Increased sensitivity to rocuronium and atracurium in mitochondrial myopathy

Josef Finsterer MD,*
Ursula Stratil MD,†
Reginald Bittner MD,‡
Paul Sporn MD†

Purpose: To describe the prolonged effect of the intermediate-acting, non-depolarising neuromuscular blocking agents rocuronium and atracurium in a 29-yr-old apparently healthy woman.

Clinical features: Because of abdominal pain the patient was scheduled for explorativelaparoscopic pelvic examination. General anaesthesia was induced with fentanyl, midazolam and propofol. Muscle relaxation was achieved with 0.6 $mg \cdot kg^{-1}$ rocuronium. Anaesthesia was maintained with nitrous oxide and propofol. Two Hz train-of-four stimulation every 15 sec evoked no twitch responses until 60 min after rocuronium. Further relaxation was achieved with 0.075 $mg \cdot kg^{-1}$ atracurium after which twitch responses recurred after 45 min. Fifteen minutes later neuromuscular blockade was successfully reversed with atropine and neostigmine. The postanaesthetic course was uneventful. Because of the increased sensitivity to rocuronium and atracurium the patient was re-evaluated postoperatively. History revealed occasional double vision, fatigue, muscle cramps, stiffness and myoglobinuria. Clinical neurological examination showed ptosis, tremor, ataxia and bradydiadochokinesia. A standardised lactate stress testing on a bicycle was pathological and, after muscle biopsy, the diagnosis of mitochondrial myopathy was established.

Conclusion: An increased sensitivity to rocuronium and atracurium may occur in patients with mitochondrial myopathy. In these patients appropriate dosing of muscle relaxants and adequate monitoring of the neuromuscular blockade are required. If an increased sensitivity to rocuronium and atracurium occurs in an apparently healthy subject, further neurological investigations should follow.

Objectif : Décrire l'effet prolongé des inhibiteurs neuromusculaires non dépolarisants à action intermédiaire, rocuronium et atracurium, chez une femme de 29 ans apparemment en bonne santé.

Aspects cliniques : La patiente a été admise pour un examen laparoscopique exploratoire du bassin à la suite de douleurs abdominales. L'anesthésie générale a été induite avec du fentanyl, du midazolam et du propofol. La relaxation musculaire a été obtenue avec 0,6 $mg \cdot kg^{-1}$ de rocuronium. L'anesthésie a été maintenue avec du protoxyde d'azote et du propofol. Une stimulation de deux Hz en train-de-quatre à toutes les 15 secondes n'a pas déclenché de contraction musculaire avant 60 minutes suivant l'administration du rocuronium. Une relaxation supplémentaire a été obtenue, avec 0,075 $mg \cdot kg^{-1}$ d'atracurium, après laquelle les contractions musculaires ont reparu 45 minutes plus tard. Après quinze minutes, le bloc neuromusculaire était renversé avec succès avec l'atropine et la néostigmine. L'évolution postanesthésique a été sans complication. La patiente a été évaluée de nouveau après l'intervention à cause de la sensibilité accrue au rocuronium. L'histoire a révélé une diplopie occasionnelle, de la fatigue, des crampes musculaires, de la raideur et de la myoglobinurie. L'examen neurologique clinique a montré de la ptose, des tremblements, de l'ataxie et de la bradydiadococinésie. Une épreuve d'effort au lactate, sur une bicyclette, s'est révélé pathologique et, après la biopsie musculaire, le diagnostic de myopathie mitochondriale a été rendu.

Conclusion : Une sensibilité élevée au rocuronium et à l'atracurium peut survenir chez les patients atteints de myopathie mitochondriale. Chez ces patients, le dosage approprié de relaxants musculaires et la surveillance adéquate du bloc neuromusculaire sont nécessaires. Si une grande sensibilité au rocuronium et à l'atracurium se manifeste chez un sujet en bonne santé apparente, des examens neurologiques complémentaires devraient être faits.

