Laparoscopic partial nephrectomy in a patient on simvastatin


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**Introduction**

Waking up from anesthesia is one of the most important concerns of anesthesiologists, patients and their families [1]. Although delay or failure in patient awakening is rare, it remains a very challenging subject for anesthesiologists. Residual effects of neuromuscular blocking agents last well beyond surgery and can have significant clinical consequences [2]. Neuromuscular block in the conscious patient can mimic unconsciousness and the response to muscle relaxants varies widely between individuals [3]. The response may be further altered by certain disease states, electrolyte imbalance and/or drug interactions [4–8]. Statins are the primary class of medication used to lower serum cholesterol concentrations for both primary and secondary prevention of coronary disease. Statins are both effective and generally safe. Although muscle toxicity remains a concern, severe myopathy is unusual, affecting perhaps 0.1% of patients [9]. The mechanism by which statins cause muscle toxicity is not well understood. The consensus is that these symptoms can be caused by statins, often in the absence of creatine kinase (CK) elevation [10]. Several authors have identified that these side effects are dose-dependent and anything elevating statin blood level will increase the likelihood of muscle toxicity [11].

**Case report**

A 55-year-old female patient (height 162 cm, weight 65 kg and body mass index BMI 24.8 kg/m²) was admitted for laparoscopic partial nephrectomy. The patient was hypertensive (3 years ago) on regular treatment with oral captopril 25 mg twice daily and oral amlodipine 5 mg once daily and hypercholesterolemic (1 year before) on regular oral simvastatin 40 mg once daily with a normal electrocardiogram (ECG). There were no abnormal laboratory findings with respect to complete blood count, blood glucose concentration, coagulation profile, kidney functions and liver functions. The patient had no history of past surgery or experience with anesthesia. On admission to the operating theatre, the patient was given i.v. midazolam 1.0 mg in the holding area. On arrival at the operating table the patient was connected to non-invasive blood pressure, ECG and pulse oximetry monitors. Her blood pressure was 132/80 mm Hg, heart rate was 65–78 beats/min and O₂ saturation 98% on room air. She did not complain of anxiety or discomfort. An arterial line was inserted through the left radial artery under local skin infiltration with lidocaine 1%. The patient was induced for general anesthesia with i.v. fentanyl 2 μg/kg body weight, propofol 2 mg/kg and rocuronium bromide 0.6 mg/kg to facilitate tracheal intubation. Anesthesia was maintained with inhalation of isoflurane 1.0–1.5% in 40% oxygen-enriched air and i.v. fentanyl 25 μg boluses. The patient did not require any additional rocuronium throughout surgery according to train of four (TOF) monitoring.

Arterial blood gas (ABG) analysis was done preoperatively, during surgery and at the end of surgery and a level within

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**Kasuistiken**

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Delayed recovery from neuromuscular blockade

Essam E. Abd El-Hakeem was the principle anesthetist who managed the patient, made substantial contributions to conception, acquisition of data and made the final design of manuscript. Abdullah M. Kaki contributed to the conception, data collection and design of the manuscript. Shady A. Almazlom was the assistant anesthetist for the patient. Ahmed J. Alsayyad performed the surgical procedure for the patient, made substantial contribution in obtaining the necessary references and drafting the manuscript. All authors have seen and approved the final version of the manuscript.

