



HYPERTHYROIDISM

Antithyroid drug-induced severe liver injury in newly diagnosed patients with Graves' Disease in Japan

BACKGROUND

Graves' disease is the most common cause of hyperthyroidism in the United States. Treatment options include antithyroid drugs ((Methimazole, MMI, and propylthiouracil, PTU), radioactive iodine treatment and surgery. Antithyroid drugs have been used since the 1940's. These drugs are very effective in controlling the hyperthyroidism and are usually very well tolerated. However, rarely, they can have severe and potentially fatal side effects, including low white blood cell counts (agranulocytosis), liver injury and inflammation of the blood vessels (vasculitis). Drug-induced liver injury has been reported in 0.03% to 0.5% of patients taking antithyroid drugs. The use of PTU has been associated to severe, potentially fatal, liver disease while MMI has been associated more with inflammation of the gall bladder tract (cholestatic disease). Again, these reaction are very rare. Recent reports from Asia have indicated that both drugs can cause either type of liver injury. The goal of this study was to evaluate the types of antithyroid drug-induced severe liver disease in patients with Graves' disease in Japan.

THE FULL ARTICLE TITLE

Suzuki N et al 2019 Analysis of antithyroid drug-induced severe liver injury in 18,558 newly diagnosed patients with Graves' disease in Japan. *Thyroid* 29:1390–1398. PMID: 31573408.

SUMMARY OF THE STUDY

The study included 18,558 patients with newly diagnosed Graves' disease who received antithyroid drugs for the first time between January 2005 and December 2016 at a single medical center in Japan. Among these, 14,271 patients received MMI and 4,287 patients received PTU. Study data was collected from the patients' medical records, and patients with prior history of liver disease were excluded.

The types of antithyroid drug-related liver disease were defined as follows: liver cell (hepatocellular) injury (levels of the liver enzyme ALT > 8 times the upper limit of normal anytime or >5 times the upper limit of normal

for more than 2 weeks), gall bladder (cholestatic) injury (serum total bilirubin levels >3 times the upper limit of normal) or mixed injury (both liver cell and gall bladder injury). The liver injury severity was graded from 1 to 5: Grade 1- mild disease; Grade 2- moderate; Grade 3- severe but not immediately life-threatening; Grade 4- life-threatening and needing urgent intervention (ALT >20 times the upper limit of normal, or 20 times the baseline if the baseline had been abnormal; or total bilirubin >10 times the upper limit of normal, or 10 times the baseline if the baseline level had been abnormal); Grade 5 - death.

A total of 461 patients (2.5% - 0.3% for males and 2.9% for females) had severe Grade 3 or 4 drug-induced liver injury. Nine women developed liver injury after exposure to both MMI and PTU. Severe liver injury was associated more often with PTU than MMI use (6.3% versus. 1.4%, respectively), and most patients (2.3%) had Grade 3 with a few patients having Grade 4 liver injury. There were no deaths or liver transplantations.

The majority of patients had a liver cell injury. Of the MMI-treated patients, 94% had liver cell injury, 2.5% had gall bladder injury (1 had Grade 4 drug-induced liver injury), and 3.5% had a mixed type. Of the PTU-treated patients, 90.9% had hepatocellular injury, 0.4% had cholestatic injury, and 0.7% had a mixed type. Severe drug-induced liver injury was more frequent in older patients treated with MMI but not PTU.

The average time to development of drug-induced liver injury was 30 days, and the average time to recovery was 28 days. The liver injury developed within 90 days after starting antithyroid drug therapy in 97% of cases. The average daily dose of MMI was 15 mg, while the average daily dose of PTU was 300 mg. No correlation between the antithyroid drug dose or serum thyroid function tests and the severity of the drug-induced liver injury was found. Half of the patients received no treatment for liver injury, while half received ursodeoxycholic acid therapy or glucocorticoids.





HYPERTHYROIDISM, continued

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

In this study from Japan, like other Asian countries, the prevalence of both PTU and MMI-induced liver disease was higher than that reported in the United States. The major type of MMI-induced liver injury was injury to the liver cells in Asian countries and elevated bilirubin in the United States. All studies have showed a higher risk of severe liver injury with PTU as compared to MMI. Thus, MMI is the preferred drug in treating hyperthyroid patients. Physicians should be aware that MMI can cause liver injury, however.

Although severe antithyroid drug-induced liver injury is rare, it can be potentially fatal. All patients who start antithyroid drug treatment should be aware of the possibility of hepatic complications and discontinue the drug if they develop symptoms concerning for liver disease. It would be advisable to refer the patients with severe antithyroid drug-induced liver injury to a specialized liver center that has the capability of performing liver transplantation.

— Alina Gavriła, MD, MMSC

ATA THYROID BROCHURE LINKS

Graves' Disease: <https://www.thyroid.org/graves-disease/>

ABBREVIATIONS & DEFINITIONS

Hyperthyroidism: a condition where the thyroid gland is overactive and produces too much thyroid hormone. Hyperthyroidism may be treated with antithyroid meds (Methimazole, Propylthiouracil), radioactive iodine or surgery.

Graves' disease: the most common cause of hyperthyroidism in the United States. It is caused by antibodies that attack the thyroid and turn it on.

Methimazole: an antithyroid medication that blocks the thyroid from making thyroid hormone. Methimazole is used to treat hyperthyroidism, especially when it is caused by Graves' disease.

Propylthiouracil (PTU): an antithyroid medication that blocks the thyroid from making thyroid hormone. Propylthiouracil is used to treat hyperthyroidism, especially in women during pregnancy.

Agranulocytosis: an acute and severe decrease in the white blood cell count that can result in life-threatening infections.

Vasculitis: inflammation of blood vessels.

Hepatocellular liver disease: a condition where there is damage to the liver cells that may affect the liver function.

Cholestatic liver disease: a condition where there is slowing of the bile flow in the liver.

Alanine aminotransferase (ALT): an enzyme normally present in the liver that is released into blood when the liver is damaged.

Bilirubin: orange-yellow pigment that results from the breakdown of red blood cells and is usually excreted in the bile. Cholestasis causes bile and bilirubin to build up in the bloodstream.

