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Thiopental intensifies the euthyroid sick syndrome after cardiopulmonary resuscitation

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Introduction

Pharmacologic treatment of anoxic brain damage has been an important issue in the field of anesthesiology and critical care. Because thiopental strongly suppresses brain electrical activity, this drug has been used for brain protection. However, the clinical outcome after thiopental therapy for the treatment of postanoxic brain damage has not been satisfactory. Recent investigations indicate that thyroid function is involved in neurologic recovery after cardiopulmonary resuscitation. Previous investigations have demonstrated that short-term thiopental administration results in a transient decrease in serum thyroid hormone levels [1]. These data suggest that the effect of thiopental on thyroid function might adversely affect neurologic recovery after cardiopulmonary arrest, although the effect of prolonged thiopental infusion on thyroid function has not been fully analyzed. In addition, various severe illnesses, including head trauma, cause typical changes in thyroid hormone called euthyroid sick syndrome (ESS). These changes consist of decreased T3 concentration and increased reverse T3 concentration. We speculated that patients who have been resuscitated from cardiopulmonary arrest also exhibit abnormal thyroid function compatible with ESS [2,3].

In this study, we report the changes in thyroid function during continuous intravenous thiopental infusion following cardiopulmonary resuscitation.

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Patients and methods

The study protocol was approved by the Human Studies Committee of the School of Medicine, Keio University. Informed consent was obtained from the patients' families.

Five subjects who received continuous intravenous thiopental following successful cardiopulmonary resuscitation at the General Intensive Care Unit of Keio University Hospital were studied (Table 1). After they had been successfully resuscitated and cardiovascular stability had been achieved, the patients received a $5\,mg\cdot kg^{-1}$ intravenous dose of thiopental followed by a continuous infusion at the rate of $3\,mg\cdot kg^{-1}\cdot h^{-1}$ over 48 to 72 h. The duration of thiopental administration was determined by clinical status, such as convulsions. Blood samples were obtained from each patient before thiopental administration (time 1), after 24 h of intravenous thiopental (time 2), at the end of thiopental administration (time 3), and 24 h after the termination of thiopental (time 4). Serum samples were separated and stored at −20°C until assayed. They were analyzed for total thyroxine (T4), total triiodothyronine (T3), free triiodothyronine (fT3), reverse triiodothyronine (rT3), and thynoid-stimulating hormone (TSH) by radioimmunoassay (RIA). Corticotropin (ACTH) was also measured to assess pituitary function in three cases (patients 2, 3, and 4).

Routine hematologic and chemical analyses were done daily, and the data were recorded. Medications such as adrenocortical steroids and dopamine, which may influence thyroid function, were administered at the physician's discretion and also recorded.

Results

The concentrations of thyroid hormones and TSH are summarized in Table 2. T4 levels decreased to below

Table 1. Demographics and clinical characteristics of five male post-cardiopulmonary resuscitation patients who received continuous thiopental infusion

Patient No.	Age (yr)	Cause of arret	Duration of thiopental infusion (h)	Dopamine	Steroids	Prognosis
1	64	Acute myocaridal infarct, VF	48	No	Yes	Complete recovery
2	48	Intraoperative massive bleeding	72	Yes	No	Complete recovery
3	82	Foreign body aspiration	72	No	No	Persistent vegetative state
4	33	Acute epiglottitis	72	Yes	No	Persistent vegetative state
5	5	Intraoperative arrythmia (VT)	72	No	Yes	Persistent vegetative state

normal range in three patients and remained within normal limits in two patients. No specific trends were found. Total T3 decreased in two patients and remained practically unchanged in the other patients 24 h after thiopental therapy. Total T3 was then undetectable by the end of thiopental therapy in all patients. Total T3 levels then increased but remained below normal 24 h after termination of thiopental in all patients. Free T3 decreased in four of the five patients after 24-h thiopental infusion. Free T3 further decreased at the end of thiopental therapy in these patients. Reverse T3 increased after thiopental administration, and remained 2 to 10 times higher than the upper limit of normal during therapy in all the patients. Reverse T3 decreased significantly 24 h after termination of thiopental in all the patients.

TSH remained normal in three patients but decreased below normal limits in the other two patients. TSH concentration was lower after 24 h of thiopental infusion and at the termination of administration than it was at baseline.

Plasma ACTH concentration measured in three patients remained within the normal range throughout the study period (8–35 $pg \cdot ml^{-1}$ in patient 2, 5–18 $pg \cdot ml^{-1}$ in patient 3, and 11–46 $pg \cdot ml^{-1}$ in patient 4).

Administration of either dopamine or steroids appeared to have no effect on the thyroid hormone concentration in the study patients. The neurologic outcomes are also listed in Table 1. There was no clear indication of hypothyroidism in the patients during and after thiopental administration. There was no relationship between suppressed thyroid function and neurologic prognosis.

Discussion

Previous studies indicated that thiopental might influence thyroid function [4]. Thiopental inhibits iodine transport, which is necessary for thyroid hormone synthesis [5]. Thiopental also has an inhibitory effect on the hydrogen peroxide generating system necessary for thyroid hormone synthesis [6]. However, no report has described the changes in thyroid function during continuous thiopental administration. We found decreased concentrations of total and free T3 and increased rT3 concentration after 48 to 72 h of thiopental infusion. The T4 and TSH levels did not change. These profiles are compatible with the ESS.

