

Dissimilar Hepatotoxicity Profiles of Propylthiouracil and Methimazole in Children

Scott A. Rivkees and Ana Szarfman

Yale Pediatric Thyroid Center (S.A.R.), Yale University School of Medicine, New Haven, Connecticut 06520; and Center for Drug Evaluation and Research (A.S.), U.S. Food and Drug Administration, Silver Spring, Maryland 20993

Background: The antithyroid drugs propylthiouracil and methimazole were introduced for clinical use about 60 yr ago and are estimated to be used in more than 6000 children and adolescents per year in the United States. Over the years that these medications have been used, reports of adverse events involving hepatotoxicity have appeared. To date, there has not been a systematic and comparative evaluation of the adverse events associated with antithyroid drug use.

Objective: Our objective was to assess safety and hepatotoxicity profiles of propylthiouracil and methimazole by age in the U.S. Food and Drug Administration's Adverse Event Reporting System (AERS).

Design: We used the multi-item gamma-Poisson shrinker (MGPS) data mining algorithm to analyze more than 40 yr of safety data in AERS. MGPS uses a Bayesian model to calculate adjusted observed to expected ratios [empiric Bayes geometric mean (EBGM) values] for every drug-adverse event combination in AERS, focusing on hepatotoxicity events.

Results: MGPS identified higher-than-expected reporting of severe liver injury in pediatric patients treated with propylthiouracil but not with methimazole. Propylthiouracil had a high adjusted reporting ratio for severe liver injury (EBGM 17; 90% confidence interval = 11.5–24.1) in the group less than 17 yr old. The highest EBGM values for methimazole were with mild liver injury in the group 61 yr and older [EBGM 4.8 (3.3–6.8)], which consisted of cholestasis. Vasculitis was also observed for propylthiouracil in children and adolescents, reaching higher EBGM values than hepatotoxicity signals.

Conclusions: MGPS detects higher-than-expected reporting of severe hepatotoxicity and vasculitis in children and adolescents with propylthiouracil but not with methimazole. (*J Clin Endocrinol Metab* 95: 3260–3267, 2010)

Graves' disease is the most common cause of hyperthyroidism in children, adolescents, and adults and is treated with antithyroid drugs, radioactive iodine, or surgery (1). In children and adolescents, the antithyroid drugs propylthiouracil and methimazole are widely used as first-line therapy for patient with Graves' disease (1). In 2008, it was estimated that 2000 pediatric patients in the United States were treated with propylthiouracil and 4000 with methimazole (2).

Propylthiouracil was introduced for clinical use in 1947 and methimazole in 1952 (2). Over the 60 yr that these medications have been used, reports of adverse events for

both medications have appeared (2), including reports of propylthiouracil-related liver failure and death in more than 30 individuals between 6 and 62 yr of age (2–4). Children also appear to be disproportionately represented in reports of propylthiouracil-induced liver injury compared with adults (2, 4, 5).

To date, there has not been a systematic evaluation of the adverse events reporting associated with propylthiouracil and methimazole use. To address this issue, we applied a novel database analysis approach to identify the overall safety reporting of propylthiouracil and methimazole and their liver-associated safety reporting in the huge

U.S. Food and Drug Administration's (FDA) Adverse Events Reporting System (AERS) database.

AERS is a spontaneous reporting database that is the primary data resource for the study and identification of adverse drug reactions in the United States. The FDA has maintained the AERS database of adverse drug events submitted to the FDA by the pharmaceutical industry and the public since 1968. AERS contains about 5 million such reports, and the FDA receives over 1200 new reports each day. AERS has over 10,000 preferred terms (codes) of adverse events in use. The large number and complexity of these reports necessitates the use of statistical algorithms to supplement traditional methods to detect drug safety problems from this large database. Using a novel approach for database mining, we used AERS data to assess the nature and relative strength of adverse events associated with propylthiouracil and methimazole, focusing on the pediatric population.

Materials and Methods

We performed data-mining analysis of the AERS database maintained by the FDA using Empirica Signal software and the multi-item gamma-Poisson shrinker (MGPS) data-mining algorithm (6, 7). MGPS was run using simultaneously all event terms and all suspect drugs in the AERS database as of December 31, 2008. The MGPS run also included custom liver injury terms defined below that combined several standard preferred terms, as follows.

Severe liver injury (custom term) included ammonia abnormal, ammonia increased, coma hepatic, hepatic necrosis, hepatitis, hepatic failure, hepatitis acute, hepatitis fulminant, acute hepatic failure, hepatitis acute, hepatocellular injury, hyperammonemia, hyperammonemic encephalopathy, liver transplant, hepatic encephalopathy, hepatotoxicity, and subacute hepatic failure.

Mild liver injury (custom term) included the absence of the above terms in the reports and reports containing any of following preferred terms: alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin abnormal, blood bilirubin increased, cholestasis, cholestasis of pregnancy, cholestatic liver injury, cholestatic pruritus, hepatic enzyme abnormal, hepatic enzyme increased, hepatic function abnormal, hepatitis cholestatic, hyperbilirubinemia, icterus index increased, jaundice, jaundice acholuric, jaundice cholestatic, jaundice hepatocellular, liver function test abnormal, neonatal cholestasis, ocular icterus, and urine bilirubin increased.

