Appropriate Intravenous Doses of L-Thyroxine and Magnesium in a Thyroidectomized Patient with Thyroid and Parathyroid Carcinomas Receiving Total Parenteral Nutrition During Acute Necrotizing Pancreatitis

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A totally thyroidectomized patient with thyroid and parathyroid carcinomas, which had developed after neck irradiation in childhood, became hypercalcemic due to pulmonary metastases. The hypercalcemia was ameliorated by intermittent iv administration of bisphosphonate for 3.5 years, but this gradually became refractory to the bisphosphonate treatment. After right thoracotomy for resection of pulmonary metastases, acute necrotizing pancreatitis developed. The patient was therefore placed on total parenteral nutrition supplemented with T₄ and a restricted dose of magnesium. Thyroxine(T₄) (30 µg/day, iv) was not sufficient to maintain euthyroidism, but a higher dose (60 µg/day) elicited mild hyperthyroidism to the same extent as that elicited by an oral dose of 100 µg/day. The present case showed that the appropriate iv dose of T₄ in this thyroidectomized patient with acute pancreatitis was about 60% of the oral dose. Furthermore, bisphosphonates (pamidronate and alendronate) and magnesium depletion were very effective in controlling the hypercalcemia.

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Key words: thyroid carcinoma, parathyroid carcinoma, acute necrotizing pancreatitis, bisphosphonate, morphine

Introduction

The appropriate oral dose of thyroxine (T₄) for maintaining hypothyroid or athyreotic patients in a euthyroid state is about 1.6–2 µg/kg body weight per day (1–3). However, there are few or no data to indicate adequate iv dose of T₄ in totally thyroidectomized patients, particularly when they are critically ill, because serum T₃ and T₄ levels are substantially decreased in non-thyroidal illnesses (NTI) (4–6).

Recently, we treated a hypercalcemic patient with parathyroid and thyroid carcinomas, which had developed 40 years after neck irradiation (7–11). The patient underwent total thyroidectomy and was maintained slightly hyperthyroid for 4 years at a daily oral dose of 100 µg T₄. Despite total resection of the tumors in the neck, hypercalcemia developed due to bilateral lung metastases (11, 12). The patient underwent right thoracotomy for resection of the metastases and amelioration of

the hypercalcemia (12). After the operation, acute necrotizing pancreatitis developed. Bisphosphonates were repeatedly injected to control the hypercalcemia (13), and the patient was placed on intravenous hyperalimentation (IVH) supplemented with L-thyroxine (30–60 µg/day) to assist the regression of the pancreatitis.

We report here the thyroid function of this totally thyroidectomized patient, who was treated with total parenteral nutrition (TPN) for more than 4 months.

Case Report

Initial clinical course

In April 1993, the patient, a 64-year-old woman, was admitted to Tokyo Women's Medical College because of hypercalcemia due to pulmonary metastases of thyroid and parathyroid carcinomas. At the age of 11 years, she underwent irradiation

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tion of the neck for treatment of atopic eczema (11). In 1981 (age 53), she noticed thyroid nodules, and left thyroid lobectomy was performed. The pathological diagnosis was papillary carcinoma of the thyroid (7, 11). In 1984, hypercalcemia developed, and a parathyroid tumor was resected. The diagnosis was parathyroid carcinoma (11). Hypercalcemia persisted, and extracorporeal shock-wave lithotripsy failed to remove renal stones in the left kidney, resulting in left hydronephrosis. In 1988, the thyroid tumor recurred in the neck. Complete thyroidectomy was performed and the tumors, which were found to have invaded into the esophagus and trachea (papillary carcinoma), were removed. She was administered T₄ at an oral dose of 125–150 µg/day to minimize thyroid stimulating hormone (TSH)-dependent tumor growth. The dose was reduced to 100 µg/day to maintain thyroid function in a slightly hyperthyroid state (14, 15) (Table 1). The serum calcium concentration gradually increased and exceeded 14 mg/dl in September 1989, accompanied by increased urinary excretion of calcium (300–490 mg/day). From November 1989, pamidronate (45–60 mg, Ciba Geigy, Osaka) was intermittently administered iv to decrease the serum calcium concentration to below 13–14 mg/dl (13). In the early period of administration, this was very effective for ameliorating the hypercalcemia, but after the 20th administration, the hypercalcemia became refractory to bisphosphonate (Fig. 1). In April 1993, it was not possible to decrease the serum calcium concentration to below 15 mg/dl, despite iv injection every 4th week. Plasma

