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THE INFLUENCE OF ANTICHOLINERGICS USED IN INCONTINENCE TREATMENT ON SLEEP IN HEALTHY VOLUNTEERS AGED 50 YEARS AND OLDER

Hypothesis / aims of study

There is strong evidence of an impact on sleep structure and sleep quality under treatment with anticholinergic substances used in incontinence treatment coming from reports of neuro-psychological side-effects and case-reports of sleep disturbances as well as from parallels to other anticholinergic substances. The aim of the study was to investigate whether sleep parameters change under treatment with oxybutynin, tolterodine and trospium in comparison to placebo within the target population for these substances, i.e. in individuals aged 50 years and older.

Study design, materials and methods

According to the guidelines of Good Clinical Practice (GCP) and the declaration of Helsinki a randomised, double-blind, placebo-controlled study was conducted in a cross-over-design. After an initial polysomnographic and thorough physical examination 25 healthy volunteers (13 female, 12 male) aged 51 to 65 years, without any sleep-disturbances were included in the study, one volunteer dropped-out.
The subjects underwent 4 periods of 2 consecutive polysomnographic nights in the sleep-lab, always separated by 12 days washout. Each first night was for adaption, the second night was the treatment-night and was used to study the impact of the medication on sleep.
Administration of medication was 2 hours before starting polysomnography. In a randomised order volunteers obtained 4 mg tolterodine, 15 mg oxybutynin, 45 mg trospium and placebo. To assess the subjective quality of sleep, a structured questionnaire had to be filled out by the volunteers before and after each polysomnographic recording. In addition “The d2 test of Attention” (d2) and a “Number Combination Test” (ZVT) were performed one hour after medication. Additionally an exploratory analysis of all objective and subjective sleep parameters as well as parameters of psychometric testing was performed using the Wilcoxon Matched-Pairs Signed-Ranks Test. All tests except that used for the primary parameters had to be interpreted on an explorative level.

Results

For statistics Friedman’s ANOVA was used to prove differences between the treatments. As target variable for polysomnography REM duration as a percentage of sleep duration (TST) showed statistically significant over-all differences ($p=0.007$) between the four treatment groups. Further analyses using the Wilcoxon Matched-Pairs Signed-Ranks Test revealed reductions in the median of REM sleep duration of 14.2% after oxybutynin ($p=0.002$) and of 15.2% after tolterodine ($p=0.012$) compared to placebo. REM duration after trospium chloride was not significantly different from placebo.
A second explorative analysis revealed a non-significant ($p=0.074$) prolongation of REM latency (time between sleep onset and first period of REM) after intake of oxybutynin and tolterodine compared to placebo and trospium chloride. No significant changes were seen for the other secondary objective parameters: duration of various sleep stages (stage 1, stage 2, slow wave sleep (SWS)) as a percentage of sleep duration (TST), sleep latencies (sleep onset latency, SWS latency), and sleep efficiency.
Subjective sleep parameters were not significantly affected by the different medications.
None of the study medications influenced the cognitive skills of the volunteers.

Interpretation of results

Incidence and intensity of central-nervous side-effects of anticholinergic drugs depend on their pharmacokinetic and pharmacodynamic properties and can be more pronounced in the elderly, even if dosage is properly adjusted to account for age-related pharmacokinetic changes. Several authors have shown relevant neuro-psychological side-effects in elderly patients treated with tertiary anticholinergic substances as oxybutynin and tolterodine. These

side-effects did not occur under treatment with the quaternary substance trospium chloride. Furthermore, sleep disturbances (pavor nocturnus) were reported in literature under oxybutynin .
In healthy volunteers aged 50 years and older, we observed a significant REM sleep reduction of about 15 % and a slightly increased REM latency under oxybutynin and tolterodine compared to placebo. Under trospium chloride, REM sleep parameters were comparable to placebo.
We did not observe any effect of the tested anticholinergics on cognitive parameters and subjective sleep parameters.
However, an impairment of cognitive function and neuro-psychological side-effects cannot be excluded, especially when elderly patients with impaired REM sleep due to various psychic diseases (e.g. depression) and/or sleep disturbances are given oxybutynin or tolterodine. Furthermore, these drugs are used in chronic diseases and it is unknown how the effects on sleep structure influence cognitive skills in the long run.

Concluding message

Individuals aged 50 years and older have a distinct impairment of REM sleep under oxybutynin and tolterodine. We suggest that for patients with cognitive impairment under therapy with these anticholinergics, a switch to trospium chlorid should be taken into consideration.

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