MGPS generated over 13 million rows of unique drug-event values across all drug and events in AERS, including values for propylthiouracil and methimazole, by year of the report and age. Results were filtered to display the results for propylthiouracil and methimazole where at least one adverse event was reported. The MGPS program calculated lower and upper bounds of 90% confidence limits for each empiric Bayes geometric mean (EBGM) value denoted as EB05 and EB95, respectively. To identify reporting differences between the two drugs, we assessed the overlapping/nonoverlapping status of (EB05, EB95) intervals of one drug with regard to the other.

The primary goal of the analysis was to assess liver injury signals in children and adolescents with propylthiouracil and methimazole. The secondary focus was to describe the age effects of these signals as well as to describe non-liver-associated adverse event signals. Adverse events associated with propylthiouracil and methimazole use during pregnancy were excluded.

MGPS data-mining method

MGPS applies a Bayesian model to simultaneously analyze disproportionality of reporting ratios for each drug event in the huge AERS database relative to all other drugs and events in the database. MGPS calculates adjusted relative reporting ratios for pairs of drug-event combinations and for higher-order (*e.g.* triplet and quadruplet) combinations of drugs and events that are significantly more frequent than their pairwise associations would predict. MGPS systematically shrinks observed to expected ratios that cannot be precisely estimated because of small counts. This approach helps reduce false-positive signals.

The MGPS program typically stratifies data in AERS by over 1300 categories, including over 40 categories by year, 11 categories by age group, and three categories by gender (male, female, and not stated) to adjust for background differences in relative reporting ratios by these variables. This stratification procedure reduces potential confounding variables, including those related to database changes over time, prescribing paradigm changes, and due to independent relationships between a drug and a stratum variable and an event and the same stratum variable.

EBGM values indicate the strength of the reporting relationship between a particular drug and event pair and reflect the relative reporting rates (after Bayesian smoothing) for the drug-event pairs studied. For example, if the EBGM is 10, then the drug-event combination is reported at 10-fold greater frequency than if there were no association between the drug and the event.

Results

From January 1, 1968, until December 31, 2008, AERS collected a total of 651 reports for propylthiouracil and 822 for methimazole across all age groups (Fig. 1). There were more methimazole than propylthiouracil reports, except in the youngest age group (<17 yr; Table 1).

The highest EBGM values for propylthiouracil in the age group of less than 17 yr and in the overall analysis in all age groups were for vasculitis events, with several EBGM values for vasculitis events greater than 50 times higher than expected (Tables 2 and 3). These problems included antineutrophil cytoplasmic antibody-positive, leukocytoclastic vasculitis, glomerulonephritis, and other forms of vasculitis. Either these events were reported only with propylthiouracil or EBGM values were higher for propylthiouracil than for methimazole (Tables 2 and 3).

When hepatotoxicity was examined in children and adolescents, major differences in the number and proportion of severe liver injury reports for propylthiouracil *vs.* methimazole were observed (Tables 2 and 4 and Fig. 2). We

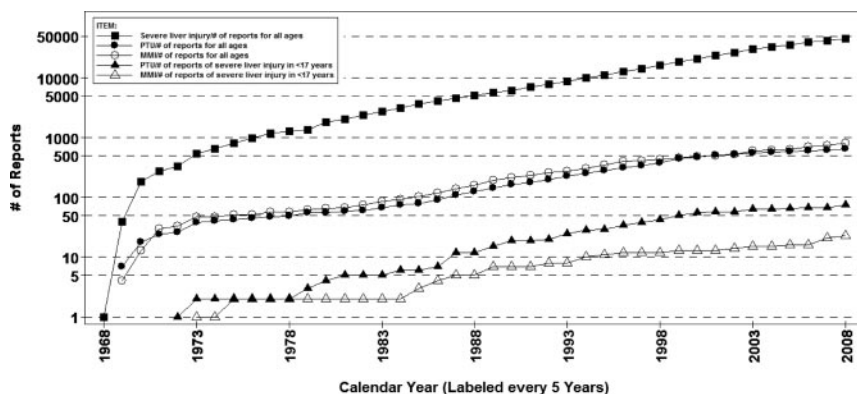


FIG. 1. Cumulative number of reports of severe liver injury (■) across all drugs in AERS. Shown are the number of reports for propylthiouracil (●) and methimazole (○) for all age groups regardless of liver injury and for propylthiouracil (▲) and methimazole (△) having severe liver injury in the age group of under 17 yr. Reports are from the FDA AERS.

observed 23 cases of severe liver injury in the age group less than 17 yr with propylthiouracil; no cases were seen with methimazole. These propylthiouracil reports accounted for 0.86% of the total reports of severe liver injury in AERS. When mild liver injury was examined in children and adolescents, we observed mild liver injury in the under-17-yr age group in four children and adolescents treated with propylthiouracil and in one child treated with methimazole (Table 4). Propylthiouracil accounted for 0.08% and methimazole 0.02% of total reports of mild liver injury in the AERS database. When we assessed these proportions regardless of age, propylthiouracil accounted for 0.17% and methimazole for 0.05% of severe liver injury and for 0.04 and 0.09% of mild liver injury (Table 4).

