Folia Medica Indonesiana Vol. 43 No. 4 October – December 2007 : 268-275

Review Article and Clinical Experience: GRAVES' DISEASE AND THYROID STORM ATD Therapy, Formulas TS – 41668, CS – 7.3.7

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ABSTRACT

Thyroid Storm (TS) or Thyroid Crisis (TC) usually develops after some specific precipitating event such as infection, sepsis, trauma, cerebrovascular accident, or radioactive iodine therapy, etc. Thyroid Crisis may present as the so called masked or apapthic thyrotoxicosis (Ghobrial et al 2002), in which case signs and symptoms of the patient may be subtle, or not previously diagnosed with thyrotoxicosis (Hughes et al 2003). The clinical picture reflexes to severely exaggerated effects of thyroid hormones (THs). Heat intolerance and diaphoresis are common in simple thyrotoxicosis but manifest as hyperpyrexia in TS. The temperature is consistently higher than 38.5°C, but frequently exceeds 40°C. Excessive sweating may be frequently exist. In addition to the thermoregulatory dysfunction, other cardinal systems, such as CNS, Gastrointestinal-Hepatic System, and Cardiovascular System are fundamentally involved. Diagnosis of TS is primarily clinical based, and no specific laboratory tests are available. However, Burch-Wartofsky Point Score (BWPS) can be used as diagnostic criteria for TS (Burch et al 1993, Tietgens et al 1995). Formula 41668 (Tjokroprawiro 2002) and the revised Formula TS 41668-24-6 (Tjokroprawiro 2005) have been routinely used in Surabaya as guidelines of specific treatment of TS and for evaluation of its therapeutic clinical outcomes. Thyroid Crisis is an acute, life-threatening emergency with extremely high mortality (90%) in USA if early diagnosis is not made and the patients is left untreated. However, with better control of tyrotoxicosis and early treatment of TS, the mortality has decreased to less than 20%. This presentation or paper is intended for residents of internal medicine, internists, candidates of endocrinologists, and associated specialists, to recognize the rational therapy of TS, the Formula TS 41668-24-6 as its practical guidelines and to know how to apply the Formula CS 737 for the rationale administration of corticosteroid treatment.

Keywords: *Thyroid Storm (TS) or Thyroid Crisis (TC), Grave's Disease, ATD Therapy, Formulas TS – 41668, CS – 7.3.7*

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INTRODUCTION

Thyroid Storm (TS) or Thyroid Crisis (TC) is a sudden, life-threatening thyrotoxicosis or those who are previously unrecognized thyrotoxicosis. The clinical features seen in uncomplicated thyrotoxicosis are generally present and often accentuated in TS, or TS is the most extreme decompensated state of thyrotoxicosis. In the past, TS commonly was observed during thyroid surgery, but today, TS occurs more commonly as a medical rather than a surgical crisis. The clinical picture relates to severely exaggerated effects of thyroid hormones (THs) can be categorized into dysfunctions of 4 cardinal systems: 1. Thermo-Regulatory System (temperature frequently exceeds 38.5°C, even higher than 40°C), 2. Central Nervous System (agitation, delirium, seizure, coma), 3. Gastrointestinal-Hepatic System (diarrhea, vomiting, abnormal pain, jaundice), 4. Cardiovascular System (tachycardia, high-output heart failure, cardiac arrhythmia, atrial fibrillation, cardiac arrest, etc). To date, 24 known precipitants of TS can be summarized in this paper. The Burch-Wartofsky-Point Score (BWPS) has been widely used in Surabaya since 2002 as a device of diagnostic criteria for TS. A score of 45 or greater is highly suggestive of TS. A score of 25-44 is suggestive of impending TS, and a score below 25 is unlikely to represent TS.

