TITLE: REVERSAL OF THE D-TUBOCURARINE BLOCK BY COMBINATION OF METHYLGUANIDINE AND NEOSTIGMINE IN VIVO

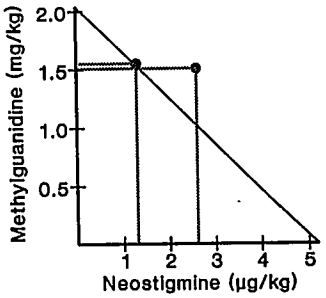
AUTHORS: K. Watanabe, M.D., H. Nagashima, M.D, Y. Ohta, M.D., F.F. Foldes, M.D.
AFFILIATION: Department of Anesthesiology, Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, NY 10467

Methylguanidine (MG) in vitro prevents and antagonizes the neuromuscular (NM) blocking effect of nondepolarizing muscle relaxants.[1] It has been reported that in rats, in vitro, the antagonist effect of combinations of MG and anticholinesterases are more than additive.[2] In the present study, the antagonism of d-tubocurarine (d-Tc) induced NM block by a combination of MG and neostigmine (NEO) was investigated in live rats.

Rats anesthetized with i.p. pentobarbital and urethane were tracheostomized and mechanically ventilated with O_2. Sciatic nerves were stimulated at gluteal region with supramaximal square impulses of 0.2 ms duration at 0.1 Hz. The force of contraction of the tibialis anterior muscle was quantitated by force transducers and recorded on a polygraph. After control measurements, d-Tc was continuously infused into the jugular vein by an infusion pump. When about 90% stable neuromuscular block had been established, either MG or NEO was injected into the contralateral jugular vein and ED50 (the doses required to restore the twitch tension to 50% of the control value) for each compound were calculated by the cumulative log dose-response analysis. ED50 of MG was also determined after the injection of 1/4 or 1/2 ED50 of NEO.

ED50 of MG and NEO were 2.04±0.17 mg/kg and 5.20±0.25 µg/kg (Mean±SEM; n=4), respectively. MG 2 mg/kg transiently increased the blood pressure by 16±3% (n=4). ED50 of MG in the presence of 1/4 and 1/2 ED50 of NEO were 1.55±0.23 and 1.51±0.30 mg/kg, respectively. Isobologram analysis indicated that the effects of the lower dose of NEO and MG were additive and those of the higher dose of NEO and MG were less than additive (figure).

Our findings indicate that NEO does not facilitate the antagonism of the d-Tc block by MG. Furthermore, the ED50 of MG caused the increase in BP. This effect is probably due to increased norepinephrine release from the right atrium (unpublished observations). The differences observed in the in vitro and in vivo interaction of MG and NEO are probably due to the absence of pharmacokinetic factors in vitro.



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A890

TITLE: MUSCULAR RELAXATION WITH ORG9426 UNDER BALANCED ANESTHESIA

AUTHORS: H. Nagashima, M.D., H.D. Nguyen, M.D., M.M. Mason, CRNA, W.S. Schiller, M.D., P.L. Goldiner, M.D., F.F. Foldes, M.D.
AFFILIATION: Department of Anesthesiology, Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, NY 10467

It has been reported[1] that the ED95 of ORG9426 under balanced anesthesia is 0.285 mg/kg. In the present study the neuromuscular (NM) effects of 0.6 mg/kg ORG9426 were investigated under balanced anesthesia.

Twenty-two patients, of ASA classification 1, 2 and 3 signed informed consents to participate in this study approved by our Institutional Review Board. Patients were premedicated with 1.0 mg/kg diphenhydramine and 1.0 mg/kg meperidine. Anesthesia was induced with 0.5 µg/kg fentanyl, 0.1 mg/kg droperidol, 2 to 3 mg/kg thiopental and N_2O-O_2 (FiO_2 30 to 35%), and maintained with N_2O and increments of fentanyl and thiopental. After induction of anesthesia the ulnar nerve at the wrist was stimulated, through surface electrodes with train-of-four (TOF) supramaximal square wave impulses of 0.2 ms duration every 12 s. The force of contraction was quantitated with a force displacement transducer and continuously recorded. After stabilization (T1, T2, T3 and T4 constant) 11 patients in Group I received an 0.1 mg/kg "priming" and 4 min later an 0.5 mg/kg "intubating" dose of ORG9426. Another 11 patients (Group II) were given a single 0.6 mg/kg intubating dose of ORG9426.

Following the priming dose T1 decreased to 89.9±6.4% (Mean±SEM) of control and T4/T1 ratio was 0.57±0.05. The NM effects of the intubating doses summarized in the Table indicate that the various NM parameters observed in Group I and II are similar. The onset time in Group I was shorter than that in Group II. This observation was, however, not statistically significant due to large individual variations in the NM effects of ORG9426. The onset time of ORG9426 observed in this study, however, was significantly shorter than those of vecuronium (354±60 s, Mean±SEM; n=15)[2], pipecuronium (216±24 s, n=22)[2] and pancuronium (222±30 s, n=10)[2] and was equal to that of 0.6 mg/kg succinylcholine (96±10 s, n=29). The intubating doses of ORG9426 had no effect on HR or BP. In 14 of the patients, residual NM block at the end of anesthesia could be reversed within 2 min with 0.5 mg/kg edrophonium + 0.015 mg/kg atropine.

In conclusion, ORG9426 in the doses used had no side effects and its onset time was more rapid than the other nondepolarizing MR.

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Parameter	Group I	Group II
Time(s) to 80% block	52.6±7.1	55.3±3.8
Onset time(s)	76.6±14.1	95.8±12.2
Clinical duration (min)	38.3±3.8	41.5±5.1
Recovery Index (min)	21.1±3.7	12.7±2.8
Recovery of T1 from 10 to 90% (min)	28.0±8.4	24.0±6.4