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ORIGINAL ARTICLE

Thionamide Associated Agranulocytosis: Low Incidence with Low Doses of Methimazole

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Agranulocytosis is an uncommon but most serious adverse side effect of thiouracil. It has been reported to affect 0.3% – 0.6% of patients treated with thiourea–derivates. Both methimazole (MMI) and propylthiuracil (PTU) can cause agranulocytosis. Some data indicate that low doses of MMI are associated with lower prevalence of agranulocytosis than either high-dose MMI or conventional doses of PTU. The aim of the present study was to determine the frequency of thionamide-associatied agranulocytosis and to clarify the role of clinical factors such as gender and age of patient, duration of antithyroid therapy, dosage and type of thionamide used, in the development of agranulocytosis.

Materials and Methods: The medical records of all patients with hyperthyroid disease, treated with either MMI or PTU in endocrine clinics, were reviewed retrospectively with regard to agranulocytosis, patient age and sex, duration of antithyroid therapy, diagnosis, dosage, and type of thionamide used. Between April 1985 and September 2004, a total of 21,800 patients with hyperthyroidism due to Graves' disease or toxic multinodular goiter received long term treatment (mean duration of treatment of 15.7±8.4 months) with either MMI or PTU at endocrine clinics of Tabriz University of Medical Sciences. Of these, 20,840 (95.6%) patients were treated with MMI and the remainder 960 (4.4%) received PTU.

Results: Classic agranulocytosis, defined as severe neutropenia, accompanied by serious symptoms and signs of infection developed in seven cases, 5 in MMI group and 2 in PTU treated patients. Thus the overall prevalence of thiomamide–associated agranulocytosis in this study is about 0.03 percent. There was no significant difference between mean ages of patients with and without agranulocytosis (42.2±14.8 vs 45.4±13.7 years). In the majority of cases, agranulocytosis occurred during the first 2 months of treatment. There was no case with agranulocytosis among 15,412 individuals treated with low doses of MMI (< 20 mg/day).

Conclusion: In conclusion the majority of cases of agranulocytosis occurred within the first few weeks of initiation of antithyroid therapy. This side effect may occur at any times, regardless of patient age, gender or duration of treatment. It seems that the likelihood of agranulocytosis is diminished at low doses of MMI.

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Introduction

Since their development in 1941, thionamides have been widely used for treatment of hyperthyroid patients. Antithyroid therapy may be associated with adverse effects.1-5 Agranulocytosis is a rare but life-threatening

side effect of thionamides, that has been reported to affect 0.3% to 0.5% of patients treated with these agents.1-9 Factors or clinical circumstances that might predispose to antithyroid-associated agranulocytosis remain largely unknown.1-4,11 Agranulocytosis occurs almost exclusively during the first ten weeks of thionamide therapy and is probably related to drug dosage.11-15 Although this serious drug-related complication can occur with any antithyroid dose, but the risk is increased in patients given larger doses, while the likelihood diminishes at MMI doses less than 30 mg/day.10,11,15 The aim of the present study was to determine the possible role of factors such as patient age and gender, dosage, duration of treatment, and type of antithyroid drug used, in the occurrence of thionamide-related agranulocytosis in a large number of patients who received long term treatment with either MMI or PTU.

Materials and Methods

The medical records of all patients with hyperthyroid disease who were treated with either MMI or PTU were reviewed retrospectively with respect to antithyroid-related agranulocytosis. Between April 1985 and September 2004, a total of 21,800 patients with hyperthyroidism due to Graves' disease or toxic multinodular goiter, received long term treatment with either MMI or PTU at endocrine clinics of Tabriz university of Medical Sciences. Data regarding patient age and sex, diagnosis, dosage and type of thionamide used, and duration of antithyroid treatment were recorded. WBC count is not routinely done in our clinics before or during antithyroid therapy, but all patients starting treatment are warned to stop and seek an urgent blood count if they develop a sore throat or other symptoms and signs of an infectious process. Thus, classic agranulocytosis was defined as severe neutropenia (granulocyte count of 0.25 × 109/L or less), accompanied by symptoms and signs of infection. To examine the possible safety of low doses of the MMI with respect to agranulocytosis, patients in MMI group were divided into those who were treated with high-dose MMI (≥ 20 mg/day) and those who received low-dose treatment (< 20 mg/day). There were 15412 patients (74%) in the low-dose and 5428 individuals (26%) in the high-dose groups. Values were expressed as mean ± SD and the unpaired students' t test was used to compare differences between mean values.

Results

During a 20-year period from 1985 to 2004, a total of 21800 patients with hyperthyroidism due to either Graves' disease or toxic multinodular goiter were treated long term with antithyroid agents in endocrine clinics of Tabriz University of Medical Sciences. Of these, 20840 patients (95.6%) received MMI and the remaining 960 individuals (4.4%) were treated with PTU. There were 17879 females (82%) and 3921 males (18%) among this population of patients with a mean age of 45.4±13.7 years. Most patients (no=15412) were started on low-dose MMI (less than 20 mg/day), while high-dose MMI (20 mg/day or more) was prescribed in 5428 patients. The duration of antithyroid therapy ranged from 4 months to 9 years with a mean of 15.7±8.4 months.