On the basis of clinical experiences, Formula TS 41668-24-6 (originally, Formula 431668 has been used since 2002) has been used as of 2005 as specific practical guideline in the treatment of TS and as its therapeutic

clinical outcomes. The Formula TS 41668-24-6 can be shortly described below. "4" means: 400 mg loading dose of PTU, with maintenance dose: 100-200 mg PTU 4 hourly. Alternatively, methimazole: 40 mg as a loading dose can be given, with maintenance dose 10 mg 4 hourly. "1" means: PTU should be administered at least 1 hour before giving iodine to establish blockade of hormone synthesis via the Wolft – Chaikoff effect. The first "6" means: 6 drops of Lugol's solution or SSKI 6 hourly to inhibit TH release from thyroid gland and should be evaluated after 6 days. The second "6" means: administration 10-40 mg propanolol (for sympathetic blockade) 6 hourly to decrease heart rate, myocardial contractility, blood pressure, and myocardial oxygen demand. Reevaluation of propanolol administration should be done after 6 days. The general supportive therapy should be well included in the specific measures, while this Formula is being performed. "8" means: 100-200 mg I.V. hydrocortisone hemisuccinate or 2 mg I.V. dexamethasone or 25 mg i.v. methylprednisolon 8 hourly to block the conversion of T4 to T3. Formula CS 737 can be used as a rule for the administration of corticosteroid (CS). Stress doses are required to replace accelerated production and degradation of cortisol induced by TH. "24" means: with adequate thyroid-suppressive therapy and sympathetic blockade, clinical improvement should occur within 24 hours. The last "6" means: adequate therapy should resolve the TS within 6 days.

Thyroid Storm or Thyroid Crisis is a sudden, life-threatening exacerbation of thyrotoxicosis (mostly), however, it may happen in patients who are not previously diagnosed with thyrotoxicosis. Diagnostic criteria for thyroid storm by using Burch-Wartofsky-Point Score (BWPS) are feasible in daily clinical practice. Formula TS 41668-24-6 can be used as a practical guideline of specific measures of thyroid storm and evaluation of its therapeutic clinical outcomes. To prevent the occurrence of adrenal gland dysfunction, Formula CS 737 may be used as a "rule" in the administration of corticosteroid.

ANTI THYROID DRUGS

Thyrotoxicosis denotes the clinical, physiological, and biochemical findings that results when the tissue are exposed to excess thyroid hormone (TH). The term hyperthyroidism should be used to denote only those conditions in which hyperfunction of the thyroid lead to thyrotoxicosis. Graves' disease is a complex autoimmune disorders characterized by hyperthyroidism, a particular opthalmopathy, and prefibial myxedema. Prophylthiouracil (PTU) and methimazole are the antithyroid drugs (ATDs) frequently used in the US and in Indonesia (carbimazole, a methimazole analogue, is used in the UK and also Indonesia). Their multiple effects include inhibition of TH synthesis (by interfering with thyroid peroxidase-mediated iodination of tyrosine residues in thyroglobulin (Tg), an important step in the synthesis of thyroxine and triiodothyronine), and a reduction in both intra thyroidal immune dysregulation, and (in the case of PTU, but not methimazole or carbimazole) the peripheral conversion of T4 to T3.

Nine (9) mechanisms of action of ATDs can be summarized as follows: decreased anti TSH-receptor antibodies, decrease ICAM-1 receptor, lowered IL-2 receptor, lowered IL-6 receptor, induced thyroid apoptosis of lymphocytes, decreased HLA-Class II expression, increased number of T-suppressor, decreased NK Cells, and decreased T Helper. Clinical use of ATDs, in general, can be devided into 2 ways: as the primary treatment for hyperthyroidism or as preprarative therapy before radiotherapy or surgery. However, ATDs are most often used as the primary treatment for patients with Graves' disease. "Remission" is usually defined as remaining biochemically euthyroid for one year after cessation of drug treatment. Nine (9) possible predictors for remission are degree of hyperthyroidism, goiter size, T3/T4 ratio in the serum (high ratio > 20: less likely for remission), Graves' Opthalmopathy, history of cigarette smoking, duration of symptoms before diagnosis, levels of anti TSH receptor antibodies, age, and sex.