From the Ludwig Boltzmann Institute for Epilepsy and Neuromuscular Disorders,* the Department of Anaesthesia and Intensive Care,† Krankenanstalt Rudolfstiftung, and the Neuromuscular Department, Anatomical Institute,‡ University of Vienna, Vienna, Austria.

Address correspondence to: Dr. J. Finsterer, Postfach 348, 1180 Vienna, Austria. Phone: 43-1-88000- 260; Fax: 43-1-4781711; E-mail: Josef.Finsterer@akh-wien.ac.at; Josef.Finsterer@2nr.nkr.magwien.gv.at

Accepted for publication April 30, 1998.

MITOCHONDRIAL disorders are a clinically and genetically heterogeneous group of disorders manifesting in impaired oxidative metabolism.[1] In some patients with mitochondrial myopathy an increased sensitivity to mivacurium, *d*-tubocurarine, and succinylcholine has been reported.[2-4] A prolonged effect of rocuronium and atracurium has not been described in these patients.

Case report

A 29-yr-old Afghani, apparently healthy woman (weight 66 kg, height 165 cm) was scheduled for laparoscopic pelvic examination under general anaesthesia because of lower abdominal pain. Preoperatively, she reported no other symptoms and her previous anaesthetic history appeared uneventful. Premedication was with 0.3 $mg \cdot kg^{-1}$ chlorazepam, *po*. Anaesthesia was induced with 0.0037 $mg \cdot kg^{-1}$, fentanyl, 0.045 $mg \cdot kg^{-1}$ midazolam and 2.3 $mg \cdot kg^{-1}$ propofol. One minute after 0.6 $mg \cdot kg^{-1}$ rocuronium, intubation was easily achieved. Anaesthesia was maintained with nitrous oxide 65% in oxygen and 2-2.5 $mg \cdot kg^{-1} \cdot hr^{-1}$ propofol. To monitor relaxation, the right ulnar nerve was stimulated supramaximally at the wrist with square pulses (duration: 0.2 msec, amplitude: 60 mA), delivered in a train-of-four (TOF) sequence at 2 Hz every 15 sec, using a Neurostim T4 stimulator. The grade of relaxation was assessed visually and tactilely by counting the resultant contractions of the right adductor pollicis muscle. Neuromuscular monitoring commenced immediately after administration of rocuronium but there was no response to stimulation for 60 min when the first twitch could be evoked. Because of this prolonged effect, increased sensitivity to rocuronium was assumed. As further relaxation was necessary, 0.075 $mg \cdot kg^{-1}$ atracurium were administered at a TOF count of 2, 65 min after administration of rocuronium. This produced profound relaxation and the first twitch response returned only after the termination of surgery, 45 min later. A further 15 min later, three twitches could be evoked and neuromuscular blockade was successfully reversed with 0.015 $mg \cdot kg^{-1}$ atropine and 0.037 $mg \cdot kg^{-1}$ neostigmine. Propofol and nitrous oxide were terminated and five minutes later, the patient awoke. Recovery of neuromuscular block was confirmed by sufficient spontaneous ventilation, head lift >5 sec and lack of TOF fade and the trachea was extubated. Total duration of anaesthesia was 130 min. The patient had been stable haemodynamically throughout the operation. The postanaesthetic course was uneventful.

Because of the increased sensitivity to rocuronium and atracurium, the patient's history was re-evaluated postoperatively. Neuromuscular disease was suspected and the patient was referred to the neurology department. The patient reported occasional muscle cramps, muscle stiffness and increased fatigability for six years. During the delivery of her third child, poor uterine contractions were observed. In the preceding two years she had observed episodes of myoglobinuria, occasional double vision and morning ptosis. A previous general anaesthetic was followed by a slightly prolonged recovery. She was not taking any medication, in particular none which could have interacted with the muscle relaxants. There was no family history of neuromuscular disease. On neurological examination a left sided ptosis, reduced mimicry, ataxia of the left arm, postural tremor and bradydiadochokinesia were found. Myasthenia gravis was assumed but was excluded by laboratory and electrophysiological investigation. Quantitative needle EMG of the right brachial biceps muscle was normal. Serum lactate increased to 1.6, 2.2, 2.4, 2.8 and 1.7 $mmol \cdot l^{-1}$ during standardised physical stress on a bicycle (upper reference limits: 1.9, 2.0, 2.1, 2.0 and 1.7 $mmol \cdot l^{-1}$ respectively). Muscle biopsy from the left deltoid muscle revealed occasional subsarcolemmal accumulation of mitochondria, partial cytochrome-c deficiency, glycogen storage within the mitochondrial matrix and abnormal proliferation of the mitochondrial cristae. Molecular genetic analysis of the leucocytic mt DNA failed to detect any of the known or new mitochondrial mutations. Based on the history, the clinical appearance, the abnormal lactate stress test and the muscle biopsy, a diagnosis of mitochondrial myopathy was established.