intact parathyroid hormone (PTH) increased steadily to 2,602 pg/ml, accompanied by a marked increase in serum alkaline phosphatase activity (3,341 IU/L). Muscle weakness, and pain in the knee joints due to pseudogout worsened, making it difficult for the patient to visit the hospital on foot.

Clinical course in the Department of Surgery

On admission, the patient weighed 37 kg, and her height was 156 cm. She complained of general fatigue and nocturia, but was mentally alert with good intellect. The serum calcium concentration was 15.7 mg/dl, P 1.9 mg/dl, Mg 0.9 mEq/L, albumin 3.8 g/dl, Blood urea nitrogen (BUN) 21.9 mg/dl, creatinine 1.0 mg/dl, Na 141 mEq/L, K 3.8 mEq/L, Cl 111 mEq/L. CT scan revealed multiple metastases in the bilateral pulmonary field (Fig. 2). On May 19, right thoracotomy was performed as part of a staged bilateral thoracotomy (12), and 57 small metastatic tumors (approximately 7 g in total) were resected. The pathological diagnosis was thyroid carcinoma (15 of the 57 tumors, chiefly the larger nodules) and parathyroid carcinoma (42 of the 57 tumors, the smaller nodules). Eight days after the operation, severe abdominal pain developed, and serum amylase increased to 2,951 U/L. Under a diagnosis of acute pancreatitis, nafamostat mesilate (Futhan, 20 mg) was administered iv. The patient was maintained by IVH (total 1,400 cal), depleted of phosphate and magnesium.

Table 1. Thyroid Function of the Patient

	1989 Oct	90 Apr	91 Feb	93 5/18	Operation ↓ 7/23	8/24	9/1	9/10	9/24
Rp) T ₄ (µg/day)	125	125	100	100	100	(–)*	30*	30*	30*
Body weight (kg)			41	37					
T ₃ (90–170 ng/dl)	152	135	114	–	102	50	87	101	123
T ₄ (5.1–11.4 µg/dl)	13.3	11.8	9.7	–	–	1.3	3.2	4.7	6.3
TSH (0.2–4 µU/ml)	<0.1	<0.1	<0.1	<0.1	<0.1	9.6	37.7	102.7	20.1
fT ₃ (2.5–5.0 pg/ml)	4.10	4.14	3.0	4.28	–	1.13	1.79	2.48	2.82
fT ₄ (0.95–1.85 ng/ml)	2.59	2.00	1.25	0.93	1.80	<0.20	0.36	0.51	0.69
Tg-Ag (<35 ng/ml)	–	150	–	268	117.0	416.0	–	823.0	834.0
Ab (<20%)	–	5.9	–	5.6	4.9	7.9	–	6.3	7.2
TBG (14.0–29.4 µg/ml)	–	–	–	–	–	19.2	24.5	22.7	–
	1994								
	10/8	10/29	11/25	12/8	12/20	1/24	2/4	2/24	
Rp) T ₄ (µg/day)	60*	75	100	0	50*	50*	50*	40*	
Body weight			39						
T ₃ (90–170 ng/dl)	148	155	169	88	129	140	153	182	
T ₄ (5.1–11.4 µg/dl)	9.6	5.9	9.7	2.5	4.9	8.3	10.1	11.0	
TSH (0.2–4 µU/ml)	0.1	0.1	<0.1	17.8	13.7	0.3	<0.1	<0.1	
fT ₃ (2.5–5.0 pg/ml)	3.47	3.87	4.50	2.05	2.90	3.4	4.14	4.43	
fT ₄ (0.95–1.85 ng/ml)	1.19	0.69	1.0	0.22	0.45	0.80	1.19	1.27	
Tg-Ag (<35 ng/ml)	–	114.0	67.5	252.0	682.0	122.0	104.0	89.2	
Ab (<20%)	–	5.5	6.3	9.6	5.0	7.5	6.8		
TBG (14.0–29.4 µg/ml)	22.5	26.0	25.3						

*indicates that T₄ was administered iv. TBG: thyroxine-binding globulin.

