

Putting Propylthiouracil in Perspective

David S. Cooper, M.D.
Division of Endocrinology and Metabolism
Johns Hopkins University
Baltimore MD

Scott A. Rivkees, M.D.
Yale Pediatric Thyroid Center
Yale University, New Haven CT

Corresponding author:

David S. Cooper, M.D.
Division of Endocrinology and Metabolism
The Johns Hopkins University School of Medicine
1830 E. Monument St., Suite 333
Baltimore, MD 21287
phone 410-502-4926
fax 410-955-8172
e-mail: dscooper@jhmi.edu

Key words: propylthiouracil, methimazole, hyperthyroidism, liver failure, pregnancy,

Word Count: 1445

Disclosure summary: The authors have nothing to declare.

The antithyroid drugs propylthiouracil (PTU) and methimazole have played central roles in management of hyperthyroidism for more than fifty years. While both drugs effectively control hyperthyroidism, observations over several decades have shown that methimazole and its pro-drug 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 methimazole be the first line drug when antithyroid thyroid 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 methimazole (2). PTU has also been used in patients with minor reactions to methimazole but, nonetheless, prefer to continue antithyroid drug therapy. PTU may also be preferable in patients with life-threatening thyrotoxicosis because of its additional inhibition of T4 to-T3 conversion.

It is in this context that continued PTU use as a second line agent, and a first line agent in pregnancy, and routinely by some practitioners, has been reevaluated at two meetings in the last six 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. 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 Figure 1). UNOS reported 16 liver transplants in adults and 7 in children between 1990 and 2007 due to PTU-induced liver failure (4,5) (Supplemental data). While methimazole can cause liver injury too, it is typically characterized by cholestatic dysfunction rather than hepatocellular inflammation (1). Indeed, over the same 17-year period when one to three PTU-related liver transplants per year occurred, 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 under-reporting, detail reports of severe liver injury in 22 adults over the past 20 years, 9 of whom died and 5 received liver transplants. Over the same period, 12 pediatric patients sustained severe liver injury resulting in 3 deaths and 6 liver transplants. The average daily dose of PTU associated with liver failure was

approximately 300 mg in both children and adults. Liver failure occurred 6 to 450 days (median 120 days) 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 (6), and the age distribution of the United States 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-quarter of patients treated with antithyroid drugs for hyperthyroidism in the United States (7). 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 (8), 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 1 or 2 individuals with Graves' disease in the United States will die or require a liver transplant following PTU exposure. UNOS and AERS data support this estimate, as there were 18 PTU-related liver transplants of adults over the past 17 years and 9 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 (7), a substantial number of individuals remain at risk for PTU-related liver failure.

Data for children suggest that risk of drug-induced liver failure may be greater than for adults. Based on PTU prescription data, 1,500 of the 4,000 children treated with antithyroid drugs receive PTU (3). Consequently, based on UNOS and FDA AERS reports that there are 1 to 2 cases of major PTU-related liver injury per year (3), PTU-treated children are at low but significant risk of liver failure (1 in 1,000 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 4,000 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 4 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 (9). 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 (10) 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 are treatment options 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 fatigue, malaise, nausea, anorexia, or pharyngitis, the medication should be immediately discontinued and white blood cell count and bilirubin, alkaline phosphatase, and transaminase levels obtained.

Regarding the antithyroid drug use in pregnant women, a recent epidemiologic study found an odds ratio of 18 [95%CI 3-121] for choanal atresia among infants with in utero methimazole exposure compared to the general population (11). 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 (12). 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 prior to 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 associated with a similarly small but finite risk of serious liver injury in the mother.

References

- 1 Cooper DS. Antithyroid drugs. *N Engl J Med* 2005;352:905-917.
- 2 Abalovich M, Amino N, Barbour LA, Cobin RH, De Groot LJ, Glinoe D, Mandel SJ, Stagnaro-Green A. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2007;92(8 Suppl):S1-47
- 3 Eunice Kennedy Shriver National Institute of Child Health and Human Development. Hepatic Toxicity Following Treatment for Pediatric Graves' Disease Meeting: October 28, 2008. Conference proceeding. <http://bpca.nichd.nih.gov/outreach/index.cfm>
- 4 Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P. Liver transplantation for acute liver failure from drug induced liver injury in the United States. *Liver Transpl*. 2004;10(8):1018-23
- 5 Rivkees SA, Mattison DR Propylthiouracil (PTU) toxicity in children and recommendations for discontinuation of use. *Intl J Pediatr Endocrinol* (in press)
- 6 Abraham-Nordling M, Törring O, Lantz M, Hallengren B, Ohrling H, Lundell G, Calissendorff J, Jörneskog G, Wallin G. Incidence of hyperthyroidism in Stockholm, Sweden, 2003-2005. *Eur J Endocrinol*. 2008;158(6):823-7.
- 7 Laura Governale, FDA Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology SDI, Total Patient Tracker. Years 2002 - 2008. Extracted 3/09
- 8 Kim HJ, Kim BH, Han YS, Yang I, Kim KJ, Dong SH, Kim HJ, Chang YW, Lee JI, Chang R. The incidence and clinical characteristics of symptomatic propylthiouracil-induced hepatic injury in patients with hyperthyroidism: a single-center retrospective study. *Am J Gastroenterol*. 2001;96(1):165-9.
- 9 Liaw YF, Huang MJ, Fan KD, Li KL, Wu SS, Chen TJ. Hepatic injury during propylthiouracil therapy in patients with hyperthyroidism. A cohort study. *Ann Intern Med*. 1993;15;118(6):424-8
- 10 Rivkees SA, Mattison DR. Ending propylthiouracil-induced liver failure in children. *N Engl J Med*. 2009;360(15):1574-5.
- 11 Barbero P, Valdez R, Rodríguez H, Tiscornia C, Mansilla E, Allons A, Coll S, Liascovich R. Choanal atresia associated with maternal hyperthyroidism treated with methimazole: a case-control study. *Am J Med Genet A*. 2008;146A(18):2390-5.

12 Van Dijke CP, Heydendael RJ, De Kleine MJ. Methimazole, carbimazole, and congenital skin defects. *Ann Intern Med.* 1987;106(1):60-1.