Perioperative endocrinological findings in a patient with Bartter's syndrome and living-related renal transplantation

Ryusuke Ueki[1], Ryu Okutani[2], Ayumi Fukushima[2], Tetsuo Tsuji[3], Hideki Ohata[3], and Chikara Tashiro[1,2]

[1] Department of Anesthesiology, Hyogo College of Medicine, 1-1 Mukogawa–cho, Nishinomiya City, Hyogo 663-8501, Japan
[2] Intensive Care Unit, Hyogo College of Medicine Hospital, 1-1 Mukogawa–cho, Nishinomiya City, Hyogo 663-8501, Japan
[3] Diagnostics Science Division, Shionogi & Co., Ltd, 2-5-1 Mishima, Settu City, Osaka 566-0022, Japan

Introduction

Bartter's syndrome is characterized by hypokalemia, metabolic alkalosis, normotensive hyperaldosterone-mia, a decreased vasopressor response to angiotensin, and hyperplasia of the renal juxtaglomerular apparatus [1–3]. About 70 cases of Bartter's syndrome have been reported in Japan, but only a few kidney transplantations have been reported worldwide for this syndrome [4–6]. In this report, we present the endocrinological findings obtained in the perioperative period when living renal transplantation was performed in a patient with Bartter's syndrome.

Case report

The patient was a 27-year-old woman scheduled for living-related renal transplantation from her mother.

Present illness

Since the age of 22 years, easy fatigability and orthostatic hypotension occurred frequently, and Bartter's syndrome was diagnosed at the age of 23 years. When she was 26, chronic renal failure developed and hemodialysis was performed three times a week. By setting the amount of water removed to 0 ml at each dialysis, a urinary output of 1000–1600 ml·day^{-1} was maintained.

Admission findings

Her height was 155 cm and her weight was 43 kg. Renal dysfunction and anemia were shown by preoperative laboratory tests. The hemodynamic response to dopamine was examined as follows. Before administration of dopamine, the blood pressure was 103/56 mmHg, and the heart rate was 72 bpm. When dopamine was infused at 2 μg·kg^{-1}·min^{-1} and then the dose was raised gradually to 12 μg·kg^{-1}·min^{-1}, the blood pressure rose only to 131/65 mmHg and the heart rate to 73 bpm, indicating a marked decrease in catecholamine reactivity. To counteract excessive angiotensin-II (AT-II) secretion, 2.5 mg·day^{-1} of enalapril was administered orally, and the AT-II concentration was controlled in the normal range (Table 1). On echocardiography, left ventricular function was normal except for grade 1 tricuspid regurgitation, and the ejection fraction was 65%.

Anesthetic course

The patient was premedicated with 0.5 mg of atropine sulfate injected intramuscularly 30 min before the operation. Anesthesia was induced with 250 mg of thiamylal and 0.1 mg of fentanyl. After administration of 8 mg of vecuronium, an endotracheal tube was inserted. After induction of anesthesia, a central venous catheter was inserted via the right internal jugular vein, and central venous pressure (CVP) was continually monitored. Anesthesia was maintained with oxygen–nitrous oxide–isoflurane, and vecuronium was administered as necessary. During the operation, fluid infusion was controlled with the aim of keeping CVP at about 10 mmHg. When reperfusion of the transplanted kidney was resumed after anastomosis of the renal vessels, the blood pressure decreased markedly (from 100/50 to 85/42 mmHg). A single dose of 1 mg of methoxamine was administered with 7 μg·kg^{-1}·min^{-1} of dopamine, but the blood pressure did not respond. However, it recovered

to 130/60 mmHg after administration of norepinephrine. Because there was still no urinary flow from the transplanted kidney, norepinephrine was replaced by $0.1 \mu g \cdot kg^{-1} \cdot min^{-1}$ of epinephrine. At that time, CVP was decreased from 10 (just before reperfusion) to 6 mmHg. Hypoproteinemia (total protein, $4.8 mg \cdot dl^{-1}$) and anemia (hemoglobin $7.1 g \cdot dl^{-1}$) were shown on the laboratory data. Therefore, 500 ml of plasma protein fraction and 2 units of concentrated red cells were given to maintain blood pressure. About 10 min later, the blood pressure was 95/55 mmHg, but it recovered to 112/58 mmHg about 20 min after that. At that point, there was a small urinary output. During surgery, parentaleral fluid without potassium was used. The serum potassium concentration was $3.9 mEq \cdot l^{-1}$ at the beginning of the operation, $3.6 mEq \cdot l^{-1}$ at the reperfusion of the transplanted kidney, and $3.1 mEq \cdot l^{-1}$ at the end of the surgery. Arrhythmia was not observed during the operation. After the end of the operation, emergence from anesthesia was prompt and the endotracheal tube was removed in the operating room. As the patient recovered from anesthesia, the blood pressure returned to normal and the dosage of epinephrine was gradually reduced.