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normal ranges. The surgical procedure was finished after 4 h from beginning surgery. At that time, all surgical wound orifices were infiltrated with 20 ml of bupivacaine 0.25% by the surgeon and isoflurane inhalation was stopped. The total fentanyl given to the patient by end of surgery was 300 μg. We attempted recovery of the patient but she was not responsive, unconscious with complete areflexia without any contractions with TOF monitoring (INNERVTOR272, Auckland, New Zealand). This profound block was confirmed with post-tetanic count (PTC) stimulation (absence of post-tetanic twitch response). At that time we wanted to administer sugammadex (a selective rocuronium-binding drug that rapidly reverses rocuronium-induced neuromuscular blockade) but it was not available in our hospital [12]. The patient was normothermic with 36.5 °C esophageal temperature and her pupils were equal with round normal size and sluggish reaction to light. The patient was continued on mechanical ventilation and investigated for ABG, serum electrolytes, blood sugar, kidney functions, liver functions and thyroid functions. During this period, when the blood pressure began to rise, isoflurane 0.5% was restarted with additionally midazolam 1.0 mg. We were considering the possibility of cerebral stroke from the hypertensive attack, therefore a brain computed tomography (CT) scan was arranged and then cancelled when the patient began to recover from the muscle relaxant as indicated from the TOF monitoring. The findings for ABG, electrolytes, blood sugar, kidney functions were within normal ranges. Also, liver functions and thyroid functions were normal as proven later after full recovery of the patient. After 2.5 h from the end of surgery the patient began to gradually recover from the skeletal muscle relaxant effect and when the TOF testing showed a satisfactory four contractions isoflurane was stopped and i.v. neostigmine 2.5 mg plus atropine 1.0 mg were administered by injection. When the patient became fully conscious with good minute ventilation 3 h after the end of surgery, the patient was safely extubated and transferred to the recovery area, where she was monitored for 2 h to be transferred to the ward after confirmation of normal ABG levels. In the recovery area the patient required i. v. meperidine 50 mg to relieve pain. In the ward the patient was twice investigated for CK but it was within the normal range. During the postoperative visit, the patient mentioned that she had had muscle pain with rapid onset of fatigue during the last 3 months before surgery.

Discussion

Recovering consciousness from anesthesia and awakening depends on various factors related to patient, anesthesia type, and duration of surgery. When surgery is prolonged, careful evaluation of various factors which might affect consciousness is necessary. The most common reason for prolonged anesthesia and patient unresponsiveness after anesthesia is persistent effects of anesthetic drugs and sedatives [1]. Opiates and benzodiazepines are the most commonly used drugs considered in this group. Furthermore, neuromuscular block is a cause of patient unresponsiveness to stimulation. A long duration between the administration of a single dose of an intermediate-acting nondepolarizing muscle relaxant and the arrival in the post anesthesia care unit does not guarantee a lack of a residual paralysis, even if this delay is longer than 2 h. Because of the wide variability of the speed of spontaneous recovery (impeded by hypothermia and interaction between halogenated agents and muscle paralysis), it is impossible to precisely determine the minimum delay after the administration of a relaxant that will be associated with complete recovery [13]. Also, it has been shown that neuromuscular blockade can persist for up to 4 h following even a single dose of muscle relaxant [14]. Residual neuromuscular blockade results in paralysis that is indistinguishable from delayed awakening although the patient is conscious and aware. After evaluating anesthetic drugs, metabolic and endocrine disorders, such as hypothyroidism [15], severe hypoglycemia or hyperglycemia, other disorders, such as hypothermia, acid-base disorders and electrolytes imbalance must be taken into consideration in the case of prolonged recovery from anesthesia [15].

Statins, which are 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, are effective in lowering blood cholesterol as well as in primary and secondary prevention of cardiovascular events. Statins are safe and effective in the majority of patients but they are associated with muscle toxicity, which, although rare can be serious and potentially life-threatening [3]. The clinical spectrum of statin-induced myotoxicity varies greatly from asymptomatic elevations of CK without muscle pain, to muscle pain or weakness with raised CK levels, myositis with biopsy-proven muscle inflammation and finally, rhabdomyolysis with muscle symptoms, high CK and potential for acute kidney injury [16]. Asymptomatic serum CK elevations and muscle pain without an increase in CK are the two most commonly (occurring in up to 33% of patients) described features of statin-induced myotoxicity [17]. It has been suggested that lipophilic statins, such as simvastatin are more likely to cause myotoxicity because they cross the cell membrane of muscle cells more readily than the more hydrophilic ones [18]. Although the precise mechanism of statin-induced side effects is unknown, they are likely caused by a combination of patient and statin characteristics. Several patient-specific risk characteristics have been identified such as older age, reduced body mass, hypothyroidism and female sex [19].

