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Case Report

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Resistance to Nondepolarizing Blocking Agents in a Patient Prolonged Treatment with Ranitidine

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ABSTRACT

We report a case of a 65-year-old man with a history of duodenal ulcer that treated preoperatively with ranitidine and underwent surgical exploration for upper gastrointestinal hemorrhage under emergency conditions. Under general anaesthesia, he showed resistance to two nondepolarizing neuromuscular blocking drugs. No obvious cause for the resistance was demonstrated except for the possibility of an interaction between ranitidine with vecuronium and mivacurium. *©2007, Fırat Üniversitesi, Tıp Fakültesi*

Key words: *Resistance to neuromuscular drug, vecuronium, mivacurium, ranitidine*

ÖZET

Uzun Süreli Ranitidin Tedavisi alan Olguda Nondepolarizan Bloker Ajanlara Karşı Rezistans Gelişimi (Olgu Sunumu)

Biz bu yazıda, 65 yaşında, duodenal ülser nedeniyle uzun süredir ranitidine tedavisi gören ve üst gastrointestinal sistem kanaması nedeniyle opere olan erkek olguyu sunduk. Genel anestezi altında opere olan olguda nondepolarizan kas gevseticilerden vekuronium ve mivakuriuma karşı rezistans gelişti. Rezistans oluşturacak mekanizmalar arasında vekuronium ve mivakuriumun ranitidin ile etkileşmesi en büyük olasılıktır. *©2007, Fırat Üniversitesi, Tıp Fakültesi*

Anahtar kelimeler: *Nöromuskuler ilaçlara reziztans, vekuronium, mivakurium, ranitidine.*

Vecuronium and mivacurium are the nondepolarizing neuromuscular blocker drugs (NDNMB) of first choice for major general surgery procedures at our institution.

Resistance to NDNMBs has been shown to occur in a large, diverse and apparently unrelated group of pathological states including burns, (1) upper and lower motor neurone lesions (2), multiple sclerosis (3), cerebral palsy (4), disuse atrophy (5) and prolonged blockade with NDNMBs themselves (6). The resistance that has been described in patients treated with phenytoin (7), carbamazepine (8), steroids (9) and aminophylline (10) may therefore, in some cases, be attributable in part to the coexisting disease for which they have been prescribed.

Ranitidine HCl (Ranitab) is a potent H_2 reseptor antagonist, indicated for treatment of gastroduodenal ulcer. We report the case of a patient with intractable duodenal ulcer who was treated preoperatively with ranitidine and who intraoperatively experienced extreme resistance to the effect of two nondepolarizing neuromuscular blocker drugs vecuronium and mivacurium. To our knowledge there is no published data on interaction between ranitidine and these muscle relaxants.

CASE REPORT

The patient was a 65-year-old male weighing 60 kg underwent emergency surgery for intractable bleeding duodenal ulcer. He was suffering for duodenal ulcer since last twenty years. He had a history of gastric burning, which still occurred occasionally, and was treated with ranitidine Hcl 150 mg twice daily since ten years. He did not receive any other medication and no operation before. His family history was unremarkable.

His physical examination was remarkable with evidence of over sensitive abdomen, and a pale skin. His preoperative laboratory test values; The haemoglobin concentration was 10.9 g dl^{-1}, haemotocrit 31%, platelet count 97 000 mm^{-3}, prothrombin time (PT) 16.6 s and APTT 33.5 s. where as other biochemistry and haemogram test results were within the normal limits. He was not premedicated.

On arrival in the operation room, basic monitoring was established with ECG, noninvasive BP, SpO_2 and temperature probe. He had an oxygen saturation of 99%, a heart rate of 98 beats.min^{-1}, and arterial pressure of 140/75 mmHg. A peripheral venous line was obtained and a 1000 cc Ringer lactat infusion was started.