Fig. 1. Clinical course of the patient.

Upper panel: serum amylase (●—●; IU/L). Middle panel: serum calcium (○—○; mg/dl), corrected serum calcium (●—●; mg/dl) (16). Lower panel: serum T₄ (■—■; µg/dl), serum T₃ (▲—▲; ng/dl), serum TSH (●—●; µU/ml), Dose of T₄ (µg/day), □ p.o., ■ i.v. NM: nafamostat mesilate, MC: morphine chloride (10 mg), CA: elcatonin 80 IU/day (im), AHPBP: pamidronate 60 mg (iv), AHBuBP: alendronate 10 mg (iv). Dotted areas indicate a normal range of serum calcium.

Clinical course in the Department of Medicine

On July 23, she was transferred to the Department of Medicine, for control of hypercalcemia and pancreatitis. The serum calcium concentration was 11.4 mg/dl, and albumin 3.6 g/dl. The corrected serum calcium concentration was 11.8 mg/dl (16). On July 30, the patient collapsed due to a syncopal attack, and became stuporous and disoriented. Under a diagnosis of metabolic encephalopathy due to hypophosphatemia (P: 0.4 mg/dl) and hypomagnesemia (Mg: 0.2 mEq/L) (17, 18), IVH was supplemented with Parental B containing phosphate (12 mmol) and Mg (4.5 mEq). The serum Mg concentration increased gradually to 1.6 mEq/L on August 9. Subsequently, the serum calcium concentration increased rapidly to 14.1 mg/dl. Severe abdominal pain developed, accompanied by ascites and pleural effusion. The serum amylase level increased

Fig. 2. CT scan of the chest. Multiple nodular lesions are present in the bilateral lung bases.

to 8,490 IU/L. Leukocytosis (23,000/mm³), hypoproteinemia (4.8 g/dl) and hypoalbuminemia (2.2 g/dl) developed (19). Abdominal CT scan revealed ascites and a pseudocyst in the enlarged pancreas (Fig. 3). The intravenous dose of nafamostat mesilate was increased to 80–120 mg. The level of amylase in the ascites was 181,575 IU/L. Following intraperitoneal administration of nafamostat mesilate (50 mg) on August 19, the ascites was markedly decreased. Calcitonin (elcatonin, 40 U twice daily, im) was administered, and this was followed by a marked decrease in the serum calcium concentration, which could have been partly due to the severe pancreatitis *per se* (20). However, escape phenomenon developed on day 6, and alendronate (10 mg) was administered iv, resulting in very effective control of the hypercalcemia (21). To ameliorate the pancreatitis induced by the hypercalcemia, alendronate (Teijin Pharmaceutical Co., Tokyo) was repeatedly administered. To assist the regression of acute pancreatitis, the patient was placed on a nothing-by-mouth regimen, and after obtaining informed consent, T₄ was added to IVH containing 1,600 kcal. To ameliorate the PTH-induced hypercalcemia, administration of magnesium was restricted to about 1 mEq/day, so that moderate hypomagnesemia persisted. The serum amylase level gradually decreased to less than 500 U/L in October, and the IVH was tapered off.

On November 2, IVH was discontinued and the patient was allowed to eat a low fat, low-calcium diet. T₄ was taken orally from October 12 at a dose of 75 µg/day, which was increased to 100 µg/day on November 3. She started muscle training again in the rehabilitation department, but complained of muscle and knee joint pain during walking. Non-steroidal anti-inflammatory drugs were prescribed, which caused abdominal pain and gastrointestinal bleeding.