For our patient, regarding the anesthetic technique there was no overdosage of fentanyl or midazolam and we observed that our patient was fully relaxed throughout surgery without any additional rocuronium. From the patient past history, she was hypertensive on regular treatment with captopril and amloidipine, and hypercholesterolemia on maximum simvastatin dosage 40 mg daily. In the beginning we tried to find a reason for the delay in patient recovery. The patient was normothermic, acid-base and electrolyte disorders were excluded. Blood sugar, liver functions, kidney functions and thyroid functions were normal. Also, a brain CT scan was arranged but was cancelled when the patient began to recover.
Abstract - Zusammenfassung

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Laparoscopic partial nephrectomy in a patient on simvastatin. Delayed recovery from neuromuscular blockade

Abstract

Delayed recovery from anesthesia remains a very challenging subject for anesthesiologists. This case report describes the clinical course of delayed recovery from neuromuscular blockade after laparoscopic partial nephrectomy in a patient on simvastatin. The patient was hypotensive on regular treatment with oxaprozin 25 mg twice daily and amlodipine 5 mg once daily and hypercholesterolemia on regular simvastatin 40 mg once daily with a normal electrocardiogram (ECG). All preoperative laboratory findings were within normal ranges. The patient was premedicated with midazolam 1 mg and general anesthesia was induced with fentanyl 2 μg/kg body weight, propofol 2 mg/kg and rocuronium bromide 0.6 mg/kg to facilitate tracheal intubation. Anesthesia was maintained with inhalation of isoflurane 1.0–1.5 % in 40 % oxygen-enriched air and 25 μg boluses of fentanyl. The patient did not require any additional rocuronium throughout surgery which was finished after 4 h. The patient most probably had preoperative simvastatin-induced myotoxicity. This potentiated the muscle relaxant effect of rocuronium bromide and was the reason for patient unresponsiveness and delayed postoperative recovery. We can conclude that anesthesiologists should preoperatively identify statin myotoxicity and to avoid neuromuscular blocking drugs for statin-treated patients. Also, preoperative adjustment of statin dosage may be recommended.

Keywords

Delayed recovery · General anesthesia · Hypercholesterolemia · Neuromuscular blockade · Simvastatin

Laparoskopische partielle Nephrektomie in einem Patient mit Simvastatin Behandlung. Verzögerte Regeneration von einer neuromuskulären Blockade

Zusammenfassung

Die verzögerte Regeneration nach einer Anästhesie bleibt ein schwieriges Thema für Anästhesisten. Dieses Fall beschreibt den klinischen Verlauf einer verzögerten Regeneration von einer neuromuskulären Blockade nach laparoskopischer partieller Nephrektomie bei einem Patienten, der mit Simvastatin behandelt wurde. Der Patient war hypotensiv bei einer regelmäßigen oralen Behandlung mit Captopril 25 mg 2-mal täglich und Amlodipin 5 mg 1-mal täglich, sowie hypercholesterämisch bei einer regelmäßigen Behandlung mit Simvastatin 40 mg 1-mal täglich bei normalem EKG-Befund. Alle präoperativen Laboregebnisse lagen im Normbereich. Als Prämedikation wurde dem Patienten Midazolam 1 mg verabreicht. Die Allgemeinästhesie wurde mit Fentanyl 2 μg/kg KG, Propofol 2 mg/kg und Rocuroniumbromid 0,6 mg/kg eingeleitet, um eine tracheale Intubation zu ermöglichen. Die Anästhesie wurde durch Inhalation von Isofluran 1,0–1,5% in 40% sauerstoffangereicherter Luft und 25 μg Fentanyl als Bolus aufrechterhalten. Der Patient benötigte während des gesamten Eingriffs, der nach 4 h abgeschlossen war, kein zusätzliches Rocuronium. Bei dem Patienten lag höchstwahrscheinlich präoperativ eine Simvastatin-induzierte Myotoxizität vor. Hierdurch wurde die muskelerelaxierende Wirkung von Rocuroniumbromid potenziert, was der Grund für die Unansprechbarkeit des Patienten und die verzögerte postoperative Regeneration war. Die Autoren schließen daraus, dass Anästhesisten eine Statin-induzierte Myotoxizität präoperativ identifizieren sollten, um Medikamente, die eine neuromuskuläre Blockade bewirken, bei mit Statinen behandelten Patienten zu vermeiden. Auch eine präoperative Anpassung der Statindosis ist zu empfehlen.

