Was a hypertensive crisis in a patient with pheochromocytoma caused by rocuronium? — A case report —

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Pheochromocytoma is an uncommon tumor that originates in the adrenal medulla or in other paraganglia of the sympathetic nervous system. If a hypertensive crisis occurs during general anesthesia in incidental or untreated pheochromocytoma, it is a life-threatening event with a mortality rate of about 80%. Anesthetic drugs such as pancuronium, atracurium, and metoclopramide can exacerbate the potentially lethal cardiovascular effects of catecholamines. We report a case of a patient with pheochromocytoma who displayed abrupt increases in systolic arterial pressure and plasma norepinephrine following rocuronium administration. This case indicates the possible involvement of elevated sympathetic nervous system to a catecholamine crisis triggered by rocuronium in pheochromocytoma.

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We report a patient with asymptomatic pheochromocytoma whose surgery was canceled, because his systolic blood pressure was increased abruptly following rocuronium administration at first anesthetic induction trial and the increasing of blood pressure by rocuronium was effectively regulated by α-blocker pretreatment at second trial.

CASE REPORT

A 67-year-old, 61-kg, man was admitted to a hospital for the evaluation of a left adrenal mass detected by abdominal ultrasonography at a health screening center. He had no known history of hypertension, diabetes mellitus, and other systemic diseases. Abdominal magnetic resonance imaging showed a 54 × 50 × 46 mm mixed cystic and solid mass arising from the left adrenal gland (Fig. 1). The tumor was suspected as a pheochromocytoma because 24-hour urine metanephrine and vanillylmandelic acid levels were found to be 4.7 mg (reference, 0 ～ 1 mg) and 6.8 mg (reference, 0 ～ 8 mg), respectively. Iodine-131 metaiodobenzylguanidine scintigram showed uptake at the left supra-renal region without metastasis. Surgery was planned without preoperative prescription of any catecholamine blockade on the recommendation of an endocrinologist because the patient had no history of hypertension and clinical sign of suspicious paroxysmal hypertensive episodes such as palpita-
tion, diaphoresis, fever, dizziness, and headache. The patient was premedicated with midazolam 7.5 mg orally, 1 h prior to the induction of anesthesia. After being admitted to the operating room, a 20-gauge catheter was placed into the radial artery to continuously monitor the blood pressure. His vital signs before induction consisted of an arterial blood pressure of 136/68 mmHg and a heart rate of 53 beats/min (bpm). The patient was preoxygenated with 100% oxygen by mask, followed by intravenous induction of anesthesia using remifentanil continuous infusion (0.25 μg/kg/min), propofol (2 mg/kg), and rocuronium (50 mg). Initial mask ventilation with sevoflurane 3 vol% in oxygen was applied without difficulty. Before attempting direct laryngoscopy for tracheal intubation, blood pressure started to rise rapidly to 340/190 mmHg. After a limited blood pressure response to nicardipine (Peridipine®, Astellas, Japan) 0.5 mg bolus, additional 1 mg and 2 mg boluses quickly caused blood pressure to drop to 118/63 mmHg. Surgery was postponed until an adequate catecholamine blocker concentration was achieved to prevent intraoperative hypertensive crisis. The patient was transferred to the postanesthetic care unit for close monitoring and was discharged without any problem. Two weeks later the patient returned to the hospital for excision of the tumor after medication with doxazocin mesylate (Cardura®, Pfizer, USA) 4 mg/day orally. The day before the scheduled operation, the patient provided consent to blood testing to identify the cause of the prior hypertensive crisis. Informed consent about risk of surgery was taken also. After premedication with 7.5 mg midazolam orally, 1 h prior to the induction of anesthesia, the patient arrived at the operation room and standard monitors including an arterial catheter insertion to measure blood pressure and to collect blood samples were applied. Bispectral index monitor (BIS) was applied to monitoring the depth of anesthesia. His vital signs consisted of blood pressure of 146/65 mmHg and heart rate of 55 bpm. At this time, the concentration of plasma norepinephrine (NE) which was measured in duplicates using the technique of high-pressure liquid chromatography (Acclaim, Dionex, USA), was determined to be 143.3 pg/ml. We started the remifentanil continuous infusion at 0.25 μg/kg/min throughout the induction of anesthesia and tracheal intubation. One minute following the start of remifentanil infusion, anesthesia was induced with propofol 2 mg/kg intravenously. After the loss of eyelash reflex, mask ventilation with sevoflurane 3 vol% in oxygen was applied. Three minutes after the injection of propofol, rocuronium 0.8 mg/kg was administered over 5 seconds. Just prior to rocuronium injection, the patient’s vital sign consisted of blood pressure of 87/47 mmHg and heart rate of 58 bpm. The concentration of plasma NE was 292.3 pg/ml. Two minutes following rocuronium administration, the patient’s systolic blood pressure rose to 166 mmHg and continued to rise to peak at 196/74 mmHg at three minutes after rocuronium injection. The concentration of plasma NE was 2338.7 pg/ml and 1,618.3 pg/ml at two and three minutes after rocuronium injection, respectively. The patient did not show any withdrawal signs, such as finger or wrist movements, caused by rocuronium injection pain. At that time, BIS value was about 40. The patient was intubated with endotracheal tube, but did not experience an xtn diastolictolic/n of an additive increase in blood pressure. One minute after intubation, the patient’s maximal blood pressure was 183/71 mmHg and the concentration of plasma NE was 582 pg/ml (Fig. 2). Afterwards, blood pressure continued to decrease to 163/62 mmHg and 133/55 mmHg at 2 and 3 minutes, respectively. A central venous catheter was placed via right internal jugular vein and central venous pressure was 1 mmHg. The patient did not show the significant increase of blood pressure during operation, such as skin incision, except during direct manipulation of mass. The patient underwent a laparoscopic adrenalectomy without incident. Histology showed a 78 × 50 × 40 mm sized pheochromocytoma.