Following pre-oxygenation, anaesthesia was induced with fentanyl 100 µg, propofol 60 mg intravenously (i.v.). The lungs were ventilated with 50% O_2, nitrous oxide and 2% sevoflurane after loss of the eyelash reflex.Vecuronium 6 mg was injected through the free running drip. After about five minutes, tracheal intubation was attempted, but the cords were mobile.

The patient was ventilated again for three minutes. Cricoid pressure was applied until the trachea was intubated, and the patient's lungs were ventilated with nitrous oxide 67%, oxygen 33%, and sevoflurane to an end-tidal concentration of 2.5%.

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A central venous catheter was placed via internal jugular vein. After surgery had started, the patient began to breath and struggle with the ventilator in ten minutes. Supplementary dose of vecuronium, 2 mg was repeated (total 12 mg) with frequent intervals but targetted muscle relaxation could not be obtained. We decided to substitude the vecuronium with mivacurium. Mivacurium 9 mg was given i.v. This dose was repeated to a total of 18 mg during the following 20 minutes. Muscle relaxation was again insufficient. Then mivacurium infusion was started beginning with 5 $\mu g^{-1}kg^{-1}$min and than rose up to 15 $\mu g^{-1}kg^{-1}$min. Although mivacurium infusion was running, patient was still spontaneously breathing. Only for short periods patient's spontaneous breathing was resolving and airway pressure was coming near the normal limits. The patient's end tidal sevoflurane concentration was kept at 2-4.5 % during the entire surgical procedure to provide some degree of muscle relaxation. Blood samples were drawn for blood gas analysis and haematologic control of the patient during the surgery. Measurement of blood gases, protein/albumin rate and electrolytes were within normal limits. Hb/Htc concentrations were 9.8/29.6, body temperature was 36.2^{o}C.

Surgeons were complained of operation conditions because of unrelaxed muscles from beginning of the surgery. Then spleen was laserated by surgeons. Following this complication mivacurium infusion was stopped and succinylcholine 1.5 $mg^{-1}kg$ was injected i.v. Following succinylcholine injection, the patient's muscles were relaxed completely. Airway pressure turned normal range and rest of the operation was uneventful and lasted more 45 minutes. Surgeons said that they now started to operate a relaxed patient and were studied comfortable conditions. Surgeons closed down abdominal muscles free of problems. The total duration of surgery was five hour and twenty minutes. At the end of surgery, the patient was still deeply anaesthetized, but breathing spontaneously with low tidal volumes. Atropine 0.5 mg and neostigmine 2.5 mg were given i.v. The adverse cardiovascular effects of neostigmine were not observed. The patient transferred to the recovery room and his respiration was assisted with a Bird respirator. 30 minutes later the patient was wide awake, and one hour later he was extubated. The rest of the postoperative period was uneventful.

We conducted some laboratory investigations to evaluate the reason of this resistance problem during the postoperatif period. Probable factors such as hypothyroidism, testiculer feminization, and atypic cholinesterase levels were eliminated through these tests in this patient. All laboratory investigations were in normal limits.

The patient was discharged after fifteen days with full recovery.

DISCUSSION

This case presentation is intended to draw attention to the possibility of drug interaction between ranitidine and nondepolarizing neuromuscular blocker drugs. Further study is needed to determine what effects, if any, it has at the neuromuscular junction or on the bioavailability of other drugs.

Most of the obvious potential causes of the failure of drug action during anesthesia were excluded. Failure of the drug to enter the blood stream was ruled out because the patient had functioning peripheral venous access via an 18G angiocath and a central venous catheter. Loss of potency of the drug was excluded by the fact that the same batches of these drugs were used successfully on other patients.

The relationship between an administered dose of a nondepolarizing muscle relaxant and the resulting degree of neuromuscular blockade is known to be modified by a multiplicity of factors. These include age, acid base status, temperature, pathologic derangements such as burns or lower motor neurone disease (1,11) and concurrent drug therapy.

