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[Case report]

Caution : Patient-specific preoperative preparations combined with procedure-specific 5-aminolevulinic acid may lead to critical events

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Abstract

5-Aminolevulinic acid (5-ALA) is orally administered 2-4 hours before surgery to identify tumor location. Hypotension is sometimes observed after 5-ALA administration.

Case reoprt

We present a case of a patient with 5-ALA-induced hypotension that resulted in the development of cerebral infarction. An 83-year-old man with a bladder tumor was scheduled for photodynamic diagnosis-assisted transurethral resection of bladder tumor (PDD-TURBT) and right radical nephroureterectomy. 5-ALA was orally administered and his ordinary antihypertensive and antianginal agents were also administered an hour after 5-ALA administration. Following this, his blood pressure dropped, and he developed muscle weakness and paralysis in his left upper extremity. Magnetic resonance imaging showed evidence of cerebral infarction.

Conclusions

We cannot conclude definitively that our patient's cerebral infarction was solely caused by 5-ALA-induced hypotension because hypotension under these circumstances is not rare. We consider that additional factors, such as patient-specific doses of antihypertensive and antianginal agents may have played a role in the development of his cerebral infarction.

Keywords : 5-aminolevulinic acid, cerebral infarction, transurethral resection of bladder tumor

Introduction

5-aminolevulinic acid (5-ALA) is an optical diagnostic agent used to visualize malignant tumors. In some types of cancer cells, 5-ALA is metabolized to protoporphyrin IX (Pp IX) while Pp IX catabolism is inhibited. This results in the accumulation of more Pp IX than what is found in normal cells. Because Pp IX is photoactive, visible blue light causes emission of red fluorescence, enabling identification of tumor location (photodynamic diagnosis, PDD)[1)]. 5-ALA is orally administered 2-4 hours before surgery to identify tumor location. Hypotension is a widely recognized complication of 5-ALA, some cases of which may even be catecholamine resistant[2)]. 5-ALA-induced hypotension has been reported before surgery and/or intraoperatively in some patients[3,4)].

Here, we report a patient who developed hypotension preoperatively, resulting in a cerebral infarction.

Written informed consent to publish details of this case was obtained from the patient.

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Case report

An 83-year-old man (height 155 cm, weight 60 kg) presented to our institution because of intermittent hematuria for several months and was diagnosed with a bladder tumor. Two years previously, he had been diagnosed with hypertension and angina pectoris, for which he was prescribed 4 mg of benidipine hydrochloride, 5 mg of nicorandil, and 0.5 mg of doxazosin mesylate to be taken orally every morning, and a 40 mg transdermal isosorbide dinitrate patch to be applied every morning. His usual blood pressure was controlled around 110-130 / 60-80 mmHg. He had no history of transient ischemic attack.

The bladder tumor was located on the anterior bladder wall and also at the right ureteral orifice, so PDD-TURBT was scheduled before radical nephroureterectomy.

Perioperative examinations were performed. An electrocardiogram showed sinus rhythm with no arrhythmias. D-dimmer was 2.7 mcg/mL. No thrombosis was detected in the ultrasound examination of the lower extremities and cardiovascular system. Blood count, creatinine, estimated glomerular filtration rate (eGFR), fibrinolytic system and coagulation tests, including activated partial thromboplastin time (APTT), prothrombin time (PT), and fibrinogen, appear in Table 1.

On the day prior to the surgery, he was admitted to our hospital, took a stimulant laxative and began fasting. He was permitted to drink clear water until 2 hours before surgery. The actual timing and volume of fluid he ingested was not documented, but he was permitted to take up to 2000 mL of clear water over 20 hours following his admission. On the day of surgery, fluid administration was initiated, and he orally took 1180 mg of 5-ALA, followed by his usual doses of antihypertensive and antianginal agents an hour after 5-ALA administration. About an hour later, he reported muscle weakness and paralysis in his left upper extremity, which turned out to be a consequence of cerebral infraction. A detailed time course is shown in Figure 1. Because the bladder tumor had been hemorrhaging, we did not administer thrombolytic therapy, but only administered antiplatelet agents, 160 mg of ozagrel sodium, 100 mg of aspirin, 75 mg of clopidogrel sulfate, and 160 mg of edaravone to prevent development of brain edema.