Once a patients has been started on an ATD, follow up testing of thyroid function every 4 to 6 weeks is recommended, at least until thyroid function is stable or the patients become euthyroid. After 4 to 12 weeks, most patients have achieved normal thyroid function, and the drug dose can be decreased while maintaining normal thyroid function. Many patients can be ultimately controlled with a relatively low dose, for example, 5mg to 10 mg of methimazole or 100mg to 200mg PTU daily. Note: hypothyroidism or goiter can develop if the dose is not decreased appropriately. After the first 3 to 6 months, follow up intervals can be increased to every 2 to 3 months, and then every 4 to 6 months. Serum thyrothropin levels remain suppressed for weeks or even months, despite a normalization of thyroid hormone levels, so a test of thyrotropin levels is a poor early measure. Furthermore, patients sometimes continue to have elevated serum T3 levels despite normal or even low T4 or FT4 levels, indicating the need to increase, not decrease, the ATD dose. If ATDs have immune suppressive effects, a higher dose or longer treatment duration might enhance the chances of remission.

Data from prospective trials with up to 4 years of follow up do not indicate that treatment for longer than one (1) year has any effect on relapse rate. In general, treatment with ATDs for 12 to 18 months is the usual practice, as recommended in a recent systemic, evidence-based review. With the exception of children and adolescent, who are often treated with ATDs for many years, ATDs are usually stopped or tapered after 12 to 18 months of therapy. Relapse increased in patients with normal serum levels of FT4 and FT3, but suppressed serum thyrothropin levels. If radioiodine therapy is selected after a relapse, the outcome may be influenced by the prior use of ATDs. When used to normalized thyroid function before radioiodine therapy, PTU, but not methimazole, increases the failure rate of the radioactive iodine. These "radioprotective" effects of PTU may be related to its ability to neutralize iodinated free radicals produced by radiation exposer, a property evidently not shared by methimazole. Side effects of methimazole are dose-related, whereas those of PTU are less clearly related to dose. Minor side effects of ATDs include cutaneous reactions (urticria or macular rashes), arthalgia and gastrointestinal upset occurred in approximately 5% of patients. The development of arthralgias, while classified as a "minor reactions" should prompt drug discontinuation, since this symptom may be a harbinger of a severe transient migratory polyarthritis known as "the anti thyroid arthritis syndrome".

Agranulocytosis an absolute granulocyte count of less than 500 per mm3 occurred in 0.37% for PTU, and in 0.35% for methimazole. Agranulocytosis could be distinguished from the transient, mild granulocytopenia (a granulocyte count of less than 1500 per mm3) that occasionally occurs in patients with Graves' disease. Most cases of agranulocytosis occur within the first 90 days of treatment, but may happen even a year or more after starting therapy. The risk of agranulocytosis is greater in older patients and that they have a higher rate of death. Agranulocytosis is thought to be autoimmune mediated, and antigranulocyte antibodies are shown by immunoflourescence and cytotoxicity assays. Antineutrophil cytoplasmic antibodies (ANCAs) may play a role, since antigen target (e.g., proteinase 3) may be expressed on the neutrophil surface. Fever and sore throat are the most common presenting symptoms of agranulocytosis, and sepsis should be suspected if there is very rapid onset of fever, chills and prostration. In such cases, ATDs should be immediately discontinued and the patient should be hospitalized. Pseudomonas aeroginosa was the specific most commonly isolated from the blood in agranulocytosis associated sepsis. The intravenous appropriate antibiotic for pseudomonas infection should be administered. The G-CFS injection may shorten the time to recovery and length of hospitalization in patients with agronulocytosis due to ATDs. Most authorities recommend using G-CSF for agronulocytosis due to ATDs.

