

Putting Propylthiouracil in Perspective

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The antithyroid drugs propylthiouracil (PTU) and methimazole (MMI) have played central roles in the management of hyperthyroidism for more than 50 yr. Although both drugs effectively control hyperthyroidism, observations over several decades have shown that MMI and its prodrug carbimazole are better than PTU in controlling more severe hyperthyroidism, having higher adherence rates, and causing less toxicity, especially when prescribed in lower doses (1). This has led to the recommendation that MMI should be the first-line drug when antithyroid drug therapy is initiated, either for primary treatment or to prepare a patient for radioiodine or surgery. An exception to this rule has been pregnancy, during which PTU has been preferred because of rare reports of birth defects associated with MMI (2). PTU has also been used in patients who had minor reactions to MMI but, nonetheless, preferred to continue antithyroid drug therapy. PTU may also be preferable in patients with life-threatening thyrotoxicosis because of its additional inhibition of T_4 to T_3 conversion.

It is in this context that continued PTU use as a second-line agent, a first-line agent in pregnancy, and routinely by some practitioners has been reevaluated at two meetings in the last 6 months. The first meeting, which was sponsored by the Eunice Kennedy Shriver National Institute of Child Health and Development on October 28, 2008, examined PTU safety in children because of accumulating reports of PTU-related liver failure and death in children (3). The second meeting, sponsored by the American Thyroid Association and the Food and Drug Administration (FDA) on April 18, 2009, reevaluated the role of PTU during pregnancy, given what is known about PTU-related hepatotoxicity and MMI-related birth defects (4). At both meetings, the world's literature on PTU hepatotoxicity was reviewed. Representatives from the FDA provided data on current PTU and MMI prescribing practices. Information pertaining to PTU hepatotoxicity from the FDA Adverse Event Reporting System (AERS) MedWatch Program was examined. Data on hepatic transplantations for PTU-related hepatotoxicity, provided by The United Network for Organ Sharing (UNOS), were also reviewed. At the second meeting, MMI-related aplasia cutis and more severe teratogenesis were discussed; however, no new information about the frequency or the cause of this problem was presented. At both meetings, mechanisms of drug-related hepatic injury were reviewed,

and the role of biochemical monitoring of liver integrity in patients taking drugs known to cause hepatic damage was discussed.

A complex and incomplete but, nonetheless, worrisome picture emerged from these meetings. There are 33 published reports of severe PTU-related liver failure in adults and 14 in children (see Supplemental Table 1 and Supplemental Fig. 1, published as supplemental data on The Endocrine Society's Journals Online web site at <http://jcem.endojournals.org>). UNOS reported 16 liver transplants in adults and seven in children between 1990 and 2007 due to PTU-induced liver failure (5, 6) (supplemental data). Although MMI can cause liver injury, too, it is typically characterized by serious cholestatic dysfunction rather than hepatocellular inflammation (1). Indeed, over the same 17-yr period when one to three PTU-related liver transplants occurred per year, there were no liver transplants in the United States attributed to MMI toxicity. The FDA AERS databases, which overlap published reports and are subject to underreporting, detail instances of severe liver injury in 22 adults over the past 20 yr, nine of whom died and five who received liver transplants. Over the same period, 12 pediatric patients sustained severe liver injury resulting in three deaths and six liver transplants. The average daily dose of PTU associated with liver failure was approximately 300 mg in both children and adults. Liver failure occurred after 6 to 450 d (median, 120 d) of treatment. In the AERS data, there were also two reports of serious maternal liver injury due to PTU during pregnancy and two reports of liver injury in fetuses whose mothers took PTU.