To promote the rehabilitation program, a morphine chloride suppository (10 mg, Ampeck) was prescribed on November 26. A few hours after rectal insertion, the patient complained of abdominal discomfort, and the serum amylase level increased to 5,190 U/L. Oral intake was stopped and IVH was again

Fig. 3. CT scan of the abdomen. CT scan on August 22, 1993 reveals ascites and an enlarged pancreas with formation of a pseudocyst. The left kidney is hydronephrotic.

started. Although the acute pancreatitis rapidly subsided, the patient did not do well. Serum alkaline phosphatase activity, the major proportion being of bone origin, exceeded 4,500 IU/L. On March 1, she fell onto the floor, resulting in bilateral femoral fracture at the diaphysis. Anemia and metabolic acidosis worsened. Pneumonia developed and the patient died of respiratory failure on March 7. Autopsy was not performed. The total doses of pamidronate and alendronate administered during the course were 1,305 mg (23 times) and 81.25 mg (9 times), respectively.

Intravenous dose of L-thyroxine

L-thyroxine (Sigma Chemical Co., St. Louis, MO, USA) was dissolved in 0.1 N NaOH and sterilized by filtering through a millipore membrane in the pharmaceutical division of the hospital. One vial contained 50 µg T₄ in 2 ml of solution (pH 10.0). While the patient was receiving TPN, T₄ was administered from a lateral tube by bolus injection.

Measurement of serum T₃, T₄, TSH and selenium concentration

To minimize the effect of blood sampling time on thyroid hormone concentration, all samples were taken at 9–10 AM in the outpatient clinic and at 5–6 AM during the admission (22). Serum levels of T₄, free T₄ and free T₃ were determined using commercial kits (Amerlex-MT₄, Amerlex-M free T₄, Amerlex M-free T₃; Nihon-Kodak, Tokyo). T₃ and thyroglobulin were determined using RIA kits (Eiken-Kagaku, Tokyo). TSH and intact PTH were determined by immunoradiometric assays (Diagnost-TSH; Hekisuto Japan, Immuno PTH-intact; Baxter, Tokyo). Serum selenium concentration was determined by atomic absorption spectroscopy (Mitsubishi Yuka BCL, To-

Fig. 4. Correlation between serum levels of intact PTH and Mg. There was a significant correlation between plasma intact PTH concentration (pg/ml) and serum Mg concentration (mEq/L) in samples taken after surgery. $Y = 1069 X + 419.7$, $r = 0.653$, $P < 0.05$ ($n = 10$).

Fig. 5. Correlation between serum levels of TSH and thyroglobulin. There was a significant correlation between serum TSH and thyroglobulin concentration in samples taken after surgery. $Y = 6.98 X + 234.7$, $r = 0.484$, $P < 0.05$ ($n = 11$).

kyo).

Thyroid function during IVH is summarized in Table 1. There was a significant correlation between the serum levels of Mg and intact PTH after the operation (Fig. 4). Furthermore, a significant correlation was also found between the serum levels of TSH and thyroglobulin (Fig. 5).

Discussion

Since the average absorption rate of T_4 in normal subjects is approximately 80% (23, 24), the dose of T_4 for iv injection should be about 20% less than that taken by mouth (1). This was proved to be the case, at a rough estimate, in the present athyreotic patient, who was placed on TPN for more than 4 months because of relapsing acute pancreatitis following thoracic surgery.

