Case Report

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The effect of long-term oral dantrolene on the neuromuscular action of rocuronium
-a case report-

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Oral dantrolene causes a dose-dependent depression of skeletal muscle contractility. A 52-year-old man treated with oral dantrolene for spasticity after spinal cord injury was scheduled to undergo irrigation and drainage of a thigh abscess under general anesthesia. He had taken 50 mg oral dantrolene per day for 3 years. Under standard neuromuscular monitoring, anesthesia was performed with propofol, rocuronium, and sevoflurane. A bolus dose of ED_{95} (0.3 mg/kg) of rocuronium could not depress T1 up to 95%. An additional dose of rocuronium depressed T1 completely and decreased the train-of-four (TOF) count to zero. There was no apparent prolongation of the neuromuscular blocking action of rocuronium. The TOF ratio was recovered to more than 0.9 within 40 minutes after the last dose of rocuronium. A small dose of oral dantrolene does not prolong the duration of action and recovery of rocuronium. (Korean J Anesthesiol 2014; 66: 153-156)

Key Words: Dantrolene, Relaxant, Rocuronium.

In 1967, Snyder et al. [1] identified dantrolene as a new class of muscle relaxant. Dantrolene is mostly used to treat spasticity due to cerebral infarction [2], neuroleptic malignant syndrome [3], and heat stroke [4], and it is also used for the prevention and treatment of malignant hyperthermia during anesthesia [5].

The sarcolemma action potential spreads into muscle fibers along the transverse tubule, and the sarcoplasmic reticulum feet subsequently function as a voltage sensor and calcium channel. Dantrolene blocks this function and inhibits the release of calcium from the sarcoplasmic reticulum to the sarcoplasm. The mechanism of action at the molecular level is not clearly known, but the ryanodine receptor isoform 1, an intracellular calcium release channel, is predicted to be involved. Hence, the prevention of muscle contraction is presumed to result from the decreased concentration of calcium in the sarcoplasm, followed by the discontinuation of excitation-contraction coupling [5].

Due to its mechanism of action, muscle weakness can occur with the administration of dantrolene [6]. In a retrospective analysis that focused on complications in patients who were administered dantrolene for malignant hyperthermia from 1987

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to 2006, the most common adverse event was muscle weakness, which occurred in 80 out of 368 patients (21.7%). The median total dose of dantrolene was 400 mg for patients who experienced a muscle weakness complication. In addition, based on logistic regression, it was reported that the likelihood of a muscle weakness complication increased by 27% when the total dose of dantrolene doubled [7].

Furthermore, dantrolene is used to treat spasticity due to spinal cord damage. It can be administered at an initial daily dose of 25 mg, which can be increased up to 100 mg 4 times a day, for a maximum total dose of 400 mg [8]. In one report, however, a patient whose dosage of oral dantrolene increased from 50 mg 4 times a day to 75 mg 4 times a day — to treat spasticity due to spinal cord injury from an accident 8 month earlier — experienced an increase in fatigue, general weakness, and serious respiratory depression; endotracheal intubation was required in this case [9]. It is assumed that the muscle relaxant action of dantrolene affected this patient, but there are extremely few studies or reported cases with regard to this effect.

In this case report, the muscle relaxant action was assessed during administration of the optimized dose of rocuronium under nerve root monitoring in general anesthesia for a patient with long-term dantrolene administration. The effect of dantrolene on muscle relaxation will be discussed.

Case Report

A 52-year-old male patient with a height of 163 cm and a weight of 65 kg was admitted to the hospital due to right femoral edema, and following a diagnosis of right femoral abscess, an incision and drainage procedure was performed.

With regard to medical history, the patient was paraplegic from the level of the fourth thoracic vertebra due to a T2-level spinal cord injury from a car accident 4 years previously. Due to tetany symptoms in both lower limbs, he had been regularly taking an oral dantrolene formula of 50 mg (Anorex® Cap. 25 mg, Yooyoung Pharmaceutical, Seoul, Korea) every night for the previous 3 years.

Prior to the operation, the patient's blood pressure was 100/60 mmHg, and his heart rate was 94 beats per minute. There was a systemic inflammation response due to the right femoral abscess, accompanied by an increase in body temperature (38.3°C); in addition, the prothrombin time was outside the normal range (INR 1.21). Hence, the decision was made to perform the operation under general anesthesia.

