Hepatic Toxicity Following Treatment for Pediatric Graves' Disease Meeting
October 28, 2008
***Eunice Kennedy Shriver* National Institute of Child Health and Human Development**
6100 Executive Boulevard
Rockville, MD

This meeting was sponsored by the Obstetric and Pediatric Pharmacology Branch (OPPB), Center for Research for Mothers and Children (CRMC), *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH), U.S. Department of Health and Human Services (HHS), in support of the Best Pharmaceuticals for Children Act (BPCA) Program.

Background and Meeting Goal

Donald R. Mattison, M.D., Captain, U.S. Public Health Service; Senior Advisor to the Directors of NICHD and CRMC; Chief, OPPB, CRMC, NICHD, NIH

BPCA legislation encourages the collection of pediatric data on drug use and consequences and offers economic considerations, including an additional 6 months of exclusivity to drug manufacturers that collect data as requested by the Food and Drug Administration (FDA). Another component of the BPCA legislation is the request that NICHD be involved in drug development. The original 2002 BPCA legislation asked NICHD to explore mostly off-patent drugs that were of use in pediatric therapeutics and collect data that would enhance labeling of those drugs. The focus of activities was off-patent drugs with specific indications. The goal was to improve knowledge on dosing, safety, and efficacy of drugs for children. The lessons learned from these initial activities were communicated to Congress. In the 2007 reauthorization of BPCA, the legislation directed NICHD to think more broadly about pediatric therapeutics. The focus of activities shifted to include not only drugs but also devices and biologics. There is a new focus on therapeutic needs within pediatric conditions. Under the new legislation, the goal of BPCA has shifted to improving knowledge on dosing, safety, and efficacy for pediatric therapeutics.

The BPCA legislation—both 2002 and 2007—asked NICHD to determine priority areas, specifically affected patient populations, unmet needs, and scientific importance. Priorities include:

- Diseases of high prevalence in the pediatric population
- Diseases with high morbidity and mortality
- Diseases with limited availability of treatment alternatives
- Treatment of rare diseases
- Label changes
- New pediatric formulations
- Diseases with public health and global scientific impact
- Compelling preclinical rationale
- Novel mechanisms of action, trial design, and/or outcome measures
- Safety concerns.

Determining priorities begins with determining therapeutic area needs by defining boundaries (for example, whether the intervention is a drug, biologic, or delivery system), gathering data (for example, from literature, databases, and labels), and consulting experts (government, academic, organizations, and parents/advocacy groups). Factors in prioritization include feasibility, public health impact, relevance to BPCA, and innovation. Subsequent activities may include clinical research, clinical drug trials, epidemiology research, and basic science research. The responsibility of prioritization is shared among NICHD, various NIH liaisons, expert panels, BPCA working groups, the FDA Pediatric Division, and the FDA Review Division. About 20 NIH institutes and centers (ICs) have contributed to the BPCA Program.

To date, 106 pediatric drugs have been discussed with experts from NIH ICs, FDA, academia, and industry. Of these 106 drugs, 61 drug–indication pairs have been identified and listed as requiring further pediatric studies. NICHD has responded to 80 percent of the written requests (WRs) received. Nineteen WRs were received. Fifteen WRs led to ongoing clinical and/or preclinical studies. The remaining four WRs presented challenges. Because of safety concerns for drugs used in pediatric therapeutics and the gaps in knowledge about safety, BPCA activities continue to follow safety signals in all studied drugs. Drugs with specific concerns are methylphenidate, propylthiouracil (PTU), and melamine. So far, 10 drugs or indications have been studied through interagency agreements and collaborations.

Several treatment strategies are available to manage hyperthyroidism in pediatric patients. Treatment strategies should be considered in the context of risks and benefits. For example, PTU, although effective in treating hyperthyroidism, appears to carry a risk for hepatic failure. This working meeting brought together individuals from organizations with interests in pediatric drug development, pediatric endocrine disease, drug regulation, drug safety, drug-induced liver failure, and pediatrics to explore the data on liver failure in children with Graves' disease. The goal of the meeting was to improve understanding of liver damage following treatment of hyperthyroidism in children.

Overview of Antithyroid Drug Therapy

David S. Cooper, M.D., Director, Johns Hopkins Thyroid Clinic, Johns Hopkins University School of Medicine

Antithyroid drugs were developed as derivatives of thiourea, which was discovered to cause goiter in rats. Thiourea was the first drug used in man, followed by thiouracil (after testing hundreds of compounds in rats). E. B. Astwood's landmark paper on the treatment of hyperthyroidism with thiourea and thiouracil was published in the *Journal of the American Medical Association* in 1943. Both compounds caused agranulocytosis in about 1 percent of patients. PTU was found to have a lower risk of agranulocytosis; methimazole (MMI), which was introduced a few years later in 1949, seems to have a lower rate still.

Some pharmacologic comparisons of PTU and MMI are as follows:

Measure	PTU	MMI
▪ Serum protein binding	75 percent	Nil
▪ Serum half-life	75 minutes	About 4–6 hours
▪ Gastrointestinal absorption	Almost complete	Almost complete
▪ Peak serum concentrations	1 hour after ingestion	1 hour after ingestion
▪ Duration of action	12–24 hours	Possibly > 24 hours
▪ Transplacental passage	Lower	Higher
▪ Levels in breast milk	Lower	Higher

Both drugs are actively concentrated by the thyroid. Their mechanisms of action remain to be completely elucidated. However, the mechanisms of action are likely related to their ability to inhibit the use of iodine in a complex way. In addition, they may have effects on the immune system to further enhance their direct effects on thyroid function to promote "remissions" in Graves' disease, which is an autoimmune disease. PTU has an effect to block peripheral T4 to T3 conversion, an effect not shared by MMI.

There are two contexts for antithyroid drugs use. The drugs are used in short-term therapy (in the range of weeks to months) to "cool down" the patient prior to radioiodine therapy. Long-term therapy (in the range of 1–2 years) is used to achieve "remission," which may or may not occur. Long-term therapy is usually followed by radioiodine therapy. Antithyroid drugs have a subsequent deleterious effect on the efficacy of radioiodine therapy.

For the treatment of thyrotoxicosis, the starting dose of PTU is 100 mg three times a day. The starting dose of MMI is 10–30 mg/day as a single dose. The potency of MMI as an inhibitor of thyroid hormone synthesis is 20–50-fold greater than the potency of PTU (on a milligram-per-milligram basis). With both drugs, a euthyroid state is achieved in 4–12 weeks, depending on baseline severity, thyroid gland size, and drug dose. Because MMI is given in a single daily dose, patient compliance is better than that for PTU.

Side effects from these drugs can be classified as *minor* and *major*. Minor side effects occur in 5–10 percent of patients and include rash, urticaria, pruritus, fever, and gastrointestinal distress. Major side effects are agranulocytosis, hepatotoxicity, and vasculitis.

A comparison of PTU and MMI side effects are as follows:

Side effect	PTU	MMI
▪ Minor (rash, fever)	5–20 percent	5–20 percent (dose-related)
▪ Agranulocytosis	0.2–0.5 percent (not clearly dose-related)	0.2–0.5 percent (dose-related)
▪ Hepatic toxicity	Hepatitis (25 percent; perhaps < 1 percent severe)	Cholestasis (few deaths)
▪ Vasculitis	Antineutrophil cytoplasmic antibody positive (ANCA+)	Very rare

With regard to which drug is considered "better," the response time for PTU and MMI are both 4–12 weeks, although MMI response time may be faster. Compliance with MMI is greater than compliance with PTU. MMI toxicity is dose-related, with no hepatitis or vasculitis. PTU toxicities include hepatitis and vasculitis (based on case reports, not randomized clinical trials). The cost of MMI is higher with high doses. The cost of PTU is lower. PTU lowers the efficacy of radioiodine therapy, whereas MMI may or may not lower the efficacy of radioiodine therapy.

