Methimazole-induced agranulocytosis in patients with Graves' disease is more likely with a daily dose of 30 mg than with 15 mg

Takata K, Kubota S, Fukata S, Kudo T, Nishihara E, Ito M, Amino N, Miyauchi A. Methimazole-induced agranulocytosis in patients with Graves' disease is more frequent with an initial dose of 30 mg daily than with 15 mg daily. Thyroid 2009;19:559-63.

SUMMARY

BACKGROUND One of the most serious side effects of antithyroid drugs (ATDs) is agranulocytosis; however, there is no conclusive evidence that the prevalence of this serious complication is related to the dose of ATDs. Although it has been reported that the side effects of methimazole (MMI) are dose-related, the studies remain inconclusive, perhaps because of the low frequency of agranulocytosis in patients treated with MMI. The aim of this study was to determine whether the prevalence of agranulocytosis is dependent on the dose of MMI.

METHODS From 1991 through 2005, 9104 patients with newly diagnosed Graves' disease were treated at Kuma Hospital in Japan. Of this group, 8260 patients received MMI as the initial therapy. Patients who dropped out within 1 year after the start of therapy (n = 1125) were excluded from the study, mainly because the authors believed that it was necessary to confirm that the side effects occurred at least 1 year after starting treatment. An additional 477 patients who were changed to propylthiouracil (PTU) or had surgery because of pregnancy or other complications were also excluded from the study. The remaining 6658 patients were enrolled into the study.

The diagnosis of Graves' disease was based on the laboratory features of hyperthyroidism, including suppressed serum thyrotropin (TSH), elevated levels of serum free triiodothyronine (T_3), and the presence of thyrotropin-binding inhibitor with or without an increase in radioiodine uptake. Agranulocytosis was defined as a neutrophil count less than 1000 per microliter. Patients were treated with an MMI dosage that was gradually tapered to maintain the euthyroid state. In some cases the MMI dosage was increased when the serum thyroid hormone levels were not declining. If a patient had fever, MMI was immediately discontinued and the white-cell count was measured.

RESULTS In all, 28 of 6658 patients (0.4%) had agranulocytosis; 30 (0.5%) neutropenia, and 650 (10%) minor side effects resulting in a switch to other treatments. In all, 5950 patients (89%) had follow-up for more than 1 year. The patients who could be followed for at least 1 year and others who had side effects during the observation period were selected as study subjects. As a result, 2087 subjects were treated with 30 mg/day of MMI and 2739 were treated with 15 mg/day of MMI.

Agranulocytosis developed in 17 patients (0.8%) in the 30-mg group, and 6 patients (0.3%) in the 15-mg group (P<0.01, comparing the prevalence of agranulocytosis in the two groups) (Figure 1). When severe agranulocytosis was defined as a neutrophil count less than 200 per microliter, there were 11 such patients (0.5%) in the 30mg group and 3 (0.1%) in the 15-mg group (P<0.05).

Neutropenia occurred in 16 patients (0.8%) in the 30-mg group and 7 (0.3%) in the 15-mg group (P<0.05). Of the 33 patients (2%) affected with agranulocytosis and neutropenia, 33 (1.6%) were in the 30-mg group and 13 (0.5%) were in the 15-mg group (P<0.001).

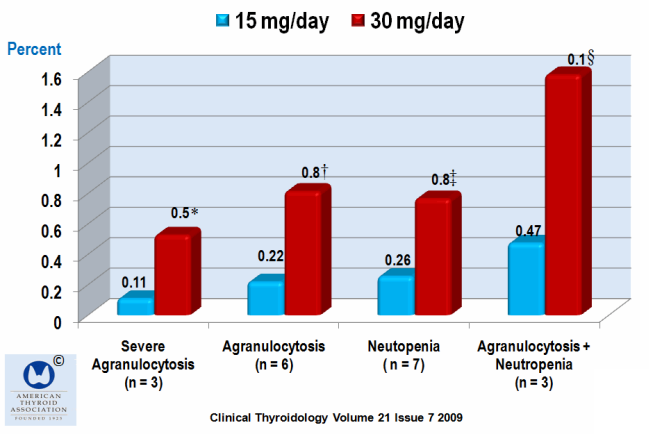

Figure 1. The incidence of side effects with 15 vs. 30 mg/day of methimazole *P = 0.02, †P = 0.006, ‡P = 0.002, §P = 0.0002) comparing 15 mg/day with 30 mg/day of MMI. Severe agranulocytosis is a neutrophil count less than 200 per microliter, agranulocytosis a neutrophil count less than 500 per microliter, and neutropenia a neutrophil count less than 1,000 per microliter.