As pretreatment for anesthesia, 0.2 mg of i.m. glycopyrrolate was administered 30 minutes prior to entering the operating room. When the patient entered the operating room, the standard anesthetic monitoring devices were applied, and the blood pressure and heart rate were 123/78 mmHg and 86 beats per minute, respectively.

The neuromuscular monitoring device (TOF-Watch®, Organon, Boxtel, Netherlands) was attached to the ulnar nerve of the left forearm flap. Propofol 2 mg/kg was intravenously administered for induction of anesthesia, and i.v. rocuronium 0.3 mg/kg (ED_{95}) was administered while ventilating with 5 L/min of oxygen and 4 vol% of sevoflurane.

The TOF ratio did not fall under 0.25 2 minutes after rocuronium administration, and 10 mg (0.15 mg/kg) of i.v. rocuronium was additionally administered. After 2 minutes, the TOF count still had not decreased to 0, and 0.15 mg/kg of i.v. rocuronium was repetitively administered. Thereafter, the TOF count decreased to 0, and endotracheal intubation was carried out.

The mandible was sufficiently relaxed at the time of endotracheal intubation; there was no movement of the vocal cord, and coughing or movement was not observed after intubation. The anesthesia was maintained with 1.2−1.5 vol% of sevoflurane and 50% N_2O during the operation.

The TOF ratio was 0.37 at the end of the operation, which was 35 minutes after the last dose of the muscle relaxant had been administered. Intravenous pyridostigmine 0.15 mg/kg and glycopyrrolate 0.003 mg/kg were administered as antagonists of the muscle relaxant. Extubation was carried out; the TOF ratio was maintained above 0.9 at around 55 minutes after the last dose of the muscle relaxant had been administered. No sign of respiratory depression was observed after extubation, and no particular signs and symptoms were observed in the recovery unit.

Three months later, the patient was diagnosed with chronic osteomyelitis, and an incision and drainage operation was planned. It was decided to perform general anesthesia in consideration of the state of systemic inflammation and the patient's preference.

As pretreatment for anesthesia, 0.2 mg of i.m. glycopyrrolate was administered 30 minutes prior to entering the operating room. When the patient entered the operating room, the standard anesthetic monitoring devices and the neuromuscular monitoring device were applied in the same manner as in the previous operation.

The blood pressure was 112/70 mmHg, and the heart rate was 93 beats per minute. The neuromuscular monitoring device (TOF-Watch® SX, Organon, Netherlands) was attached to the ulnar nerve of the right forearm flap. Loss of consciousness was confirmed after administration of 2 mg/kg of i.v. propofol, and then 2.5 vol% of sevoflurane was administered as an inhalation anesthetic.

After the loss of consciousness, stabilization and calibration were carried out to establish the initial value of the spasm height prior to the administration of rocuronium. For the calibration of

the spasm reaction, a 50 Hz tetanic stimulation was conducted for 5 seconds, which was then changed to a 2 Hz TOF stimulation with 15-second intervals, and the calibration was initiated by pressing the CAL switch on the TOF-Watch® SX (CAL 2 mode). The TOF response change was within 10% 2 minutes after the calibration, and this was considered as the stabilization of the spasm response. The muscle relaxant was then administered.

At 180 seconds following the i.v. administration of rocuronium 0.3 mg/kg (ED_{95}), a block of more than 80% of T_1 failed; therefore, additional i.v. rocuronium 0.3 mg/kg was administered, and a 100% block of T_1 was achieved at just past 300 seconds. Endotracheal intubation was then carried out. The anesthesia was maintained with 1.5–2.0 vol% of sevoflurane and 50% of N_2O during the operation. The time taken to recover T_1 to 25% after the administration of the second dose of the muscle relaxant was 4 minutes and 36 seconds.

Twenty-five minutes after endotracheal intubation, T1 had recovered more than 25%; hence, an additional 7.5 mg of rocuronium was administered. With the recovery of the muscle relaxation, the time taken for T1 to recover from 25% to 75% was 9 minutes and 1 second.

The TOF ratio was 0.33 5 minutes after ceasing sevoflurane administration on completion of the operation. Neostigmine 0.05 mg/kg and glycopyrrolate 0.005 mg/kg were administered to antagonize the muscle relaxation.