Hepatotoxicity (ATD-induced hepatic side effect) is another major side effect of ATDs (0.1 to 0.2%) and the estimation may be difficult, since in up to 30% of patients with normal aminotransferase levels who are treated with PTU, transient acute increases in those levels develop, ranging to 1.1 to 6 times the upper limit of normal levels that may resolve while therapy is continued. PTU-related hepatotoxicity takes the form of an allergic hepatitis accompanied by laboratory evidence of hepatocellular injury, often markedly elevated aminotransferase levels and submassive or massive hepatic necrosis on biopsy. Therapy consists of immediate cessation of PTU along with expectant management of the potential complications of hepatic failure. The rare hepatic abnormalities associated with methimazole and carbimazole are typical of a cholestatic process. Biopsy specimens show preserved hepatocellular architecture, along with intracanalicular cholestasis and mild periportal inflammation. Complete, but slow, recovery is the rule after drug discontinuation.

Vasculitis is the 3rd major toxic reaction seen with ATD treatment, more commonly found in connection with PTU than with methimazole. Serologic evidence consistent with LE develops in some patients, fulfilling the criteria for drug-induced lupus (ATD-induced lupus). ATD-induced ANCA-positive vasulitis has also been reported, especially in Asian patients treated with PTU. It has been hypothesized ATDs, especially PTU, can react with myeloperoxidase to form reactive intermediates that promote autoimmune inflammation. ATD-induced ANCA positive vasculitis syndrome includes acute renal dysfunction, arthritis, skin ulceration, vasculitic rash, and upper and lower respiratory symptoms (sinusitis and hemoptysis). Although this syndrome generally resolves after drug discontinuation, high-dose glucocorticoid therapy or cyclophospamide may be needed in severe cases, and some patients have required short-term hemodialysis.

Antithyroid drugs during pregnancy should be started at the time of diagnosis, since thyrotoxicosis itself presents a risk to the mother and fetoes. PTU has been preferred in North America because it was reputed to cross the placenta minimally as compared with methimazole; however, recent studies suggest that PTU does, in fact, cross the placenta and clinical data do not show any differences in the thyroid function at birth between fetuses exposed to PTU as compared with those exposed to methimazole. However, in North America, PTU remains the treatment of choice during pregnancy, because congenital anomalies have been reported with

methimazole, particularly aplasia cutis, usually described as single or multiple lesion of 0.5 to 3 cm at the vertex or occipital area of the scalp. The use of methimazole is also associated with a very rare teratogenic syndrome termed "methimazole embryopathy". In contrast, however, another study found no increased in the frequentcy of conginetal abnormalities, including aplasia cutis, among 243 infants who were exposed to methimazole in utero; however, only external anomalities were reported. The FDA has categorized both PTU and methimazole as class D agents (i.e, drugs with strong evidence of risk to the fetus) because of potential for fetal hypothyroidism. Hence, the dose of ATDs should be minimized to prevent fetal hypothyroidism. If the maternal FT4 is maintained at or slightly above the upper limit of normal, the risk of fetal hypothyroidism is negligible. Even if fetal thyroid effects do occur, they are likely to be mild, and follow-up studies of children exposed in utero have not shown developmental or intellectual impairment. By the 3rd trimester, approximately 30% of women can discontinue ATD therapy altogether and still remain euthyroid. For mothers during lactation, both ATDs (PTU and methimazole) are considerable safe (in 2001, both drugs are approved for nursing mothers by the American Academy for Pediatrics). Both appear in breast milk but in low concentrations. Clinical studies of breast-fed infants have shown normal thyroid function and normal subsequent intellectual development in exposed infants.

