Acute pancreatitis is significantly increased among methimazole, but not propylthiouracil users. Evidence from a nationwide, case-crossover, and case-control study.

Thomas H. Brix[1], Lars C. Lund[2], Daniel P. Henriksen[2], Lars Folkestad[1], Steen J. Bonnema[1], Jesper Hallas[2] and Laszlo Hegedüs[1]

[1] Department of Endocrinology and Metabolism, Odense University Hospital, Odense, Denmark

[2] Clinical Pharmacology and Pharmacy, University of Southern Denmark, Odense, Denmark

Background: The antithyroid drugs (ATD) methimazole and its prodrug carbimazole (hereafter MMI for both drugs) and propylthiouracil (PTU) are currently used worldwide as the primary treatment for hyperthyroidism. Although serious side effects, such as agranulocytosis and hepatic dysfunction occur in 0.5-1.0% of current users the drugs are generally well tolerated. In January 2019, owing to six case reports on acute pancreatitis (AP) associated with MMI, The European Medicines Agency sent out a warning, and the product labelling was changed to include AP as a serious side effect. Currently there are no data regarding PTU use and risk of AP. This prompted us to examine the association between use of the different ATD and AP in a nationwide controlled study.

Design and Methods: Registry-based study nested within a cohort of all ever-users (≥ one prescription) of MMI (N=103.852) or PTU (N=14.824) in Denmark during 1995-2018. Cases were all Danish residents with a hospitalization due to first-time AP (ICD-10;K85.x). Two approaches were used; A) a case-crossover technique evaluating the risk of AP in ongoing MMI or PTU users. B) a case-control study (each case with AP matched for sex and age with 4 controls) exploring a possible cumulative dose effect of MMI and PTU. Odds ratios (OR) and 95% confidence intervals (CI) for AP associated with each doubling of cumulative MMI and PTU dose, were calculated.

Results: 43,580 cases with AP were identified and 226 (0.5%) and 19 (0.04%) were ongoing MMI or PTU users, respectively. The case-crossover analysis yielded an OR of 1.51 (95% CI: 1.12-2.02) and 1.16 (0.46-2.93) for AP among ongoing MMI and PTU users, respectively. In the case-control study there was no increased risk of AP when comparing highest vs lowest quartile of cumulative dose of ATD [OR_{MMI} 0.98 (0.74-1.32) and OR_{PTU} 0.86 (0.37-2.04)] Doubling of cumulative MMI or PTU dose did not affect the risk of AP [OR_{MMI} 1.00 (0.96-1.05) and OR_{PTU} 1.00 (0.88-1.13)].

Conclusions: In this nationwide registry-based study, ongoing MMI, but not PTU use was associated with an increased risk of acute pancreatitis. No evidence of a cumulative dose effect of MMI or PTU on the risk of AP was found. In our view, the warning by The European Medicines Agency is justified since the frequency of AP in MMI users is of a similar magnitude as reported for agranulocytosis and hepatic dysfunction.