Table 1. Plasma concentrations of angiotensin and aldosterone before and after enalapril $2.5 mg \cdot day^{-1}$ per os

Hormone level—$pg \cdot ml^{-1}$ (normal value)	Before-medication	Medication	
		day 3	day 7
Angiotensin I (<110)	1400	—	520
Angiotensin II (<22)	59	27	12
Aldosterone (29.9–159)	2500	640	490

Postoperative course

On entering the intensive care unit, the patient had a blood pressure of 100/50 mmHg without administration of epinephrine. By fluid loading using mannitol, a urine output of $200–300 ml \cdot h^{-1}$ was maintained. However, the renogram obtained on the morning of the first postoperative day showed that blood flow in the transplanted kidney was extremely poor, and therefore the diuresis seemed to be from the patient's own kidneys. To improve perfusion to the transplanted kidney, the dose of oral enalapril was increased from 10 mg a day on the first postoperative day to 20 mg daily on the fourth postoperative day. Satisfactory urine flow from the transplanted kidney was then obtained. Although the serum urea nitrogen, creatinine, and potassium values were high, hemodialysis was not performed. The renal function data, serum potassium, and blood levels of enalapril, AT-II, catecholamines, atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and adrenomedullin (AM) during the perioperative period are shown in Table 2.

Discussion

The etiology of Bartter's syndrome has not been clarified in several respects. The flow of sodium toward the distal nephrons is increased due to abnormal reabsorption of Na^+ and Cl^- in the ascending limb of the loop of Henle. To counter the loss of Na^+, the activity of the renin–angiotensin–aldosterone (RAA) system is enhanced, the Na^+-K^+ and Na^+-H^+ channels of the distal renal tubules are activated, and hypokalemia and metabolic alkalosis develop [1–3]. AT-II has a strong direct

Table 2. Changes in renal functions and in plasma concentrations of enalapril and of hormones

Time	P-Cr (mg·dl⁻¹)	UV (ml·day⁻¹)	Enalapril Dosage (mg·day⁻¹)	Concentrations (ng·ml⁻¹)	AT-II (ng·ml⁻¹)	ANP (pg·ml⁻¹)	BNP (pg·ml⁻¹)	AM (fmol·ml⁻¹)
6POD 6:00 A.M.	5.81	1538	2.5	9.9	110	9.3	6.8	24.6
Preanesthesia	5.28		2.5	3.8	64	81	68	28.6
Renal reperfusion				7.9	150	50	67	33.4
In ICU 6:00 P.M.	4.83			8.6	89	320	100	326
12:00 P.M.	4.93	4130	2.5	9.5	55	140	320	78.2
1POD 6:00 A.M.	5.13			10.2	29	210	540	52.8
6:00 P.M.	5.68	2390		24.6	29	160	680	48.6
2POD 6:00 A.M.	6.57			21.7	23	270	410	48.2
6:00 P.M.	6.72	2905	7.5	27.9	5	280	380	47.2
3POD 6:00 A.M.	7.56	3150	10	33.6	11	290	330	38.4
4POD 6:00 A.M.	8.16	3435	10	56.1	9	310	310	32.6
5POD 6:00 A.M.	8.19	3884	10	120.1	6	230	230	28.6
14POD 6:00 A.M.	5.8	4000	10	—	6	320	120	14.6

