THERAPY

Propylthiouracil use associated with severe hepatotoxicity in children

Propylthiouracil therapy should be discontinued in children in favor of alternative approaches, say US researchers, after a systematic and comparative evaluation of the adverse events associated with antithyroid drug use revealed severe hepatotoxicity and vasculitis in children and adolescents treated with propylthiouracil but not with methimazole.

"Our group became aware of what appeared to be a cluster of propylthiouracil-induced liver failure cases in children," recounts investigator Scott A. Rivkees from Yale University School of Medicine (New Haven, CT, USA). The investigators reported these findings to the US FDA and the National Institute of Child Health and Development.

Rivkees and Szarfman now report a detailed analysis on hepatotoxicity profiles of propylthiouracil and methimazole stratified by age, for which they analyzed more than 40 years of safety data in the FDA's Adverse Event Reporting System.

The investigators assessed adverse events related to antithyroid drug use for each drug by organ system. In addition, specific focus was directed at identifying liver-related adverse events that were mild or severe.

> "...the use of propylthiouracil in children is no longer justifiable..."

Their data showed a major safety concern related to propylthiouracil use and liver injury and vasculitis—safety signals that are much less frequent with methimazole therapy. "These observations are in agreement with numerous reports that have accumulated in the medical literature showing more adverse events with propylthiouracil than methimazole, especially in children," says Rivkees.

"At present, the first trimester of pregnancy is now the only situation where propylthiouracil is the drug of choice based on potential teratogenic concerns of methimazole," comments Rivkees. "The potential risks of antithyroid drugs to mother and fetus are now a major area of investigation for our group."

The researchers recommend that the use of propylthiouracil in children is no longer justifiable, with the exception of children who have had toxic reactions to methimazole. If used, propylthiouracil therapy should only be short-term until treatment by surgery or radioactive iodine can be provided.

In accordance with the findings of Rivkees and Szarfman, in April 2010—63 years after propylthiouracil was introduced for clinical use—the FDA issued a 'box warning' on its label on the serious adverse events associated with the use of this medication.

Linda Koch

Original article Rivkees, S. A. & Szarfman, A. Dissimilar hepatotoxicity profiles of propylthiouracil and methimazole in children. *J. Clin. Endocrinol. Metab.* doi:10.1210/jc.2009-2546