PATHOGENESIS OF THYROID STORM OR THYROID CRISIS

The following hypotheses or theories of the pathogenesis of thyroid storm (TS) have been proposed (Tietgens et al 1995, Singhal 2003). First, the rapidity with which the hormone levels rise may be more important than the absolute levels in determining the clinical presentation. One mechanism for a sudden change in hormone levels would be a change in the levels of the binding protein (Colebunders et al 1984). A drop in binding proteins, which might occur postoperatively, might cause a sudden rise in free hormone levels. A rapid rise in TH levels also may occur when the gland in manipulated during surgery or by vigorous palpation during physical examination. This has been noted to occur postoperatively and in patients with systemic nonthyroidal illness. The production of thyroid hormone-binding inhibitor(s), which has been demonstrated in the sera from several patients with nonthyroidal systemic illnesses, could decrease the binding affinity of thyroid hormones and increase free hormone levels. Hughes et al (2003) reported thyroid crisis, a 55-year-old woman, following a tibial fracture, who was not previously diagnosed with hyperthyroidism, experienced a cardiac arrest secondary to thyroid crisis. Second, adrenergic receptor activation is another hypothesis. In this theory, sympathetic nerves innervate the thyroid gland, and catecholamines can stimulate TH synthesis. This increased TH then increases the density of beta-adrenergic receptors, thereby enhancing the effect of catecholamines. This hypothesis is supported by the dramatic response of TS to beta blockers and the occurrence of TS after accidental ingestion of adrenergic drugs such as pseudoephedrine. Third, the last proposed theories include: tissue tolerance to THs; presence of a unique catecholamine like substance in thyrotoxicosis; a direct sympathomimetic effect of TH as a result of its structural similarity to catecholamines. Mostly, FT3 and FT 4 correlate poorly with severity of clinical manifestation: condition is essentially an inability of end-organs to modulate their response to excess thyroid hormone.

LABORATORY STUDIES

Never forget that the diagnosis for thyroid crisis is clinically based; no laboratory tests are diagnostic. If the patient's clinical picture is consistent with thyroid crisis, never delay treatment to await laboratory confirmation of thyrotoxicosis. As to thyroid studies, the result of thyroid studies usually are consistent with hyperthyroidism and are useful only if the patient has not been diagnosed previously. Test results may not come back quickly and usually are unhelpful for immediate management. Usually findings include elevated triiodothyronine (T3) and thyroxine (T4), elevated free T4, increased T3 resin uptake, suppressed TSH, and an elevated 24-hour iodine uptake. TSH is not suppressed if the etiology is excess TSH secretion. CBC reveals mild leukocytosis, with a shift to the left. Liver function tests commonly show nonspecific abnormalities such as elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), creatin kinase, alkaline phosphatase, and serum bilirubin (jaundice may be present). Blood gases, electrolytes, and urinalysis testing may be performed to assess and monitor short-term management.

KNOWN PRECIPITANTS OF THYROID STORM OR THYROID CRISIS

In most cases of Thyroid Storm (TS) or Thyroid Crisis (TC), precipitating events (precipitants) can be identified. Known precipitants of TS (Burch et al 1993, Tietgens et al 1995, Hall et al 1999, Turner et al 2003,

Greenspan et al 2004) can be summarized as seen in Table 1. In thyroid crisis, the fever and tachycardia tend to be out of proportion to the illness.

TABLE – 1 (24) Known Precipitants of Thyroid Storm

Burch et al 1993, Tietgens et al 1995, Hall et al 1999, Turner et al 2003, Greenspan et al 2004
(Summarized : Tjokroprawiro 2002 - 2006)

1 Infection	14 Hypoglycemia
2 Thyroid Surgery	15 Sympathomimetic Drugs : Pseudoephedrine, Amiodarone, etc
3 Non-Thyroid Surgery	16 "Healthy Food" Preparation Containing Sea weed or Kelp
4 Iodinated Contrast Dyes	17 Congestive Heart Failure
5 Withdrawal of Antithyroid Drug Therapy	18 Toxemia of Pregnancy
6 Radioiodine Therapy	19 Bowel Infarction
7 Diabetic Ketoacidosis	20 Tooth Extraction
8 Parturition	21 TH Ingestion
9 Severe Emotional Stress	22 Burn Injury
10 Pulmonary Embolism	23 Sepsis
11 Cerebral Vascular Accident	24 Childbirth
12 Trauma : Fracture, etc.	
13 Vigorous Thyroid Palpation	

