

COGNITIVE SAFETY AND OVERALL TOLERABILITY OF IMIDAFENACIN IN ROUTINE CLINICAL USE : LONG-TERM, OPEN-LABEL, POST-MARKETING SURVEILLANCE STUDY

Hypothesis / aims of study

Overactive bladder (OAB) is common in elderly people, many of whom are at risk of impaired cognition. There are reports of anticholinergics causing a dementia-like syndrome in otherwise healthy individuals. Newer anticholinergics appear to have no adverse effect in cognitively intact elderly people, but there are a few clinical data on those at risk. The aim of this study was to investigate the influence of imidafenacin (IM) on cognitive function in OAB patients with mild cognitive impairment (MCI). IM is the novel anticholinergic; its superiority to placebo and noninferiority to propiverine have been demonstrated in placebo- and propiverine-controlled clinical studies [1], and it has been marketed in Japan since 2007. IM also showed bladder-selectivity for the bladder over the salivary gland, heart, colon, brain and no influence on cognitive function in animals.

Study design, materials and methods

This was an open-label, post-marketing surveillance study focused on MCI, cognitive progression to dementia, with a monitoring period of one year. It was performed in the setting of 52 medical institution in Japan. This study was approved by local Ethics Committee. We recruited 192 patients with OAB who were on suspicion of MCI and newly administered IM (0.1mg twice a daily). The registration of patient was performed by the central registration system through postal mail or facsimile. All patients underwent a systematized lower urinary tract symptom (LUTS) questionnaire, physician-based monitoring of adverse drug reactions (ADRs), and cognitive tests (Mini-Mental State Examination [MMSE]: range 0–30, lower scores indicating worse cognition). Men and women with symptom of urinary urgency, urinary frequency (>8 voids/24h), urge incontinence (>1 episodes/week) were eligible for inclusion. Exclusion criteria included: no demonstrable MCI evaluated by MMSE; disabling symptom of decline in cognitive function; patients diagnosed with dementia; patients with concomitant administration of donepezil hydrochloride. Rate of progression of MCI to dementia was calculated as a proportion of those recruited at baseline rather than those that survived to follow-up, as this most closely resembles clinical practice when attempting to give estimates of prognosis. We also calculated person years of observation in this study. MMSE scores between before and after treatment was calculated that short-term analysis set, from baseline to 12-14 weeks, and long-term analysis set, from baseline to over 48 weeks. Statistical assessments were performed using the paired t test, and P <0.05 was considered statistically significant.

Results

Case report forms of 192 patients were collected from 52 medical institutions. Safety analysis was performed 187 patients in overall analysis except for 5 patients who didn't revisit institution. The underlying diseases are cardiovascular disease in 88 patients, benign prostatic hyperplasia in 27 patients, Parkinson's disease in 18 patients, etc. Consequently, 42 patients met exclusion criteria, and the safety analysis set of MCI was 145 patients. The average age was 75±9.1 years [33-93 years] in overall analysis and 75±9.4 years in patients with MCI. Average duration of drug use is 283±173.3 day. OAB symptom such as urgency, urinary frequency, and incontinence were improved with time, and overall improvement ratio was 80.7%. The tolerability of IM was good. ADRs reported in 15 patients (8.02%) but no specific tendency in the occurrence of the ADRs was noted. Further, cognitive progression to dementia was confirmed in 4 of the 145 MCI patients, with an annual conversion rate of 3.6%, and this rate did not exceed those reported in the past epidemiological studies (6.8 – 16.1 per year). No significant difference was noted in MMSE scores between before and after treatment (24 weeks or 48 weeks after starting IM therapy; 24.8±2.9 to 25.8±2.7 or 25.7±2.7, respectively).

Interpretation of results

This is the first report to focus on the conversion rate of MCI to dementia in OAB patients treated with anticholinergic. Although there are reports of anticholinergics causing a dementia-like syndrome in otherwise healthy individuals, cognitively vulnerable patients with OAB were common. Thus, it is important to investigate the relationship between anticholinergic medications and the cognitive function in OAB patients. There is a report that individuals with MCI appear to be at an increased risk of developing Alzheimer disease at the rate of 10% to 12% per year [2]. It is also reported that the annual conversion rate that Mild Memory Impairment /not Dementia shifted to AD is calculated on 8.5% per 100 person-year, and shifted to dementia on 16.1% per 100 person-year in a population-based cohort study in Japan [3]. In our study, the conversion rate from amnesic MCI to dementia was 5.9% per 100 person-year and this conversion rate under run the previous epidemiological survey.

Concluding message

In real-life conditions, therapeutically effective doses of IM can be used safely for cognitively vulnerable patients with OAB. The results of this study should give confidence to clinicians treating OAB in this at-risk group of older people.

References

1. Urology. 68(2):318-23, 2006
2. Arch Neurol, 56,303-308, 1999
3. Int J Geriatr Psychiatry, 21,134-139, 2006

Disclosures

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