Several studies have reported similar changes in thyroid hormone in critically ill patients [7]. Two studies investigated hormonal changes in patients with severe brain damage. Hackl et al. [8] demonstrated that mean T3 concentration decreased to $60 \pm 10\,ng \cdot dl^{-1}$ and mean rT3 concentration increased to $46.9 \pm 9.9\,ng \cdot dl^{-1}$ after acute traumatic brain injury in patients whose scores on the Glasgow Coma Scale were below 6. Masson et al. [9] reported that brain-dead patients who previously had received thiopental therapy (0.77 ± 0.11 *vs* $1.63 \pm 0.34\,ng \cdot dl^{-1}$) had significantly lower free T3 concentrations than patients who did not receive thiopental, although they did not analyze thyroid function during thiopental therapy. In this case report, the study population was quite small, and the etiology of cardiopulmonary arrest and the prognosis varied considerably. Therefore the relationship between neurologic outcome and thyroid function was quite equivocal. However, several reports indicate that significant change in thyroid function occurred when the patient became brain dead or did not survive [10,11]. We think it is reasonable to assume that the plasma concentrations of T3, T4, and rT3 change similarly regardless of the patient's neurologic function in this acute setting.

Our data showed that the changes in thyroid function during thiopental administration were even more profound. The total and free T3 concentrations remained basically unchanged during 24 h of thiopental therapy. Thereafter these parameters decreased below the normal range during the therapy. We also found that hormone concentrations returned toward normal after thiopental was terminated. Reverse T3 concentration increased after 24 h of thiopental therapy and stayed high during the therapy. We speculate that the conversion of T4 to rT3 was accelerated in the early phase of

Table 2. Serum concentrations of thyroid hormones in five post-cardiopulmonary resuscitation patients who received continuous thiopental

Patient	Total T4 (μg·dl^{-1})[a]				Total T3 (ng·dl^{-1})[b]				Free T3 (ng·dl^{-1})[c]				Reverse T3 (ng·dl^{-1})[d]				TSH (μU·ml^{-1})[e]			
No.	Time 1	Time 2	Time 3	Time 4	Time 1	Time 2	Time 3	Time 4	Time 1	Time 2	Time 3	Time 4	Time 1	Time 2	Time 3	Time 4	Time 1	Time 2	Time 3	Time 4
1	4.3	4.4	3.7	3.3	36	46	<25	27	0.9	0.8	0.8	0.7	57	106	102	76	1.49	1.1	0.76	0.64
2	2.7	3.7	3.7	5.1	<25	<25	<25	<25	1.7	0.9	<0.6	<0.6	24	295	384	300	0.83	0.21	<0.1	<0.1
3	4	3.3	3.3	4.6	43	<25	<25	31	1.5	<0.6	<0.6	1.0	75	181	118	105	1.28	0.79	0.6	0.74
4	6.3	7.4	5.7	6.1	91	81	<25	36	2.4	1.0	<0.6	<0.6	18	159	152	90	1.11	0.41	<0.1	<0.1
5	6.7	7.4	5.3	4.6	105	37	<25	38	3.1	1.5	0.8	1.4	5	199	204	41	0.79	0.22	0.38	0.27

Time 1, before thiopental administration; time 2, 24 h of thiopental; Time 3, termination of thiopental; time 4, 24 h after termination

[a] Normal value of total T4 is 4–12 μg·dl^{-1}

[b] Normal value of total T3 is 70–180 ng·dl^{-1} and sensitivity of the assay is 25 ng·dl^{-1}

[c] Normal value of free T3 is 2–6 ng·dl^{-1} and sensitivity of the assay is 0.6 ng·dl^{-1}

[d] Normal value of rT3 is 3–43 ng·dl^{-1}

[e] Normal value of TSH is 0.3–4 μU·ml^{-1} and sensitivity of the assay is 0.1 μU·ml^{-1}

thiopental administration and that thereafter an actual decrease in total and free T3 took place. Furthermore, the pituitary gland appeared to be functioning in these patients, since the TSH and ACTH concentrations remained within normal. These findings strongly suggest that thiopental affects thyroid hormone synthesis and metabolism and intensifies ESS after brain damage. The effects of adrenocortical steroids [12] or dopamine [13–15] on thyroid function are somewhat conflicting. We cannot elaborate the reason why there was no obvious relationship between thyroid hormone concentration and these medications in our study.

Previous studies suggested that three mechanisms are responsible for ESS: decreased conversion of T4 to T3, accelerated metabolism of thyroid hormone, and decreased rate of thyroid hormone synthesis. An increased concentration of tumor necrosis factor has also been reported to contribute to this syndrome [16]. Further study is warranted to clarify the exact mechanism by which thiopental influences this syndrome. ESS is regarded as an adaptive mechanism during critical illness, and there are many debates about whether hormone supplementation is beneficial [17,18]. One of the disadvantages of thiopental administration is that it frequently causes hemodynamic instability [19]. This may be the reason that it does not afford protection during cardiopulmonary resuscitation. Since thyroid hormone can significantly affect cardiac function [20], the suppressive effect of thiopental on thyroid function may contribute to circulatory disturbance. It is possible that maintaining adequate thyroid function may be beneficial for patients with severe head trauma, since suppressed thyroid function correlates significantly with disturbances of consciousness in such patients [21]. Thus, hormone supplementation may be clinically meaningful when thiopental is used after anoxic brain damage.

In conclusion, we found decreased T3 and increased rT3 concentrations during thiopental administration in five patients after cardiopulmonary arrest from various causes and resuscitation. These changes were considerably greater than those found in previous reports in which thiopental was not infused. The concentrations of these thyroid hormones returned toward the normal range after thiopental was stopped. Although we cannot delineate the exact reason for these changes, thiopental administration may contribute to the observed changes in these post-CPR patients, which are compatible with ESS.

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