A number of pregnancy complications have been reported in hyperthyroid women. Maternal complications include preeclampsia, pregnancy-induced hypertension, preterm labor, congestive heart failure, placental abruption, and thyroid storm. Fetal complications include small for gestational age, fetal growth restriction (that is, intrauterine growth restriction), prematurity, stillbirth, fetal/neonatal hyperthyroidism, and central congenital hypothyroidism. PTU and MMI have been used to treat hyperthyroidism during pregnancy. Older data suggest that transplacental passage of MMI is greater than that for PTU. However, newer data have challenged this finding. With regard to teratogenic effects, associations with MMI include possible aplasia cutis and embryopathy, including choanal atresia, esophageal atresia, tracheoesophageal fistula, and athelia. Because there are no known teratogenic associations with PTU, it is the preferred drug to treat hyperthyroidism during pregnancy. Both PTU and MMI have been shown to be safe in lactating women, with preservation of normal neonatal thyroid function.

The extent of the problem of PTU-induced hepatitis is not known. Using data from a number of studies and information sources, the total annual number of cases of PTU-induced hepatitis in the United States can be roughly estimated.

- The annual number of cases of adult hyperthyroidism in the United States is about 63,000. About half of these cases will be treated with PTU. Assuming the incidence of severe hepatitis is 0.1 percent (1/1,000), 31 adults will develop severe hepatitis each year.
- There are about 4,000,000 births per year in the United States. Graves' disease occurs in 1/500–1/1,000 of pregnant women. Therefore, Graves' disease occurs in 4,000–8,000 women each year, and virtually all of them are treated with PTU. A severe hepatitis rate of 0.1 percent yields 4–8 cases per year, depending on the frequency of Graves' disease in pregnancy.
- There are about 80 million U.S. children between age 0 and 19 years. Assuming the incidence of hyperthyroidism is 25 percent of the adult incidence (10/100,000), there will be about 8,000 cases per year of pediatric hyperthyroidism. Assuming half the cases are treated with PTU and the incidence of severe hepatitis is 0.1 percent (1/1,000), 4 children will develop severe hepatitis each year.
- The total annual number of cases of PTU-induced hepatitis in the United States is 40–50 (31 adults, 4–8 pregnant women, and 4 children). Depending on the frequency of PTU-induced hepatitis (1/500–1/2,000), and the prevalence of PTU usage, the total number of annual cases could be as low as 20 or as high as 100.

Both PTU and MMI are effective antithyroid drugs. MMI has many advantages (for example, efficacy, compliance, and toxicity profile) over PTU, making it the drug of choice in hyperthyroidism. PTU may be favored in pregnancy because of possible teratogenic effects of MMI, not because of a difference in transplacental passage. PTU causes severe hepatitis in an

unknown fraction of patients (likely 1/500–1/2,000). What is not currently known about the use of antithyroid drugs during pregnancy is whether the risk of MMI-induced aplasia cutis or embryopathy outweighs the risk of PTU-induced hepatotoxicity.

Graves' Disease in Children: Treatment Options and Adverse Events

Scott Rivkees, M.D., Associate Chair of Pediatric Research, Director, Yale Child Health Research Center, Chief, Section of Developmental Endocrinology and Biology, Professor of Pediatrics, Department of Pediatrics, Yale University School of Medicine

Graves' disease in the pediatric population accounts for 95 percent of cases of hyperthyroidism.[1,2] In 1996, it was estimated that about 38,000 children (10–19 years old) had Graves' disease.[3] The disease is six times more frequent in females than in males.[1,2] With regard to age distribution, 5 percent of cases occur in children 5 years old and younger, 15 percent of cases occur in children 6–9 years old, and 80 percent of the cases are in children 10–18 years old. When treated medically (that is, with antithyroid drugs), children have lower remission rates than do adults. Pediatric remission rates range from 15 to 30 percent.[1,2]

The management of Graves' disease is the same for adults and children. There are three basic treatment options for Graves' disease in children: surgery, antithyroid drugs, and radioiodine therapy. Adverse events (AEs) are associated with each treatment option. There are some controversies for the treatment options and the associated AEs.

Some practitioners[4] consider surgery as the optimal treatment for pediatric Graves' disease. Although no studies of complication rates in children were provided, the complication rates for adults (1–5 percent) were applied to children. A recent study of clinical and economic outcomes of thyroid surgery in children found an average cost of $35,000 per operation.[5] The major complication rate related to total thyroidectomy (not for cancer) varied by type of surgeon: 18 percent for pediatric surgeons, 12 percent for general surgeons, and 4 percent for endocrine surgeons. This study concluded that (1) children with Graves' disease should be cared for at high-volume expert endocrine surgery centers and (2) the surgery is not an optimal option for many children.

Other practitioners consider radioiodine (^{131}I) as an optimal treatment for Graves' disease in children.[6] The goal of contemporary ^{131}I therapy is ablation of the thyroid. A ^{131}I dose greater than 150 μCi/gm (125 Gy; 12,500 Rads) is associated with a 95 percent cure rate with a single dose.[7] The current cost is about $800, and acute side effects are rare. Lingering fears with this treatment option include thyroid cancer, nonthyroid cancers, and reproductive injury. The lower age limit for radioiodine therapy is not known.

Medical therapy with the antithyroid drugs PTU and MMI is the first-line therapy for more than 95 percent of children with Graves' disease. Serious AEs have been reported for PTU and MMI. AEs for antithyroid drugs are very prone to underreporting. A recent literature search found the following:

- Published AEs include 42 case reports of PTU-related liver failure, 10 case reports of PTU-related deaths, and 5 case reports of PTU-related liver transplants.[8–42] About 30 percent of

these cases involved children patients (Table 1).[8,12,14,21,22,25,26,29,31,35,37,39,41,43] There are considerably fewer reports of serious AEs for MMI. Serious AEs include hepatocellular injury, agranulocytosis, and vasculitis.

- From 1970 to 1997, MedWatch reported the following AEs in children younger than 18 years of age: 14 cases of PTU-related liver injury, 2 cases of PTU-related liver transplants, and 3 cases of PTU-related death (Table 2). MMI-related AEs were far fewer and did not include liver injury or death.[44]
- Results of several cohort studies found that PTU is associated with a 5–30 percent incidence of minor AEs and up to a 5 percent incidence of major AEs. MMI is associated with a 5–13 percent incidence of minor AEs and up to a 2 percent incidence of major AEs.[45–51] These cohorts included more than 550 PTU-treated patients. AEs related to PTU use occurred in 15–35 percent of children, except for one report that described AEs in 1 of 63 patients.
- In 2004, drug-induced liver injury was reported to account for 15 percent of liver transplants in the Organ Procurement and Transplantation Network (OPTN), United Network for Organ Sharing (UNOS) database.[52] Acetaminophen accounted for 50 percent of drug-related transplants, followed by isoniazid (17 percent).[52] PTU was the third most common cause of drug-induced liver failure, accounting for 10 percent of drug-related transplants.[52] The age range of PTU-related transplant recipients was 6–69 years.[52]
- Study of antithyroid drug-induced agranulocytosis in 31,798 patients revealed incidence rates of 0.35 percent for MMI and 0.37 percent for PTU.[53] About 90 percent of the cases developed within 90 days of treatment onset.
- In a long-term follow-up study of the occurrence of ANCA and associated vasculitis in patients with hyperthyroidism treated with antithyroid drugs, there was a 30 percent incidence with PTU and a 5 percent incidence with MMI.[54]

Table 1. Case Reports of PTU-Related Liver Injury in Pediatric Patients

Author, date	Age (years)	Gender	Daily dose (mg)	Duration of PTU (months)	Liver abnormality	Outcome
Moore, 1946[8]	12	Female	300	0.5	Liver injury	Recovery
Parker, 1975[12]	9	Female	300	2	Portal inflammation cholestasis	Recovery
Reddy, 1979[14]	10	Female	300	1.2	Hepatitis	Recovery
Bloch, 1985[21]	12	Male	450	2	Hepatitis	Recovery
Garty, 1985[22]	12	Female	300	1	Hepatitis	Recovery
Limaye, 1987[24]	6	Female	300	4	Hepatitis	Recovery
Jonas, 1988[25]	13	Female	300	7	Massive necrosis	Death
Baker, 1989[26]	9	Female	300	3	Hepatitis	Recovery
Kirkland, 1990[29]	9	Female	300	4	Liver failure	Transplant/ recovery
Levy, 1993[31]	11	Female	300	14	Liver failure	Death
Deidiker, 1996[41]	13	Female	250	4	Liver failure	Transplant/ death

Williams, 1997[43]	14	Female	450	4	Liver failure	Transplant/ recovery
Testa, 2005[35]	17	Female	450	6	Liver failure	Transplant/ recovery
Sipe, 2006[37]	7	Female	300	9	Liver failure	Transplant/ recovery

Table 2. MedWatch-Reported AEs from 1970 to 1997 in Individuals ≥ 18 Years of Age

AE	PTU	MMI
Total number	34	14
Hospitalizations	18	3
Deaths	2	0
Liver injury: mild	1	0
Liver injury: serious	13	0
Liver transplantation	2	0
Liver injury-related death	2	0
Agranulocytosis	1	1
Leukopenia	3	1
Thrombocytopenia	1	0
Renal injury	3	
Vasculitis	3	1
Arthritis	1	2
Arthralgia	1	1
Rash/urticaria	5	9

Pediatric endocrinologists continue to use PTU to treat Graves' disease in children, even though there is a 5–30 percent incidence of minor AEs and a 5 percent incidence of major AEs. Hepatotoxicity is a major current concern. There have been at least one to three cases of PTU-related liver failure per year in the United States for decades. PTU toxicity is not just a pediatric problem. A similar hepatic safety signal is not apparent with MMI. Therefore, antithyroid medication use should not be viewed as trivial in children.