P-Cr, plasma creatinine; UV, urine volume; AT-II, angiotensin-II; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; AM, adrenomedullin; POD, postoperative day; ICU, intensive care unit

vasoconstrictor activity, which is many times greater than that of noradrenaline on a molecular basis. AT-II also indirectly causes vascular smooth muscle contraction by stimulating ganglion cells and cholinergic or noradrenergic nerve endings. Therefore, the levels of circulating catecholamines, such as noradrenaline, are elevated, and this leads to down-regulation of catecholamine receptors and decreased reactivity to exogenous catecholamines. To explain why the blood pressure remains in the normal range despite enhancement of the RAA system, impairment of angiotensin receptors was assumed to be present in the past. Recently, however, down-regulation in response to the chronic high levels of renin and aldosterone has been considered to be the cause [7–10]. In Bartter's syndrome, the increase in intracellular calcium ions is suppressed at the second messenger level, and therefore vascular and myocardial reactivity is decreased [11–15]. In the present patient, extremely low reactivity was found in the dopamine loading test before surgery. Therefore, the choice of vasopressor drugs for hypotension during operation was a problem. Although correction of enhanced RAA system activity was attempted by oral administration of an angiotensin-converting enzyme(ACE) inhibitor for 1 month before the operation, recovery of the response to catecholamines was still insufficient. To correct low volume hypotension at the time of resumption of renal perfusion, the peripheral vascular resistance was increased by infusion of norepinephrine in addition to rapid fluid loading. However, although the blood pressure was elevated, administration of norepinephrine severely decreased the blood flow in the transplanted kidney, probably because the catecholamine receptors in this kidney were normal. When epinephrine was substituted for norepinephrine, the blood pressure was maintained and urinary output increased. Unfortunately, a Swan-Ganz catheter was not inserted for monitoring of the hemodynamics in this patient.

A major problem of anesthetic management in a patient with Bartter's syndrome is the reduction in the sympathetically mediated reflex to adjust blood pressure. It is considered that anesthetic agents will reduce this reflex further [16]. This phenomenon suggests that anesthetics suppress the baroreflex further in a patient with Bartter's syndrome.

Generally, hypokalemia is the major problem in anesthetic management in a patient with Bartter's syndrome [17–19]. However, in this case hypokalemia did not exist before surgery because of chronic renal failure.

Various hormones were measured perioperatively in the present patient. Shortly after operation, the plasma AT-II concentration unexpectedly became abnormally high, and this may have induced vasoconstriction in the transplanted kidney and reduced urinary output. When AT-II was normalized by increasing the dose of enalapril, an ACE inhibitor, the vascular tone of the transplanted kidney was normalized, renal blood flow increased, and the transplanted kidney started to function. The levels of ANP, BNP, and AM increased markedly after the operation. This was probably because atrial dilation was caused by fluid loading from the time of resumption of renal perfusion. Because ANP antagonizes AT-II, the increase in ANP might help to normalize the AT-II level, in addition to the increase in the dose of enalapril. AM is a peptide with a strong vasodilatory action that also antagonizes AT-II, and the AM level returned to normal with normalization of renal function and AT-II level. Yokoyama et al. found that when blood flow in the transplanted kidney was adequate, the RAA system, plasma bradykinin, and urinary prostaglandin F1α concentration were normalized within 2 weeks after operation [4]. There is no agreement as to the mechanism of normalization of these hormones. If the etiology of Bartter's syndrome is a renal tubular abnormality, these hormones should not be normalized as long as the abnormal host kidneys are retained. Thus, it is interesting that the levels of these hormones were actually normalized in our patient by kidney transplantation. In the case reported by Yokoyama et al., urinary flow from the native kidneys was 0 ml, whereas in the present case, urinary flow from the native kidneys was 1000–1600 ml·day^{-1}, and estimation of urine flow from the transplanted kidney was difficult. In their case, the RAA system was rapidly normalized after transplantation without the use of enalapril. In the present case, however, reduction of the AT-II level by administration of enalapril appeared to be important, judging from the changes in this hormone. A decrease in Na$^+$ and Cl$^-$ ions in the distal renal tubules stimulates renin secretion.

Postoperatively, the oral dosage of enalapril should be adjusted according to blood pressure, urine volume, blood urea nitrogen, plasma creatinine, and ultrasound echo finding of the transplanted kidney, because the results of each hormone value were not available immediately after blood sampling. Many points about these mechanisms still require clarification, and further studies on the etiology of Bartter's syndrome seem to be necessary.

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