At 5 minutes and 30 seconds after administration of the antagonist, T1 had recovered more than 95%, and the TOF ratio had recovered to more than 0.9. Therefore, extubation was carried out. There was no sign of respiratory depression after extubation in the recovery unit.

Discussion

The authors confirmed that long-term administration of oral dantrolene for the treatment of spasticity does not significantly affect the muscle relaxant action of rocuronium.

Regarding the induction of muscle relaxation in the second operation, T1 did not decrease more than 84% 3 minutes and 30 seconds after the administration of 0.3 mg/kg of rocuronium. Hence, an extra dose of 0.3 mg/kg of rocuronium was administered.

A more than 95% reduction in T1 was observed 5 minutes after the administration of the first dose of the muscle relaxant. In both of the operations, the total amount of rocuronium required for endotracheal intubation was twice the ED_{95} (0.6 mg/kg).

For the maintenance of muscle relaxation, the clinical duration (the time taken from the administration of the intubating dose until 25% recovery of T1) was 24 minutes and 36 seconds, which was not extended any further. For the recovery of muscle relaxation, the recovery index (the time taken for T1 recover from 25 to 75%) in the second operation was 9 minutes and 1 second, and the time taken for the TOF ratio after the last dose of the muscle relaxant to be greater than 0.9 was 22 minutes and 30 seconds, which was not extended any further.

Nakayama et al. [10] reported the case of an 8-year-old patient who had been taking oral dantrolene 20 mg daily for the treatment of spasticity for 2 years prior to an operation. When 75 μg/kg of vecuronium was administered for general anesthesia, the recovery index was 7 minutes, and the recovery time of T1 to 90% was 25 minutes, which was not extended.

After the operation, neostigmine and atropine were used as antagonists of the muscle relaxant when T1 had recovered to 25%. Six minutes after the administration of the antagonists, T1 recovered to 75%. There were no signs of muscle weakness after the operation.

However, there are reports that do not accord with the above findings. Flewellen et al. [6] evaluated the dose-dependent effect of dantrolene on the muscle relaxant action in adults without a particular medical history, and 75% twitch depression was observed when 2.4 mg/kg was intravenously administered with the additional administration of 0.1 mg/kg of dantrolene every 5 minutes. However, there was no significant change in maximum expiratory flow rate, lung capacity, or respiratory rate per minute.

Driessen et al. [11] reported the case of a 60-year-old female patient who was administered 350 mg (5.3 mg/kg) of dantrolene for 28 hours prior to an operation for the prevention of malignant hyperthermia. when 45 μg/kg of vecuronium was administered for general anesthesia, the spasm response of the 90% recovery time on the electromyogram was extended to 47 minutes.

Furthermore, Watson et al. [12] described the case of a 5-year-old female patient who was administered 2 doses of 1 mg/kg oral dantrolene every 6 hours for the prevention of malignant hyperthermia. After the second dose, the patient manifested muscle weakness and partial obstruction of the soft tissue of the upper respiratory tract under respiration.

The patient in this case had been administered 50 mg of oral dantrolene once a day, and in both operations, the total dose of muscle relaxant (0.6 mg/kg) required for endotracheal intubation was not particularly different from the dose required in other patients [13]. In addition, the recovery time was not extended. After extubation, signs of muscle weakness such as respiratory depression were not observed.

These results can be attributed to the fact that the patient was taking 0.76 mg/kg of dantrolene, and the elimination half life of dantrolene is 15.8 ± 6.0 h. As the first operation was at 4 p.m. and the second operation was at 1 p.m., the operations were carried out 21 hours and 18 hours after the administration of dantrolene, respectively. Therefore, the reduction in the serum concentration of dantrolene that was administered the day before

the operation is considered to be one of the factors influencing the results [14].

The perioperative administration of dantrolene may cause a delay in the recovery of muscle relaxation in a dose-dependent manner, and the timing of preoperative administration is especially important as it is associated with the serum dantrolene concentration. Therefore, for patients taking a high dose of dantrolene, it is helpful to consider the half life of the medication when making decisions about the timing of medication discontinuation [8,15]. However, there are individual differences in pharmacokinetics. For the use of a muscle relaxant, neuromuscular monitoring must be performed for patients taking dantrolene who are undergoing general anesthesia.

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