When data were examined using MGPS across age groups, the EBGM values for severe liver injury with propylthiouracil were higher in younger (<17 yr) than older individuals (≥17 yr), regardless of whether we assessed the individual severe preferred terms or the severe liver injury custom term (Fig. 3). Side-by-side comparison of overlapping/nonoverlapping status of (EB05, EB95) intervals for severe liver injury adverse events for all age groups showed them to be higher with propylthiouracil

TABLE 1. Distribution of unique reports for propylthiouracil and methimazole by age group in the FDA AERS

Subset (yr)	Propylthiouracil	Methimazole	Total
<17	81	46	122
≥17–40	194	216	407
≥41–60	139	190	329
≥61	98	119	217
Unknown	139	251	386
Total	651	822	1461

The column totals are not the sums of the preceding columns because a single report may mention both drugs.

than methimazole, and the propylthiouracil EBGM values were higher and did not overlap with the methimazole values (Figs. 2 and 3). Side-by-side comparison for mild liver injury for all age groups showed (EB05, EB95) intervals to be higher with methimazole than with propylthiouracil, and the methimazole EBGM values were in general higher and did not overlap the propylthiouracil values (Fig. 4). The highest EBGM values with methimazole were with mild liver injury in the group 61 yr and older [EBGM 4.8 (3.3–6.8)] and consisted mainly of cholestasis (Fig. 4).

Discussion

Our analysis of FDA AERS data reveals a concerning number of reports describing severe hepatotoxicity associated

TABLE 2. Top propylthiouracil and methimazole EBGM values for the age group of less than 17 yr

Item	n	EBGM (EB05-EB95)
Propylthiouracil		
Antineutrophil cytoplasmic antibody positive	5	96 (41.9–195) ^a
Leukocytoclastic vasculitis	6	90.5 (43–172.8) ^a
Glomerulonephritis	7	66.3 (33.5–120.7) ^a
Goiter	5	60.8 (26.3–124.3) ^a
T ₃ increased	4	60.4 (21.9–137.9) ^a
Vasculitis	10	53.9 (30.8–89.1) ^a
Henoch-Schonlein purpura	4	38.4 (7.5–94.6) ^a
Basedow's disease	3	38.1 (3.3–126.3) ^a
Liver transplant	4	35.8 (6.2–89.8) ^a
Antinuclear antibody positive	6	32.7 (14.2–64.4) ^a
Methimazole		
Hypothyroidism	4	15.9 (2.8–53.1)
Proteinuria	3	9.3 (1.6–52.9)
Arthralgia	8	8 (3.4–19)
Collagen disorder	2	6.4 (1–74.2) ^b
Raynaud's phenomenon	2	5.9 (0.9–68.7) ^b
Toxic epidermal necrolysis	3	5.3 (1.4–32) ^b
Leukopenia	4	3.1 (1.3–6.6)

Liver-associated events are shown in *bold*. Goiter, T₃, Basedow's disease, and hypothyroidism reflect coding of the condition being treated.

^a Events with higher and nonoverlapping EBGM values for propylthiouracil than for methimazole or events reported only with propylthiouracil.

^b Events with higher and nonoverlapping EBGM values for methimazole than propylthiouracil or events reported only with methimazole.

TABLE 3. Top propylthiouracil and methimazole EBGM values for all ages

Item	n	EBGM (EB05-EB95)
Propylthiouracil		
Glomerulonephritis	14	197.3 (123.7–301.9) ^a
rapidly progressive		
Antineutrophil	13	166.1 (102.2–258.3)
cytoplasmic		
antibody positive		
Antibody test positive	23	93.6 (65.4–130.6)
Goiter	21	78.5 (53.9–111.2)
Pulmonary alveolar	10	72.1 (41.2–119.2) ^a
hemorrhage		
Blood TSH decreased	12	68.8 (41.4–108.9) ^a
T ₃ increased	7	68.4 (34.6–124.5)
Glomerulonephritis	18	62.3 (41.4–90.8) ^a
Wegener's	5	61 (26.4–124.8) ^a
granulomatosis		
Leukocytoclastic	13	50.2 (30.9–78) ^a
vasculitis		
Methimazole		
Uveitis	42	106.8 (82.2–136.9) ^b
Antineutrophil	6	58.8 (27.9–112.4)
cytoplasmic		
antibody positive		
Cutaneous vasculitis	6	43.6 (20.5–84)
Hyperthyroidism	32	43.1 (31.9–57.2)

Goiter, blood TSH decreased, and T₃ increased reflect coding of the condition being treated.

^a Events with higher and nonoverlapping EBGM values for propylthiouracil than for methimazole or events reported only with propylthiouracil.

^b Events with higher and nonoverlapping EBGM values for methimazole than propylthiouracil or events reported only with methimazole.

with propylthiouracil use in children and adolescents, a risk that is not present with methimazole. These observations are consistent with case reports and liver transplantation data, which reveal serious liver injury associated with propylthiouracil use in children and adolescents, but not with methimazole (2, 3, 5).

AERS data show that whereas there were more overall reports for propylthiouracil than methimazole, propylthiouracil-associated reports were more common than those with methimazole in the pediatric population. When pediatric propylthiouracil reports were evaluated, two major safety signals were observed, vasculitis and hepatotoxicity, which were very low for methimazole in children and adolescents.

