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Certain Clinical Features and Treatments May Be Associated with Increased Mortality in Thyroid Storm

Stephen W. Spaulding

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SUMMARY

Background

This group previously reported 38 fatalities in 356 patients with "definite" or "suspected" thyroid storm in a Japan-wide consortium of hospitals between 2004 and 2008. Mortality was increased 10-fold if multiple organ failure was present and was increased 4-fold if shock or disseminated intravascular coagulopathy were present (previously reviewed in this journal, 1). Many of these cases occurred when intercurrent illnesses developed in non-compliant or untreated patients, but some cases occurred rather suddenly, even in apparently euthyroid patients. (Note that patients with thyroid storm who are seen in Japan may be slightly different from patients in parts of the world where dietary iodine intake is lower and toxic nodular goiter is more common). The authors now present analyses of this retrospectively collected data that indicate that certain clinical and therapeutic factors were associated with increased mortality rates.

Methods

The correlation of mortality with clinical and laboratory parameters, including disease severity scores (Acute Physiology and Chronic Health Evaluation [APACHE II]) plus Sequential Organ Failure Assessment [SOFA]), was assessed using Fisher's exact test and Wilcoxon and Kruskal–Wallis tests, as well as Spearman's rank correlation coefficient. To assess independence between associated factors, some clinical data were first converted to a more normal distribution using Box–Cox power transformations, followed by logistic-regression analysis or stepwise multiple regression analysis.

Results

Severity of disease (based on APACHE II and SOFA scores) was significantly correlated with mortality ($P<0.0003$ by Spearman's rank correlation. On the other hand, free T_3 and the ratio of free T_3 to free T_4 were correlated with disease severity but did not correlate with mortality. The mortality rate in the 248 patients in whom a precipitating factor had been identified did not differ from the rate in the 108 without a known precipitating factor. Similarly, mortality in the 89 patients with infections was the same as in the remainder of patients.

Antipyretics were used in 96 patients (the majority took acetaminophen), and their use was associated with higher body temperatures but not with mortality, disease severity, or thyroid hormone levels.

There was no difference in mortality between the 323 who had been given antithyroid drugs and the 33 who were not, nor did the two groups differ in disease severity or in free T_3, free T_4, or free T_3/free T_4. There also was no difference between the 276 given MMI

alone and the 45 given PTU alone. However, mortality and disease severity were significantly higher in the 41 patients given MMI intravenously rather than orally (n = 47 vs. 231; 21.2% vs. 7.8%; P<0.05 by Fisher's exact test).

Glucocorticoid use (216 vs. 140) was significantly associated both with mortality and disease severity. Although stepwise multivariate analysis confirmed that mortality was associated with disease severity, it did not find glucocorticoid use to be an independent factor. Glucocorticoid use was associated with KI use, but not with antithyroid drug use.

KI was given to 296 patients with thyroid storm (range of doses, 10 mg to 2 g; median, 0.1 g), whose disease severity was higher than in the 59 not given KI, but mortality did not differ between the two groups. Stepwise analysis indicated that administration of KI was associated with the free T_3 and free T_4 levels, but they were not associated with the dose of KI.

A nonselective beta1-adrenergic antagonist (propranolol or carteolol) was given to 190 patients, a selective beta1-adrenergic antagonist (atenolol, bisoprolol, betaxolol, metoprolol, or landiolol) to 66, both a selective and a nonselective drug to 3, and an alpha/beta-adrenergic antagonist (carvedilol or arotinolol) to 18, whereas the type of antagonist was not identified in 9, and it was not known whether any beta-adrenergic agents were used in 19. No beta-adrenergic antagonists were given to 51 patients. The overall use of a beta1-adrenergic antagonist was not associated with greater disease severity or mortality, but stepwise multivariate analysis indicated that those given a nonselective adrenergic antagonist alone or in combination with a beta1-selective agent had higher mortality than those given only a selective beta1-selective adrenergic antagonist. In 28 of the 193 patients given a nonspecific beta-blocker, the mortality rate was significantly higher (14.5%) than in the 4 of 93 (4.3%) treated with "other" beta1-adrenergic antagonists (66 were given beta1-specific blockers, 18 alpha/beta-blockers; in 9, the type was unknown; P<0.006 by a one-tailed Fisher's exact test). There was no significant difference in free T_3, free T_4 or free T_3/free T_4 between the group given beta1-specific agents versus the group given nonspecific agents.

Of the 181 patients receiving antithyroid drugs plus KI plus glucocorticoids, the mortality rate was 13.3%, whereas of the 94 patients who received only antithyroid drugs and KI, the mortality was 5.3%, although no statistical analysis of the difference was provided in the text.

