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THE EFFECTS OF DARIFENACIN AND TOLTERODINE ON HEART RATE (HR) IN PATIENTS WITH OVERACTIVE BLADDER (OAB)

Hypothesis / aims of study

Adverse cardiac effects from non-cardiac drugs are of major concern, especially in patients at risk of cardiovascular disease. Antimuscarinic drugs may exert cardiac effects (particularly increased HR) through muscarinic M_2 receptor antagonism. This could exacerbate pre-existing heart failure, myocardial ischaemia or angina and could undo the effects of cardiovascular therapy, such as beta blockers, used to treat a variety of cardiac conditions. This issue is particularly relevant for older patients.

Antimuscarinic drugs used to treat OAB differ regarding M_2 receptor binding and blockade. Darifenacin shows a 59-fold greater in-vitro binding affinity for the M_3 subtype (which mediates detrusor contraction) than for the M_2 subtype, whereas tolterodine shows only a 3.6-fold difference [1]. A double-blind trial of darifenacin and tolterodine has been conducted in patients with OAB, key outcomes of which were included in a pooled analysis of darifenacin phase III trials [2]. This trial forms the subject of the present post-hoc analysis comparing the cardiovascular safety of darifenacin, tolterodine and placebo.

Study design, materials and methods

Patients (aged 21–93 years, 38.4% ≥65 years, 84% female) with OAB for ≥6 months were randomized to 12 weeks' treatment with darifenacin (15 mg once daily), immediate-release tolterodine (2 mg twice daily) or placebo (n=112, 223 and 115, respectively). At baseline, the darifenacin, tolterodine and placebo groups included 33, 58 and 35 patients with hypertensive disease; 23, 42 and 31 patients taking antihypertensives; and 10, 22 and 8 patients taking beta blockers, respectively. OAB symptoms, adverse events (AEs) and discontinuations were recorded. Cardiovascular safety was investigated as spontaneously reported AEs and change in HR from baseline to last observation.

Results

Compared with baseline, median (percentage) changes in the number of incontinence episodes per week were –11.4 (–83.3%) for darifenacin, –10.3 (–73.7%) for tolterodine and –9.0 (–70.9%) for placebo ($p<0.05$ vs darifenacin, $p>0.05$ vs tolterodine). The most common AEs of dry mouth (34.8%, 26.9% and 9.6%) and constipation (25.0%, 12.6% and 6.1%) led to discontinuation in 2.7%, 1.8% and 0% patients on darifenacin, tolterodine or placebo, respectively. Treatment-related cardiovascular AEs (e.g. hypertension, palpitations) occurred in 1.8%, 4.0% and 0% patients receiving darifenacin, tolterodine and placebo, respectively. Tachycardia was reported by only 3 patients (all received tolterodine). One treatment-related serious AE was reported: irregular heartbeat and congestive heart failure in a patient receiving tolterodine. HR data showed greater increases from baseline to last observation with tolterodine than with placebo. The proportions of patients with HR increases of ≥5 or ≥10 beats per minute (bpm) were higher with tolterodine than either placebo (significantly [p=0.0046] for ≥5 bpm; p=0.0807 for ≥10 bpm) or darifenacin (p=0.0042 and p=0.0248, respectively). In contrast, darifenacin was associated with similar or lower HR at last observation relative to baseline than placebo (Table).

Table. Effects of treatment on HR

	Darifenacin 15 mg (n=108)	**Tolterodine (n= 219)**	**Placebo (n=112)**
Baseline (bpm)			
Mean (SD)	72.6 (8.8)	70.1 (7.8)	71.0 (7.7)
Median	72.0	70.0	72.0
Change from baseline to last observation (bpm)			
Mean (SD)	-0.9 (8.5)	3.3 (8.9)	0.5 (8.1)
Median	-0.5	2.0	0.0
p-value versus baseline (t-test)	0.27	<0.0001	0.51
Number (%) patients with change from baseline to last observation			
<5 bpm[a]	83 (76.8%)	133 (60.7%)	86 (76.8%)
≥5 bpm	25 (23.2%)	86 (39.3%)*†	26 (23.2%)
<10 bpm[a]	95 (88.0%)	169 (77.2%)	96 (85.7%)
≥10 bpm	13 (12.0%)	50 (22.8%)†	16 (14.3%)

[a] Includes patients who had a decrease in HR
*p<0.05 versus placebo; †p<0.05 versus darifenacin (Fisher's exact test, 2-sided)

Interpretation of results

Increases in HR are a potential concern for all patients, especially older patients at risk of cardiovascular disease. The proportion of patients with varying degrees of HR increase following darifenacin treatment was the same or lower than with placebo, whereas significantly higher proportions had a HR increase with tolterodine treatment. In addition, 9.9%

patients on tolterodine were being treated with beta blockers – the actions of which may be compromised by a HR increase; only three patients on tolterodine reported tachycardia as an AE – suggesting underreporting of HR effects.
A clinically relevant increase of ≥10 bpm in 22.8% patients on tolterodine is of particular note, and an important finding for older patients who are at increased risk of cardiovascular comorbidities and sudden cardiac death.
The overall efficacy, tolerability and safety of darifenacin in this study are consistent with the pooled analysis of phase III studies, which included 671 patients treated with darifenacin [2], and reported treatment-related cardiovascular AE rates of 0.9% for darifenacin 15 mg/day, and 0.3% for placebo.

Concluding message

These findings indicate that darifenacin treatment has effects on HR comparable to placebo, a profile that may be explained by its M_3 receptor selectivity. This cardiac safety profile is of clinical relevance for all patients with OAB and is likely to be of particular importance for older patients at risk for cardiovascular comorbidities, and those on polytherapy.

References:

1. Napier C, Gupta P. Darifenacin is selective for the human recombinant M3 receptor subtype. Neurourol Urodyn 2002;21(4):275–472 (abs445).
2. Chapple, C et al. A pooled analysis of three phase III studies to investigate the efficacy, tolerability and safety of darifenacin, a muscarinic M3 selective receptor antagonist, in the treatment of overactive bladder. BJU Int 2005;95:993–1001.

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CLINICAL TRIAL REGISTRATION: **This clinical trial has not yet been registered in a public clinical trials registry.**

HUMAN SUBJECTS: **This study was approved by the an independent review board at each trial centre and followed the Declaration of Helsinki Informed consent was obtained from the patients.**