Although the primary focus of our report was liver injury, a major vasculitis safety signal associated with propylthiouracil use in children and adolescents was observed. Vasculitis associated with methimazole use was also observed, but strength of association scores were lower than those observed for propylthiouracil. These observations are in accord with reports of vasculitis associ-

TABLE 4. Number and proportion of unique reports for severe and mild liver injury by age group

Type of liver injury by age group (yr)	Propylthiouracil		Methimazole		Total reported in AERS
	Reports (n)	%	Reports (n)	%	
Severe					
<17	23	0.86	0	0.00	2,668
≥17–40	23	0.28	4	0.05	8,242
≥41–60	11	0.09	9	0.08	11,622
≥61	7	0.06	6	0.05	11,245
Unknown	13	0.11	4	0.03	11,760
Total	76 ^a	0.17	23	0.05	45,537
Mild					
<17	4	0.08	1	0.02	5,273
≥17–40	14	0.08	21	0.13	16,590
≥41–60	4	0.02	26	0.11	23,812
≥61	6	0.02	22	0.09	25,822
Unknown	5	0.02	15	0.07	20,401
Total	33	0.04	85	0.09	91,898

^a A total of 76 reports instead of 77 appeared in the overall assessment regardless of age group, probably due to a duplicate report.

ated with antithyroid drug use and children and adolescents (8–11) and reports showing a higher risk of developing antineutrophil cytoplasmic antibodies with propylthiouracil than methimazole (12).

Propylthiouracil-associated severe hepatotoxicity was seen at all ages, but age-related data showed that reports and signals of propylthiouracil-associated hepatotoxicity were greatest in individuals less than 17 yr of age. In comparison, there was no methimazole-associated hepatotoxicity signal in children and adolescents. Methimazole hepatotoxic signals in adults were seen in the oldest age group and consisted largely of cholestasis.

To date, more than 30 cases of propylthiouracil-induced liver failure have been reported in individuals with ages ranging between 6 and 62 yr of age (2, 3, 5). Recovery from liver failure without transplant occurred in 18 individuals, transplantation occurred in three persons, and nine deaths were reported. Of these cases, 14 were pediatric patients (2, 3, 5). There were three deaths in propylthiouracil-treated pediatric patients (2, 3, 5). Five children who underwent liver transplantation have been reported as well (2, 3, 5). The MGPS analysis of FDA AERS data support the impression in the published literature that children and adolescents are more vulnerable to propylthiouracil-mediated hepatotoxicity than adults.

Studies reporting outcomes of pediatric Graves' disease treated with propylthiouracil, in which adverse events were discussed, also reveal propylthiouracil-related adverse events. These cohorts included more than 550 propylthiouracil-treated patients (2). Adverse events related to propylthiouracil use occurred in 15–35% of children and adolescents (13–15), except for one report that de-

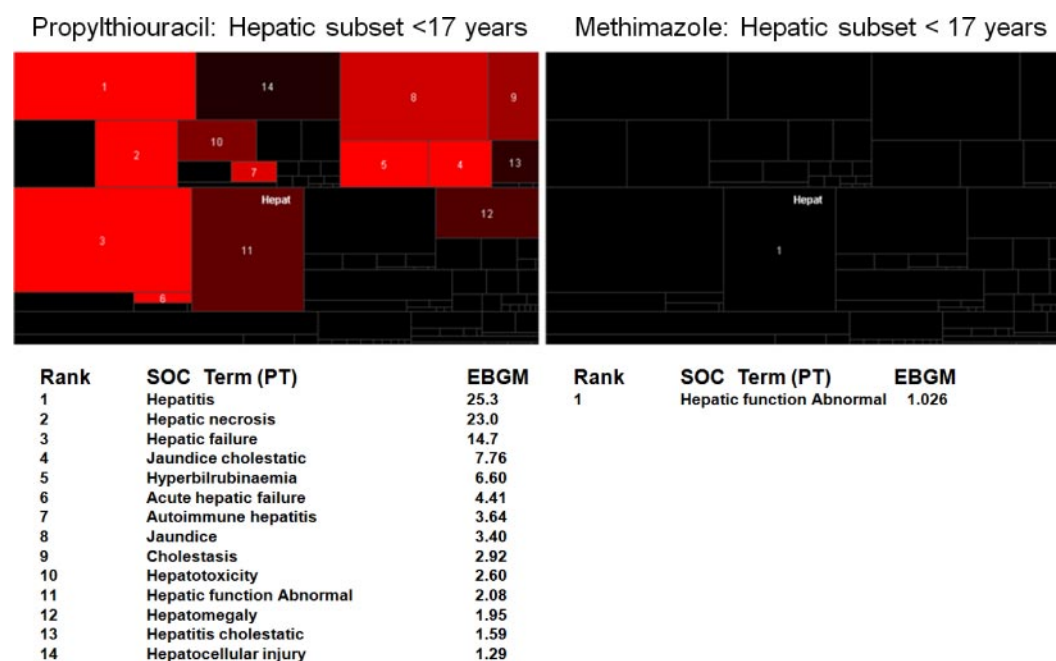


FIG. 2. Comparative sector map (heat map) display of adverse events in the MedDRA Hepatic System Organ Class for propylthiouracil (*left*) and methimazole (*right*) in individuals less than 17 yr of age. The numbers indicate the ranking of EBGM values for each preferred term (PT). Preferred terms are grouped by higher-level terms and by higher-level groups in MedDRA. The size that each preferred term occupies in the graphic display reflects its association with serious outcomes in AERS across all drugs (the larger the space, the higher is its association with a serious outcome.) For example, hepatitis, hepatic necrosis, and hepatic failure (events ranked 1, 2, and 3 with propylthiouracil) occupy a larger space in the graph because they are more highly associated with a serious outcome than jaundice cholestatic (ranked 4 with propylthiouracil) that occupies a smaller space. Liver transplant appears in the surgical system organ class (SOC) and, therefore, is not listed here. For Figs. 2–4, MGPS performed analyses for each age group after stratifying the AERS data by over 40 categories by year and three categories by gender (male, female, and not stated).