No 1 - 13 are Known Precipitants presented by Burch and Wartofsky-1993

EFFECT OF PREGNANCY ON THYROID FUNCTION

Due to the involvement of parturition, toxemia of pregnancy, and childbirth in the Table 1, the effect of pregnancy on thyroid function should be recognized (Turner et al 2003, Summarized: Tjokroprawiro 2005). Thyroid Stimulating Hormone (TSH) is within normal limit in pregnancy. However, it is suppressed in 13.5% in 1st trimester, 4.5% in 2nd trimester and 1.2% in 3rd trimester due to hCG thyrotropic effect. Positive correlation between FT4 and hCG levels and negative correlation between TSH and hCG levels in first half of pregnancy. Thyrotropin Releasing Hormone (TRH) is also normal. Iodide stores decreases due to increased renal clearance and transplacental transfer to foetus. Thyroid size increases in thyroid volume by 10-20% due to hCG stimulation and relative iodide deficiency. Thyroglobulin also increases corresponding to the rise in thyroid size. Thyroid Binding Globulin (TBG) has twofold increase in concentration as a result of reduced hepatic clearance and increased synthesis stimulated by estrogen. Concentration plateaus at 20 weeks of gestation, and falls again post partially. Total T4 and T3 have increased concentrations, corresponding to rise in TBG, while free T4 and T3 have small rise in concentration in the first trimester due to hCG stimulation then fall into normal range.

AMIODARONE AND THYROID FUNCTION

Amiodarone is also listed in the TABLE-1, hence, the effects of this drug are shortly low (Greenspan et al 2004, Summarized: 2005). Amiodarone contains 39% iodine by weight. On a dose of amiodarone between 200-600 mg daily, 7-21 mg iodine is made available each day (the optimal daily iodine intake is 150-200 µg). Amiodarone is distributed in several tissues from where it is slowly released. Importantly, the terminal elimination half-life of amiodarone averaged 52.6 days with a standard deviation 23.7 days. Abnormalities of thyroid function occur in up to 50% of patients. In the UK and USA, 2% of patients develop thyrotoxicosis (AIT = amiodarone-induced thyrotoxicosis) and about 13% develop hypothyroidism (AIH = amiodarone-induced hypothyroidism). However, AIT occurs more frequently in regions with low iodine intake. AIT may present several months after discontinuing the drug (long half-life); AIH is commoner in women and in patients with thyroid auto antibodies. Thyroid function tests should be monitored every 6 months in amiodarone treated patients. The high iodine content of amiodarone may inhibit TH synthesis and release of TH causing AIH, or loading to iodine-induced thyrotoxicosis. Thyrotoxicosis resulting from iodine excess (induced TH synthesis) is referred to as AIT Type-I, whereas thyrotoxicosis due to a direct toxic effects of amiodarone is referred as to AIT Type-II (Table 2).

Drug induced destructive thyroiditis results in leakage of thyroid hormones from damaged follicles into the circulation, and like subacute thyroiditis can be followed by a transient hypothyroid state before euthyroidism is restored.

Table 2. Characteristics of Amiodarone induced Thyrotoxicosis

	AIT Type-I	AIT Type-II
Aetiology	Iodine toxicity	Thyroiditis
Signs of clinical thyroid disease	Yes	No
Goiter	Frequent	Infrequent
Thyroid antibodies	Positive	Negative
Radioiodine uptake	Normal	Decreased
Thyroglobulin	Normal or slightly elevated	Very elevated
Serum IL-6	Normal	Very elevated
Late hypothyroidism	No	Possible
Vascularity (Doppler)	Increased / Normal	Reduced

The management of Amiodarone-induced Thyrotoxicosis is briefly described as follows (Greenspan et al 2004, Summarized: 2005). Amiodarone should be stopped and ß-blocker therapy should be instituted if possible. The following therapies are administered: antithyroid drugs: Tapazole, 40 – 60 mg/dl, potassium perchlorate, 200 mg every 6 hours, cholestyramine or Colestipol, 20 – 30 g/d, prednisone, 40 mg/d, for acute thyroiditis (IL-6 levels should be monitored), and thyroidectomy.