Investigations of Graves' disease are needed to better understand current treatment practices, to determine better predictors of remission, and to better understand risks of radioiodine therapy. Guidelines are needed for the monitoring of children on antithyroid drugs. Comparative studies of risks and benefits of each treatment option and studies of long-term outcomes of Graves' disease treatments are also needed.

1. Rivkees SA. The treatment of Graves' disease in children. *J Pediatr Endocrinol Metab* 2006;19(9):1095-111.
2. Rivkees SA, Sklar C, Freemark M. Clinical review 99: The management of Graves' disease in children, with special emphasis on radioiodine treatment. *J Clin Endocrinol Metab* 1998;83(11):3767-76.

3. Jacobson DL, Gange SJ, Rose NR, Graham NM. Epidemiology and estimated population burden of selected autoimmune diseases in the United States. *Clin Immunol Immunopathol* 1997;84(3):223-43.
4. Lee JA, Grumbach MM, Clark OH. The optimal treatment for pediatric Graves' disease is surgery. *J Clin Endocrinol Metab* 2007;92(3):801-3.
5. Sosa JA, Tuggle CT, Wang TS, et al. Clinical and economic outcomes of thyroid and parathyroid surgery in children. *J Clin Endocrinol Metab* 2008.
6. Rivkees SA, Dinauer C. An optimal treatment for pediatric Graves' disease is radioiodine. *J Clin Endocrinol Metab* 2007;92(3):797-800.
7. Rivkees SA, Cornelius EA. Influence of iodine-131 dose on the outcome of hyperthyroidism in children. *Pediatrics* 2003;111(4 Pt 1):745-9.
8. Moore FD. Toxic manifestations of thiouracil therapy. *JAMA* 1946;130:315-9.
9. Colwell AR, Jr., Sando DE, Lang SJ. Propylthiouracil-induced agranulocytosis, toxic hepatitis, and death. *JAMA* 1952;148(8):639-41.
10. Eisen MJ. Fulminant hepatitis during treatment with propylthiouracil. *N Engl J Med* 1953;249(20):814-6.
11. Fedotin MS, Lefer LG. Liver disease caused by propylthiouracil. *Arch Intern Med* 1975;135(2):319-21.
12. Parker LN. Letter: Hepatitis and propylthiouracil. *Ann Intern Med* 1975;82(2):228-9.
13. Mihas AA, Holley P, Koff RS, Hirschowitz BI. Fulminant hepatitis and lymphocyte sensitization due to propylthiouracil. *Gastroenterology* 1976;70(5 pt.1):770-4.
14. Reddy CM. Propylthiouracil and hepatitis: a case report. *J Natl Med Assoc* 1979;71(12):1185-6.
15. Weiss M, Hassin D, Bank H. Propylthiouracil-induced hepatic damage. *Arch Intern Med* 1980;140(9):1184-5.
16. Pacini F, Sridama V, Refetoff S. Multiple complications of propylthiouracil treatment: granulocytopenia, eosinophilia, skin reaction and hepatitis with lymphocyte sensitization. *J Endocrinol Invest* 1982;5(6):403-7.
17. Parker WA. Propylthiouracil-induced hepatotoxicity. *Clin Pharm* 1982;1(5):471-4.
18. Safani MM, Tatro DS, Rudd P. Fatal propylthiouracil-induced hepatitis. *Arch Intern Med* 1982;142(4):838-9.
19. Fedotin MS. Correction. Propylthiouracil and hepatitis. *Arch Intern Med* 1984;144(10):2100-1.
20. Hanson JS. Propylthiouracil and hepatitis. Two cases and a review of the literature. *Arch Intern Med* 1984;144:994-6.
21. Bloch CA, Jenski LJ, Balistreri WF, Dolan LM. Propylthiouracil-associated hepatitis. *Arch Intern Med* 1985;145(11):2129-30.
22. Garty BZ, Kauli R, Ben-Ari J, et al. Hepatitis associated with propylthiouracil treatment. *Drug Intell Clin Pharm* 1985;19(10):740-2.
23. Seidman DS, Livni E, Ilie B, Blum I. Propylthiouracil-induced cholestatic jaundice. *J Toxicol Clin Toxicol* 1986;24(4):353-60.
24. Limaye A, Ruffolo PR. Propylthiouracil-induced fatal hepatic necrosis. *Am J Gastroenterol* 1987;82(2):152-4.
25. Jonas MM, Eidson MS. Propylthiouracil hepatotoxicity: two pediatric cases and review of the literature. *J Pediatr Gastroenterol Nutr* 1988;7(5):776-9.

26. Baker B, Shapiro B, Fig LM, et al. Unusual complications of antithyroid drug therapy: four case reports and review of literature. *Thyroidology* 1989;1(1):17-26.
27. Maggiore G, Larizza D, Lorini R, et al. Propylthiouracil hepatotoxicity mimicking autoimmune chronic active hepatitis in a girl. *J Pediatr Gastroenterol Nutr* 1989;8(4):547-8.
28. Morris CV, Goldstein RM, Cofer JB, et al. An unusual presentation of fulminant hepatic failure secondary to propylthiouracil therapy. *Clin Transpl* 1989:311.
29. Kirkland JL. Propylthiouracil-induced hepatic failure and encephalopathy in a child. *DICP* 1990;24(5):470-1.
30. Peter SA. Propylthiouracil-associated hepatitis. *J Natl Med Assoc* 1991;83(1):75-7.
31. Levy M. Propylthiouracil hepatotoxicity. A review and case presentation. *Clin Pediatr (Phila)* 1993;32(1):25-9.
32. Westphal SA. Hepatotoxicity from propylthiouracil. *South Med J* 1994;87(9):943-7.
33. Hardee JT, Barnett AL, Thannoun A, et al. Propylthiouracil-induced hepatotoxicity. *West J Med* 1996;165(3):144-7.
34. Ruiz JK, Rossi GV, Vallejos HA, et al. Fulminant hepatic failure associated with propylthiouracil. *Ann Pharmacother* 2003;37(2):224-8.
35. Testa G, Trevino J, Bogetti D, et al. Liver transplantation for propylthiouracil-induced acute hepatic failure. *Dig Dis Sci* 2003;48(1):190-1.
36. Aydemir S, Ustundag Y, Bayraktaroglu T, et al. Fulminant hepatic failure associated with propylthiouracil: a case report with treatment emphasis on the use of plasmapheresis. *J Clin Apher* 2005;20(4):235-8.
37. Sipe WE, Su M, Posselt A, et al. Propylthiouracil-associated liver failure presenting as probable autoimmune hepatitis in a child with Graves' disease. *Pediatr Transplant* 2006;10(4):525-8.
38. Khovidhunkit W, Farese RV, Jr. Resolution of propylthiouracil-induced hepatic failure after treatment of thyrotoxicosis. *West J Med* 1997;167(5):353-6.
39. Brand F, Liegeois P, Langer B. One case of fetal and neonatal variable thyroid dysfunction in the context of Graves' disease. *Fetal Diagn Ther* 2005;20(1):12-5.
40. Waseem M, Seshadri KG, Kabadi UM. Successful outcome with methimazole and lithium combination therapy for propylthiouracil-induced hepatotoxicity. *Endocr Pract* 1998;4(4):197-200.
41. Deidiker R, deMello DE. Propylthiouracil-induced fulminant hepatitis: case report and review of the literature. *Pediatr Pathol Lab Med* 1996;16(5):845-52.
42. Ozenirler S, Tuncer C, Boztepe U, et al. Propylthiouracil-induced hepatic damage. *Ann Pharmacother* 1996;30(9):960-3.
43. Haddow JE, Palomaki GE, Allan WC, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med* 1999;341(8):549-55.
44. Rivkees SA, Sklar C, Freemark M. The management of Graves' disease in children, with special emphasis on radioiodine treatment. *J Clin Endocrinol Metab* 1998;83(11):3767-75.
45. Glaser NS, Styne DM. Predicting the likelihood of remission in children with Graves' disease: a prospective, multicenter study. *Pediatrics* 2008;121(3):e481-8.
46. Hamburger JI. Management of hyperthyroidism in children and adolescents. *J Clin Endocrinol Metab* 1985;60(5):1019-24.

