Topic: SIDE EFFECTS OF ANTITHYROID DRUGS

Title: Antithyroid drug-induced aplastic anemia.

Authors: Thomas D, Moisidis A, Tsiakalos A, Alexandraki K, Syriou V, & Kaltsas G (Athens, Greece)

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SUMMARY

Background: Antithyroid drugs (ATD) have been used for more than 50 years for the management of hyperthyroidism. Most patients tolerate treatment well but some may develop life threatening side effects such as agranulocytosis and aplastic anemia (AA). The authors review all cases of antithyroid drug induced AA and describe, as illustrative cases, two women with Graves' disease who developed AA after 8 and 24 weeks of carbimazole (CMI) and methimazole (MMI) treatment respectively.

Patients Findings and Summary: To date, at least 34 cases of aplastic anemia (AA) due to ATD [(1 with CMI, 31 with MMI, and 2 with propylthiouracil (PTU)] have been published, not including the 2 patients described here. In addition, at least another 14 patients in whom AA developed after treatment with ATD (11 with CMI, and 3 with MMI) have been reported in Yellow Card Scheme data analysis. Patients with AA usually exhibit sudden onset of symptoms after a relative short time of exposure to the drugs, and all have concomitant agranulocytosis. Most have a rapid recovery following discontinuation of the drug and supportive treatment. Although only two ATD-induced AA deaths have been published, the mortality rate was higher in the Yellow Card Scheme data analysis.

Conclusions: Aplastic anemia associated with ATD treatment is rarer than ATD associated agranulocytosis. The prognosis of patients with ATD induced AA is good overall, but may not be as favorable as that of ATD-induced isolated agranulocytosis.

COMMENT

Antithyroid drugs (ATD) are extremely effective in correcting rapidly thyrotoxicosis. However, ATD are occasionally associated with life threatening side effects such as agranulocytosis and, more rarely, aplastic anemia (AA). The risk of agranulocytosis is believed to occur in 3-4/1.000 patients receiving PTU or MMI. The risk of AA, defined as pancytopenia with bone marrow hypocellularity, is even more rare (less than 40 case reports in literature). This rare occurrence (with the potential bias that it concerns only published reports) is to be compared to more than 400 cases published to date with agranulocytosis. I shall personally emit some doubt about the validity of such ‘literature’ statistics. For instance in my own experience of treating 2.000-3.000 patients/yr with various thyroid disorders over the last 40 years, we have encountered 8 cases with isolated complete agranulocytosis (but none has been published!).

In this article, the authors report their personal experience with two patients who presented life threatening AA after receiving carbimazole (CMI) and methimazole (MMI) for the treatment of Graves' disease. Patient 1 (young female) received CMI (30 mg/d) for 45 days and developed pancytopenia. She recovered progressively (after 9-10 days), after receiving G-CSF (30 mg for 5 days and 48 mg for the next 6 days). Patient 2 (middle aged woman) has been treated with MMI
(30 mg/d) for 6 months, before developing pancytopenia. She was treated by subcutaneous injections of G-CSF (300 µg/day) during 10 days and recovered gradually her hematopoietic function during this period of time.

The review of the literature indicates that 50% of the patients who developed AA during ATD administration did so within the first 15 weeks of therapy. The pathogenesis of ATD-mediated AA is thought to be immune-mediated bone marrow aplasia, although a direct toxic effect of ATD on bone marrow cannot be excluded. One important finding is that all cases reported with AA had concomitant agranulocytosis. Therefore, the pathogenesis of both complications probably shares common pathogenic mechanisms.

One clinical question that is frequently raised when confronted with such cases concerns the need to administer G-CSF. It is generally admitted that such patients recover spontaneously in 10-15 days, and that G-CSF administration shortens the recovery period by a couple of days. Since this condition is life threatening, it seems reasonable to use all therapeutic means that are available to give patients the best possible chance to recover from such rare – but extremely severe – side effects of ATD treatment.

Partial or complete clinical and laboratory recovery was observed in 90% of the patients, within 9 to 35 days. Finally, the overall prognosis of ATD-induced AA is good, with a survival rate greater than 94% in the 36 published cases reviewed by the authors.

(Daniel Glinoer, M.D.; Ph.D.)

See Figure below