scribed problems in one of 63 patients (16). Cohort studies describing adverse events related to methimazole are few. In a recent study of the methimazole analog carbimazole, of 147 treated children, eight children developed rash and one child developed agranulocytosis (17).

One issue of potential concern that was not possible for us to address in this cohort was the possibility of toxic effects of propylthiouracil on the fetus. However, we have been made aware of a newborn with lethal fulminant hepatitis born to a mother treated with propylthiouracil during pregnancy (S. Harada, Tokyo, Japan; personal communication).

In comparison with reports of propylthiouracil-induced hepatocellular necrosis, liver-related problems associated with methimazole use are related to cholestasis, which has been reported in 20 adults (18–27). Methimazole-related cholestasis is associated with high doses and older age (25). There is one case report of methimazole-related liver failure leading to death in a 43-yr-old man with hyperthyroidism and hepatitis B (28). The death of a 20-yr-old woman treated with 90 mg/d methimazole for 8 months has been reported (29). Similar to the published literature, there were no AERS reports of methimazole-related liver failure, liver transplants, or deaths in pediatric patients. AERS data also revealed that methimazole hepatotoxic adverse events were most likely to occur in older adults.

Review of the Organ Procurement and Transplantation Network, United Network for Organ Sharing, data (30) reveals that propylthiouracil is the third most common cause of drug-induced liver failure in children and adolescents, accounting for 10% of drug-related transplants (30). From 1990–2007, 23 propylthiouracil-related liver transplants were performed (2). Ten of the liver transplant recipients were pediatric patients. No methimazole-related liver transplants occurred over this period in children or adults (2, 3, 5). The MGPS analysis of FDA AERS data also indicates that the risks for liver failure and the need for liver transplantation were associated with propylthiouracil use. It is important to note that not all cases of propylthiouracil-induced liver failure leading to transplantation included in the United Network for Organ Sharing database were present in AERS data. In addition, whereas some narratives described the need for liver transportation, they were not coded as liver transplant.

It is also important to note that AERS reporting is dependent on submissions by consumers, practitioners, and manufacturers and is thus prone, in general, to underreporting. The determination of observed to expected ratios using the total number of AERS reports as a surrogate for exposure, however, has been shown to provide a reasonable approach to approximating relative reporting in datasets where the denominator is unknown, as with