Classic agranulocytosis, defined as severe neutropenia (granulocyte count < 0.25 × 10^9/L), accompanied by symptoms and signs of infection including fever, chills, mouth ulcers, sore throat and sepsis developed in 7 cases, 5 in MMI treated patients and 2 in the PTU group. A mother and her daughter were among patients who developed agranulocytosis with MMI. Thus, the overall prevalence of thionamide-induced agranulocytosis in this report was approximately 0.03%. The prevalence of agranulocytosis was 0.02% in 20840 patients who received MMI, and 0.2% in 960 thyrotoxic patients treated with PTU (Fig. 1).

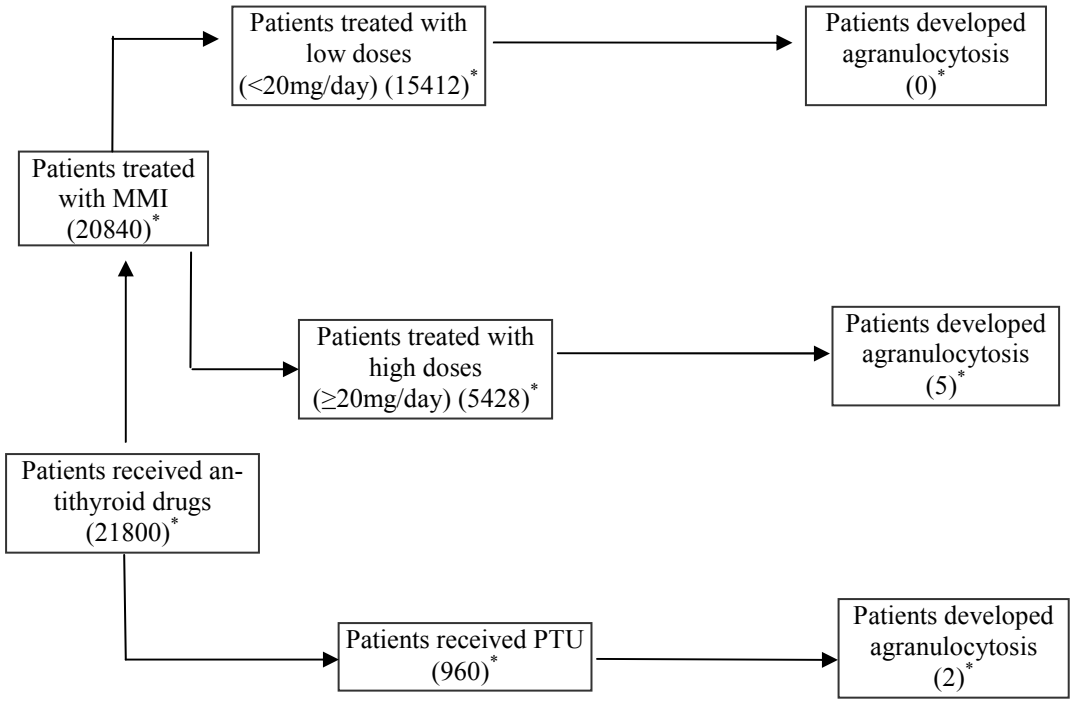

Fig.1. Thionamide-associated agranulocytosis: effect of dosage and type of thionamide used (MMI or PTU) * No. of patients

Table 1. Clinical and laboratory features of patients with agranulocytosis

Case	Sex / age	Cause of hyperthyroidism	ATD	Dosage (mg/day)	duration (days)	granulocyte (count × 10^6/L)	outcome
1	F/44	Graves' Disease	PTU	300	17	96	Recovery
2	F/27	Graves' Disease	MMI	45	12	148	Recovery
3	F/51	Graves' Disease	MMI	30	21	195	Recovery
4	F/65	TMNG	MMI	40	21	230	Recovery
5	F/21	Graves' Disease	MMI	20	270	170	Recovery
6	F/48	Graves' Disease	PTU	300	60	130	Recovery
7	M/40	Graves' Disease	MMI	40	30	110	Died of sepsis

ATD: antithyroid drug, MMI: methimazole, PTU: propylthiuracil, TMNG:toxic multinodular goiter

Clinical and laboratory findings of 7 patients with agranulocytosis have been shown in Table 1. The mean age of patients with thionamide-associated agranulocytosis was 42.2±14.8 years. In the majority of cases, agranulocytosis occurred during the first few weeks of treatment. Mean duration of treatment with thionamide before development of agranulocytosis in six of seven cases was 26.8±17.2 days. In one patient, agranulocytosis occurred approximately 9 months after starting therapy with MMI. All 5 cases with agranulocytosis, among patients who received MMI, occurred in the high-dose group (mean dose of MMI of 35 mg/day). There was no case with agranulocytosis among 15412 individuals treated with low doses of MMI (Fig. 1). Patients with agranulocytosis presented with symptoms and signs of infection including septic fever, shaking chills, mouth ulcers, sore throat and sepsis. They were admitted to hospital and treated with intravenous fluids, broad spectrum antibiotics, and high doses of corticosteroids. Six patients recovered gradually within 2-3 weeks of admission. A 40 year-old Kurdish man who remained neutropenic, died of sepsis and septic shock, 8 days after hospitalization.