Table 1. (preoperative blood examinations)

	Data	Reference range
Hb (g/dl)	12.6	13.7-16.8
Hct (%)	37.4	40.7-50.1
Plt (×10/ mcl)	212	158-348
Crea (mg/dl)	1.24	0.65-1.07
eGFR (ml/min/1.73)	43.1	60-200
PT-INR	0.93	
PT% (%)	116	70-130
APTT (sec)	24.7	24-35
Fibrinogen (mcg/ml)	298	180-400
D-dimmer (mcg/ml)	2.7	<1.0

By the following day, his muscle weakness and paralysis in his left upper extremity had completely resolved. We had to postpone surgery but, because the tumor is malignant, surgery is planned as soon as his general condition permits.

Discussion

We here present a case of cerebral infarction, likely due to hypotension induced by 5-ALA, exacerbated by antihypertensive and antianginal agents.

5-ALA-induced hypotension is not a rare phenomenon. Therefore, extra factors combined with 5-ALA-induced hypotension likely contributed to development of cerebral infarction in our patient.

The mechanism by which 5-ALA induces hypotension is not clearly understood ; however, nitric oxide released from vascular endothelial cells may be involved in vessel dilation, which in turn depresses blood pressure[5]. Also, nicorandil and isosorbide dinitrate are vasodilators that acts as nitric oxide donors[6]. Nitric oxide has a vasodilatory effect that could accelerate 5-ALA induced hypotension. Ivan *et al.* reported that antihypertensive drugs could be a risk factor in 5-ALA-induced hypotension[7]. Our patient took a calcium antagonist, alpha-blocker, nicorandil, and also applied a transdermal isosorbide dinitrate patch an hour after 5-ALA administration. These drugs, which have vasodilatory effects, could have exacerbated the subsequent hypotension. Since we did not measure blood pressure in short intervals after administration of 5-ALA, the patient may have been taking antihypertensive and antianginal agents even after his blood pressure began to drop. In most case, antihypertensive drugs like calcium channel blocker and α1-adrenergic receptor antagonist are continued during perioperative periods[8]. Generally, antianginal agents that act as nitric oxide donors, which in our case were nicorandil and a transdermal isosorbide dinitrate patch, were administered throughout the perioperative period[9]. If we had been aware of this patient's high

risk of hypotension, we might have withheld them and, if necessary, administered them intravenously during surgery.

Although our patient had not been diagnosed with renal failure, renal dysfunction was observed prior to the operation. Miyakawa *et al.* reported that age >80 years, BMI >25, and estimated glomerular filtration rage (eGFR) <45 are significant risk factors for the development of severe hypotension after oral ALA administration[10]. Thus, our patient was at high risk for developing hypotension with oral administration of 5-ALA.

Additionally, our patient was scheduled to undergo both PDD-TUR-BT and right radical nephroureterectomy. This required preoperative abdominal preparation, which is not usually done for PDD-TUR-BT alone. Although the patient was hydrated from the time of admission, the stimulant laxative and glycerin enema may have contributed to dehydration, which, in turn, could have led to the development of hypotension.

We managed the hypotension by passive leg raising procedure and fluid therapy only. Retrospectively, we should have considered administering vasoactive agents immediately to facilitate the normalization of cerebral perfusion.

The time of onset of our patient's cerebral infarction was unclear. That it was a wake-up stroke was unlikely because he did not report any abnormalities before 5-ALA administration. We speculated that the cerebral infarction occurred while the patient remained quietly in bed, covered by a blanket to shield him from the light, after 5-ALA administration.

Generally, a DWI–FLAIR mismatch, which means cerebral infarction, occurs within 3 or fewer hours after an ischemic event[11]. In our case, both DWI and FLAIR images exhibited high signals, indicating that a cerebral ischemic event may have occurred 3 or more hours prior to the scan. This would mean that his cerebral ischemic event had already occurred before the hypotension was first noted and confirmed on a bed-side monitor. Since the patient's blood pressure wasn't closely monitored after administering 5-ALA at that time, it is difficult to determine exactly when the hypotension occurred.