Discussion

In the reported patient an increased sensitivity to 0.6 $mg \cdot kg^{-1}$ rocuronium and 0.075 $mg \cdot kg^{-1}$ atracurium was assumed, since neuromuscular block lasted for 60 and 45 min with TOF stimulation respectively. This prolonged effect prompted further neurological investigations leading to the diagnosis of mitochondrial myopathy. In such a patient non-depolarising muscle relaxants have to be used with caution and under adequate neuromuscular monitoring.

Increased sensitivity to muscle relaxants has been previously reported in patients with mitochondrial myopathy and may be the first indication of their disease.[2-4] Exaggerated relaxation has been observed especially after mivacurium[2] and d-tubocurarine.[3] Reports of succinylcholine in patients with mitochondrial myopathy are controversial. On the one hand succinylcholine has been suggested to be safe,[4,5] on the other hand a prolonged recovery after succinylcholine has been observed.[4] An uneventful anaesthetic course has been seen only for vecuronium,[4,6,7] pancuronium[5,8] and atracurium.[4,6,7,9] An increased sensitivity to rocuronium has not been reported before in patients with

mitochondrial myopathy.[8] The normal duration of neuromuscular blockade after 0.6 mg·kg^{-1} rocuronium is said to be 29 ± 20 min.[10] Thus, our observation of 60 min is above the upper end of the normal range, disregarding the great variation in response to neuromuscular blocking agents in individual patients.[11] The prolonged effect to rocuronium may be explained with altered pharmacokinetics and dynamics due to the combination of a chronic metabolic acidosis (lactate increase already at low levels of effort) and a compensatory respiratory alcalosis.[4] The prolongation of action of atracurium may be explained with a possible potentiation of atracurium by rocuronium.[12,13]

Dosage reduction of muscle relaxants may normalise the prolonged effect of patients with mitochondrial myopathy to these agents, but in severe cases or during delivery it might be wise to avoid muscle relaxants entirely.[14] Which muscle relaxants require dose reduction and which should be avoided, remains unknown. In our patient, the muscle relaxant was changed to atracurium because of its different pharmacokinetic properties compared with rocuronium. No potentiating and synergistic effect with the combination of rocuronium and atracurium has been reported although synergy between atracurium and vecuronium, atracurium and pancuronium, atracurium and pipercuronium and rocuronium and mivacurium is well documented.[12,13]

To avoid problems during anaesthesia in patients with mitochondrial myopathy, the diagnosis should be established before operation. Unfortunately, one of the main characteristics of mitochondrial myopathies is their clinical and genetic heterogeneity making diagnosis difficult. The same phenotype may be due to different mutations and, conversely, a single mutation may lead to widely differing clinical presentations. A single phenotype may depend not only on the type of the affected gene but also on the abundance of the mutation, the distribution of the mutation within a single and different tissues and the time at which a mutation occurs. Additional factors may be age and environment.[1]