Drug interactions described to date generally have involved the potentiation of neuromuscular blockade, most notably antibiotics. Chen et al. reported that a patient being treated with phenytoin therapy requires approximately 80% more pancronium than control patients to maintain a stable level of neuromuscular blockade. Metteo et al (6) reported that plasma protein binding affects the free drug levels of d-tubocurarine available to exert pharmacological action. Increased binding of this drug can reduce its effectiveness. Duvaldestin and her co-workers (12) have demonstrated that liver disease increases the distribution volume necessitating more drug-pancuronium-to produce a given degree of blockade.

Mishra and et al. (13) were investigated in the rat phrenic nerve-hemidiaphragm preparation in-vitro study. They suggested ranitidine augmented the indirectly-evoked muscle response at concentrations between 30 and 160 microM but at higher concentrations, between 300 and 1800 microM, produced neuromuscular paralysis. These data indicate that higher than clinically relevant concentrations of ranitidine produce neuromuscular paralysis and may potentiate the action of vecuronium. Low concentrations of ranitidine may antagonize the action of vecuronium.

Cross-resistance among chemically dissimilar neuromuscular blocking agents poses a difficult patient management problem and supports a pharmacodynamic basis of resistance to these agents. This would suggest that significant extrajunctional acetylcholine receptor proliferation is an unlikely mechanism (14).

Since none of the causes described above adequately explains the resistance observed in our patient, we think that this resistance can be attributed to an interaction between ranitidine and nondepolarizing muscle relaxants resulting from some undefined pharmacodynamic alterations. But, McCarthy et al. (15) investigated the effects of oral administration of ranitidine 150 mg 90 min before anaesthesia on the neuromuscular blocking effects of atracurium or vecuronium. There were no significant differences in any of the variables following ranitidine pretreatment. A single dose ranitidine has been used in this study. In contrast to this report, it is important that the patient had prolonged treatment with ranitidine for 10 years. We want to stress that whatever a drug may existence serious advers effects, if it uses in very long time.

The preceding only one report (16)'s described to resistance d-tubocurarine and pancuronium with ranitidine. As far as we are aware, this is the first report decribed with vecuronium and mivacurium resistance with ranitidine. Our report would strengthen the paper to indicate that vecuronium and mivacurium by same mechanism as d-tubocurarine and and pancuronium. Thus, the observation would act as a confirmation of the interaction between the non-depolarizing and H_2 antagonists. This is probably more important than claming a first observation, as vecuronium and mivacurium are used mainly so clinical practice at nowadays.

Because neuromuscular monitoring is not essential a monitorization device, we were not planned to place neuromuscular monitoring in this patient because he had no history of a muscle disease or drug allergy. The evidence for the lack of relaxation is clinical; we had no access to a peripheral nerve stimulator to confirm this finding. Although Parr et al 9 did not use a neuromuscular monitarization; they suggested that neuromuscular resistance can be established as clinically. Our clinical observation and evidence based experience were very important and helpful in diagnosis and problem solving in this patient as Parr experienced. There is no doubt that neuromuscular monitorization would make richer the patient's findings. Both vecuronium and mivacurium did not adequately caused muscle relaxation in the patient. We thought, because of inadequate relaxation, spleen was lacerated by surgeons. Only following depolarizan muscle relaxant, abdominal muscles were effectively relaxed.

Although no clinical findings, hypothyroidism could be the reason for the resistance. In addition to this, increased level of endogenous testosterone and steroidal-core structure of vecuronium may explain the increased tolerance to vecuronium in this patient. Regarding as far as plasma cholinesterase is concerned, ıncreased plasma cholinesterase activity might be the clinical discovery. In the patient, all laboratory investigations were in normal limits. That is to say, supporting neuromuscular resistance of patient was no laboratory result.

We want to stress that some drugs may cause vital advers effects being used in over time

In conclusion, we would like to point out that anesthesiologists should be aware that ranitidine can cause resistance to vecuronium and mivacurium.

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