Probably the most curious finding was that 8 patients did not receive any antithyroid drugs. The patients' thyroid status was not appreciated until their critical conditions had been managed: the diagnosis of storm was established retrospectively, based on thyroid-function tests and clinical symptoms. Unfortunately, no follow-up information concerning subsequent endocrine evaluation or antithyroid treatment was provided, but only 1 fatality was reported in those 8 patients, a rate of 13.3%, which is not different from the 12.5% mortality rate in the remaining 348 patients.Presumably these patients had Graves' disease, but no followup information concerning subsequent endocrine evaluation or anti-thyroid treatment was provided.

Unfortunately, the three supplementary figures and eight supplementary tables were not made available, despite repeated requests.

Conclusions

Mortality was higher in patients with more severe disease, but was the same whether patients were treated with MMI or PTU. Treatment with KI was associated with disease severity but not with mortality. No differences in mortality were found with use of KI, glucocorticoids, or beta-adrenergic antagonists. However, mortality was higher in patients given a nonselective beta-adrenergic antagonist than in those given a selective beta1-adrenergic antagonist.

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ANALYSIS AND COMMENTARY

It will be important to identify clinical or laboratory features that improve the accuracy of the diagnosis and/or prognosis in cases of possible thyroid storm. Unfortunately, the rarity and the protean manifestations of thyroid storm make it necessary to lump together patients with very disparate clinical findings. In the future, tissue-specific markers of thyrotoxicity might provide useful information, in view of the tissue-specific differences in thyroid hormone receptor levels and myriad interacting factors, hormone transporters, and downstream pathways they regulate. Furthermore, it is difficult to decide which patients to include in such studies. For example, in the current study, a "precipitating factor" was identified in 248 of the patients, but it is not clear how many additional patients with hyperthyroidism were excluded because an underlying disease appeared to be responsible for fever, impaired consciousness, heart failure, or liver failure — despite the fact that such preexisting conditions can trigger thyroid storm (1). Patients with more severe disease are likely to get more intensive therapy and also are more likely to die, but finding an association between a therapy and mortality does not necessarily indicate that the therapy caused the mortality. Thus, patients given intravenous MMI (not available in the United States) did have a higher SOFA score and a higher free T_4 level, but those patients might have been more likely to die whether or not MMI was given intravenously.

Hyperthyroid patients commonly display increased heart rate, myocardial contractility, and diastolic relaxation, presumably reflecting changes in myocardial proteins involved in contraction and electrochemical signaling, which respond — directly or indirectly — to T_3. Patients with thyroid storm often have more severe cardiovascular disorders. In this study, symptoms of congestive heart failure were found in about 50% of the patients and atrial fibrillation in about 40%. Large doses of propranolol can reduce circulating T_3 levels, although this is not an antiadrenergic effect. Furthermore, patients given a nonspecific beta-blocker did not have significantly lower free T_3, free T_4, or free T_3/free T_4. The metabolism of propranolol is unpredictable, being affected by at least three cytochrome P-450 enzymes, and also by a variable first-pass effect in the liver, so a case could be made for using more specific intravenous beta1-adrenergic antagonists that have predictably short half-lives. However, the apparent decrease in mortality in patients receiving a beta1-specific adrenergic antagonist is problematic because, rather than entirely excluding the 9 patients whose beta-blocker was not known, they were included as part of the group of 93 given a selective beta1- or an alpha/beta-adrenergic antagonist. Furthermore, even beta1-specific short-acting antagonists have occasionally been reported to exacerbate some clinical features of patients with thyroid storm.

Patients with a critical illness often have a low circulating T_3 level, a factor that might have contributed to the 2% of patients with thyroid storm who had a normal free T_3 level (but who had a high free T_4 and a suppressed TSH level). At any rate, this study did not find that mortality was associated with free T_4, free T_3, or T_3/free T_4, although the latter two levels were negatively associated with disease severity.

Use of KI was associated with higher disease severity, free T_3, and free T_4 levels, but not with increased mortality. Thus, perhaps administration of KI may have had some benefit, because even if it did not actually reduce mortality, these were the sicker patients. The statistical basis for stating that combining antithyroid drugs, KI, glucocorticoids, and selective beta1-adrenergic receptor blockers may improve outcomes in severe thyroid storm is not clear, although it would seem reasonable.

The 8 patients with unappreciated and untreated thyroid storm do raise an interesting question. Can the sudden development of a severe disease in a patient with a previously unknown predisposition for

hyperthyroidism cause thyroid storm out of the blue? When their concomitant disorders were treated, most of these patients apparently became clinically euthyroid without any antithyroid treatment. It would be interesting to know whether any of the 7 untreated survivors subsequently had anti-thyrotropin receptor antibody levels determined, or eventually underwent antithyroid treatment.

Reference

1. Spaulding SW. A large nationwide survey of patients hospitalized with thyroid storm has been used to develop a different approach to characterizing the disease. Clin Thyroidol 2012; 24(6):5-7.