47. Kaguelidou F, Alberti C, Castanet M, et al. Predictors of autoimmune hyperthyroidism relapse in children after discontinuation of antithyroid drug treatment. *J Clin Endocrinol Metab* 2008.
48. Lippe BM, Landaw EM, Kaplan SA. Hyperthyroidism in children treated with long term medical therapy: twenty-five percent remission every two years. *J Clin Endocrinol Metab* 1987;64(6):1241-5.
49. Ma C, Kuang A, Xie J, Liu G. Radioiodine treatment for pediatric Graves' disease. *Cochrane Database Syst Rev* 2008(3):CD006294.
50. Somnuke PH, Pusuwan P, Likitmaskul S, et al. Treatment outcome of Graves' disease in Thai children. *J Med Assoc Thai* 2007;90(9):1815-20.
51. Van Vliet G. Neonatal hypothyroidism: treatment and outcome. *Thyroid* 1999;9(1):79-84.
52. Russo MW, Galanko JA, Shrestha R, et al. Liver transplantation for acute liver failure from drug induced liver injury in the United States. *Liver Transpl* 2004;10(8):1018-23.
53. Tajiri J, Noguchi S. Antithyroid drug-induced agranulocytosis: how has granulocyte colony-stimulating factor changed therapy? *Thyroid* 2005;15(3):292-7.
54. Slot MC, Links TP, Stegeman CA, Tervaert JW. Occurrence of antineutrophil cytoplasmic antibodies and associated vasculitis in patients with hyperthyroidism treated with antithyroid drugs: A long-term followup study. *Arthritis Rheum* 2005;53(1):108-13.

Hepatic Toxicity Following Treatment for Pediatric Graves' Disease—The Multi-Item Gamma Poisson Shrinker (MGPS) Data Mining Signals

Ana Szarfman, M.D., Ph.D., Medical Officer, Office of New Drugs, Office of Translational Sciences, Center for Drug Evaluation and Research (CDER), FDA

Medical data are inherently noisy. In this noisy environment, generating valid safety signals in a proactive, systematic, and reproducible way requires the implementation of a careful data management strategy. The solution involves a continuous iterative process that enhances the ability of multiple specialists to (1) understand and validate the evolving data cleaning and configuration decisions and the tools being built and (2) interpret the evolving signaling results within this context.

Interactive systems need to provide the ability to drill down into individual patient profiles and narratives or notes to (1) observe the behavior that is taking place when making data extraction and transformation decisions and (2) drill down into an effective representation of the data configuration, without guesswork. At the end, the validated data processes and tools speed the development of better data and better analytical tools.

There is a need to speed the identification of drug safety issues, especially with serious emergent safety signals. Accessibility and speed are important during more mundane activities, such as when assessing new dose increases, new combination products, new drugs for the same indication, new "me-too" drugs, and labeling updates. Accessibility and speed are also important when assessing potential drug–drug interactions and syndromes, as well as subpopulations of higher risk patients. Together with the need to speed detection of safety signals comes the need to speed the confirmation of safety signals.

More than 10 years ago, FDA started developing a data mining system for simultaneous detection of AEs in the Adverse Events Reporting System (AERS) database. The data mining engine is based on the MGPS empirical Bayesian algorithm developed by William DuMouchel, Ph.D. In general, data mining is statistical analysis applied to large databases without any a priori hypotheses.

The AERS database is a computerized system that stores voluntarily reported drug-related AEs. There have been more than 3 million reports from 1968 to the present. There are more than 1,500 new reports a day. The reports generally include only a small number of data elements (for example, drugs, events, age, and sex). Much of the information is sparse or missing certain elements.

MGPS is routinely applied to compute signal scores for all of the millions of drug-event combinations represented in large data repositories, including:

- FDA's AERS
- World Health Organization's Vigibase
- Medicines and Healthcare products Regulatory Agency of the United Kingdom
- National Cancer Institute's Surveillance Epidemiology and End Results
- Johns Hopkins University outcome data
- Department of Defense health care data.

The process of computing signal scores in large repositories of safety data can be completed in a few hours. Because of the need for speedy identification of drug safety issues and the need for speedy confirmation of safety issues, the Institute of Medicine recognized the value of MGPS in two reports. *The Future of Drug Safety* of 2006 recommended a more active use of MGPS, WebVDME (pharmacovigilance signal detection and signal management software), and the sector map. *The Emergent Science of Drug Safety* of 2007 described the supportive use of MGPS to help identify new medications lacking specific toxicities.

The MGPS data mining program handles complex stratification (more than 1,000 categories: 9 for age, 3 for gender, and 40 for year of report). Stratification helps adjust for background differences in relative reporting by these variables. The MGPS data mining program uses statistical modeling to systematically "shrink" volatile estimates due to small counts. The goal of shrinking is to estimate the true relative reporting ratio (RR). A true RR of 350 indicates that a drug–event combination occurs 350 times more than expected under the assumption of independence between drugs and events. The empirical Bayes geometric mean (EBGM) estimates the RR. Because expected counts are often so small that a single report will yield a huge RR, it is necessary to shrink the RR. Shrinkage dramatically reduces the false positive rate.

AERS sector reports were used to create MGPS sector maps to detect hepatotoxicity signals of PTU and MMI in pediatric patients. PTU had higher signals from pediatric reports than from reports in adults. The EBGM values had wide confidence limits, probably due to the low number of reports. For MMI, there were no serious liver events signals in pediatric reports.

Both case reviews and data mining provide insight into the drug AEs. Case reviews may give insight into the correctness of the diagnosis and occasionally into the causal relationship between the drug and the event. Data mining provides a systematic insight into how the reporting frequency of the AE compares with background reporting rates or to reporting rates for other drugs.

OPTN Data on Drug-Induced Acute Liver Failure in Pediatrics

Wida Cherikh, Ph.D., Senior Biostatistician, Department of Research, UNOS

UNOS is a nonprofit organization that administers the OPTN, which was established by Congress under the National Organ Transplant Act of 1984. UNOS is the only organization to manage the OPTN and has administered this HHS contract for more than 20 years. The OPTN is a unique public–private partnership that links all of the professionals involved in the donation and transplantation system. The primary goals of the OPTN are to increase the effectiveness and efficiency of organ sharing and equity in the national system of organ allocation and to increase the supply of donated organs available for transplantation. The OPTN's secure transplant information database contains all national data on the candidate waiting list, organ donations and matching, and transplantation. This system is critical in helping organ transplant institutions match waiting candidates with donated organs. Institutions rely on the database to manage time-sensitive, life-critical data of all candidates, before and after their transplants.

Numerous entities submit data to the OPTN database, including:

- All transplant centers performing solid organ transplantation for data on transplant candidates, transplant recipients, and living donors
- All organ procurement organizations for data on deceased donors
- All histocompatibility laboratories for tissue typing and cross-match information for donors and recipients.

Numerous data are collected for liver transplant candidates and transplant recipients, and follow-up data are collected for transplant recipients. The purpose of the current study is to identify pediatric candidates on the liver wait list with drug-induced acute liver failure diagnosis from the OPTN database; to tabulate drugs reported as cause of liver failure, characteristics of cohort, and wait list outcomes; and to summarize transplant outcomes.