DIAGNOSTIC CRITERIA FOR THYROID STORM

The diagnosis of thyroid storm (TS) or thyroid crisis (TC) is clinically based, and there is no one specific set of diagnostic criteria that can be used reliably to make the diagnosis in all patients. Burch and Wartofsky (1993) have devised a diagnostic point scale (Burch-Wartofsky Point Score = BWPS) to distinguish uncomplicated thyrotoxicosis, impending TS, and established TS on a semi quantitative basis (TABLE 3). There are no laboratory criteria to diagnose TS, although patients have findings consistent with thyrotoxicosis. As seen in Table 3, in patients with severe thyrotoxicosis, points are assigned to the highest weighted description applicable in each category and scores totaled.

When it is not possible to distinguish the effects of an intercurrent illness from those of the severe thyrotoxicosis per se, points are awarded such as to favor the diagnosis of storm and hence empiric therapy. A score of 45 or greater is highly suggestive of thyroid crisis, a score of 25-44 is suggestive of impending storm, and a score below 25 is unlikely to represent thyroid crisis. In thyroid crisis: fever and tachycardia tend to be the two most important points in BW Score.

MANAGEMENT OF THYROID STORM

The management of thyroid crisis (TS) can be classified into Supportive Care and Specific Measures (Burch et al 1993, Tietgens et al 1995, Tjokroprawiro 2002, 2005, Belchet et al 2003, Hughes et al 2003, Singhal et al 2003, Turner et al 2003, Greenspan et al 2004)

SUPPORTIVE CARE OF THYROID STORM

The general supportive therapy may include: NG-tube, which is essentially needed for oral medicines; fluid balance, glucose infusion for nutrition; oxygen; cardio respiratory status; cooling blanket; acetaminophen (Avoid Aspirin: since this drug will displace T4 from TBG, resulting in an increase in FT4 serum levels. Chlorpromazine (50-100 mg I.M) can be used to treat agitation and because of its effect in inhibiting central thermoregulation, hence it may be useful in treating the hyperpyrexia; phenobarbital, which may be a useful sedative since it stimulates T4 metabolism via the hepatic microsomal enzyme system; and multivitamin.

SPECIFIC MEASURES OF THYROID STORM

On the basis of clinical experiences, Formula TS 41668-24-6 or TC 41668-24-6 (Tjokroprawiro 2005) has been routinely used in Surabaya, and the essential drugs should be given in a sequent number of such a Formula as follows: The Formula TS or TC 41668-24-6 (Tjokroprawiro 2005), the revision of the previous Formula 41668 (Tjokroprawiro 2002) is a practical guideline of the specific measures of TS and can be used to reach the desired clinical outcomes. The description of this Formula is as follows: "4" means: 400 mg loading dose of PTU, with maintenance of PTU 100-200 mg 4 hourly. PTU is given to inhibit synthesis of TH by preventing organification and trapping of iodide to iodine and by inhibiting coupling of iodotyrosines; also inhibits peripheral conversion of T4 to T3, an important component of management. Methimazole: inhibits synthesis of TH by preventing organification of iodide to iodine and coupling of iodotyrosines. Although at least 10 times more potent than PTU on a weight basis, it does not inhibit peripheral conversion of T4 to T3. Initial dose of methimazole: 40 mg per oral, with maintenance dose: 10 mg every 4 hours. "1" means: minimally 1 hour after initiation of PTU, iodides may be started.