Symptoms and signs that are reported in patients with mitochondrial myopathy include ptosis, double vision, limb weakness, muscle pain, cramps, jerks, fatigue, reduced endurance, stiffness, myoglobinuria (neuromuscular involvement), seizures, syncope, vertigo, headache, dystonia, unconsciousness, impaired visual acuity, neuropsychological deficits, hypacusis (CNS involvement), anginal pain, rhythm abnormalities, dyspnea, edema (cardiac involvement) and polyphagia, polydipsia, impotence, hyperhidrosis (endocrinological involvement). Clinical neurological investigation may reveal short stature, facial and limb weakness and wasting, visual impairment, ophthalmoplegia, nystagmus, impaired hearing, normal, reduced, absent or exaggerated deep tendon reflexes, hypotonia or spasticity, ataxia, dystonia, impaired sensation and gait abnormalities. Often, symptoms and signs are only mildly expressed and may be overlooked so that anaesthetic management should begin with thorough review of the history and physical examination.[14] Even slight abnormalities should be taken seriously.[15]

It is concluded that increased sensitivity to rocuronium and atracurium may occur in patients with mitochondrial myopathy. In these patients, appropriate dosing of muscle relaxants and close monitoring of the neuromuscular blockade are required. An increased sensitivity to rocuronium and atracurium in apparently healthy subjects should also provoke detailed neurological examination which may lead to the diagnosis of a formerly unrecognised neuromuscular disorder.

References

1 *Morgan-Hughes JA.* Mitochondrial diseases. *In:* Engel AG, Franzini-Armstrong C (Eds.). Myology. Basic and Clinical. New York: McGraw-Hill, 1994: 1610–51.

2 *Naguib M, El Dawlatly AA, Ashour M, Al-Bunyan M.* Sensitivity to mivacurium in a patient with mitochondrial myopathy. Anesthesiology 1996; 84: 1506–9.

3 *Robertson JA.* Ocular muscular dystrophy. A cause of curare sensitivity. Anaesthesia 1984; 39: 251–3.

4 *Wiesel S, Bevan JC, Samuel J, Donati F.* Vecuronium neuromuscular blockade in a child with mitochondrial myopathy. Anesth Analg 1991; 72: 696–9.

5 *D'Ambra MN, Dedrick D, Savarese JJ.* Kearns-Sayer syndrome and pancuronium-succinylcholine-induced neuromuscular blockade. Anesthesiology 1979; 51: 343–5.

6 *Breucking E, Mortier W, Lampert R, Brandt L.* Anaesthesia and intensive care for a patient with mitochondrial myopathy and general condition similar to that seen with malignant hyperthermia. (German) Anaesthesist 1993; 42: 719–23.

7 *Klockgether-Radke A, Henze T, Braun U, Kettler D.* Anesthesia in two patients with mitochondrial myopathy. (German) Anaesthesist 1993; 42: 111–4.

8 *Ciccotelli KK, Prak EL, Muravchick S.* An adult with inherited mitochondrial encephalomyopathy: report of a case. Anesthesiology 1997; 87: 1240–2.

9 *Thompson VA, Wahr JA.* Anesthetic considerations in patients presenting with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome. Anesth Analg 1997; 85: 1404–6.

10 *Mayer M, Doenicke A, Hofmann A, Peter K.* Onset and recovery of rocuronium (ORG 9426) and vecuronium under enflurane anaesthesia. Br J Anaesth 1992; 69: 511–2.

11 *Magorian T, Flannery KB, Miller RD.* Comparison of rocuronium, succinylcholine, and vecuronium for rapid-sequence induction of anesthesia in adult patients. Anesthesiology 1993; 79: 913–8.
12 *Kim DW, Joshi GP, White PF, Johnson ER.* Interactions between mivacurium, rocuronium, and vecuronium during general anesthesia. Anesth Analg 1996; 83: 818–22.
13 *Rautoma P, Meretoja OA, Erkola O, Kalli I.* The duration of action of mivacurium is prolonged if preceded by atracurium or vecuronium. Acta Anaesthesiol Scand 1995; 39: 912–5.
14 *Rosaeg OP, Morrison S, MacLeod JP.* Anaesthetic management of labour and delivery in the parturient with mitochondrial myopathy. Can J Anaesth 1996; 43: 403–7.
15 *Finsterer J.* Mitochondriopathies. (German) Akt Neurologie 1997; 24: 231–41.