Characteristics of the study cohort are as follows:

- Pediatric candidates (age at listing younger than 18 years old) added to the liver wait list between April 1, 1994, and March 31, 2008, with primary or secondary diagnosis of drug-induced acute hepatic necrosis or other, specify.
- Before April 1, 1994, diagnosis was not collected on the wait list or on the transplant candidate registration form.
- There were 12,389 pediatric registrations—or 10,408 unique pediatric patients—between April 1, 1994, and March 31, 2008.
- There were 275 pediatric registrations—or 269 unique pediatric patients—between April 1, 1994, and March 31, 2008, with drug-induced acute liver diagnoses. The five most common

drugs were acetaminophen (63.5 percent), PTU (about 4 percent), unknown (13 percent), and other (about 20 percent).

- Of the 269 patients, 14 had more than one registration either before April 1, 1994, with no diagnosis; or between April 1, 1994, and March 31, 2008, with diagnosis of non-drug-induced acute liver failure or listed at older than 17 years of age.
- Among the pediatric patients listed due to drug-induced acute liver failure between April 1, 1994, and March 31, 2008, 76 patients were removed for a liver transplant. Of the 29 acetaminophen patients who received a transplant, 24 received a deceased donor transplant and 5 received a living donor transplant. All six PTU patients received a deceased donor liver transplant.

Characteristics of the study cohort of PTU patients are as follows:

- Between April 1, 1994, and March 31, 2008, there were 10 unique pediatric patients with PTU-induced acute liver failure diagnosis.
- Among the 10 patients, 1 had three registrations between April 1, 1994, and March 31, 2008; one registration before April 1, 1994, with unknown diagnosis; and one registration between April 1, 1994, and March 31, 2008, with non-PTU-induced acute liver diagnosis.

In summary, the incidence of drug-induced acute liver failure in pediatric liver wait list patients was relatively low. The most commonly reported drug was acetaminophen. Across all drugs, acute liver failure seemed to occur more frequently in White female patients between the ages of 12 and 17 years. Most patients were listed in urgent medical status categories. More than half of the acetaminophen-induced patients were removed for improved condition, whereas more than half of the PTU-induced patients were removed for a transplant. The incidence of PTU-induced acute liver failure was very low among pediatric wait list patients in the study cohort. Most of the 10 patients were in urgent status category while on the wait list. Six received deceased donor liver transplants. One of the six patients was listed five times, had three transplants, and died. Five of the six patients were reported alive and with a functioning graft.

Pediatric Acute Liver Failure (PALF) Study Group

Robert Squires, Jr., M.D., Clinical Director, Gastroenterology, Children's Hospital of Pittsburgh; Professor of Pediatrics, University of Pittsburgh

The etiology of acute liver failure (ALF) has historically been defined by single site experiences. One of the issues with single site studies is the length of time (often decades) to accumulate data from a cohort of adequate size. In addition, management strategies change over time. Worldwide, infections are the predominant cause of PALF.

The PALF Study Group began in 2005 as an ancillary component of an adult ALF study led by William M. Lee, M.D., of the University of Texas Southwestern. The PALF Study Group is funded by the National Institute of Diabetes and Digestive and Kidney Diseases through 2010. It is a multicenter, multinational study in three countries: the United States (17 sites) Canada (1 site in Toronto), and the United Kingdom (2 sites, London, Birmingham). The study collects clinical and laboratory data, plus serum daily for 7 days. Endpoints are death, transplant, and discharge. Biological samples include DNA, bile, liver tissue, fibroblasts, and urine. A randomized clinical

trial is investigating N-acetylcysteine treatment for non-acetaminophen PALF. Core ancillary studies are investigating acetaminophen adducts, fatty acid oxidation defects in PALF, and natural killer cell dysfunction in PALF.

In adults, ALF is traditionally defined as acute hepatic dysfunction (jaundice, coagulopathy, etc.) and development of encephalopathy within 8 weeks. Children are different: Encephalopathy is difficult to assess and may not develop until terminal stages. The PALF Study Group developed a consensus definition of ALF in children, which served as the entry criteria for the study:

- No evidence of chronic liver disease
- Evidence of acute liver injury
- Coagulopathy unresponsive to vitamin K
  - Prothrombin time > 15 seconds or international normalized ratio (INR) > 1.5 with encephalopathy
  - Prothrombin time > 20 seconds or INR > 2.0 with/without encephalopathy.

The natural course of PALF has only two outcomes: life or death. No longer is there a way to assess natural course because of the arbitrary intervention of liver transplant, which can occur at any time along the continuum of natural disease course. Clinicians may observe prodrome signs, but there are no indicators of time zero, or exactly when liver failure began. This makes it difficult to extrapolate what is observed in the data set with clinical signs and symptoms. Defining parameters and measuring biomarkers early in the disease course would allow better characterization, which could lead to earlier transplants and higher survival rates.

The PALF Study Group has enrolled about 700 children. Most of the children were younger than 3 years of age at time of enrollment. The top three causes of ALF in infants younger than 4 weeks of age are metabolic disease, viral hepatitis (primarily herpes), and neonatal iron storage disease. From 9 weeks to 1 year of age, the primary cause of ALF is "indeterminate" (45 percent of patients). During this period, patients begin to show autoimmune markers (about 5 percent of patients). From 1 and 10 years of age, about 60 percent of ALF cases result from indeterminate causes. In patients older than 10 years, autoimmune disease appears in about 10 percent of ALF cases. Drug-induced ALF increases from 1–4 percent in children younger than 10 years to about 7 percent in children older than 10. Valproic acid, PTU, phenytoin, isoniazid, and iron caused about half of the cases (11 of 24 patients) of drug-induced hepatitis. Twenty-one-day outcomes for drug-induced hepatitis were 19 percent dead, 33 percent transplant, and 48 percent alive. Of the patients with acetaminophen-induced hepatitis, about 93 percent were alive at day 21, about 5 percent received transplants, and 3 percent died. Two of these transplant recipients appeared to have abnormalities in fatty acid oxidation.

The PALF Study Group examined drug exposure 1 month before recognition of PALF. Twenty-one-drug classes were recognized. The top five classes were antibiotics (258 cases), acetaminophen (188 cases), nonsteroidal anti-inflammatories (116 cases), anticonvulsants (69 cases), and antacids (41 cases). Some cases were exposed to several classes of drug in the 1 month before recognition of PALF. Two patients in the PALF Study Group data set had PTU-induced ALF. Both had massive hepatic necrosis and received transplants.

Of all the children in the PALF Study Group, about 47 percent had ALF due to indeterminate causes; 13 percent of the cases were caused by acetaminophen and narcotics; and 40 percent were caused by drug, viral, metabolic, and "other" causes. Within different age groups, the etiology of PALF is quite different and evolves with age.

Hepatic Toxicity Following Treatment for Pediatric Graves' Disease: Frequency of Drug Use

James Korelitz, Ph.D., Associate Director and Senior Epidemiologist, Westat

This study used administrative claims data from Medicaid and commercially insured pediatric populations to estimate the prevalence of Graves' disease and frequency of outpatient prescription drug use among children with Graves' disease. The databases included 10.7 million children (ages 0–17 years) from 11 states with Medicaid coverage in 2003, and 4.3 million children from 50 states with commercial insurance during 2004–2005. The primary research questions were as follows:

- What percentage of children had a medical claim with a diagnosis of Graves' disease or other thyroid disorder?
- What percentage of all children had one or more claims for antithyroid medications?
- Among children with Graves' disease, what percentage had one or more claims for antithyroid medications?

Study results corresponding to the three research questions are shown in Tables 1–3.