Schlüsselwörter

Verzögerte Regeneration · Allgemeinanästhesie · Hypercholesterolemie · Neuromuskuläre Blockade · Simvastatin

from the muscle relaxant at that time. It is well known that increased sensitivity to muscle relaxants is seen in patients with muscle dystrophy [20]. Neuromuscular blockade or muscle relaxation, is a necessary component of many surgical procedures [21]. Patients undergoing general anesthesia are treated with a neuromuscular blocking drug before surgery in order to facilitate intubation, to decrease patient movement and to improve operating conditions [21, 22]; however, the use of neuromuscular blocking drugs has been associated with negative side effects, as an increased incidence of postoperative respiratory failure, expressed as reintubation and unplanned intensive care unit (ICU) admission post-surgery, after use of intermediate acting neuromuscular blocking drugs [23]. Neuromuscular blockade is intended to be temporary and must be reversed when it is no longer required [22]. If complete recovery from the effects of neuromuscular blocking drugs is not achieved after surgery, prolonged muscle relaxation may lead to residual muscle weakness, breathing problems and delayed recovery [24]; therefore, successful recovery from muscle relaxation is necessary to avoid unintended complications. To minimize patient morbidity and optimize use of operating room time, monitoring of neuromuscular blockade is essential during the perioperative period. During profound non-depolarizing neuromuscular block, there may be no response to TOF or single twitch stimulation. In such circumstances, a PTC may be useful and is generally used to ensure profound muscle block, such as during microsurgery, ophthalmic surgery, and when “bucking” on the endotracheal tube could have disastrous consequences [25]. Reversal of non-depolarizing neuromuscular blocking agents, such as rocuronium and vecuronium traditionally has been achieved by using acetylcholinesterase inhibitors.
[26]; however, these agents cannot adequately reverse profound neuromuscular blockade [27]. Sugammadex rapidly and effectively reverses rocuronium-induced neuromuscular blockade, including profound blockade [28]. Sugammadex is a selective relaxant binding agent, that is used to reverse muscle relaxation and it is becoming increasingly available across many healthcare settings [29]. Sugammadex selectively binds to neuromuscular blocking agents (rocuronium or vecuronium) and reverses muscle relaxation by encapsulating these drugs and reducing their effect on the neurological system [24]. Due to its unique mechanism of action, sugammadex has the potential to rapidly and reliably reduce neuromuscular blockade and concurrently decrease the likelihood of residual muscle weakness after surgery, unlike existing alternatives [29]. Our patient most probably had simvastatin skeletal myotoxicity before surgery, which potentiated the muscle relaxant effect of rocuronium and was the reason for patient unresponsiveness during recovery from anesthesia.

Conclusion

Our patient most probably had simvastatin-induced myalgia or myopathy before surgery. This caused potentiation of the skeletal muscle relaxant effect of rocuronium and was the reason for patient unresponsiveness and prolonged recovery. We recommend that anesthesiologists should be careful when managing patients on statins to define the myotoxic effects before surgery and it is possibly better to avoid using muscle relaxants or at least to adjust the relaxant dose. Also, adjustment of statins dosage preoperatively may be recommended.

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Compliance with ethical guidelines

Conflict of interests. E.E. Abd El-Hakeem, A.M. Kaki, S.A. Almazlom and A.J. Alsayyad declare that they have no competing interests.

This article does not contain any studies with human participants or animals performed by any of the authors. Consent was obtained from all patients identifiable from images or other information within the manuscript. In the case of underaged patients, consent was obtained from a parent or legal guardian.

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