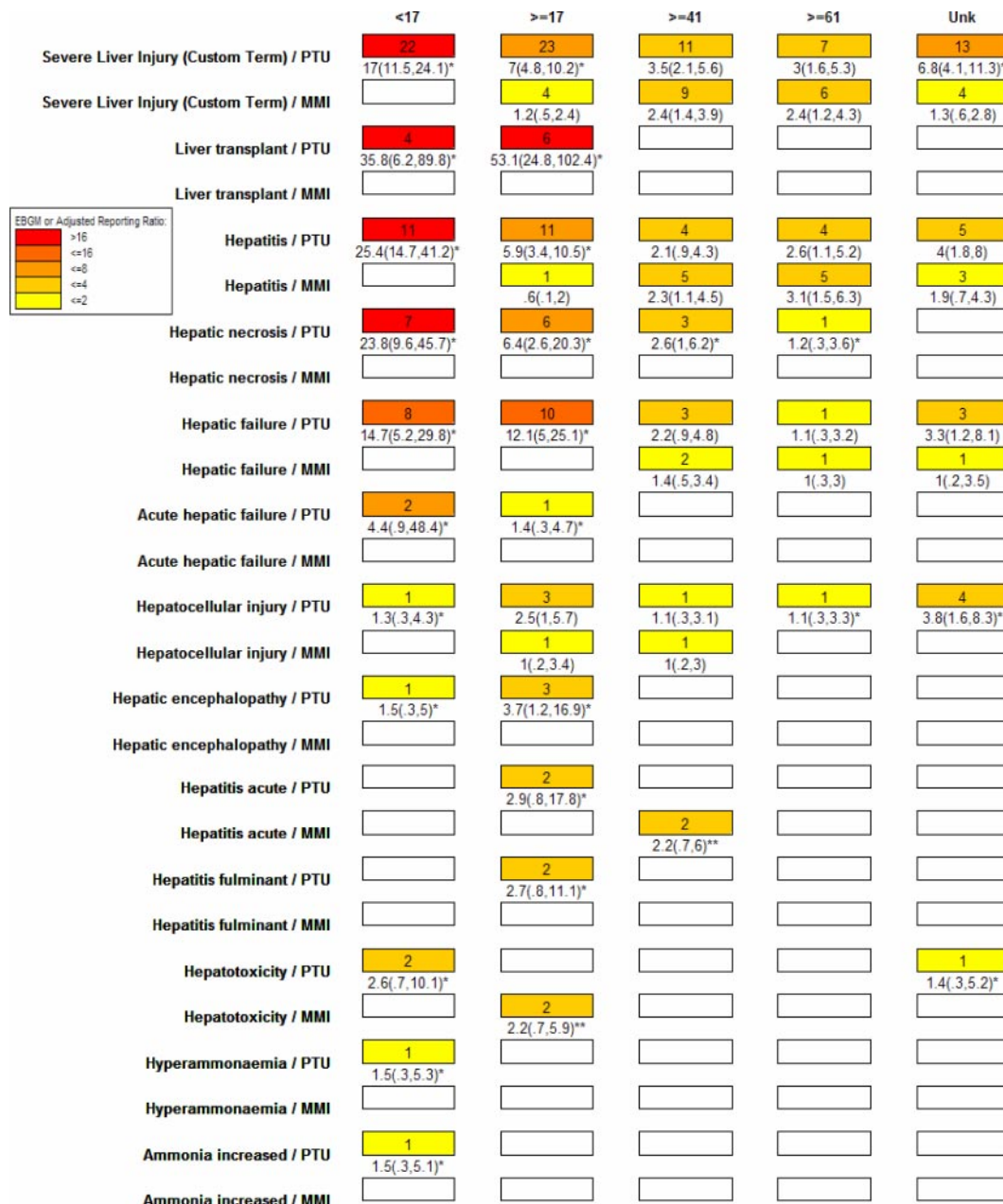


FIG. 3. Paired EBGM values by drug and age group for the custom term that defines severe liver injury and for the individual preferred terms included in the custom term. Note the signal strength (EBGM value by color and by the annotation below each minigraph also containing the EB05-EB95 values) and the count of reports (number within each minigraph). *, Events with higher and nonoverlapping EBGM values for propylthiouracil (PTU) than for methimazole (MMI) or events reported only with propylthiouracil; **, events with higher and nonoverlapping EBGM values for methimazole than propylthiouracil or events reported only with methimazole. The higher the EBGM score indicates a higher strength of association of the adverse event with the drug. For each event, we show the propylthiouracil data in one row and the methimazole data in another. Note that at all ages, the EBGM values are higher for propylthiouracil than for methimazole and the confidence intervals do not overlap. Note that propylthiouracil is associated with many more liver-related adverse events at young ages than methimazole.

spontaneous data (7, 31). Considering the recent alerts that have been sent to practitioners by the FDA and endocrine organizations and in publications about the risk of hepatotoxicity (3–5, 32), it will be important to reassess if liver-related and other adverse events associated with propylthiouracil decline. It will also be important to monitor methimazole adverse events, because this drug will have preferred use as the antithyroid medication.

Over the six decades that propylthiouracil has been used, reports of propylthiouracil-related liver failure and death in children, adolescents, and adults have accumulated in the published literature and FDA databases. In comparison, we are unaware of reports of death and liver failure in children and adolescents taking methimazole, and there are far fewer and less serious adverse events reported for methimazole than propylthiouracil in gen-

