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POSTER DISCUSSION IX

A1067

Title: THE DOSE RESPONSE OF ORG 9426 IN CHILDREN ANESTHETIZED WITH HALOTHANE

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Introduction: This study has been undertaken to determine the neuromuscular (NM) potency of ORG 9426 in children.

Methods: The legal guardians of 48, ASA classification 1 and 2 pediatric, surgical patients of 4 to 14 years of age signed informed consent allowing participation in this study, approved by the IRB. Patients were premedicated with i.m. 0.01-0.015 mg/kg atropine. Anesthesia was induced with a mixture of 3 L/min N_2O - 2 L/min O_2 containing up to 3% and subsequently 0.8-1.5 (v/v) halothane administered through a face mask. Ventilation was manually assisted or controlled. After induction of anesthesia, the ulnar nerve at the wrist was stimulated, through surface electrodes, with supramaximal, square wave impulses of 0.2 ms duration every 12 sec. The isometric force of adduction of the thumb (P) was quantitated with a force displacement transducer and continuously recorded. After P became stable 4 groups of 12 patients each received, randomly, 0.12, 0.16, 0.20 or 0.24 mg/kg ORG 9426. After development of its maximal effect, the first dose of ORG 9426 was supplemented to 0.3 mg/kg. If necessary, additional 0.025-0.1 mg/kg increments of ORG 9426 were administered until P became <10% of control. At this time, the trachea was intubated. Increments of 0.1 or 0.125 mg/kg, ORG 9426 were given whenever P became >25% of control. Spontaneous recovery of NM transmission was allowed to proceed for as long as possible. If at the end of anesthesia T4/T1 ratio was <0.75 the residual NM block was antagonized by a mixture of 0.5 mg/kg edrophonium + 0.01-0.015 mg/kg atropine. Heart rate (HR) and blood pressure (BP) were recorded before and after administration of the first dose and after the 0.3 mg/kg total dose of ORG 9426.

Results: Irrespective of their size the time to the development of the maximal NM effect of the initial doses of ORG 9426 was similar, 2.3 ± 0.1 (mean ± SEM) (range 0.8 - 3.9 min). The ED_{50}, ED_{90} and ED_{95} of ORG 9426, determined with the log-probit method were 0.181, 0.338 and 0.403 mg/kg respectively (see table). The clinical duration of the first 0.100 and 0.125 mg/kg maintenance doses of ORG 9426 were 5.9 ± 0.4 (n=26) and 8.1 ± 0.6 (n=12) min respectively. Recovery rate was 8.2 ± 0.4 (n=46). HR increased from its control value of 112.0 ± 2.9 (mean ± SEM) to 127.9 ± 2.0 ($p<0.001$; paired t test) after 0.3 mg/kg ORG 9426. There was no change in systolic or diastolic BP.

Discussion: As indicated by the ED_{50}, ED_{90}, and ED_{95} values, ORG 9426 under halothane is less potent in children than in adults (see table). The difference in potency is less at the ED_{90} and ED_{95} than at the ED_{50} level. There is no difference in the recovery indices of ORG 9426, 8.2 ± 0.4 min in children and 8.0 ± 0.5 min in adults (Tullock W.E.). The administration of 0.3 mg/kg ORG 9426 in 2 increments, about 3 min apart, caused a 14% increase in HR.

Neuromuscular Potency of ORG 9426

	Children (4 to 14 years)	Adults *	Relative † Potencies (%)
ED_{50} (mg/kg)	0.181	0.111	61
ED_{90} (mg/kg)	0.338	0.274	81
ED_{95} (mg/kg)	0.403	0.353	88

*Personal communication Tullock WE, MD, Montefiore Hospital/ University of Pittsburg, PA 15213.

† Relative potencies in children at the levels indicated.

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TITLE: INFUSION REQUIREMENTS OF ORG 9426 IN PATIENTS RECEIVING BALANCED, ENFLURANE OR ISOFLURANE ANESTHESIA

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Introduction

ORG 9426 is a nondepolarizing neuromuscular blocking agent related to vecuronium. Animal studies indicate that it possesses a fast onset and a short to intermediate duration, and, like vecuronium, is free from cardiovascular side effects. Early studies in man show that the ED95 dose has a more rapid recovery than vecuronium (1). This recovery rate profile suggests that it would be an ideal drug for administration by continuous infusion, allowing rapid changes in blockade intensity during and after surgery. The major aim of this study is to find the infusion rates for ORG 9246 appropriate to maintain surgical relaxation during commonly used anesthetic techniques.

Methods

The study involves three groups of 8 patients, randomly allocated to receive one of three anesthetics: enflurane, isoflurane or nitrous oxide-barbiturate-narcotic. Following establishment of stable anesthesia, a 1.5xED95 bolus dose of ORG 9426, 0.45 mg/kg (1), was administered to facilitate tracheal intubation. An infusion of ORG 9426 was commenced when the evoked twitch responses have returned to 5% of control, and adjusted to maintain this intensity of blockade. Two-way analysis of variance was used to examine differences in infusion rates between groups, and across time (repeated measures).

Results

The twitch heights and infusion rates at half-hourly intervals are shown in the Table. The earliest values indicate the "catch-up" rates required to compensate for the delay in commencement of the infusion.

Discussion

The new muscle relaxant, ORG 9426, demonstrated potentiation by the inhalation agents. Enflurane and isoflurane potentiate the other nondepolarizing relaxants, similarly by about 40%.

Table: Mean values during the infusion of ORG 9426, at half-hourly intervals.

	Groups		
	Balanced	Enflurane	Isoflurane
Infusion rates, mcg/kg/min			
30 min	12.5	8.0	8.0
60 min	11.0	6.6	6.4
90 min	10.6	5.8	6.1
120 min	10.2	5.1	6.1
Twitch, % of Control			
30 min	20	9	10
60 min	10	6	6
90 min	7	5	6
120 min	5	6	5

Reference

1. Nagashima H, et al. The human dose response of ORG 9426. Anesthesiology 71:A773, 1989.