When patients with low serum T_4 and T_3 concentrations recover from NTI, the level of TSH first increases, followed by a gradual increase in serum T_4 concentration and a subsequent increase of T_3 (25, 26). On the assumption that T_4 treatment of the euthyroid sick state of NTI patients is not beneficial, and may impair an important beneficial adaptation to illness in man (4), we started T_4 infusion at a low dose of 30 $\mu\text{g}/\text{day}$. T_4 was converted effectively to T_3 , resulting in an increased ratio of T_3/T_4 , a good predictor for survival (25). Despite steadily increasing levels of T_3 and T_4 , TSH increased transiently to 100 $\mu\text{U}/\text{ml}$, suggesting that the underlying illness was in the recovery phase (25). However, daily infusion of 30 μg T_4 for 30 days was not sufficient to maintain the patient in a euthyroid state (TSH < 4 $\mu\text{U}/\text{ml}$). Therefore, the dose of T_4 was doubled for an additional 18 days, resulting in suppression of TSH (< 0.1 $\mu\text{U}/\text{ml}$). Since 4 to 6 weeks is generally required for the daily dose of T_4 to

reach equilibration in human subjects (1), these clinical data suggest that the adequate iv dose for maintaining euthyroidism in this patient (weighing 39 kg) was more than 30 but less than 60 $\mu\text{g}/\text{day}$ during the convalescent phase.

On the assumption that the appropriate dose of T_4 was 50 μg per day and that 80% would be absorbed (23, 24), T_4 (75 μg) was given orally. However, the serum T_4 level decreased to 5.9 $\mu\text{g}/\text{dl}$, and thereafter, the dose of T_4 was increased to 100 $\mu\text{g}/\text{day}$, resulting in a slightly hyperthyroid state (T_4 9.7 $\mu\text{g}/\text{dl}$, TSH < 0.1 $\mu\text{U}/\text{ml}$). Since the serum T_4 level at this dose was very close to that while the patient was receiving an iv dose of 60 $\mu\text{g}/\text{day}$ (T_4 9.6 $\mu\text{g}/\text{dl}$, TSH < 0.1 $\mu\text{U}/\text{ml}$), we estimated that about 60% of oral T_4 was absorbed in the present patient, which is in good accordance with the estimate reported by Hays and Nielsen in patients with pancreatic diseases (23, 24).

After the second relapse of acute pancreatitis, the patient was placed on TPN again. T_4 was not employed for the first 14 days, resulting in a decrease of serum T_4 from 9.7 $\mu\text{g}/\text{dl}$ to 2.5 $\mu\text{g}/\text{dl}$, the T_4 level expected on the basis of the half-time of T_4 in serum (6–7 days). It should be stressed that such a decreased T_4 level can be frequently observed in patients with NTI, suggesting that thyroid hormone secretion is markedly decreased or its catabolism is markedly enhanced in critically ill states (4). From December 8, T_4 was infused constantly at a daily dose of 50 $\mu\text{g}/\text{day}$. Serum T_4 increased gradually to 10 $\mu\text{g}/\text{dl}$, suggesting that the patient's requirement for, or consumption of T_4 was decreasing. The T_4 dose was decreased to 30 $\mu\text{g}/\text{day}$ after the femur fracture, and discontinued at the terminal stage. At the present time, we still do not know the optimum dose of T_4 for patients in such a critically ill state.

Type I iodothyronine-5'-deiodinase, a selenocysteine-containing enzyme (28), plays a key role in converting T_4 to T_3 , and selenium deficiency is known to be responsible for low T_3 and high T_4 levels in experimental animals (28). Although the serum selenium concentration in the present patient was slightly decreased, a low T_3 state was not seen (Table 2), reflecting the fact that a period of more than one year is required before selenium deficiency occurs in human subjects (29). The serum T_3/T_4 ratio was rather increased during IVH compared to that when the patient was attending the outpatient clinic, suggesting that she was well-nourished by the IVH. Indeed, her body weight at this time was increasing (Table 1). It is well known that overfeeding and a carbohydrate-rich diet increases the T_3/T_4 ratio (30), which is due at least partly to increased secretion of insulin, a potent stimulator of iodothyronine-5'-deiodinase (31).