Table 1. Prevalence of Thyroid Disorders (per 100,000 Children)

ICD-9-CM Code	Disorder	Medicaid, 2003	Commercial, 2004–2005
240-246	Disorders of the thyroid gland	176.0	240.0
240-242	Goiter or thyrotoxicosis	49.5	81.4
242.0	Toxic diffuse goiter, includes Graves' disease	8.8	12.8

Table 2. Frequency of Medication Use Among All Children

Medication	Medicaid, 2003 Number and Percentage with Dispensed Medication (*N* = 10,728,026)	Commercial, 2004–2005 Number and Percentage with Dispensed Medication (*N* = 4,266,479)
Any antithyroid agent	1,433 (0.013 percent)	620 (0.014 percent)
MMI	722 (0.007 percent)	379 (0.009 percent)
PTU	533 (0.005 percent)	147 (0.003 percent)
Potassium iodine	176 (0.002 percent)	134 (0.003 percent)

Table 3. Frequency of Medication Use Among Children with Graves' Disease (ICD-9 242.0)

Medication	Medicaid, 2003 Percentage with Dispensed Medication (*N* = 946)	Commercial, 2004–2005 Frequency with Dispensed Medication (*N* = 7090)
Any antithyroid agent	53.6 percent	49.6 percent
MMI	33.5 percent	38.8 percent
PTU	19.3 percent	15.0 percent

Additional results of the study are as follows:

- Graves' disease is relatively rare in children: about one case per 10,000 children. Graves' disease accounts for about 16 percent of all goiter or thyrotoxicosis cases and about 5 percent of all disorders of the thyroid gland cases. There is a higher prevalence among females than among males (3:1). There is an increasing prevalence with age.
- The frequency of use of antithyroid drugs is rare in the general population, but about 50 percent of children with Graves' disease were dispensed an antithyroid drug. MMI was dispensed about twice as often as PTU.
- Additional analyses are required to look at other treatments that may have been received by children with Graves' disease, especially those who were not dispensed an antithyroid drug.
- Large databases are generally required to study drug use among children with medical conditions of low prevalence.

PTU and MMI Prescription Data

Vicky Borders-Hemphill, Pharm.D., LCDR, U.S. Public Health Service Commissioned Corps; Drug Utilization Analyst, Division of Epidemiology, Office of Surveillance and Epidemiology, CDER, FDA

Laura Governable, Pharm.D., Drug Utilization Data Specialist Team Leader, Office of Surveillance and Epidemiology, CDER, FDA

Three databases were analyzed to collect PTU and MMI prescription data:

- IMS Health, IMS National Sales Perspectives: Retail and Non-Retail
- SDI Vector One: National (VONA)
- SDI Physician Drug and Diagnosis Audit (PDDA).

IMS Health, IMS National Sales Perspectives: Retail and Non-Retail database, which includes national projections, measures of the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and nonretail markets. Retail market outlets include chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Nonretail market outlets include clinics, nonfederal hospitals, federal facilities, health maintenance organizations, long-term care facilities, home health care, and other miscellaneous settings.

SDI VONA, which includes national projections, measures retail dispensing of prescriptions. Database sources include national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. VONA receives more than 2 billion prescription claims per year, representing more than 160 million unique patients. Since 2002, VONA has captured information on more than 8 billion prescriptions representing 200 million unique patients. Prescriptions are captured from a sample of about 59,000 pharmacies throughout the United States. These pharmacies account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. SDI receives all prescriptions from about one-third of the stores and a significant sample of prescriptions from the remaining stores.

SDI PDDA, which also includes national projections, is a monthly survey of prescribers from U.S. office-based physician practices. Data are collected from about 3,100 office-based physicians representing 29 specialties that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit, and treatment patterns.

In 2007, more than 246,000 prescriptions of MMI were dispensed to patients 0–17 years of age. These prescriptions represent 19 percent of overall MMI prescriptions (about 1.3 million) dispensed in 2007. In 2007, nearly 9,000 prescriptions of PTU were dispensed to patients 0–17 years of age. These prescriptions represent about 2 percent of overall PTU prescriptions (about 413,000) dispensed in 2007.

The top three diagnosis codes reported by physicians prescribing PTU or MMI were:
- ICD-9 242.0 toxic diffuse goiter
- ICD-9 242.9 thyrotoxicosis NOS
- ICD-9 244.9 hypothyroidism (for MMI) or ICD-9 648.1 thyroid dysfunction in pregnancy (for PTU).

The results of the data analysis are as follows:
- MMI was more commonly dispensed to pediatric patients, 0–17 years of age, compared with PTU during the entire time period studied.
- MMI dispensed prescriptions increased by 61 percent and PTU dispensed prescriptions decreased (–44 percent) for pediatric patients from 2002 to 2007.
- In 2007, nearly twice the amount of MMI prescriptions were dispensed to patients 0–11 years of age compared with patients 12–17 years of age.
- In 2007, nearly three times the amount of PTU prescriptions were dispensed to patients 12–17 years of age compared with patients 0–11 years of age.

Postmarketing Review of AERS Cases Associated with PTU and MMI in the Treatment of Graves' Disease

Joslyn Swann, Pharm.D., Safety Evaluator, Division of Pharmacovigilance I, Office of Surveillance and Epidemiology, CDER, FDA

A postmarketing review of AERS was conducted to determine the number of cases associated with PTU and MMI in the treatment of Graves' disease. Strategies for searching the AERS included the following:

- Drugs: PTU or MMI
- AERS outcome: All
- Drug role: Suspect
- MedDRA terminology used:
  - Hepatic failure and associated disorders (HLT)
  - Hepatic necrosis (PT)
  - Hepatitis fulminant (PT)
  - Liver transplant (PT)
- Timeframe: U.S. approval (for PTU, July 1947; for MMI, June 1950) through October 6, 2008.

Cases were defined as severe life-threatening liver injury as follows:

- Severe liver injury with secondary encephalopathy or coagulopathy in the setting of acute liver injury (elevated transaminases, bilirubin, or jaundice)
- Clinical diagnosis of liver failure or liver necrosis, without supporting clinical or laboratory data
- Death from liver injury, liver transplantation, or placement on a liver transplant list.

Case selection criteria were severe life-threatening liver injury and temporal relationship associated with use of PTU or MMI. The results for crude counts revealed that there were 44 reports of severe life-threatening liver injury associated with PTU and 5 reports associated with MMI. After report adjudication, there were 10 duplicate cases associated with PTU, which yields 34 cases (24 adult, 12 pediatric). For MMI, there were five cases, all adult.

Changing Concepts of the Mechanisms of Hepatic Drug Toxicity

James L. Boyer, M.D., Ensign Professor of Medicine, Director, Liver Center, Section of Digestive Diseases, Department of Internal Medicine, Yale University School of Medicine

In the traditional view, there are two types of drug hepatotoxicity: direct and idiosyncratic. Classic clinical characteristics of direct hepatic toxicity include:

- High incidence (100 percent)
- Dose-dependence
- Reproducible in animals
- No latent period
- No signs of immunologic response; absence of fever, rash, or eosinophilia
- Necrosis often zonal; no inflammatory component.

Classic clinical characteristics of idiosyncratic drug hepatotoxicity (IDH) include:

- Low incidence (1/1,000 to 1/10,000)
- Not dose-dependent
- Not reproducible in animals
- Often mimics viral hepatitis
- Signs of immunologic response; fever, rash, and eosinophilia may occur
- Latent period (shortened by rechallenge)
- Most cases will get better if the drug is stopped.

Although the exact mechanisms in IDH are not clearly understood, a number of risk factors are known to play a role. Risk factors for hepatic drug toxicity include age, sex, nutritional status, use of alcohol and other drugs, exposure to environmental agents, preexisting liver disease such as viral infections, and genetic determinants of drug metabolism and transport. It has been shown that underlying inflammation due to viral infections (for example, HIV and hepatitis C) increases the relative risk of drug hepatitis and incidence of idiosyncratic reactions.

The concepts of the pathogenesis of IDH are evolving beyond the traditional views. Several hypotheses and mechanisms for pathogenesis have been proposed, including the hapten hypothesis (immunologic pathway) and the reactive toxic metabolite hypothesis (metabolic pathway). These pathways may not be mutually exclusive, and there may be interplay between them. Another hypothesis is the danger hypothesis.

The hapten hypothesis proposes that drugs, or more commonly reactive metabolites of drugs, act as haptens and irreversibly bind to proteins or other macromolecules. (A hapten is a small molecule that can elicit an immune response only when attached to a large carrier such as a protein; the carrier may be one that also does not elicit an immune response by itself.) These altered proteins are "perceived" as foreign and induce an immune response. In most individuals, this immune response is asymptomatic, but in a few cases, it leads to pathology. The steps in the process are:

- Exposure to drug
- Metabolic formation of a reactive metabolite
- Inadequate detoxification of metabolite
- Covalent binding to macromolecules
- Formation of neoantigens
- Antigen presentation to T cells
- Immune recognition of neoantigens
- Formation of cytotoxic antibodies or lymphocytes
- Subsequent liver toxicity.