Fig. 1. Abdominal magnetic resonance imaging showing the left adrenal mass.
DISCUSSION

The anesthetic management of patients with pheochromocytoma is a challenge to most anesthesiologists. Arterial hypertension and arrhythmia are known to be induced by catecholamine release from pheochromocytoma in response to manipulation of tumor during surgery or even palpation of abdominal wall with tumor [3]. However, it is unlikely that acute catecholamine release from the pheochromocytoma itself is solely responsible for hypertensive crisis. A recent review suggested that the elevation of sympathetic activity is also responsible for hypertensive crisis, and mechanisms of elevated sympathetic activity are likely due to the loading of sympathetic vesicles with catecholamine, increase of sympathetic neuronal impulse frequency and a selective desensitization of presynaptic α2-adrenergic receptors [4]. It suggests that any stimulus to sympathetic nervous system such as drugs, anxiety, pain may lead to hypertensive crisis associated with significant release of the catecholamines in sympathetic nerve ending.

In this case, mask ventilation with sevoflurane is unlikely to cause hypertension because it was very easy and manipulated gently. Previous reports showed that sevoflurane did not induce the increase of catecholamine concentration and hemodynamic responses during induction of anesthesia via mask in humans [5]. Also, unlike desflurane, it has been known that the neuro-circulatory excitation associated with rapid increases of sevoflurane did not occur. Propofol has been reported to have been apparent in hypertensive crisis associated with severe injection pain [6]. So, propofol would be thought as one plausible trigger to the hypertensive crisis. However, propofol has been reported to block the catecholamine and hemodynamic responses during induction and endolaryngeal procedures [7]. In this case, the patient received propofol after infusion of remifentanil and complained of no pain during the infusion of propofol and blood pressure fell further after its administration. Therefore, injection pain of propofol is unlikely to cause the catecholamine crisis nevertheless it can’t be fully excluded in this setting.

Rocuronium has to be considered as a trigger factor of development of hypertensive crisis in this study because the abrupt increase in blood pressure and catecholamine occurred immediately following its administration. The release of catecholamine stored excessively from sympathetic nerve terminals by rocuronium administration is likely to mainly contribute to an abrupt increase in blood pressure, although the mechanism by which the crisis triggered has not been confirmed. Non-depolarizing muscle relaxants have been reported to have anti-muscarinic effects (M2 subtype) which leads to increased NE release at the presynaptic terminal of postganglionic sympathetic nerve, and they had relative order of potency for the M2 muscarinic receptors [8]. Sato et al [9] have reported, at equipotent concentrations used in clinical practice, that rocuronium enhanced the release of NE from sympathetic nerve terminals in atrial tissue, although to a somewhat lesser extent. In our case, first operation was postponed because hypertensive crisis was occurred after rocuronium injection in preoperative asymptomatic and hemodynamically stable patient. We presumed that the cause of the alarming increase of blood pressure might be rocuronium. So, we checked plasma NE concentration and found elevation of its level after rocuronium injection during anesthesia at second operation. Even though the degree of elevation of blood pressure was attenuated by α-blocker pretreatment compared with the first anesthesia, blood pressure was raised with significance after rocuronium injection.