Prior to this case, we had experienced several cases of 5-ALA-induced hypotension that was recognized in the operating room ; in one case, surgery was aborted. In other cases, surgery was managed by maintaining anesthesia while using vasopressors and catecholamines. The occurrence of

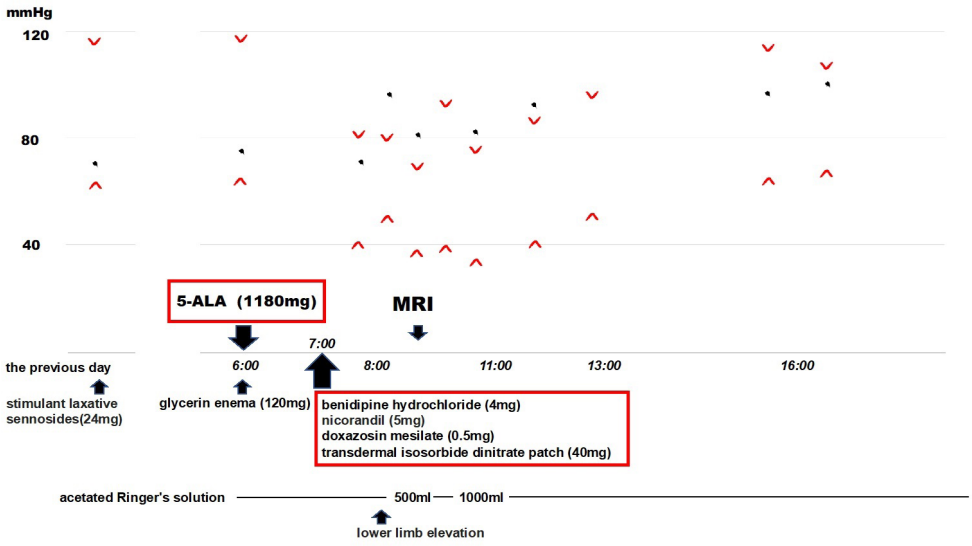

Fig. 1. On the night of admission, the patient took 24 mg of sennosides (a stimulant laxative). At 06 : 00 the next morning, he took oral 5-ALA, followed by administration of a 120 mL glycerin enema. Intravenous acetated Ringer's solution was then started. At 07 : 00, the patient received 4 mg of benidipine hydrochloride, 5 mg of nicorandil, 0.5 mg of doxazosin mesylate, and a 40 mg transdermal isosorbide dinitrate patch was applied. At 07 : 50, the patient reported nausea and hypotension was noted. This was managed by lower limb elevation and fluid administration. By 08 : 30, the patient had developed muscle weakness and paralysis in his left upper extremity. At 09 : 30, an emergency MRI was performed. Blood pressure had returned to almost normal six hours after administration of 5-ALA.

ischemic attack symptoms fortuitously allows preoperative awareness. If the anesthesia had proceeded without symptoms, further severe hypotension could have occurred due to anesthesia, possibly resulting in significant stroke sequelae. Had the hypotension been detected prior to taking the usual antihypertensive or antianginal agents, they could have been discontinued. Therefore, we conclude that patients at high risk of developing hypotension after 5-ALA administration would be better observed where blood pressure could be monitored regularly.

We were unable to determine the mechanisms of our patient's cerebral infarction. The infarction was only in the cortex area, suggesting that it was embolic. Even though the preoperative D-dimer was elevated, deep vein thrombosis of the lower extremities and intracardiac thrombus were not detected during preoperative examination. And also, we did not detect atherosclerotic stenosis nor thrombosis by either carotid artery ultrasound or magnetic resonance imaging.

D-dimmer could be elevated even in the absence of thrombosis because most cancers are associated with hypercoagulable state[12]. In this condition, thrombosis could have been formed after hypoperfusion with 5-ALA-induced hypotension.

Since the patients took antihypertensive and antianginal agents after administration of 5-ALA, in both these contributed to the sustained hypotension in our case. The relationship between 5-ALA-induced hypotension and the cause of cerebral infarction is not clear because 5-ALA-induced hypotension is not rare. Therefore, it is likely that the hypotension caused by 5-ALA was accelerated by the antihypertensive and antianginal agents, and the dehydration caused by laxatives and enemas might contribute to the hypotension, resulting in development of his cerebral infarction

Conclusion

We here report a patient who developed a cerebral infarction during 5-ALA-induced hypotension. Fortunately, the infarction was so small that there were no life-threatening complications. However, a larger infarction could have been of greater consequence.

We concluded that we need to check carefully for evidence of hypotension after administering 5-ALA, especially in older, high-risk patients with impaired renal function who are taking antihypertensive and antianginal agents.

Abbreviations

5-ALA : 5-aminolevulinic acid
PDD-TUR-BT : photodynamic diagnosis-assisted transurethral resection of bladder tumor
Pp IX : protoporphyrin IX
eGFR : estimated glomerular filtration rate
DWI : diffusion-weighted imaging
FLAIR : fluid-attenuation inversion recovery
MRI : magnetic resonance imaging

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