Reactive toxic metabolites such as N-acetyl p-benzoquinone imine from acetaminophen are known to cause IDH. Although acetaminophen metabolism has been studied for decades, it is still not known how the formation of protein adducts leads to cell death. IDH due to reactive toxic metabolites has led to the withdrawal of several drugs from market even after rigorous clinical testing as part of the FDA approval process. Examples of these drugs are benoxaprofen (Oraflex), bromfenac (Duract), iproniazid, nefazodone (Serzone), tienilic acid (Ticrynafen), and

troglitazone. There are a number of drugs with some evidence for reactive metabolites and, therefore, black box warnings, including dacarbazine, isoniazid, trovafloxacin, and valproic acid. There may be some evidence of reactive metabolites for PTU. PTU can be oxidized to immunogenic metabolites by neutrophiles and macrophages to PTU sulfonate, PTU disulfide, and propyluracil-2-sulfide. In addition, a high incidence of ANCA+ response in neutrophils is associated with PTU.

The erratic temporal and dose relationships that characterize idiosyncratic drug responses suggest the possibility that some event during the course of therapy renders tissues peculiarly susceptible to toxic effects of the drug. For example, episodes of inflammation are commonplace in people, and results of numerous studies in animals indicate that a modest inflammatory response can enhance tissue sensitivity to a variety of toxic chemicals. These observations have led to the hypothesis that an episode of inflammation during drug therapy could decrease the threshold for drug toxicity and thereby render an individual susceptible to a toxic reaction that would not otherwise occur. The danger hypothesis can explain the features of drug idiosyncrasy using fundamental pharmacologic principles, and results of recent animal studies are supportive of this. The exact nature and range of stimuli that can act as the danger signal remain to be determined, but certainly, cell damage must be a major stimulus for the production of the danger signal. According to the danger hypothesis, IDH occurs when inflammation (the danger signal) exceeds a certain threshold, interacts with the drug, and decreases the threshold for toxicity.

Another proposed mechanism of pathogenesis involves the innate or "adaptive" response to drug-induced injury. The liver is an organ with predominant innate immunity, playing an important role not only in host defenses against invading microorganisms and tumor transformation but also in liver injury and repair. In the adaptive response to IDH, a drug is metabolized to a toxic metabolite, which induces a stress response and hepatocyte death. Depending on the innate immune response, hepatocyte death may lead to severe injury or no injury.

Other factors that may play a role in IDH include drug dose, genetic determinants of drug metabolism and transport, and drug–drug interactions. With regard to the role of dosing, almost all drugs that cause IDH are administered in daily doses of 100 mg or more. The likelihood of IDH is greatly reduced with drugs that are more potent. There are very rare examples of IDH at doses less than 10 mg/day. For example, rosiglitazone (4–8 mg/day) and pioglitazone (15–45 mg/day) have the same glitazone structure as troglitzone (400 mg/day), yet IDH from rosiglitazone and pioglitazone are very rare. Troglitazone was taken off the market because of a high incidence of IDH. It is noteworthy that PTU is administered in 100 mg doses three times per day compared with MMI being administered in single 10–30 mg daily doses.

In summary:

- Drug hepatotoxicity is often associated with formation of reactive metabolites.
- Idiosyncratic reactions may depend on a "second hit" that involves inflammatory responses that lower the threshold for toxicity.
- Dose plays a role as do other risk factors including age, gender, nutritional status, use of other drugs and alcohol, and polymorphisms in drug transporters.

Drug-Induced Liver Failure

John R. Senior, M.D., Associate Director for Science, Office of Surveillance and Epidemiology, CDER, FDA
Mark Avigan, M.D., C.M., Director, Division of Pharmacovigilance I, Office of Surveillance and Epidemiology, CDER, FDA

Idiosyncrasy is an old and often misunderstood concept. Idiosyncrasy is basically "one's own mixture of characteristics," "one's own temperament," or "one's own constitution." Idiosyncrasy does not mean "rare," "unexplained," or "mysterious." Within the context of drug-induced drug liver failure, idiosyncrasy means that different people respond differently to the same stressor. Over a person's life, environmental factors may cause adaptive changes in gene expression, which may somewhat explain IDH.

The liver is a highly adaptive organ that can sustain a lot of injury and still recover. There is, however, a distinction between loss of hepatocytes (that is, injury) and the loss of function of the whole organ. Loss of function is reflected in measures such as total bilirubin. Standard measures of liver injury include serum transaminases such as aspartate transaminase and alanine transaminase (ALT). The combination of the specificity of bilirubin and the sensitivity of ALT led to Hy's law. Hy's law is a prognostic indicator that a pure drug-induced liver injury leading to jaundice, without a hepatic transplant, has a case fatality rate of 10–50 percent. ALT measures are not predictive of injury. Nor is Hy's law predictive on an individual level. Hy's law may, however, be predictive for populations.

Definitions for the levels of severity for drug-induced liver injury are being developed:
- Level 1—elevated enzyme measures
- Level 2—extent of hepatocyte injury begins to affect overall liver function
- Lever 3—clinically recognizable, serious liver injury requiring hospitalization
- Level 4—acute liver failure with secondary injurious effects on other organs
- Level 5—death of liver and death of patient.

Because of concurrent risk factors, it may not be easy to attribute liver injury to a particular drug. Patients may be on more than one drug, and comorbidities may contribute to hepatopathy. Ruling out other causes of hepatotoxicity is a difficult exercise and requires differential diagnosis. High-quality clinical data are needed for such differential diagnoses. Because spontaneous reporting tends to be inadequate, it is generally not useful in making a differential diagnosis. Different levels of likelihood for drug-induced liver injury can be determined, and when combined with levels of severity, can inform differential diagnoses.

Information on drug-induced liver injury is posted on the FDA Web site. This information outlines the evolution in thinking about IDH. Much is now known about how the liver metabolizes drugs, how drugs in the liver interact, and how drug metabolites affect the liver.

Clinicians generally agree that IDH is dose-related. In the susceptible person, the dose range shifts to a much lower zone. Idiosyncratic responses may not be rare. For example, in people

hospitalized with medical complications from alcoholism, the rate of liver injury may be as low as 15 percent. Of people who take isoniazid, about 20 percent will develop elevated levels of transaminases. Idiosyncratic drug-induced liver responses are dose-related and are not rare. These responses are reproducible in animals. There is a variety of mechanisms for idiosyncratic responses because people are different in the way they respond to drugs.

There are several challenges to understanding PTU-induced hepatotoxicity. The first is the PTU phenotype and the mechanisms of toxicity. There is no direct measure of these mechanisms. There is some heterogeneity among PTU patients in how they present, when they present, and the tempo of disease progression. This heterogeneity is similar to other liver injury-inducing drugs. The second challenge is the lack of a quantitative measure of risk for PTU-induced hepatotoxicity. This event is rare, and there is no clinical trial database to determine "denominators" and "numerators" to calculate risk. PTU-related data sources are various, of different ages, and not always comparable. Another challenge to understanding PTU-induced hepatotoxicity is the role of the background effects of the liver, concurrent risk factors, and the potential for genetic predisposition to autoimmune disease.

There is an impressive signal for PTU-induced toxicity. Although the usage of PTU is decreasing, an extrapolation of the available data indicates that PTU is a bigger quantitative risk than MMI, without the measure of the risk. The effect of dose on the risk of hepatotoxicity is still not clear. The pediatric dose of PTU was not determined in a clinical development program to conclude a well worked out therapeutic index of dose. The metabolic pathways that lead to the toxic intermediates and the disposal of the drug are not known. The practitioner societies have not firmly agreed on the algorithm for patient management for Graves' disease. There is no well-publicized guidance for treating this disease. Finally, there is no good plan for managing risk in a treated patient. It is not clear how well monitoring would work in risk management.

An action plan for studying hepatotoxicity after treatment for pediatric Graves' disease includes:

- Dosing
- Metabolic pathways in animal models and human surrogates
- Outcomes in sufficiently powered observational cohort
- Communication plans for practitioner societies
- Risk management of thyroid disease
- A surveillance network.

