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Severe Metabolic Acidosis due to Thiamine Deficiency during Intravenous Hyperalimentation : A Case Report and Review of the Literature

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Abstract An 86-year-old woman, who underwent biliary stenting for bile duct cancer 3 months before, had liver metastasis and was readmitted to our department because of anorexia. Intravenous hyperalimentation (IVH) was administered without vitamin supplementation. Nineteen days after the start of IVH, drowsiness, tachypnea and hypotension with severe metabolic acidosis suddenly manifested. The discontinuation of IVH and the administration of sodium bicarbonate and thiamine corrected the acidosis. Seven days later, IVH with the same contents as the previous one was readministered with daily thiamine supplementation, but no episode similar to the previous one occured. We believe that severe metabolic acidosis in this patient was due to thiamine deficiency.

Key Words: Severe metabolic acidosis, Thiamine deficiency, Intravenous hyperalimentation

Introduction

Intravenous hyperalimentation (IVH) is regarded as a safe and convenient method of nutritional supplementation for malnourished patients. However, several cases of severe metabolic acidosis have recently been attributed to IVH without thiamine supplementation. We report herein such a case.

Case report

An 86-year-old woman underwent biliary stenting for bile duct cancer in our department. Three months later she had anorexia, and a computed tomography (CT) revealed metastatic tumor in the liver. She was readmitted to our department 4 months after biliary stenting. After admission, she could eat very little ; subsequently, IVH, which contained 700 ml of 35.7% glucose solution and 400 ml of 11.4% amino acid solution with added electrolytes, was administered daily to compensate for malnutrition. However, vitamins were not supplemented to IVH because her diet had not been stopped. Laboratory data of eighteen days after the start of IVH are shown in Table 1. At that time, mild liver dysfunction was noted and the patient weighed about 25 kg. The following day, drowsiness, tachypnea and hypotension of 50 mmHg systolic suddenly developed. Arterial blood gases (F_IO_2 0.21) at the time showed a pH of 6.944 ; PaO_2, 114.1 mmHg; $PaCO_2$, 18.7

Table 1. Laboratory data of eighteen days after the start of IVH

WBC	5800 /mm³	T.P.	6.0 g/dl
RBC	278×10⁴ /mm³	Alb	3.4 g/dl
Hb	9.1g /dl	T.B.	1.5 mg/dl
PH.	5.1×10⁴ /mm³	GOT	34 IU
Na	139 mEq/dl	GPT	37 IU
K	4.2 mEq/dl	LDH	693 IU
Cl	107 mEq/dl	ALP	1193 IU
BUN	44 mg/dl	γ-GTP	394 IU
Cr	0.5 mg/dl	Glu	223 mg/dl
Amy	57 IU	ChE	0.2 △pH
CRP	1.5 mg/dl	Chol	119 mg/dl

mmHg ; HCO_3^-, 3.8 mEq/l ; base excess -26.5 mEq/l, and anion gap of 30.2 mEq/l. Blood glucose was 445 mg/dl and urine ketones was not detected by Ketostix® . Serum Na^+ and Cl concentrations were 143 and 109 mEq/l, respectively. After resuscitation with 200 ml of 5% plasma albumin, 4 mg etilefrine hydrochloride, 500 mg hydrocortisone, and 40 mEq sodium bicarbonate intravenously, she immediately became alert, and her systolic blood pressure rose to 100 mmHg. The brain CT was normal. One hour later, she remained tachypnea, and her blood examination showed a pH of 7.057 ; PaO_2, 116.9 mmHg ; $PaCO_2$, 16.1 mmHg ; HCO_3^-, 4.3 mEq/l ; base excess -24.8 mEq/l, and glucose 407 mg/dl. In the absence of urine keton bodies, liver failure, renal failure, and septic shock, thiamine deficiency was suspected. IVH was discontinued and

