Interactions between ORG9426 and Other Non-depolarizing Neuromuscular Blocking Agents in Rats In Vivo

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In this study, combined neuromuscular blocking effects of ORG9426 with other non-depolarizing neuromuscular blocking agents were investigated. About 20% steady state neuromuscular block was established by a continuous infusion of one of 6 neuromuscular blocking agents (ORG9426, vecuronium, pancuronium, pipecuronium, d-tubocurarine and metocurine). Then 1/7 of the ED50 of ORG9426 or one of other neuromuscular blocking agents was administered in a single injection, and the increase in the neuromuscular block was observed. The combined neuromuscular blocking effect of ORG9426 and d-tubocurarine or ORG9426 and metocurine was significantly (P<0.05) greater than that of each corresponding control (the combination of same neuromuscular blocking agent). The effect of d-tubocurarine was also potentiated by vecuronium, pancuronium and pipecuronium. These potentiations were not observed between ORG9426 and pancuronium, pipecuronium or vecuronium. Possible mechanisms of these synergistic interactions were discussed. (Key words: neuromuscular transmission, neuromuscular blocking agent, ORG9426, drug interaction)


ORG9426 is a new non-depolarizing neuromuscular blocking agent (NMBA), which is the 3-hydroxy-2-morpholino-16-allyl-pyrrolidine derivative of vecuronium (fig. 1). It was reported that the duration of action of ORG9426 is similar to that of vecuronium, but the onset of action is considerably faster than that of vecuronium or pancuronium in man1.

It has been reported that in in vitro experiments2-5, and in clinical studies6-11, interaction of two different non-depolarizing NMBA can be more than additive.

In the present study, the interactions of ORG9426 with other non-depolarizing NMBA (d-tubocurarine, metocurine, pancuronium, pipecuronium and vecuronium) were investigated in rats in vivo.

Methods

All experiments were performed on anesthetized male Sprague-Dawley rats weighing between 300-350g. Anesthesia was induced by intraperi-
Fig. 1. Chemical structure of ORG9426 and vecuronium.

Fig. 2. Schematic representation of experiments performed.
After a steady state, about 20%, neuromuscular block was produced by continuous infusion of one of the NMBA, one seventh of the ED50 of ORG9426 or one of the other NMBA was administered in a single injection. Resulting decrease in the force of contraction was observed.

toneal administration of a mixture of 40 mg·kg⁻¹ pentobarbital and 500 mg·kg⁻¹ urethane. Animals were ventilated with oxygen via tracheostomy with a Harvard Rodent Ventilator at the rate of 60 per minute with a tidal volume of 1 ml per 100g body weight. The common carotid artery and both external jugular veins were cannulated for monitoring of arterial pressure and administration of drugs, respectively. Rectal temperature was maintained at 36.5–37.5°C using a heating lamp. Bipolar platinum electrodes were placed on the sciatic nerves at the gluteal region. The nerves were crushed with a ligature proximal to the electrodes. The distal tendon of tibialis anterior muscle was dissected and connected by a light steel wire to a force displacement transducer (Grass, FT-03). The nerve was stimulated with supramaximal square wave stimuli of 0.2 ms duration at 0.1 Hz with a stimulator (Grass, S88). The force of contraction of the tibialis anterior muscle was continuously recorded on a polygraph (Grass, 7D).