barbiturate-nitrous oxide-opioid anesthesia averaged approximately 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and were reduced in the presence of enflurane and isoflurane. The maintenance of rocuronium-induced paralysis by infusion appears to have little advantage over that obtained with vecuronium.

References

1. Oris B, Vandermeersch E, Van Aken H, Crul JF: Dose-response relationship of ORG 9426 during halothane, isoflurane, enflurane and intravenous anesthesia (abstr). ANESTHESIOLOGY 75:A1063, 1991

2. Shanks CA: Pharmacokinetics of the nondepolarizing neuromuscular relaxants applied to calculation of bolus and infusion dosage regimens. ANESTHESIOLOGY 64:72–86, 1986

3. Cannon JE, Fahey MR, Castagnoli KP, Furuta T, Canfell PC, Sharma M, Miller RD: Continuous infusion of vecuronium: The effect of anesthetic agents. ANESTHESIOLOGY 67:503–506, 1987

4. Wierda JM, de Wit AP, Kuizenga K, Agoston S: Clinical observations on the neuromuscular blocking action of Org 9426, a new steroidal non-depolarizing agent. Br J Anaesth 64:521–523, 1990

5. Mayer M, Doenicke A, Angster R, Hoffman A, Peter K: ORG 9426: The increase of dose shortens the onset time (abstr). ANESTHESIOLOGY 75:A1070, 1991

6. Mellinghoff H, Diefenbach C, Buzello W: Neuromuscular and cardiovascular properties of ORG 9426 (abstr). ANESTHESIOLOGY 75: A807, 1991

7. Wierda MJKH, Kleef UW, Lambalk LM, Kloppenberg WB, Agoston S: The pharmacodynamics and pharmacokinetics of ORG 9426, a new non-depolarizing neuromuscular blocking agent, in patients anaesthetized with nitrous oxide, halothane and fentanyl. Can J Anaesth 38:430–435, 1991

8. Foldes FF, Nagashima H, Nguyen HD, Schiller WS, Mason MM, Ota Y: The neuromuscular effects of ORG9426 in patients receiving balanced anesthesia. ANESTHESIOLOGY 75:191–196, 1991

9. Tullock WC, Wilks DH, Brandom BW, Cook DR: ORG 9426: Onset, intubating conditions, and clinical duration (abstr). ANESTHESIOLOGY 75:A789, 1991

10. Dubois M, Shearrow T, Tran D, Kataria B, Rever L, Gadde P, Lea D: ORG 9426 used for endotracheal intubation: A comparison with succinylcholine (abstr). ANESTHESIOLOGY 75:A1066, 1991

11. Cantineau JP, Porte F, Homs JB, Liu N, Duvaldestin P: Neuromuscular blocking effect of ORG 9426 on human diaphragm (abstr). ANESTHESIOLOGY 75:A785, 1991

‖ Tullock WC, Wilks DH, Brandom BW, Diana P, Cook DR: ORG 9426 single-dose response onset and duration with halothane anesthesia (abstr). ANESTHESIOLOGY 73:A877, 1990.