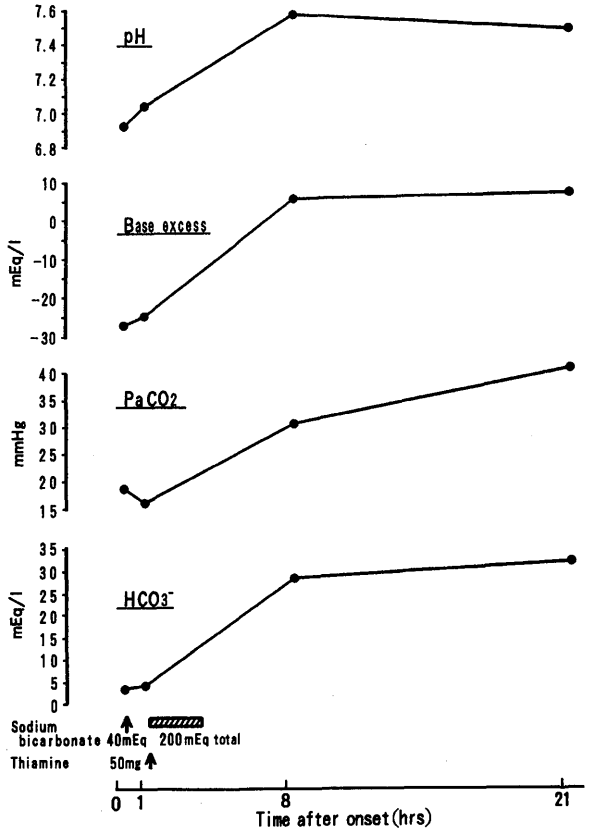

Fig 1. The time course of laboratory indexes after the onset of acidosis.

changed to a solution containing 10% glucose with added electrolytes. She was given 50 mg thiamine and received sodium bicarbonate (200 mEq total/2.5 hours) intravenously. Over the subsequent 7 hours she showed improvement of tachypnea as well as evident improvement in laboratory parameters of acid base equilibrium (pH 7.528 ; PaO_2, 104.8 mmHg ; $PaCO_2$, 30.3 mmHg ; HCO_3^-, 28.8 mEq/l ; base excess 6.4 mEq/l). The acidosis was corrected without further administration (Fig.1). Although the patient had received 1000 ml of 10% glucose solution with added electrolytes daily for the following seven days, she was incapable of ingesting sufficient food to satisfy her nutritional requirements, and IVH with the same contents as before was resumed with daily 100 mg thiamine supplementation. No similar episode occurred, while her bile duct cancer advanced and she died 55 days after the resumption of IVH.

Discussion

In 1967, Dudrick et al. devised a method of intravenous nutritional maintenance and the concept of IVH[1]. Since then IVH has been often utilized in gastrointestinal surgical services in preparation for operation, in postoperative management, and as a part of the treatment of malnourished patients suffering from either inoperable or recurrent malignant tumors.

Our patient had severe metabolic acidosis. The most common cause of this condition is diabetic ketoacidosis, but differential diagnoses include all causes of inadequate tissue perfusion (e.g., sepsis and hypovolemia), all causes of hypoxia (e.g., hypothermia and strenuous exercise), several systemic disorders (e.g., severe liver disease, leukemia, and other cancers), and thiamine deficiency. In our patient, although urine ketones were negative, diabetic ketoacidosis was not completely neglected because the measurement of serum 3-hydroxybutyrate, which was not detected by Ketostix®, was not performed. However, as the patient's condition improved without administering insulin or hydration, diabetic ketoacidosis could be ruled out, nor was the patient associated with sepsis, hypovolemia or hypoxia. Furthermore, though the patient had bile duct cancer with liver metastasis, her condition was far from a systemic disorder because there was no similar episode after the resumption of IVH. On the other hand, no specific measurements of lactate, pyruvate, thiamine, and transketolase were made and we could not prove that her severe metabolic acidosis responded to the administration of either bicarbonate or thiamine. However, we believe that our patient was thiamine deficient because an episode similar to the previous one did not occur when IVH with same contents as before was readministrated with thiamine supplementation. Rovelli et al. stated that thiamine deficiency should be considered even if the levels of lactate, pyruvate, thiamine, and transketolase were not measured, when there was no other cause of severe metabolic acidosis with the highly increased anion gap during IVH without vitamin supplementation[2].

Thiamine is essential for two enzymes involved in aerobic metabolism: pyruvate dehydrogenase and α-ketoglutarate dehydrogenase. In the absence of thiamine, pyruvate that is metabolized from glucose, fructose, or xylitol cannot enter the Krebs cycle, resulting in pyruvate accumulation and conversion to lactate. In addition, the generation of reduced nicotinamide adenine dinucleotide (NADH) within the Krebs cycles is prevented, stimulating anaerobic glycolysis and further lactate production[3,4].