Discussion

The overall incidence of thionamide-induced agranulocytosis in this study was about 0.03 percent. Clinico-laboratory characteristics of our seven patients with thionamide-related agranulocytosis have been shown in Table 1. The female to male ratio of 6 to 1 was similar, with the expected preponderance of female patients. There was no significant difference in the mean ages of patients with and those without agranulocytosis (42.2±14.8 years versus 45.4±13.7 years). Three of our seven patients were 40 years old or less. The mean duration of treatment with antithyroid drug before diagnosis of agranulocytosis in six cases was 26.8±17.2 days. In one patient agranulocytosis occurred 9 months after initiation of MMI therapy. Thus, thionamide-induced agranulocytosis occurred irrespective of patient age and sex and duration of antithyroid treatment.

Agranulocytosis is a rare but life threatening side effect of thionamides.[1-5] In the largest series, its incidence has been reported to range between 0.3% to 0.6%.[1-9] Although the exact responsible mechanism is unknown, it is thought to have an autoimmune basis.[16-18,23] The presence of antigranulocytic antibodies has been shown in patients with thionamide-related agranulocytosis, and it has been suggested that antineutrophil cytoplasmic antibodies play an important role in its pathogenesis.[19-23] These antibodies may cause agranulocytosis by direct cytotoxicity or through mechanisms that inhibit growth of progenitor cells.[19,24,25]

A strong positive association between HLA class II genes and MMI-induced agranulocytosis has been reported in Japanese patients with Graves' disease.[26] The susceptibility to thionamide-related agranulo-cytosis may have a genetic basis and be HLA-linked, suggesting that cellular autoimmunity may be involved in its development.[26,27] Since its etiology is not known, at present, it is impossible to predict which patient may be at risk for development of thionamide-related agranulocytosis.[1-5] Because of rapid onset of agranulocytosis and its low frequency, despite its simplicity, the routine practice of monitoring of white blood cell (WBC) count has not been considered cost-effective and still remains controversial.[1-5,28] In one study granulocytopenia (granulocyte count of $< 0.5\times10^9$/L) was detected by routine WBC count monitoring before agranulocytosis occurred, suggesting the onset may be more gradual than previously thought. In patients with graunlocytopenia, prompt discontinuation of thionamide led to an increase in granulocyte count.[33] However, due to the low incidence of agranulocytosis the cost effectiveness of routine monitoring should be questioned.

Cooper et al. investigated the role of patient age, dosage and type of thionamide used, in development of agranulocytosis[11]. Their results showed that low doses of MMI (< 30 mg/day) were associated with a lower incidence of agranulocytosis than were higher doses of MMI or conventional doses of PTU, and increased patient age was associated with an excess risk of agranulocytosis.[11,29] Three European prospective studies, comparing high and low doses of antithyroid drugs, showed more frequent side effects including agranulocytosis with higher doses.[30] Although agranulocytosis has been reported to be more common with higher doses of MMI, researchers have not found a similar relation to PTU therapy.[31] On the other hand in 1989 Tamai et al. published their experience with thionamide-related agranulocytosis[8] and concluded that agranulocytosis after MMI may occur irrespective of dose, age of patient, duration of treatment, whether or not a previous course of antithyroid therapy has been given (second exposure). Werner and his co-workers studied 389 patients with Graves' hyperthyroidism receiving either high PTU or MMI daily doses, to evaluate whether adverse effects including agranulocytosis were related to the type of thionamide or its daily dose regimen. Their results showed that adverse effects of thionamides were similar in both high-and low-dose regimens.[32]

In conclusion, the overall incidence of thionamide-induced agranulocytosis in this study was about 0.03%. This is nearly ten times less than those reported from the West and Japan.[1-9] This can be attributed to low-dose regimens of MMI employed in nearly three-fourths of our patients and the possible safety of MMI in comparison with PTU, as the vast majority of patients in this series (95.6%) received MMI. The majority of cases developed during the first few weeks of initiation of antithyroid therapy. Thionamide-associated agranulocytosis occurred irrespective of patient age and sex and duration of treatment. Low-dose methimazole seemed to be safer than high-dose methimazole or conventional doses of propylthiuracil with respect to agranulocytosis. Fever, chills, mouth ulcers, and sore throat due to exudative pharyngitis were the most common presenting manifestations of agranulocytosis.

Based upon the results of this investigation we recommend that firstly all patients should be instructed to discontinue the thionamide and contact a physician immediately if fever, sore throat, mouth ulcers or symptoms of sepsis develop. A WBC and differential should be obtained immediately. Secondly methimazole, at low doses, is less often associated with agranulocytosis; for this reason, it is preferable to propylthiuracil. Thirdly it seems reasonable to avoid antithyroid drug therapy in hyperthyroid relatives of patients who have developed thionamide-induced agranulocytosis

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