Antipsychotics and QTc Prolongation

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BACKGROUND:
Case reports have linked antipsychotic drugs with QTc prolongation, torsades de pointes, and sudden deaths.  "Black box" warnings regarding these risks have been added to the PDR for the older antipsychotics thioridazine and mesoridazine.  A new antipsychotic, sertindole, was not registered in the U.S. because it caused QTc prolongation and sudden death.

AIM:
To determine the risk of sudden cardiac death in antipsychotic users.

METHODS:
Retrospective cohort study of Tennessee Medicaid enrollees (481,744 persons with 1,282,996 person-years of follow-up, 1988-1993).  Multivariate rate ratios were calculated, adjusting for age, sex, race, cardiovascular disease and noncardiovascular illness.

MAIN FINDINGS:
Corrected risk ratios for sudden cardiac death:
Moderate-dose antipsychotic use vs. nonuse 2.39 (95% CI 1.77-3.22; p<.001)
Low-dose antipsychotic use vs. nonuse 1.30 (95% CI 0.98-1.72; p=.003)
Moderate-dose antipsychotic use in patients with severe cardiovascular disease vs. nonuse 3.53 (95% CI 1.66-7.51; p<.001).
There were 1,487 sudden unexpected cardiac deaths, or 11.6 per 10,000 person-years in moderate-dose antipsychotic users (and 367 per 10,000 person-years in users who had severe cardiovascular disease).

CONCLUSIONS:
This study demonstrates relative and absolute increases in the risk of sudden death in patients taking moderate doses of antipsychotics.

LIMITATIONS:
The study design does not allow any conclusions about causality. The data are from a time before the new “atypical” antipsychotics (risperidone, olanzapine, quetiapine, ziprasidone) became available. Information on smoking status and obesity was not available, so it could not be controlled for. They are both major potential confounding factors, very common in patients with chronic serious mental illness. The authors did control for smoking-related respiratory disease and for coronary artery disease (CAD). However, sudden death may be the first symptom of CAD and this could not be controlled for without autopsies.

IMPACT ON INTERNAL MEDICINE:
While several antipsychotics have been documented to cause torsades de pointes and sudden death, the biggest risk is with thioridazine (See Related Reference). No association has been found with olanzapine, quetiapine, risperidone, or ziprasidone (though the latter does prolong QT and is new). It would be prudent to ask any patient who is to receive antipsychotic medication (or is already on one) regarding any history of syncope, and any family history of unexplained sudden deaths and/or long QT syndrome. Patients with known heart disease or at high risk for it, or on other drugs that can prolong QT should have a pre-treatment EKG. People with pre-treatment prolonged QT should be monitored with periodic EKGs, and for those patients, preference should be given to antipsychotics that do not prolong QT.
RELATED REFERENCES: