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TITLE: A Comparison of Onset and Recovery of Neuromuscular Block after ORG9426 and Vecuronium
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ORG9426 is an investigational non-depolarizing muscle relaxant similar in structure to vecuronium. Initial studies show a rapid onset of action and a duration in the intermediate range. This study is designed to compare ORG9426 and vecuronium directly using case control methodology, to determine relative rates of onset and rate of recovery.

Methods: Seven ASA I or II patients having elective surgery were studied as control subjects and received vecuronium. Each was paired with a patient from a group of 60 who had received ORG9426 in an identical protocol. Pairing was based on degree of block attained without knowledge of onset time. When possible, patients were matched to achieve the same distribution of age and weight and sex. The study was reviewed and approved by the IRB. All patients gave written informed consent.

After premedication with diazepam 100-150µg/kg p.o., anesthesia was induced with thiopental 4-8µg/kg and fentanyl 4-8 µg/kg. Intubation was accomplished under enflurane 2%ET and N2O/O2 without use of any muscle relaxant. After the enflurane had been stable at 1%ET for 15-20 min, patients received vecuronium 0.02mg/kg or ORG9426 (160-240µg/kg). The force of thumb adduction was monitored using train of four stimulation of the ulnar nerve at the wrist every 12 s. Time to achieve set fractions of the final block level was tabulated and compared. Ratios of these times (Vec/9426) were calculated for each patient vs their control. This was further analyzed in a model that states that: measured time = constant (transit delay) + onset time; and onset time (vecuronium) = factor X onset time (9426). Values were compared by t test with p < 0.05 as significant

Results: Paired patients (Vec vs 9426) were close in age 40±10 vs 40±9 years, weight 77±15 vs 74±15 kg and sex distribution (% female) 71% vs 57%. Maximal first twitch depression also agreed closely (table 1). Block onset was significantly faster at all tested times for ORG9426. Analysis of onset time yielded a transit delay of 0.1±0.1 minutes and an average ratio of Time(vecuronium)/Time(ORG9426) of 2.4±0.2.

Recovery index was similar for both drugs.

Discussion: ORG 9426 is significantly faster in onset than vecuronium (2.4 times on average). Times to achieve half maximal block were in the range of 1 minute even for a dose less than the ED95. ORG9426 looks promising as a drug for the rapid onset of neuromuscular blockade especially in situations where a non depolarizing agent is preferred.

Drug	T1 %	Time (min) to % of Maximum Block				Recovery 10-25%
		5%*	50%*	75%*	90%*	
Vec	16.8 (24)	1.49 (0.62)	2.51 (0.69)	3.25 (0.68)	4.01 (0.59)	4.85 (0.41)
9426	16.4 (23)	0.75 (0.21)	1.07 (0.31)	1.39 (0.54)	1.80 (0.79)	4.52 (1.25)
Ratio V/9	1.08 (0.2)	2.06 (0.96)	2.39 (0.52)	2.46 (0.46)	2.42 (0.41)	1.16 (0.41)

All values mean (SD).

* Significant differences between drugs.

Reference:

1. British Journal of Anaesthesia 1990; 64:521-523.

A1072

TITLE: ORG-9426 INFUSION REQUIREMENTS IN CHILDREN DURING HALOTHANE ANESTHESIA
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INTRODUCTION: We administered ORG-9426, a steroidal, nondepolarizing neuromuscular blocking drug, by titrated infusion to children during nitrous oxide-halothane anesthesia. **METHODS:** 43 children (ASA I-II) of 1 to 5 years of age were studied after informed consent was obtained from a parent. Anesthesia was induced with nitrous oxide (70%), oxygen (30%), and halothane (up to 4% inspired). An iv catheter was placed and atropine (10 µg·kg⁻¹) was given. End-tidal halothane concentration was adjusted to 0.8 ± 0.05%, and fentanyl (1-3 µg·kg⁻¹) was given as needed. The ulnar nerve was stimulated supramaximally with trains-of-four stimuli (2 Hz for 2 sec at 10-sec intervals) at the wrist with surface electrodes. The evoked compound electromyogram of thumb adduction was recorded using a Datex NMT monitor. The degree of neuromuscular block was described as percent of control in that the height of the first train-of-four response (T₁) was compared to the control.

After incremental boluses of ORG-9426 produced at least 90% depression of T₁, spontaneous recovery to 25% was observed. Another bolus of at least 100 µg·kg⁻¹ of ORG-9426 was administered to produce greater than 90% blockade. Then an infusion of 600 µg·ml⁻¹ of ORG-9426 in 0.9% NaCl was begun at a rate of either 7 or 12 µg·kg⁻¹·min⁻¹, and titrated to produce about 95% blockade. Effective infusion requirements (IR) were calculated as the average rate of ORG-9426 infusion during the time when neuromuscular blockade was 89-99%. All 43 patients received infusions of ORG-9426 for at least 30 min with T₁ in the desired range for at least 80% of the time. Spontaneous recovery occurred after termination of the infusion. Times to recovery of 10, 25, and 75% of T₁ and to train-of-four ≥ 0.75 were noted. Standard errors are shown for all mean values. Paired t-test and regression analysis were used where appropriate. Statistical differences were considered significant at P ≤ 0.05.

RESULTS: The average duration of ORG-9426 infusion was 79.2 ± 4.6 min (33.1-174.4). Whether the infusion was started at 7 (N=25) or at 12 (N=17) µg·kg⁻¹·min⁻¹ IR was significantly greater in the first fifteen min of infusion, 15.5 ± 0.8 µg·kg⁻¹·min⁻¹, than it was thereafter (Table 1). After the first 15 min, IR was 12.3 ± 0.5 µg·kg⁻¹·min⁻¹ or 278 ± 11 µg·m⁻²·min⁻¹. There was no significant relationship between IR (µg·kg⁻¹·min⁻¹) and age or duration of infusion. After termination of infusion, T₁₀₋₂₅ (Table 1) was statistically significantly (p<0.001) longer by 1.1 min compared to T₁₀₋₂₅ after incremental boluses. The time from termination of infusion to recovery of the train-of-four ratio to ≥ 0.75 was 28.5 ± 1.6 min (17.0-42.5). T₂₅₋₇₅ was significantly related (p<0.001) to the duration of the infusion (R=0.63).

DISCUSSION: The IR of ORG-9426 in children 1 to 5 years of age is about 12 µg·kg⁻¹·min⁻¹, about 7 times that of vecuronium (1). Spontaneous recovery rate from infusion of ORG-9426 appears similar to that after infusion of vecuronium (1). **REFERENCE:** 1. Anesthesiology 71:A1039, 1989.

Table 1. Infusion Requirements and Recovery Thereafter

	IR min > 15 µg·kg ⁻¹ ·min ⁻¹	T ₁₀₋₂₅ min	T ₂₅₋₇₅ min
X	12.3	4.7	12.6
SEM	0.5	0.3	4.4
Range	3.6-21.5	2.5-9.5	7.2-28.0
N	43	39	37