Discussion

Based on the above information and an extensive discussion, the following observations and estimates can be made:

- The prevalence of pediatric Graves' disease in the United State is about 1 in 10,000 children. About 4,000 pediatric patients per year with Graves' disease are being treated with antithyroid drugs in the United States. In 2004, 40 percent of children with Graves' disease were treated with PTU. Over the past 4 years, the number of PTU prescriptions for children with Graves' disease has decreased by about 50 percent, whereas the number or prescriptions for MMI has increased by about 50 percent.

- The risk of PTU-induced liver failure leading to transplantation is about 1 in 2,000–4,000 children. (There are about 0.5 PTU-related liver transplants per year in children; about 1,000 to 2,000 children per year take PTU.) Once PTU-induced liver failure occurs, it is rapidly progressive with a low chance of reversibility. The long-term survival rate for children receiving a liver transplant due to PTU hepatotoxicity is about 60 percent. The number of children developing PTU-induced liver injury that is reversible is estimated to be at least 10-fold greater than the number of children who develop liver failure requiring transplantation.
- Routine biochemical surveillance of liver function and hepatocellular integrity (serum bilirubin, alkaline phosphatase, and transaminase levels) will not be useful in identifying children who will develop PTU-induced liver failure.
- Children are at higher risk for PTU-induced liver injury than are adults.
- PTU-induced liver injury is an important concern for the adult population. The number of adults with Graves' disease is at least four-fold higher than the number of children with Graves' disease. The proportion of adult patients prescribed PTU for Graves' disease is currently greater than the proportion of pediatric patients prescribed PTU. Although the proportion of children prescribed PTU for Graves' disease has decreased over the past 4 years, PTU prescribing practices have remained steady in the adult population.
- MMI is not associated with a risk liver failure in the pediatric population.
- PTU is associated with much higher risk of ANCA development and vasculitis than is MMI.
- PTU and MMI have comparable rates of agranulocytosis (0.3 percent in adults). The risk of agranulocytosis is dose-dependent with MMI but not with PTU. The risk of agranulocytosis is very low with low doses of MMI.
- MMI use during pregnancy is associated with an increased risk of birth defects (aplasia cutis, choanal atresia, esophageal atresia, tracheoesophageal fistulas, and athelia). PTU use during pregnancy is not associated with birth defects. Women should be informed of the potential risks of PTU-induced hepatotoxicity and risks of MMI-associated fetal minor malformations when considering antithyroid drug use during pregnancy.
- Based on recent prescribing data, it is estimated that at least 2,000 children in the United States are currently taking PTU.

In the concluding general discussion, the meeting participants identified research needs, identified clinical options for treating hyperthyroidism and specifically Graves' disease in children, proposed actions, and noted areas of disagreement.[1]

The following research was proposed:
- Compile epidemiological data of Graves' disease in children
- Conduct etiological studies of Graves' disease (and general research on thyroid disease)
- Quantify magnitude of the problem of severe PTU-induced hepatic toxicity (and other AEs) of PTU in pediatric population
- Elucidate mechanisms of action and metabolism of PTU and MMI
- Elucidate mechanisms of hepatic toxicity of PTU and MMI
  - Effects of dose

[1] These areas were not necessarily differences among the meeting participants, but between them and the medical community at-large.

  - Risk factors
  - Genetic determinants
  - Drug–drug interactions
- Determine effects of antithyroid drugs on radioiodine efficacy
- Conduct studies to improve management of hyperthyroidism during pregnancy, including
  - Risk of aplasia cutis or MMI embryopathy vs. risk of PTU-induced hepatotoxicity
  - Incidence of MMI-induced teratogenicity/embryopathy
  - Effects of PTU dose on teratogenic effects
- Identify current treatment practices of Graves' disease in children
- Determine predictors of remission (Who warrants trials of antithyroid drugs vs. initial definitive therapy?)
- Elucidate radioactive iodine radiation risks (need formal dosimetry for whole-body radiation exposure in children)
- Conduct comparative studies of risks and benefits of each treatment option
- Determine long-term outcome of Graves' disease treatments (thyroid, nonthyroid cancers; medical problems)
- Conduct prospective studies of Graves' disease management, AEs, and treatment outcomes
- Conduct studies of antithyroid drug dosing in children.

The following clinical options were identified:
- American Thyroid Association standards of care/guidelines for management of hyperthyroidism
- PTU vs. MMI use during pregnancy
- PTU vs. MMI use in children with Graves' disease
  - Short-term therapy (weeks–months; "cool down" prior to radioiodine therapy)
  - Long-term therapy (1–2 years; "remission" usually followed by radioiodine therapy)
- Antithyroid drugs vs. radioiodine therapy
- Alternative treatments such as surgery
- Liver function monitoring during PTU therapy (frequency/length of testing)
  - Serum transaminases
  - Patient self-monitoring
  - Options to monitoring
- Defining levels of severity of liver injury.

The following actions were proposed:
- Develop guidelines for monitoring children on antithyroid drugs
- Raise awareness with pediatric endocrinologists
- List AEs associated with PTU in *Physicians' Desk Reference*
- Have FDA communicate treatment guidelines and AEs to practitioners for generic/off-label drugs; post information on FDA Web site; strengthen labeling language
- Develop a network of pediatric endocrinologists to track management and outcomes of Graves' disease network
- Fund a database for the network

- Convene an advisory committee to discuss PTU issues in an open forum, which would provide the basis for a white paper. The white paper would lay out the strengths and weaknesses of the different therapeutic approaches.
- Assess changes in practices for treating pediatric Graves' disease.

The following areas of disagreement were noted:
- Value of monitoring liver function during PTU therapy
- Estimates of prevalence of Graves' disease in children
- The need for a black box warning for PTU and MMI
- A ban on PTU (Is it an essential drug?)
- Whether there is value in conducting any pediatric PTU studies.

Participants

Mark Avigan, M.D., C.M., CDER, FDA, HHS
Vicky Borders-Hemphill, Pharm.D., CDER, FDA, HHS*
James L. Boyer, M.D., Yale University School of Medicine
Eric Caplan, The Lewin Group
Wida S. Cherikh, Ph.D., UNOS
David S. Cooper, M.D., Johns Hopkins University School of Medicine
Elizabeth L. Durmowicz, M.D., CDER, FDA, HHS
Amy G. Egan, M.D., M.P.H., CDER, FDA, HHS
George P. Giacoia, M.D., NICHD, NIH, HHS
Clifford Goodman, Ph.D., The Lewin Group
Laura Governale, Pharm.D., CDER, FDA, HHS*
Gilman D. Grave, M.D., NICHD, NIH, HHS
Lei Guo, National Center for Toxicology Research (NCTR), FDA, HHS
Lisa Kaeser, J.D., NICHD, NIH, HHS
Ralph E. Kauffman, M.D., University of Missouri–Kansas City
James J. Korelitz, Ph.D., Westat
Bernard F. Kozlovsky, M.D., M.S., Division of Transplantation, Health Resources and Services Administration, HHS
Jan L. Leahey, NICHD, NIH, HHS
Naomi Lowy, M.D., Division of Metabolism and Endocrinology Products, FDA, HHS
Saul Malozowski, M.D., Ph.D., M.B.A., National Institute of Diabetes and Digestive and Kidney Diseases, NIH, HHS
Donald R. Mattison, M.D., NICHD, NIH, HHS
Suzanne Morris, Ph.D., NCTR, FDA, HHS
Mary H. Parks, M.D., CDER, FDA, HHS
Zhaoxia Ren, M.D., Ph.D., NICHD, NIH, HHS
Scott A. Rivkees, M.D., Yale University
John R. Senior, M.D., CDER, FDA, HHS
David Siegel, M.D., NICHD, NIH, HHS
Robert H. Squires, Jr., M.D., University of Pittsburgh
Joslyn Swann, Pharm.D., R.Ph., CDER, FDA, HHS

Ana Szarfman, M.D., Ph.D., CDER, FDA, HHS
Perdita Taylor-Zapata, M.D., NICHD, NIH, HHS
Surendra K. Varma, M.D., Texas Tech University Health Sciences Center
Karen K. Winer, M.D., NICHD, NIH, HHS

*Attended via teleconference.