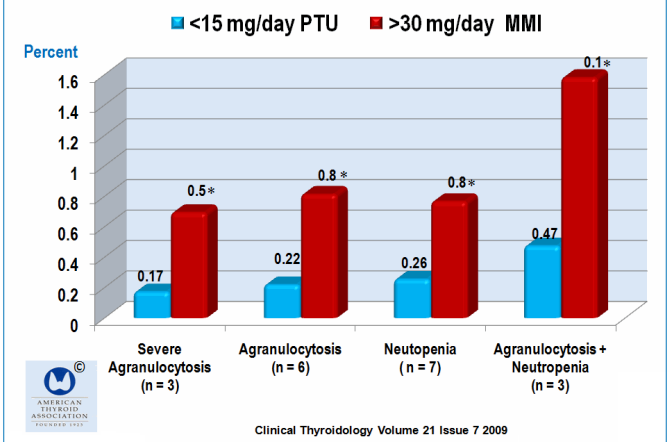

Figure 2. The incidence of side effects in the group of patients treated with less than 15 mg/day of PTU versus patients treated with more than 30 mg/day of MMI. *P<0.001 comparing <15 mg PTU with >30 mg MMI.

When the group treated with more than 20 mg/day of MMI was compared with those treated with less than 15 mg of PTU, 22 (0.7%) of 3174 patients had agranulocytosis in the high-dose group, and 6 (0.2%) of 3484 patients had agranulocytosis in the low-dose group (Figure 2). No patients treated with less than 10 mg/day of MMI had agranulocytosis, and 3 had neutropenia. No deaths from agranulocytosis occurred in the study subjects.

CONCLUSION Methimazole-induced agranulocytosis in patients with Graves' disease is more likely with a daily dose of 30 mg than with 15 mg.

COMMENTARY

The initial treatment of Graves' disease varies according to geographic location. Nonetheless, antithyroid drugs are the initial therapy of choice for the majority of patients with Graves' disease treated in Europe and Japan and elsewhere in Asia (1, 2). Although the superiority of either PTU or MMI is not fully established (3), MMI is in many ways better than PTU. For example, with MMI serious toxicity is less common, adherence rates to treatment are higher, and the thyroid hormones levels fall faster as compared with PTU (4, 5). Moreover, MMI is generally preferred when antithyroid drugs are given to prepare a patient for radioiodine therapy or surgery.

Yet, PTU is still the drug of choice during pregnancy as a consequence of the rare reports of birth defects, especially MMI-related aplasia cutis, that occur in women treated with MMI during the first trimester. In addition, PTU is most commonly recommended for patients with life-threatening thyrotoxicosis, mainly because of the reduction of T_3 production, although the clinical response to this effect is difficult to prove.

The most important issue concerning the choice of antithyroid drugs is the occurrence of life-threatening complications. MMI has less toxicity than PTU, especially when prescribed in lower doses (6, 7). In contrast, PTU can produce life-threatening hepatotoxicity that seems especially severe in children and has been reported to occur in pregnant women and in the fetus (7). A recent editorial by Cooper and Rivkees (7) suggests that approximately 4000 pregnant women per year would be expected to be treated with antithyroid drugs, most of whom would be treated with PTU, according to current practice guidelines. They also estimated that 15 adults with Graves' disease will develop severe PTU-related hepatotoxicity and that each year one or two individuals with Graves' disease in the United States will die or require a liver transplant after PTU exposure. Although MMI also can cause liver injury, it typically produces serious cholestatic dysfunction rather than severe hepatocellular inflammation. Cooper and Rivkees (7) concluded that considering the intricacies of care and risks involved for a pregnant women with thyrotoxicosis, treatment with radioactive iodine or surgery before pregnancy should be strongly considered for women who desire future pregnancy.

Agranulocytosis is the other life-threatening complication of antithyroid drugs that is of great concern. In this issue of Clinical Thyroidology, Takata et al. suggest that although a few studies suggest that agranulocytosis is related to the dose of MMI, the data are sparse (8).

The study by Takata et al. of 2087 subjects treated with 30 mg/day of MMI and 2739 treated with 15 mg/day of MMI found that the prevalence of agranulocytosis in the 30-mg group was almost fivefold greater than that in the 15-mg group ($P<0.01$). Likewise, the prevalence of agranulocytosis plus neutropenia was also about fivefold greater in the 30-mg group as compared with that in the 15-mg group ($P<0.001$). The authors' conclusions that MMI-induced agranulocytosis is dose-related is underpinned by their large study, which provides robust evidence to support this conclusion. Considering both the effectiveness of MMI and the risk of serious side effects with larger doses, the authors recommend 15 mg/day of MMI as the starting dose for the treatment of Graves' disease. This makes sense.

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