Table 3. Diagnostic Criteria for Thyroid Storm or Thyroid Crisis
(Burch and Wartofsky, 1993, Summarized: Tjokroprawiro 2005)

Thermoregulatory Dysfunction		Cardiovascular Dysfunction	
Temperature		1). Tachycardia	
37.2-37.7 ˚C	5	99-109	5
37.8-38.3 ˚C	10	110-119	10
38.4-38.8 ˚C	15	120-129	15
38.9-39.4 ˚C	20	130-139	20
39.5-39.9 ˚C	25	≥140	25
≥ 40 ˚C	30	2). Congestive Heart failure	
Central Nervous System Effects		* Absent	0
* Absent	0	* Mild	5
* Mild	10	- Pedal edema	
- Agitation		* Moderate	10
* Moderate	20	- Bibasilar rales	
- Delirium		* Severe	15
- Psychosis		- Pulmonary edema	
- Extreme lethargy		3). Atrial fibrillation	
* Severe	30	* Absent	0
- Seizure		* Present	10
- Coma			
Gastrointestinal-Hepatic Dysfunction		Precipitant History	
* Absent	0	* Negative	0
* Moderate	10	* Positive	10
- Diarrhea			
- Nausea/vomiting			
- Abdominal pain			
* Severe	20		
- Unexplained jaundice			

A score of 45 or greater is highly suggestive of thyroid crisis
A score of 25-44 is suggestive of impending thyroid crisis
A score below 25 is unlikely to represent thyroid crisis

The first "6" means: 6 drops 6 hourly of Lugol's solution or SSKI can be started 1 hour after PTU, and should be evaluated after 6 days. High concentrations of iodides will inhibit the synthesis of thyroid hormone (Wolff-Chaikoff effect) and also the release of TH from the thyroid gland. Lithium carbonate also can be used if patients are hypersensitive to iodine. The second "6" means: every 6 hours, 10-40 mg propanolol orally should be given to decrease heart rate, myocardial contractility, blood pressure, and myocardial oxygen demand. Reevaluation should be done after 6 day administration of propanolol, or 0.5 -1 mg intravenously every 3 hours, monitoring its effects of cardiac rate. Beta blocker is mainstay therapy to control autonomic effects of TH. It also blocks peripheral conversion of T4 to T3. Esmolol, a short-acting selective beta 1-antagonist, has been used successfully in children, as has labetalol in adults. Propanolol is often the only adjunctive drug necessary to control thyroid crisis. "8" means: 100-200 mg intravenous injection of hydrocortisone hemisuccinate, or 2mg intravenous injection of dexamethasone every 8 hours to block the conversion of T4 to T3. Use of steroids has been associated with improved survival. Stress doses are required to replace accelerated production and degradation of cortisol induced by TH. If steroids are not administered, acute glucocorticoid deficiency theoretically might occur because demand may outpace production. Steroid may suppress immune function, but benefit outweighs risk in serious conditions such as thyroid crisis. "24" means: with such a regimen, clinical improvement should be achieved within 24 hours.
The last "6" means: adequate therapy with such a regimen should resolve the crisis within 6 days. The precipitant of the thyroid storm is often the cause of death.

If indicated, cholestyramine or colestipol can be given 20-30 g/day (Greenspan et al 2004). Initially, for life saving, the timing of corticosteroid (CS) injection can be done "out of rule" (anytime, but with fixed 8 hour interval). For further administrations of corticosteroid

(CS), and to avoid the occurrence of to the adrenal gland dysfunction, then follow the Formula CS 737. It means: the first injection of CS is administered at 07.00 a.m., the second at 13.00 (01.00 p.m.) and the third injection is done at 17.00 (05.00 p.m.). Rapid dosage reduction should be done as the clinical situation improves. The tapering-off regimen of CS administration: the third injection (17.00) should be firstly omitted, and then followed by the second one (13.00), and finally the omission of the first injection (07.00).

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