Table 2. Serum Selenium Concentration and Thyroid Function

	August '91	January '94	February '94
Serum T_3 (ng/dl)	170	140	182
Serum T_4 ($\mu\text{g}/\text{dl}$)	15.0	8.3	11.0
Serum rT_3 (ng/dl)	54	23	73
T_3/T_4 ratio	11.3	12.0	16.5
Serum selenium ($\mu\text{g}/\text{dl}$)	18.6	13.4	10.9

It should be pointed out that acute pancreatitis, which developed postsurgically, became exacerbated twice after the patient was transferred to the Department of Medicine: once accompanied by an increase in the serum calcium concentration after correction of hypomagnesemia, and immediately after the insertion of a morphine chloride suppository.

In subjects with normal parathyroid glands, chronic hypomagnesemia causes hypocalcemia by impairing the secretion of PTH and its action on target organs (17). After the patient developed metabolic encephalopathy due to hypomagnesemia and hypophosphatemia (17, 18), IVH was supplemented with Parenteral B containing 12 mmol P and 4.5 mEq Mg. Correction of the hypomagnesemia rapidly increased the serum calcium concentration (32), leading to acute exacerbation of necrotizing pancreatitis (Fig. 3). Although the level of plasma intact PTH was not determined at the time of hypercalcemic crisis, correction of hypomagnesemia is reported to stimulate PTH secretion (17), and in fact, a significant correlation was found between the levels of serum Mg and intact PTH after thoracotomy (Fig. 4). To impair PTH secretion, Mg was depleted again from IVH until the serum Mg level had decreased to 0.5 mEq/L. Thereafter, Mg was infused at a dose equivalent to the level excreted into urine the day before (usually <1 mEq/day). Therefore, we suggest that the following IVH regimen was most suitable for this patient with parathyroid carcinoma: glucose and amino acids, 0.5 M K₂HPO₄ (20–30 ml), 7.5% NaHCO₃ (Meiron, 60–100 ml), MgCl₂ (Magnesol, 1 mEq (1 ml), and multi-vitamins depleted of vitamin D (total volume, 3,000–3,500 ml, total calorie; 1,400 kcal content, urinary Na excretion 200–300 mEq/day). With this calcium-free IVH regimen, urinary calcium excretion was decreased to 30–60 mg/day.

Needless to say, morphine chloride is contraindicated for patients with acute pancreatitis (33). This was also the case in the recovery, even though it was administered as a suppository. Since no such warning is described in the specifications for the suppository, caution should be exercised in its use. As an analgesic in the present case, buprenorphine hydrochloride (Repetan) was most efficacious for control of pain without any adverse effect on pancreatic function.

Finally, it should be pointed out that the bisphosphonates, pamidronate and alendronate, were very effective for control of hypercalcemia in this patient for a prolonged period (21, 34, 35). There was no adverse effect during or after iv administration, and the patient was able to maintain a good quality of life for at least 3 years, with intermittent injections of pamidronate at the outpatient clinic. These agents will be widely applicable for patients with parathyroid carcinoma as well as parathyroid adenoma, which for any reason have not been completely resected. Although bone fracture occurred 7 days before death, this would have been unrelated to the prolonged administration of both bisphosphonates. The patient had been receiving IVH depleted of calcium, magnesium and vitamin D for more than 8 months (Fig. 1), and the marked increase in serum alkaline phosphatase activity of bone origin suggested osteomalacia. In addition, a decreased bone mineral content in the cortical bone

of long bones with a relatively normal BMD in the trabecular bone of the vertebrae is a salient clinical feature of primary hyperparathyroidism (36).

In summary, the appropriate iv dose of T₄ in this totally thyroidectomized patient was approximately 60% of the oral dose during the convalescent phase of acute necrotizing pancreatitis. However, the dose was decreased when the general condition deteriorated. Second, correction of hypomagnesemia increased the serum calcium concentration in patients with primary hyperparathyroidism, and may have aggravated acute pancreatitis. Therefore, IVH was supplemented with a restricted dose of magnesium to ameliorate the PTH-induced hypercalcemia. Third, a morphine chloride suppository was contraindicated in this patient with acute pancreatitis even though it was absorbed gradually. Fourth, intermittent administration of bisphosphonate (pamidronate and alendronate) was very effective for ameliorating the hypercalcemia for a prolonged period (3.5 years).

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