Title: PHARMACODYNAMICS OF ORG 8764, ATRACURIUM AND VECURONIUM: A COMPARISON OF VOCAL CORD, DIAPHRAGM AND TIBIAL MUSCLE RELAXATION

Authors: H. Gilly Ph.D., M.M. Hirschl, K. Steinbereithner M.D.

Affiliation: L. Boltzmann Institute of Experimental Anesthesiology and Research in Intensive Care, Spitalgasse 23, A-1090 Vienna, Austria

Introduction. In addition to the criteria formulated by Savarese & Kitz[1] for an ideal muscle relaxant we think rapid onset of the drug at the vocal cords (VC) would be desirable to warrant immediate optimal intubating conditions. At the same time the the muscle activity of the diaphragm (DIA) should be sufficiently depressed. We tested ORG 8764 with regard to these properties in comparison with atracurium (ATR) and vecuronium (VEC) using a 3-muscle in vivo rat model.

Methods. 21 Sprague Dawley rats (3 randomized groups; n=7) were anesthetized (thiopental i.v.) and normoventilated with O2:air=1:1. Heart rate, blood and airway pressure and body temperature were continuously monitored and maintained within the physiological range. For quantitation of neuromuscular block (nm) evoked responses of M.tibialis (TIB), VC and DIA were recorded after supramaximal stimulation of the sciatic, laryngeal and both phrenic nerves. Isometric twitch tension (MMG) was recorded from TIB and DIA, electromyographical signals (EMG) were obtained from TIB and VC. Drug dosage was chosen to block mechanical depression in TIB about 90% (ED90: ORG 8764: 4800µg/kg, ATR 800µg/kg, VEC: 300µg/kg). Statistical evaluation: Wilcoxon's U-test, level of significance being 5%.

Results. In the vocal cord onset time was shorter with ORG 8764 than with ATR or VEC ($p<0.05$), ATR showing the slowest onset. DIA relaxation was also significantly more enhanced after ORG 8764 compared to the other drugs. Rather small differences were found in duration of action, VEC induced depression being shortest (see table for mean values ±SD; n=7). No signs of cumulation were observed. Tachycardia (transient heart rate increase by 20 to 30% of control) accompanied by a drop in mean arterial pressure of about 10% after bolus injection were noted. Compared with ATR and VEC the potency of ORG 8764 is rather low.

Discussion. ORG 8764 was investigated with respect to its pharmacodynamic properties in three different muscles. In contrast to both VEC and ATR ORG 8764 showed an extremely rapid onset in VC. Various factors influencing pharmacodynamics have to be discussed for explanation. Assuming that the relaxants do not change blood perfusion per se blood-tissue partition coefficient (BTPC) and drug diffusion into the biophase might become predominant factors determining onset[2]. A higher BTPC and/or enhanced diffusion into the biophase could be ascribed to ORG 8764. Whereas ATR and VEC produced rather weak diaphragmatic depression, relaxation induced by ORG 8764 was twice as intense in this muscle. This difference might be explained by a higher degree of receptor occupation (caused by increased concentration in the "diaphragm compartment"); own preliminary observations point to a dose-response shift to the left in DIA.

Conclusion. ORG 8764 could represent a further step towards the "ideal" muscle relaxant as far as VC and DIA relaxation is concerned. However, due to its cardiovascular side effect the drug does not fulfill some other requirements of major importance.

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References.

1. Savarese JJ, Kitz RJ: The quest for a short acting non-depolarizing neuromuscular blocking agent. Acta Anaesthesiol. Scand. 53 (Suppl):43-58,1973
2. Hennis PJ, Stanski DR: Pharmacokinetic and pharmacodynamic factors that govern the clinical use of muscle relaxants. Seminars in Anesthesia 4:21-30,1980

Table: Pharmacodynamics in different muscle groups

Drug	Atracurium	ORG 8764	Vecuronium
Onset (seconds)			
MMG-TIB	117±14	90±13	79±10
MMG-DIA	66±10	59±8	53±7
EMG-TIB	106±11#	90±12	69±15*
EMG-VC	63±9#	24±5	54±5*
maximal block (%)			
MMG-TIB	89±7	91±7	88±13
MMG-DIA	31±11#	68±14	26±7 *
EMG-TIB	92±4	93±6	89±14
EMG-VC	89±9	96±4	90±7
duration to 75% recovery (seconds)			
MMG-TIB	351±47	310±68	241±49*
MMG-DIA	149±22	168±36	100±15*
EMG-TIB	396±54	333±65	283±72
EMG-VC	301±40	296±66	203±42*

#: $p<0.05$ ATR vs ORG 8764; *: $p<0.05$ VEC vs ORG 8764

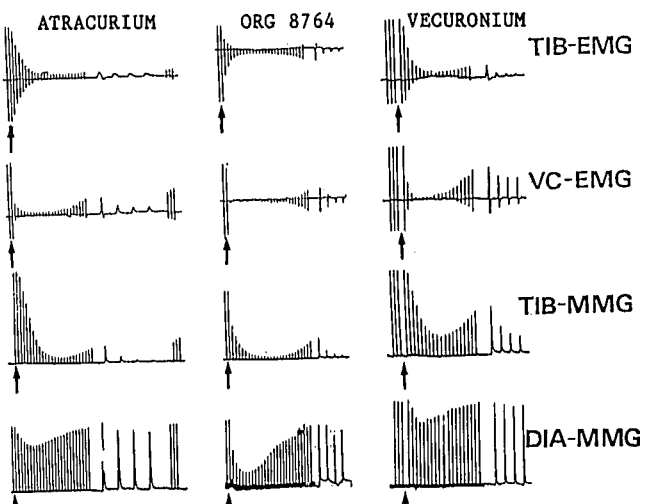

Figure. Time course of nm blockade in TIB, VC and DIA until 25% recovery of TIB mechanical twitch. Bolus doses used were ATR 800µg/kg (left), ORG 8764 4800µg/kg (mid) and VEC 300µg/kg (right panel). Time of drug injection marked by arrow↓. Stimulation pattern: single twitch at 0.1Hz; TOF at 25% recovery.