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Title: THE PROTEIN BINDING OF ORG9426 AND ITS INHIBITORY EFFECT ON HUMAN CHOLINESTERASES

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Introduction. It has been suggested[1] that after i.v. administration the speed of onset and intensity of action of nondepolarizing muscle relaxants (MR) are inversely proportional to their binding to plasma proteins and to their inhibitory effect on acetylcholinesterase (AChE). These considerations prompted the investigation of the protein binding and AChE inhibitory effect of ORG9426, a new steroid type MR.

Methods. In this study, approved by our IRB, the protein binding of ORG9426 was determined by a method based on its inhibitory effect on plasma butyrylcholinesterase (BuChE) in assay systems containing 50% or 5% heparinized human plasma respectively.[1] BuChE and red cell AChE activities were measured with a null-point potentiometric titration method.[1]

Results. The I50 of ORG9426 for BuChE was higher when its plasma concentration was 50% than when it was 5% (see table). The protein binding calculated from these data indicate that 72% of the ORG9426 added to plasma was bound to plasma proteins. In contrast the protein binding of the structurally similar, vecuronium, was 91%.[1] The I50 of ORG9426 for AChE and BuChE, respectively (see table), are 15.9 and 21.4 times higher than the I50 of vecuronium for human AChE (6.6×10^{-5}M)[1] or BuChE (6.9×10^{-7}M).[1]

Discussion. Since in man the intubating dose of ORG9426 is 6 times and its free plasma level is 3 times higher than that of vecuronium it may be expected that after i.v. injection the concentration of ORG9426 at the endplate is about 18 times higher than that of vecuronium. This should favor the shorter onset time of ORG9426[2] than that of vecuronium. The higher concentration of ORG9426 should compensate for the fact that its anti-AChE effect is 16 times lower than that of vecuronium. Therefore it is unlikely that its low AChE inhibitory potency would contribute to the difference of the onset time of the 2 MR.

Inhibition of Human Plasma BuChE and Red Cell AChE by ORG9426*

Source of Enzyme	I50 (M)	I90 (M)	r2	Protein Binding
Plasma (5%)	1.48×10^{-5}	1.51×10^{-4}	0.99	72%
Plasma (50%)	3.13×10^{-5}	2.61×10^{-4}	0.99	
Red Cell (5%)	1.05×10^{-3}	1.75×10^{-2}	0.99	

*Figures in parenthesis indicate concentration (v/v) of plasma or red cell in assay system. The concentration of ACh was 2.2×10^{-2}M in plasma BuChE and 3×10^{-3}M in the red cell AChE experiments. Assay temperature 37°C.

References.

1. Handbook of Experimental Pharmacology. Kharkevich ED (ed), Springer-Verlag, Berlin 1986. pp 225-31.
2. Anesthesiology 73:A890, 1990

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TITLE: NEUROMUSCULAR BLOCKADE FOLLOWING ORG 9426 IN CHILDREN DURING N2O-HALOTHANE ANESTHESIA

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ORG 9426, a new non depolarising neuromuscular blocking agent with minimal cardiovascular effects, is the latest agent to become available in man. Pediatric data so far is limited (1). The aim of this study was to determine onset, duration of action and recovery characteristics in the child during N2O-halothane anesthesia.

Eleven ASA status I-II children, aged between 1.5 and 7.5 years were studied following institutional approval and written informed consent from parents. All patients were scheduled for minor non-hemorrhagic surgery requiring the use of neuromuscular blocking agents. No premedication was given. Anesthesia was induced with N2O (60%) in O2 and halothane. An intravenous infusion was commenced following peripheral vein cannulation. The trachea was intubated and anesthesia was maintained with an end-tidal halothane concentration of 1 MAC (age adjusted). Ventilation was controlled to maintain an end-tidal CO2 between 30 and 36 mmHg. Monitoring included EKG, non invasive blood pressure, core temperature, end-tidal CO2, end-tidal halothane and SpO2. The ulnar nerve was stimulated supramaximally via skin electrodes at the wrist using a TOF stimulation every 10 sec. The force of contraction of the adductor pollicis was measured using a pediatric force transducer. After a stable recording had been achieved for 5 minutes, 0.8 mg.kg-1 of ORG 9426 was injected intravenously over 10 sec and flushed immediately. Following maximal blockade the stimulation rate was reduced to once every 20 sec. Onset time (time from injection to maximal blockade), clinical duration (time from injection to 25% recovery), recovery index (time from 25% recovery to 75% recovery), total duration (time from injection to 90% recovery) and the time from injection until T4 recovered to 70% of T1 were measured. All results are expressed as mean ± SD. Systolic blood pressure and heart rate prior to injection and every five minutes after were compared using ANOVA following by appropriate post-hoc test($p < 0.05$ was considered statistically significant).

Results are displayed on the table. All patients showed 100% block with the dose used. No significant changes of hemodynamic parameters following ORG 9426 were observed: systolic blood pressure was 95 ± 11 mmHg and 92 ± 9 mmHg respectively before and 5 min following injection of ORG 9426; similarly heart rate was 108 ± 15 bpm and 111 ± 13 bpm.

Table	mean ± SD	range
onset (sec)	28.2 ± 8.7	20 - 40
clinical duration (min)	32.3 ± 12.4	17 - 56
recovery index (min)	8.6 ± 3.4	4 - 13
total duration (min)	46.9 ± 16.7	23 - 75

Previous work has demonstrated the ED95 of this drug to be in a range of 0.3-0.4 mg.kg-1 in the adult (2). As it is usually considered that the intubating dose is twice the ED95, we therefore used 0.8 mg.kg-1. Following this dose the onset time (28 sec) is much more rapid than estimated equipotent doses of vecuronium in children during N2O-halothane anesthesia (3). The recovery index however remains similar. In conclusion, at the dose of 0.8 mg.kg-1. in children ORG 9426 is a neuromuscular blocker which produces 100% blockade with a short onset time and an intermediate duration of action.

References: 1) Anesth. Analg. 72: S326, 1990
2) Br. J. Anaesth. 64: 521-523, 1990
3) Anesth. Analg. 62: 1083-1088, 1983.