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Short Report

Neuromuscular Blocking Actions of the Aminoglycoside Antibiotics Sisomicin and Micronomicin in the Rabbit

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[1]*Division of Intensive Care Medicine, Tohoku University Hospital,* [2]*Department of Anesthesiology, Tohoku University School of Medicine, and* [3]*Division of Operating Theater, Tohoku University Hospital, Sendai 980-77*

Matsukawa, S., Suh, J.-H., Hashimoto, Y., Kato, M., Satoh, D., Saito, S., Endo, K. and Saishu, T. *Neuromuscular Blocking Actions of the Aminoglycoside Antibiotics Sisomicin and Micronomicin in the Rabbit.* Tohoku J. Exp. Med., 1997, **181** (4), 471-473 —— The neuromuscular blocking actions of sisomicin sulfate (SISO), micronomicin sulfate (MCR) and d-tubocurarine (dTc) were studied in 20 rabbits anesthetized with halothane. The i.v. administration of SISO 20-40 mg/kg, MCR 40-80 mg/kg or dTc 0.1-0.3 mg/kg resulted in dose-dependent decreases in twitch tension. The ED_{50}s for SISO, MCR and dTc were 23.5, 58.2 and 0.2 mg/kg, respectively. SISO- and MCR-induced neuromuscular blockade was partially antagonized by neostigmine or by calcium. ——
sisomicin; micronomicin; d-tubocurarine; neuromuscular transmission

The aminoglycoside group of antibiotics have been reported to induce neuromuscular blockade in clinical and experimental studies (Sokoll and Gergis 1981). Sisomicin sulfate (SISO) and micronomicin sulfate (MCR) are structurally related to the aminoglycoside group of antibiotics. However, no studies have made quautitative measurements of the neuromuscular blocking actions produced by those antibiotics. Therefore, the present study was undertaken to determine the neuromuscular blocking potencies of SISO and MCR in the rabbit.

Materials and Methods

We obtained approval from our institutional committee on animal research. Twenty rabbits weighing 2.2-4.4 kg were studied. Anesthesia was induced with

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thiopental sodium (25 mg/kg) i.v., and maintained with halothane (1–1.5%) in oxygen. A tracheostomy was performed after the induction of anesthesia. Ventilation was controlled mechanically to keep $PaCO_2$ between 35–45 mmHg. A carotid artery was cannulated for blood pressure monitoring and arterial blood gas analysis. The external juglar veins were cannulated for fluid (5% D/W at the rate of 10 ml/kg/hr) and drug administration. The left gastrocnemius tendon was cut and secured to a Shinko U-gage force-displacement transducer. Heating pad was used to maintain body and the muscle temperature above 36°C and the muscle was housed in a clear enclosure warmed by a heat lamp. A thermistor (CTM-303; Terumo, Tokyo) in contact with the surface of the muscle measured muscle temperature. The left tibial nerve was cut after dissection from the sciatic nerve and was covered with mineral oil pool. The cut tibial nerve was directly stimulated by 27 gage thin-walled steel-needle electrodes using a stimulator (SEN-1101; Nihon Kohden, Tokyo). Supramaximal square-wave pulses of 0.1 msec duration were delivered at a rate of 0.1 Hz. The resultant isometric force of twitch tension and arterial blood pressure were recorded continuously on a Nihon Kohden polygraph.

When a steady control twitch was obtained, we randomly administered the initial dose of SISO (20 mg/kg, $n=7$), MCR (40 mg/kg, $n=7$) or d-tubocurarine (dTc; 0.1 mg/kg, $n=6$) as an i.v. bolus and maximum percentage of depression of twitch tension was determined. The additional increments of SISO (10 mg/kg), MCR (20 mg/kg) or dTc (0.1 mg/kg) were given to study the responses to more than 90% of twitch depression. Using linear regression, we determined the log • dose-% response relationship for SISO, MCR and dTc. To compare the potency of 2 antibiotics and dTc, we calculated an ED_{50} for each drug from the linear regression analysis. The antagonizing effects of neostigmine sulfate (0.05 mg/kg) or calcium chloride (8 mg/kg) i.v. were also studied.

Results and Discussion

For SISO, MCR and dTc, dose-dependent reductions were found in twitch tension (Fig. 1). The cumulative ED_{50}s for neuromuscular blocking actions of SISO, MCR and dTc were 23.5, 58.2 and 0.2 mg/kg, respectively. The relative neuromuscular blocking potencies of SISO and MCR which are equipotent to dTc (=1,000) are 8.5 and 3.5, respectively. SISO- or MCR-induced blockade was partially antagonized by neostigmine or by calcium.

The neuromuscular blockade produced by the aminoglycoside group of antibiotics is a combination of both pre- and post-junctional actions. In the frog, aminolycosides decrease the quantal release of acetylcholine by the inhibitory action on presynaptic membrane and post-junctional receptor sensitivity (Singh et al. 1982). The present study suggests that the characteristics of neuromuscular blocking properties of SISO and MCR are similar to those of other members of the aminolycosides (Singh et al. 1978).

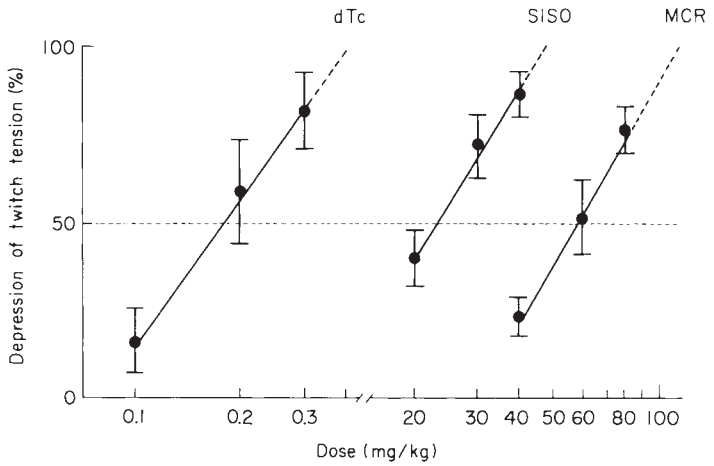

Fig. 1. Dose-response relationships for sisomicin (SISO, $n=7$), micromicin (MCR, $n=7$) and d-tubocurarine (dTc, $n=6$) during halothane anesthesia. A least-squares regression analysis was used to calculate the ED_{50} values. The values represent the means±S.E.M. Ordinate: depression of twitch tension (% of control). Abscissa: dose of drug (mg/kg i.v.).

Although the extrapolation of these data between different species may present difficulty, the relative neuromuscular blocking potencies of SISO and MCR in man seem to be minimum. However, several clinical situations may cause a neuromuscular blockade leading to respiratory depression owing to overdosage of these aminoglycosides or owing to interaction with anesthetics and/or nondepolarizing muscle relaxants (Dupuis et al. 1989). In addition, since both neostigmine and calcium partially counteract the neuromuscular blocking actions of 2 antibiotics, maintenance of the artificial ventilation should be mandatory until spontaneous respiration becomes adequate.

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