However, in this case, the levels of NE and blood pressure dropped more rapidly than clearance of rocuronium. Pharmacokinetics of drugs may be affected by cardiac output and infusion rate. Previous reports showed that a drug that alters cardiac output could affect the initial kinetics of rocuronium, and the initial arterial concentration of rocuronium after bolus injection was inversely related to cardiac output [10,11]. In this case, infusion of remifentanil combined with propofol would reduce significantly cardiac output as a consequence of a decrease...
in stroke volume. This reduction of cardiac output would lead to increase transiently the concentration of rocuronium in the patient’s heart. Furthermore, after an intravenous drug injection or rapid intravenous infusion, the first-pass arterial concentration emerging from the right heart-lung system was more rapidly decreased compared with the total concentration (the sum of the first-pass and recirculated concentration) [10]. Taken together, in pathologic condition such as pheochromocytoma associated with chronic volume deficiency and elevated sympathetic activity, rapid injection of rocuronium would cause transient increase of its concentration lead to significant catecholamine release from sympathetic nerve endings, although it was reported that rocuronium had not affinity for M2 receptor within the range of concentrations achieved with clinical use [8].

After the peak record of blood pressure by rocuronium injection, subsequent laryngoscopy and intubation did not result in additive increase of blood pressure. On the contrary, a decrease in blood pressure and plasma catecholamine was observed. This is thought to have resulted from rapid decrease of the concentration of rocuronium or the lack of time needed to reuptake of the catecholamine in the sympathetic nerve terminals after excessive release of catecholamine.

In this case, the patients did not show elevation of blood pressure by intra-arterial catheterization, which might also cause significant pain, prior to anesthesia and did not show any withdrawal signs caused by rocuronium injection pain. So it was presumed that pain from intra-arterial catheterization or rocuronium injection was not the source of hypertensive crisis. However, no withdrawal sign cannot fully deny the possibility of injection pain, because rocuronium causes significant pain on injection by direct activation of C-nociceptors of which mediator release are not correlated with intensity of pain [12]. Also, the increase in blood pressure following the administration of rocuronium might be caused by light anesthesia, but it is unlikely cause of the increase in blood pressure in this case because we administered adequate doses of remifentanil and sevoflurane in sufficient time, and the BIS value was maintained below 40 during induction of anesthesia and endotracheal intubation.

As noted above, considering the initial kinetics of rocuronium, volume deficiency might also have played a major role in the occurrence of crisis during induction of anesthesia in the patient. Therefore, preoperative adequate fluid loading is important to minimize hemodynamic changes by anesthetic drugs per se or pharmacokinetics of anesthetic drugs.

As shown in our case, pharmacological pretreatment with α-blocker can prevent hypertensive crisis. The typical symptoms of pheochromocytoma were known to be headache (80%), diaphoresis (57%) and palpitations (64%) [4]. However, diagnosis can be difficult because symptoms may be varied and some patients are completely asymptomatic. A recent review reported that 13% of patients with pheochromocytoma had normal blood pressure [4] and about half of all pheochromocytoma were detected by an abdominal imaging method performed for a reason unrelated to elevated blood pressure [13]. It suggests that preoperative α-adrenergic blocker should be used for patients with pheochromocytoma whether the patient had previous hypertension history or not. If the hypertensive crisis were occurred under general anesthesia in incidental or untreated pheochromocytoma, it could be a life threatening event with high mortality rate. Therefore, we should have treated with α-blocker before performed the first operation whether the patient had a symptom or not. It was known that selective α1-blocker reduced blood pressure and pressure responsiveness to NE, therefore, we expected that α1-blocker could attenuate the hemodynamic changes at 2nd anesthetic induction. Phenoxybenzamine preparation for the prevention of hypertensive crisis in pheochromocytoma patient over a time up to 2 weeks preoperatively remains popular but preparation with other drugs, such as prazosine and doxazosin has been suggested [14]. Also, since α1-blocker was reported not to interfere with the regulation of NE release and the adrenomedullary component of the sympathetic nervous system [15], we checked the level of plasma NE for evaluating anesthetic drugs by which NE release were provoked.

In conclusion, rapid injection of rocuronium might have caused hypertensive crisis due to the significant increasing of catecholamine release from sympathetic nerve endings. The goal of the anesthetic technique is to maintain adequate blood pressure at all times, so it is important to notice that catecholamine crisis may be triggered by some of anesthetic drugs as well as surgical manipulation of tumor. Furthermore, it is necessary to understand pharmacokinetics and adequate titration of anesthetic drug.

REFERENCES