Because the true incidence of severe liver injury among patients taking PTU is unknown, efforts were made at the two meetings to define this figure more precisely. Based on published age-specific annual incidence data for hyperthyroidism (7) and the age distribution of the U.S. population from the 2000 census, it can be calculated that approximately 60,000 adults develop hyperthyroidism each year. Based on data reported at the two meetings, PTU is prescribed to one fourth of patients treated with antithyroid drugs for hyperthyroidism in the United States (8). Approximately 15,000 adults are, therefore, estimated to begin PTU therapy per year. If the frequency of PTU-related severe liver damage is approximately

0.1% in adults, based on available data (9), approximately 15 adults will develop related severe hepatic injury annually in the United States. If 10% of these individuals develop liver failure resulting in liver transplantation or death (1:10,000 incidence), each year one or two individuals with Graves' disease in the United States will die or require a liver transplant after PTU exposure. UNOS and ARES data support this estimate because there were 18 PTU-related liver transplants of adults over the past 17 yr and nine patients who died (3). Although the frequency with which PTU is being used in the United States has declined significantly, with 101,000 PTU-treated patients in 2008 and more than 340,000 PTU prescriptions written (8), a substantial number of individuals remain at risk for PTU-related liver failure.

Data for children suggest that the risk of drug-induced liver failure may be greater for children than for adults. Based on PTU prescription data, 1500 of the 4000 children treated with antithyroid drugs receive PTU (3). Consequently, based on UNOS and FDA AERS reports that there are one to two cases of major PTU-related liver injury per year (3), PTU-treated children are at low but significant risk of liver failure (1 in 1000 incidence).

With regard to PTU use during pregnancy, there are 4 million births per year in the United States, and with a 0.1% frequency of Graves' disease in pregnancy, approximately 4000 women per year would be expected to be treated with antithyroid drugs. Most of them would be treated with PTU, per current practice guidelines. Consequently, it can be estimated that four women per year will have severe PTU-related hepatic complications, based on generally reported rates of severe liver injury in adults, although no pregnancy-specific data are available.

It seems unlikely that monitoring liver function tests would benefit patients who might develop severe PTU-related hepatotoxicity based on experience with other hepatotoxic drugs. Monitoring has not been shown to decrease risk of severe liver injury for most of these agents. Isolated serum transaminase increases are often reversible despite continuing the drug (10). Drug-related hepatotoxicity has an unpredictable latency after initiation of treatment, *e.g.* days to years in the case of PTU. Biochemical screening may not be cost-effective when dealing with rare events such as PTU-related hepatotoxicity.

Despite the limitations of this information, one could reasonably conclude that PTU should never be used as a first-line agent in either children (11) or adults, with the possible exceptions of pregnant women and patients with life-threatening thyrotoxicosis. PTU use should be restricted to circumstances when neither surgery nor radioactive iodine is a treatment option in a patient who has developed a toxic reaction to MMI and antithyroid drug therapy is needed. In this situation, patients should be informed of the risk of liver failure. If patients taking PTU develop jaundice, fatigue, malaise, nausea, anorexia, or pharyngitis, the medication should be discontinued immediately and white blood cell count and bilirubin, alkaline phosphatase, and transaminase levels should be obtained.

Regarding antithyroid drug use in pregnant women, a recent epidemiological study found an odds ratio of 18 (95% confidence interval, 3–121) for choanal atresia among infants with *in utero* MMI exposure compared with the general population (12). The authors could not exclude the possibility that hyperthyroidism itself may be associated with this and other developmental defects. Aplasia cutis has also been reported with prenatal MMI use, although it has been

suggested that this risk (0.03%) is not above background (13). Because of our limited understanding of the relative risks of birth defects associated with Graves' disease and the use of antithyroid drugs, until we have additional information on MMI drug safety for the fetus, it is reasonable to recommend that pregnant hyperthyroid women be treated with PTU during the first trimester rather than with MMI. This is in accord with The Endocrine Society guideline (2). The risk of PTU for expectant mothers can be reduced by limiting PTU use to the first trimester and then changing to MMI. Furthermore, antithyroid drugs can be stopped in about 30% of women by the third trimester.

Whether hyperthyroid women who desire to become pregnant in the near future should be treated preferentially with PTU is an unanswerable question at this time. Considering the intricacies of care and risks involved for a woman with active thyrotoxicosis during pregnancy, treatment with radioactive iodine or surgery before pregnancy should be strongly considered for those who desire future pregnancy. Doing so can avoid the dilemma of choosing between a drug associated with a small risk of fetal birth defects and another drug associated with a similarly small but finite risk of serious liver injury in the mother.

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