To our knowledge 43 cases of severe metabolic acidosis due to thiamine deficiency during IVH have been documented in the literature[5-28], ours being 44th case (Table. 2). Of these 44 patients, 6 had benign disease that caused absorptive disorders and 22 had malignant diseases. Goodgame et al. suggested that lactic acidosis was related to the neoplastic utilization of intravenously infused hypertonic glucose[28]. The interval between the start of administration of IVH and the time of onset ranged from 4 days to 52 days (mean 22.1 days). Abdominal pain was recognized in 8 patients and 11 patients received exploratory laparotomy because the presence of intraabdominal lesions that caused severe metabolic acidosis was suspected. The levels

Table 2. Reported cases of severe metabolic acidosis due to thiamine deficiensy during IVH

Year	Author (Ref.)	Case No.	Age	Sex	Underlying disease	Duration of IVH before the onset (days)	Supplementation of thiamine before the onset	pH	Base excess (mEq/l)	Lactate (mg/dl)	Vit. B1 (ng/ml)	Abdominal pain at the onset	Laparotomy after the onset	Administration of thiamine after the onset	Outcome
1975	Blennow (6)	1	14	M	iatrogenic esophageal perforation	21	−	?	-12.5	?	?	−	−	+	recovered
1981	Merritt (7)	2	13	M	acute lymphocytic leukemia and abdominal lymphoma	7	+	7.07	?	118	?	−	−	−	recovered
		3	2	M	abdominal Burkitt lymphoma	6	+	7.08	?	198.1	?	−	−	−	died
1982	Shimizu (8)	4	59	M	short bowel syndrome	47	−	6.99	-25.1	?	?	+	+	−	died
1985	Velez (5)	5	76	M	gastric cancer	10	−	7.14	?	97.0	?	−	+	+	died
		6	51	M	iatrogenic small intestinal fistula	14	−	7.04	?	?	?	−	+	+	recovered
		7	48	M	gastric ulcer	7	−	6.70	?	185.5	?	−	+	+	recovered
1986	La Selve (9)	8	12	F	ulcerative colitis	30	+	7.06	?	103.6	?	+	−	+	recovered
1988	Mattioli (10)	9	22	M	ulcerative colitis	17	+	?	?	22.2	?	−	−	+	recovered
1989	ASPEN (3)	10	59	F	short bowel syndrome	20	−	?	?	?	?	−	−	−	died
		11	29	F	abdominal gun shot wound	35	−	?	?	?	?	−	−	−	died
		12	27	M	ulcerative colitis	35	−	?	?	?	?	−	−	−	died
1990	Klein (11)	13	37	F	rectal villous adenoma	21	−	6.96	-25.3	218.8	?	−	+	+	recovered
		14	44	F	chronic pancreatitis	21	−	7.17	-18.3	205.3	?	−	+	+	recovered
1990	Rovelli (2)	15	3	M	acute monocytic leukemia	22	+	7.17	-18	?	?	−	−	+	recovered
1990	Wilmanns (12)	16	66	F	gastric cancer	11	−	6.83	?	191.8	?	−	−	+	recovered
		17	19	F	Crohn's disease	28	−	7.04	?	160	?	−	−	+	recovered
		18	24	M	pancreatitis	21	−	6.94	?	120	?	−	+	+	recovered
		19	26	M	Crohn's disease	49	−	6.97	-28	222	?	+	−	+	recovered
1991	Roll (13)	20	2	M	ileus	21	−	7.0	-20	?	?	−	+	+	recovered
1991	Oriot (14)	21	3	M	acute lymphoblastic leukemia	20	−	6.82	-30	270	19	−	−	+	recovered
1992	Vortmeyer (15)	22	62	M	cerebral aneurysm	25	−	?	?	?	?	−	−	−	died
1992	Lange (16)	23	2	M	blind loop syndrome	28	?	7.0	-20	252.1	?	−	+	+	recovered
1992	Naidoo (17)	24	25	F	small intestinal tuberculosis	30	+	?	?	?	?	−	−	+	recovered
1993	Barrett (18)	25	4	M	short bowel syndrome	8	−	7.37	-10.5	65.7	?	−	−	+	recovered
1993	Nakasaki (19)	26	53	M	gastric cancer	21	−	7.134	-19.5	116	?	−	−	−	recovered
		27	69	M	gastric cancer	23	−	7.048	-25.6	289	1.0	−	−	−	died
		28	68	F	chronic hepatitis and chronic parcreatitis	18	−	6.942	-23.0	156	2.2	−	−	−	died
1993	Matsuda (20)	29	27	F	ulcerative colitis	18	−	7.143	-16.5	371	25	−	−	+	recovered
1993	Kitamura (21)	30	65	F	gastric cancer	15	−	6.76	-28	162.1	10	+	+	−	died
		31	60	F	gastric cancer	23	−	7.05	-24.4	225.1	10	+	+	+	recovered
1994	Yoshita (22)	32	63	F	thyroid cancer	21	−	7.0	-24	219	?	−	−	+	recovered
		33	45	F	breast cancer	4	−	7.0	-28	135	16	−	−	+	recovered
1992	Miyake (4)	34	59	F	gastric cancer	21	−	7.05	-20	159.6	10	+	−	+	recovered
1996	Muramoto (23)	35	61	M	jejunal cancer	20	−	?	-22.6	?	8	+	−	+	recovered
1996	Toda (24)	37	68	M	gastric cancer	13	−	7.250	-16.8	?	?	−	−	−	died
		38	79	M	rectal cancer	25	−	6.765	-30.7	?	?	−	−	+	recovered
1997	Nomura (25)	36	86	F	pancreatic cancer	21	−	7.193	-16.6	117.1	13	+	−	+	recovered
1997	Okabe (26)	39	72	M	ileus	30	−	6.717	-35.3	?	?	−	−	+	recovered
1997	Wakabayashi (27)	40	41	F	gastric cancer	52	−	7.222	-16.9	117	?	−	−	+	recovered
		41	70	M	hepatocellular carcinoma	29	−	7.300	-13.5	107	?	−	−	+	recovered
		42	64	M	pancreatic endocrine tumor	23	−	7.16	-18	119.5	?	−	−	+	recovered
		43	60	M	pancreatic cancer	21	−	7.296	-17.7	168	?	−	−	+	recovered
1999	Nakamura	44	86	F	bile duct cancer	19	−	6.944	-26.5	?	?	−	−	+	recovered

