QT interval prolongation and hydroxyzine: a retrospective cohort analysis on hospitalized elderly patients

S. Montagnani[1], C. Blandizzi[1,2], A. Marino[1], G. Pasqualetti[3], A.A. Qasem[3], S. Cottone[3], A. Capogrosso-Sansone[1], S. Mantarro[1], I. Convertino[2], A. Saporiti[1], S. Salvadori[4], M. Fornai[1], L. Antonioli[1], F. Monzani[3], M. Tuccori[2]

[1]Dept. of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy
[2]Unit of Adverse Drug Reaction Monitoring, University Hospital of Pisa, Pisa, Italy
[3]Geriatrics Unit, Dept. of Clinical and Experimental Medicine, University Hospital of Pisa, Pisa , Italy
[4]Institute of Clinical Physiology, National Research Council, Pisa, Italy

The European Medicines Agency (EMA) has recently issued a warning concerning a potential association of hydroxyzine, a first generation antihistaminic employed off-label as sedative in the elderly, with long QT syndrome. In particular, to minimize the risk of arrhythmias, EMA has recommended that in elderly patients hydroxyzine should be used at the maximum dose of 50 mg/day. The aim of the present analysis was to evaluate the effect of hydroxyzine on corrected QT (QTc) interval in hospitalized elderly patients. This retrospective cohort analysis was conducted at the University Hospital of Pisa on patients ≥65 years-old, enrolled between July 2012 and July 2014 in the ANCESTRAL program, an observational study aimed at detecting adverse drug reactions in elderly patients admitted to Emergency Department (ED) and hospitalized in the geriatric ward. The ANCESTRAL database contains demographic data and clinical information assessed at ED admission. Patients were included if their medical records reported a complete medical history for at least 3 months prior cohort entry. Patients entered in the cohort if hospitalization was required after the ED visit. During the first week of hospitalization, each patient was routinely evaluated with an electrocardiogram (ECG). After cohort entry, each patient was followed up until the first ECG, discharge or death. The main outcome was defined by abnormal QTc (>451 ms for males, and >471 ms for females). Current exposure was defined at cohort entry by at least one record for hydroxyzine use in the 3 months preceding hospitalization. Relative risk (RR) for abnormal QTc was estimated by Poisson regression and adjusted for the following covariates assessed at baseline: age, gender, exposure to drugs known to affect QTc interval, heart diseases, and electrolyte abnormalities. The final cohort included 182 patients. No patient died or was discharged before an ECG was performed. 34 patients (41% females, mean age: 86.26±8.53) were classified as exposed to hydroxyzine [dose: 12.5 mg/day (n=13) and 25 mg/day (n=21)] and 148 (61% females, mean age: 79.36±7.49) as not exposed. In exposed and not exposed patients QTc ranged from 401 to 492 ms (mean QTc: 442 ms) and from 334 to 500 ms (mean QTc: 410 ms), respectively. The proportion of patients with abnormal QTc were 29% (n=10) in the hydroxyzine group and 10% (n=15) in the control group (RR:2.90; 95% CI 1.30 to 6.45; p=0.014). After adjusting for covariates, RR was not significant (RR:1.87; 95%CI 0.77 to 4.58; p=0.16). According to our analysis, current exposure to hydroxyzine up to the dose of 25 mg/day is not associated with a significant increment of QTc interval as compared to not-exposed patients. Further studies with a larger sample of patients are required to confirm this finding.