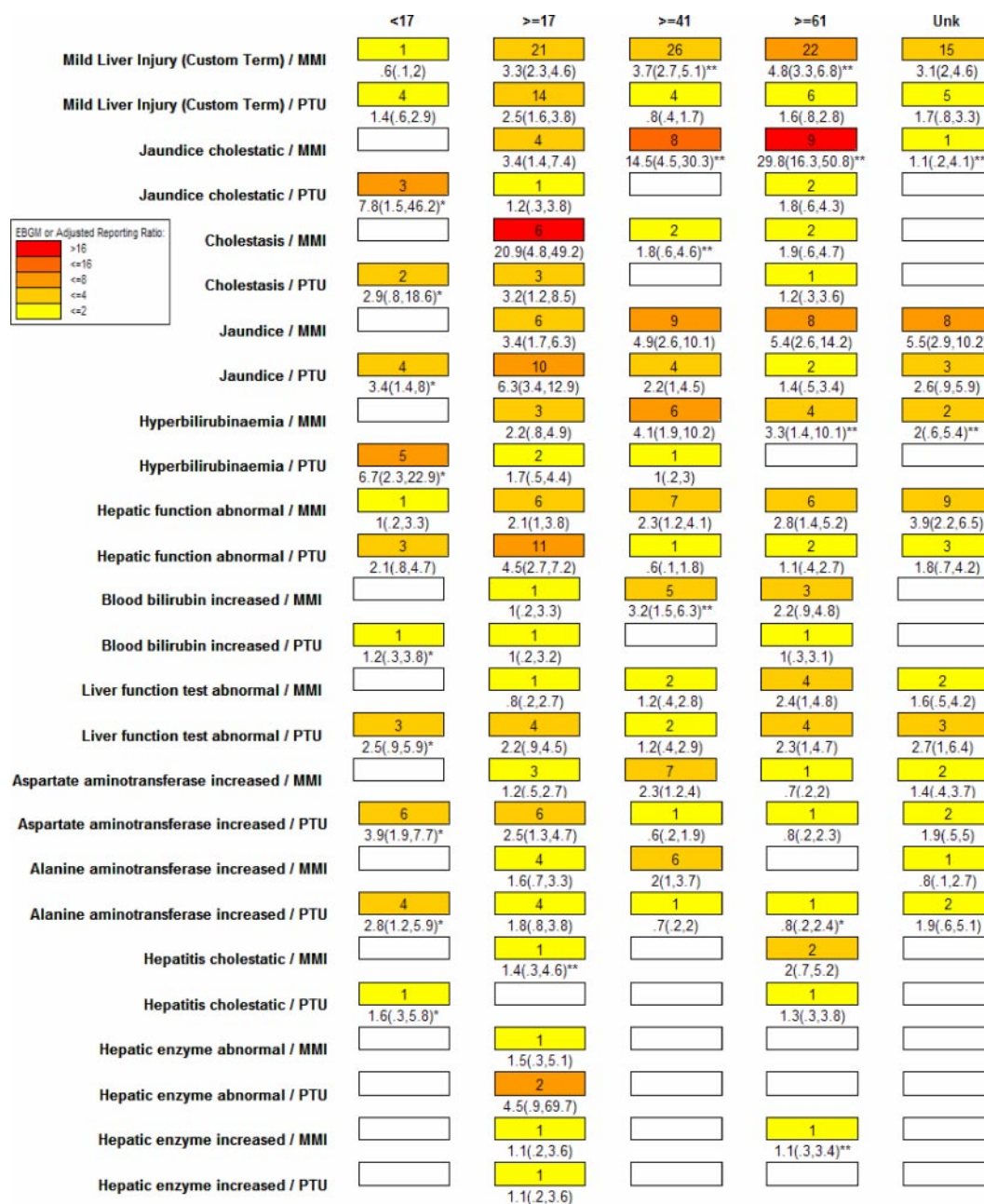


FIG. 4. The EBGM values by age group and drug for the custom term that defines mild liver injury and for the individual preferred terms. Note the signal strength (EBGM value by color and by the annotation below each minigraph also containing the EB05-EB95 values) and the count of reports (number within each minigraph). The higher the EBGM score indicates a higher strength of association of the adverse event with the drug. For each event, we show the propylthiouracil (PTU) data and the methimazole (MMI) data. Note that at the older age group, the EBGM values are higher for methimazole than propylthiouracil. *, Events with higher and nonoverlapping EBGM values for propylthiouracil than for methimazole or events reported only with propylthiouracil; **, events with higher and nonoverlapping EBGM values for methimazole than propylthiouracil or events reported only with methimazole.

eral. The risk of severe propylthiouracil hepatotoxicity is also a concern for the adult population. Considering the above, our observations support the recommendations that propylthiouracil use should be avoided (3–5, 32), especially in the pediatric population.

Our observations also highlight the utility of the systematic analysis of adverse event reports in large databases using methods that decrease false-positive rates due to small numbers while preserving stable signals with small

number of reports. This effect is important for early detection of signals as well as for detection of signals in subgroups at risk and drug-drug interactions where the problem with small numbers intensifies. There is also a need to link disparate databases such as AERS, transplantation databases, and electronic medical records currently not automatically linked with each other to help quickly confirm signals across several data resources. We also need to speed the detection of dissimilar safety profiles among

treatment alternatives to aid the identification of safer treatments in subgroups at risk.

Acknowledgments

Address all correspondence and requests for reprints to: Scott A. Rivkees, M.D., Yale Pediatric Thyroid Center, Section of Developmental Endocrinology and Biology, Yale University, 464 Congress Avenue, New Haven, Connecticut 06520. E-mail: scott.rivkees@yale.edu.

Disclosure Summary: The authors have nothing to disclose.