of arterial blood pH, arterial blood base excess, serum lactate, and blood thiamine ranged from 6.70 to 7.37 (mean 7.04), from -10.5 mEq/l to -35.3 mEq/l (mean -21.7 mEq/l), from 22.2 mg/dl to 371 mg/dl (mean 168.7 mg/dl) and from 1.0 ng/ml to 25 ng/ml (mean 11.4 ng/ml), respectively. There are no significant relations between these levels and patients' outcomes.

Eleven patients died without improvement of acidosis, and the overall mortality rate was 25.0%. But only one (3.1%) died in 32 patients who had been given thiamine. So the patient's outcome would be good if the patients were given thiamine immediately. Velez et al. recommended that 100 mg thiamine should be given immediately and repeated every hour until a satisfactory clinical and biochemical response was achieved. They also stated that overdosage with thiamine was unlikely, but respiratory depression had been reported at doses over 350 mg/kg, a level that would hardly be given to human[5]. Therefore, in any patients who develop an unexplained severe acidosis during IVH, the possibility of thiamine deficiency should be considered, and measurement of blood thiamine should be in order. The discontinuation of IVH to prevent pyruvate accumulation and thiamine replenishment should be performed immediately without waiting for the results of thiamine meaurement. In that case, less thiamine than Velez et al. recommended would be effective to acidosis in malnourished patients who are as emaciated as was our patient. On the other hand, as Matsuda et al. reported, lipid metabolism is also disordered by thiamine deficiency, nutritional support of lipids might be difficult[20]. Consequently, IVH had to be readministered with thiamine supplementation in order to improve the patient's nutritional conditions as soon as thiamine deficiency became clear. While waiting for the results of thiamine measurement, restriction of nutritional support would be unavoidable, although the patient's nutritional condition becomes poor.

Twenty of the 44 cases have been reported in Japanese literature. But there have been no cases in the USA since American Society for Parenteral and Enteral Nutrition (ASPEN) estimated that intravenous multivitamin preparation was crucial for patients who used IVH[3]. On the other hand, uniform vitamin supplementation, especially for patients whose diet is not stopped, is unallowed by Japanese law. Consequently, we stress that routine monitoring of arterial blood pH and base excess or serum lactate or blood thiamine should be performed for the early detection of thiamine deficiency when IVH is used for patients having malignant disease or absorptive disorder.

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