Propylthiouracil-Induced Hepatotoxicity and Death. Hopefully, Never More

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Addressing the dissimilar toxicities of the two most commonly used antithyroid medications, propylthiouracil (PTU) and methimazole (MMI), and focusing particularly on hepatotoxicity and death in children, Rivkees and Szarfman bring to the forefront an issue that time and time again has fallen off our radar screen: the use of PTU can result in tragic consequences and should never be used in children (1). The same statement could be made for adults, with the exception of use during early pregnancy when PTU use may avoid the potential for fetal malformations that may occur with MMI (2). However, the MMI teratogenic link seems tenuous.

Rivkees and Szarfman (1) provide an in-depth history of these drugs and recount their well-known similar and distinct mechanisms of action. More importantly, using an elegant methodological approach focused on data mining, they underscore the following central issues.

PTU is identified as being the third most frequent cause of drug-induced liver transplant in the United States (3), and administration can lead to severe liver injury and death. This seems clearer in children, and the rate is 17 times higher than the expected rate of liver failure in those not exposed. In the 40-yr period reviewed in Ref. 1, 14 of 23 (33%) cases of death from liver disease after PTU administration were in pediatric patients.

In addition to causing fatal liver disease, PTU is also linked to a greater risk of vasculitis; glomerulonephritis and associated positive titers of antineutrophil cytoplasmatic antibody are 50 times higher than expected. However, these complications are generally clinically mild.

MMI can also induce liver toxicity, but these effects are milder, confined to cholestasis, not associated with liver failure, and more frequent in people older than 61 yr of age. In children, in addition to the risk of liver failure, mild liver injury associated with PTU is four times higher than with MMI.

As in most drug-induced hepatotoxicity, there are no effective tests or means to predict or prevent serious complications. With PTU, complications can occur at any time during treatment and are not dose related.

Because many other therapeutic modalities are available that do not result in these complications, the recommendation that PTU should not be used in children seems crystal clear.

The information provided in the article by Rivkees and Szarfman (1) complements the report by Emiliano *et al.* (4) on PTU and MMI, which appeared in the April issue of *JCEM* and describing prescription practices for MMI and PTU in the United States between 1998 and 2008, showing substantial increases in the use of these drugs. A shift from PTU to MMI as the most common antithyroid drug occurred in 1996 and has led to MMI dominance of the market; the authors speculate that this may have been fueled by the availability of a generic version of MMI. Women were prescribed PTU more frequently than were men. The only group where MMI use was lower was in females of childbearing age. The authors suggest that this tendency may be due to the previously described potential for fetal malformations associated with MMI during pregnancy. Data from this article also suggest that the use of other modalities for the initial treatment of hyperthyroidism—radioactive iodine and/or surgery—have been displaced by the use of these medications. Of concern is that these data indicate that in 22% of patients receiving an-

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For article see page 3260

Abbreviations: MMI, Methimazole; PTU, propylthiouracil.

tithyroid medication PTU continues to be used as the drug of first choice and that this rate has remained unchanged in the period studied, keeping the unease about hepatic toxicity unabated.

These articles allow us to debunk the characterization that PTU liver damage is rare. In the absence of adequate data to properly assess drug use, the term "rare" properly suggests to the prescribing physician that complications may never occur. This mistaken message may, in turn, be conveyed to the patient. Data from the first article (1) indicate that the risk of severe liver damage in pediatric patients receiving PTU is quite alarming. Of concern is that a drug that is prescribed to a very limited number of patients is listed as the third cause of drug-induced liver transplantation, secondary to any medications in the United States. This puts this the term "rare complications" in a completely different light. The hope of Rivkees and Szarfman, Emiliano, and their co-workers is that the knowledge gained from these important studies will lead to a more restrictive use of PTU.

It is important to note that, as stated by the authors, PTU-induced liver toxicity was recognized soon after this medication was introduced in 1947, and cases of liver injury have occurred year after year (5). How then it is possible that it took more than 60 yr to incorporate a black box into its label?

Although it is impossible to properly answer this question, and we can only speculate, many factors contributed to the "hidden" hepatotoxicity signal. The process by which drugs were reviewed when these medications were introduced to the market more than six decades ago had different and less stringent requirements. Even if studies for approval were performed under current standards, it is very difficult to address rare events like severe hepatotoxicity, given that the conditions they treat are rare.

One example of these rare conditions is hyperthyroidism in children. Because of the availability of different treatment modalities for hyperthyroidism, large series addressing a single pharmacological agent to treat it, both in children and adults, are usually retrospective analyses and seldom include more than 100 subjects. For complications that may occur in 1 of 2000 exposed individuals, the universe for a case to emerge would be approximately 6000 patients (6). Even if it were feasible to power a study to detect this problem, executing the study at the present time would be unethical. We believe that the most experienced pediatric thyroidologists and even the busiest centers in the world may never see in excess of hundreds of children that may need antithyroid drugs.

Given that cases of liver damage are infrequent and that there is not a sophisticated database for patients over age 40, it would have been difficult to compile and analyze emerging information that may have resulted in labeling changes.

In addition, the well-known level of underreporting of adverse events (7), particularly in children (8), further increased our inability to put all of the events filed throughout the years into the proper perspective and trigger a regulatory action. Given all of these variables, it is easy to understand how the PTU liver toxicities were never addressed before.

Dr. Ana Szarfman has been working for years on mining the adverse event report system using algorithms that allow for ascertainment of rare and common events in an unbiased manner for many drugs undergoing preapproval evaluations as well as those already on the market (9, 10). The partnership with Scott Rivkees was triggered by his suspicions that the liver complications were more common than initially thought and should be characterized as "common" rather than "rare." Nevertheless, many barriers needed to be overcome. Because the system relies on spontaneous reports, mostly provided by health care professionals, these reports are compiled under numerous and distinct labels, although they may reporting an identical event. The first step was to assess which events fit where and whether they all met the same definitions. Once this was done, the number of events was compared to what is expected in the general population. This comparison ability is built into the mining process.

The results that are conveyed in the Rivkees and Szarfman report (1) were previously reviewed by many stakeholders from numerous private and government institutions including, among others, representatives of numerous Food and Drug Administration (FDA) offices, the National Institute for Child Health and Human Development, the National Institute for Diabetes and Digestive and Kidney Diseases, and the United Network for Organ Sharing, as well as the Lawson Wilkins Pediatric Endocrine Society, The Endocrine Society, and the American Thyroid Association (ATA) at a special workshop that was held under the sponsorship of the Best Pharmaceuticals for Children Act (BPCA) on October 28, 2008 and at a meeting jointly sponsored by the FDA and the ATA on April 18, 2009 (11). These discussions underscored the presence of these severe events and in turn led to a thoughtful reassessment by the FDA and the addition of a black box into the label (12).

Approximately 2 yr of hard work were needed to bring the safety alert related to PTU-induced hepatotoxic to generalized attention. Hopefully, this information will put an end to the continued prescribing of PTU other than as needed in pregnancy. In turn, this information should encourage the selection of alternative therapies for the treatment of hyperthyroidism, particularly in children.

Equally as important as the uncovering of the PTU hepatotoxicity problem are the lessons learned in the process. The role of individual clinicians reporting drug-induced adverse events and reporting them to manufacturers and the FDA should be reemphasized. Without this information, the regulatory agencies cannot update their knowledge and in turn enhance our ability to safely prescribe medications. These experiences also teach us that close relationships among prescribers, academic organizations, and federal agencies can promote drug safety. Finally, the value of investing in the application of modern new computer-based methodology that can monitor and link prescribing and adverse event data is clearly apparent.

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