References

- Rivkees SA 2006 The treatment of Graves' disease in children. *J Pediatr Endocrinol Metab* 19:1095–1111
- Eunice Kennedy Shriver National Institute of Child Health and Human Development 2009 Hepatic toxicity following treatment for pediatric graves' disease meeting: October 28, 2008. <http://bpca.nichd.nih.gov/outreach/index.cfm>
- Cooper DS, Rivkees SA 2009 Putting propylthiouracil in perspective. *J Clin Endocrinol Metab* 94:1881–1882
- Rivkees SA, Mattison DR 2009 Ending propylthiouracil-induced liver failure in children. *N Engl J Med* 360:1574–1575
- Rivkees SA, Mattison DR 2009 Propylthiouracil (PTU) hepatotoxicity in children and recommendations for discontinuation of use. *Int J Pediatr Endocrinol* 2009:132041
- DuMouchel W, Pregibon D 2001 Empirical Bayes screening for multi-item associations. *Proc Conference on Knowledge Discovery and Data*, San Diego, CA, 2001, pp 67–76
- Szarfman A, Machado SG, O'Neill RT 2002 Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database. *Drug Saf* 25:381–392
- Gao Y, Chen M, Ye H, Yu F, Guo XH, Zhao MH 2008 Long-term outcomes of patients with propylthiouracil-induced anti-neutrophil cytoplasmic auto-antibody-associated vasculitis. *Rheumatology (Oxford)* 47:1515–1520
- Bonaci-Nikolic B, Nikolic MM, Andrejevic S, Zoric S, Bukilica M 2005 Antineutrophil cytoplasmic antibody (ANCA)-associated autoimmune diseases induced by antithyroid drugs: comparison with idiopathic ANCA vasculitides. *Arthritis Res Ther* 7:R1072–1081
- Sera N, Ashizawa K, Ando T, Abe Y, Ide A, Usa T, Tominaga T, Ejima E, Yokoyama N, Eguchi K 2000 Treatment with propylthiouracil is associated with appearance of antineutrophil cytoplasmic antibodies in some patients with Graves' disease. *Thyroid* 10:595–599
- Yarman S, Sandalci O, Tanakol R, Azizlerli H, Oguz H, Alagöl F 1997 Propylthiouracil-induced cutaneous vasculitis. *Int J Clin Pharmacol Ther* 35:282–286
- Huang CN, Hsu TC, Chou HH, Tsay GJ 2004 Prevalence of perinuclear antineutrophil cytoplasmic antibody in patients with Graves' disease treated with propylthiouracil or methimazole in Taiwan. *J Formos Med Assoc* 103:274–279
- Glaser NS, Styne DM 1997 Predictors of early remission of hyperthyroidism in children. *J Clin Endocrinol Metab* 82:1719–1726
- Glaser NS, Styne DM 2008 Predicting the likelihood of remission in children with Graves' disease: a prospective, multicenter study. *Pediatrics* 121:e481–e488
- Hamburger JI 1985 Management of hyperthyroidism in children and adolescents. *J Clin Endocrinol Metab* 60:1019–1024
- Lippe BM, Landaw EM, Kaplan SA 1987 Hyperthyroidism in children treated with long term medical therapy: twenty-five percent remission every two years. *J Clin Endocrinol Metab* 64:1241–1245
- Kaguelidou F, Alberti C, Castanet M, Guitteny MA, Czernichow P, Leger J 2008 Predictors of autoimmune hyperthyroidism relapse in children after discontinuation of antithyroid drug treatment. *J Clin Endocrinol Metab* 93:3817–3826
- Arab DM, Malatjalian DA, Rittmaster RS 1995 Severe cholestatic jaundice in uncomplicated hyperthyroidism treated with methimazole. *J Clin Endocrinol Metab* 80:1083–1085
- Lersch C, Seige M, Natrath W, Heidecke W, Wittekind C, Classen M, Schepp W 1995 Cholestasis induced hyperthyroidism after liver transplantation. *Digestion* 56:429–432
- Schwab GP, Wetscher GJ, Vogl W, Redmond E 1996 Methimazole-induced cholestatic liver injury, mimicking sclerosing cholangitis. *Langenbecks Arch Chir* 381:225–227
- Hung YT, Yu WK, Chow E 1999 Delayed cholestatic hepatitis due to methimazole. *Hong Kong Med J* 5:200–201
- Mikhail NE 2004 Methimazole-induced cholestatic jaundice. *South Med J* 97:178–182
- Ramos-Bonner LS, Goldberg TH, Moyer S, Anastasopoulou C 2007 Methimazole-induced cholestatic jaundice in an elderly hyperthyroid patient. *Am J Geriatr Pharmacother* 5:236–240
- Gemma R, Suzuki Y, Tanaka I, Taminato T, Yoshimi T, Kanno T 1992 Lactate dehydrogenase (LDH)-linked immunoglobulin in a patient with Graves' disease treated with methimazole. *Intern Med* 31:377–379
- Woeber KA 2002 Methimazole-induced hepatotoxicity. *Endocr Pract* 8:222–224
- Schmidt G, Börsch G, Müller KM, Wegener M 1986 Methimazole-associated cholestatic liver injury: case report and brief literature review. *Hepatogastroenterology* 33:244–246
- Mamianetti A, Munoz A, Ronchetti RD, Maccione E, Poggi U, Mugnolo R, Gallo O 1995 [Acquired sideroblastic anemia and cholestasis in a hyperthyroid patient treated with methimazole and atenolol]. *Medicina (B Aires)* 55:693–696 (Spanish)
- Kang H, Choi JD, Jung IG, Kim DW, Kim TB, Shin HK, Kim BT, Park CK, Yoo JY 1990 A case of methimazole-induced acute hepatic failure in a patient with chronic hepatitis B carrier. *Korean J Intern Med* 5:69–73
- Baker B, Shapiro B, Fig LM, Woodbury D, Sisson JC, Beierwaltes WH 1989 Unusual complications of antithyroid drug therapy: four case reports and review of literature. *Thyroidology* 1:17–26
- Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P 2004 Liver transplantation for acute liver failure from drug induced liver injury in the United States. *Liver Transpl* 10:1018–1023
- van Puijenbroek E, Diemont W, van Grootheste K 2003 Application of quantitative signal detection in the Dutch spontaneous reporting system for adverse drug reactions. *Drug Saf* 26:293–301
- Bahn RS, Burch HS, Cooper DS, Garber JR, Greenlee CM, Klein IL, Laurberg P, McDougall IR, Rivkees SA, Ross D, Sosa JA, Stan MN 2009 The role of propylthiouracil in the management of Graves' disease in adults: report of a meeting jointly sponsored by the American Thyroid Association and the Food and Drug Administration. *Thyroid* 19:673–674