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EFFECTS OF DARIFENACIN AND TOLTERODINE ON HEART RATE IN SUBJECTS ≥ 50 YEARS OF AGE: RESULTS OF A RANDOMIZED, DOUBLE-BLIND, 3-WAY CROSSOVER STUDY

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INTRODUCTION AND OBJECTIVE: Small increases in average heart rate (HR) and reductions in HR variability (HRV) are known risk factors for cardiovascular (CV) morbidity and mortality. Risk is higher in older (≥ 50 yrs) patients (pts) with CV disease.¹⁻³ Since the prevalence of overactive bladder (OAB) increases with age and up to 47% of OAB pts also have CV disease,⁴ the additional potential impact of antimuscarinic OAB treatments on CV risk through effects on HR/HRV is of major concern. In a prior study,⁵ the antimuscarinics darifenacin (DAR) and tolterodine (TOL) showed different effects on HR/HRV. This study evaluated effects of DAR and TOL in healthy volunteers similar in age to OAB pts.

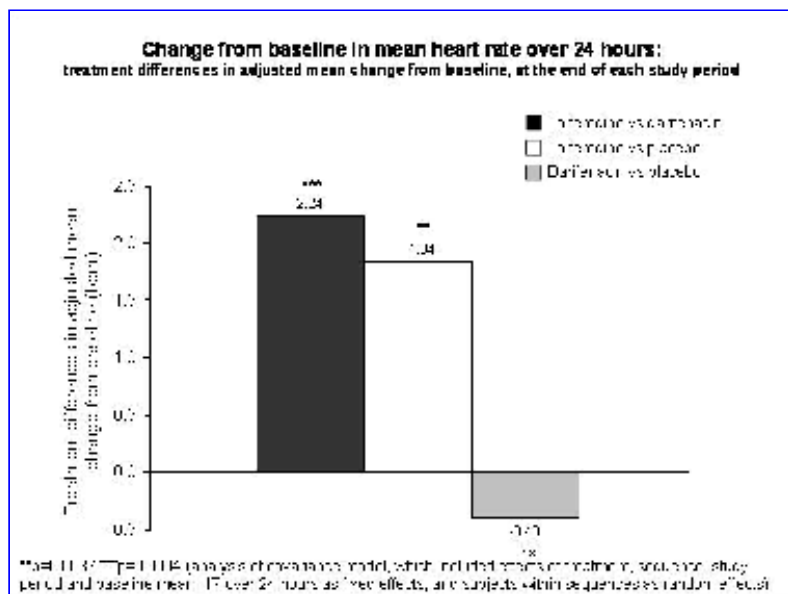
METHODS: In this crossover study, healthy subjects (≥ 50 yrs of age) were randomized to 1 of 6 different treatment sequences, each comprising three 7-day dosing periods (DAR 15 mg, TOL 4 mg, placebo [PBO]) separated by 14-day washouts. Mean (primary endpoint), minimum and maximum HR and HRV per 24 hours (h) were assessed at baseline and steady-state exposure (day 7 of each dosing period) using 24-h ambulatory ECG monitoring (Holter). Mean HR at hour of anticipated T_{max} and hourly mean HR were also assessed.

RESULTS: Of 117 randomized subjects (mean age 58.4 yrs, 63.2% women), 108 completed all 3 dosing periods. TOL statistically significantly increased mean HR per 24 h vs. DAR and vs. PBO (Figure). TOL statistically significantly reduced 2 of 3 HRV parameters per 24 h vs. DAR (both $p < 0.01$) and 1 of 3 HRV parameters vs PBO ($p = 0.0219$). In contrast, DAR did not affect any HR or HRV parameters vs. PBO. Most common adverse event (AE) was dry mouth (13.3% DAR, 5.4% TOL, 0.9% PBO). Discontinuation due to AEs was rare (0.9% DAR, 0% TOL, 1.8% PBO). There was one serious AE (hypersensitivity with DAR).

CONCLUSIONS: In healthy subjects similar in age to typical OAB pts, TOL increased HR and decreased HRV compared with DAR, which had similar effect on either parameter as PBO. As increased HR and reduced HRV are associated with increased CV risk, careful selection of antimuscarinics for OAB pts could minimize this risk.

References:

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