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Brief Communication

Effect of tolterodine on sleep structure modulated by CYP2D6 genotype

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Abstract

Objective: Tolterodine, a drug for the treatment of overactive bladder symptoms, has a limited entry into the brain, which makes cognitive side effects seldom. However, some case reports have described central-nervous side effects such as sleepiness. The aim of this retrospective analysis was to investigate whether tolterodine-related effects on sleep stage parameters could be explained by different CYP2D6 metabolizer characteristics of subjects.
Methods: Data were taken from two randomized, double-blind, placebo-controlled studies conducted in a cross-over design. Forty-eight volunteers underwent 4 two-night attended polysomnographic studies. Subjective quality of sleep and cognitive function were assessed. A single dose of 4 mg tolterodine or placebo was administered before sleep. Forty-four volunteers gave informed consent for genotyping. We found 19 extensive metabolizers (EM), 20 intermediate metabolizers (IM), 4 poor metabolizers (PM) and 1 ultra-rapid metabolizer. There were no significant differences between the groups regarding demographic data.
Results: Rapid eye movement (REM) sleep duration as a percentage of total sleep time showed significant reduction ($p = 0.019$) in the group carrying one or more deficient alleles (IM + PM). No significant difference was found with two active alleles of CYP2D6 in the EM group. REM latencies under tolterodine displayed a tendency towards prolongation, which was irrespective of the metabolizer status. Subjective sleep parameters did not show statistically significant changes after tolterodine. Cognitive skills were not affected.
Conclusion: Our retrospective analysis reveals that a decrease of REM sleep under tolterodine is found only in individuals carrying one or two deficient CYP2D6 alleles.

Keywords: Tolterodine; CYP2D6; Anticholinergics; Sleep; REM sleep; Drug side effects

1. Introduction

Tolterodine is a potent competitive antagonist at muscarinic receptors used for the treatment of overactive bladder symptoms [1–3]. It is extensively metabolized via CYP2D6 to an active metabolite (5-hydroxymethyl-tolterodine) [4,5]. The drug effect is based upon the concentration of the plasma unbound 'active moiety' (sum of tolterodine + 5-hydroxymethyl-tolterodine). However, about 7% of the Caucasian population are poor metabolizers without any active CYP2D6 allele. These subjects transform tolterodine via CYP3A4 into the inactive metabolite *N*-dealkylated tolterodine.

Tolterodine's entry into the brain is limited by its relatively low lipid solubility. This is probably the reason why cognitive side effects are rather seldom [3,6]. However, some case reports have described memory impair-

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ment and hallucinations [7,8], dizziness, sleepiness and nervousness [9,10].

We investigated the influence of different anticholinergic substances on the structure and quality of sleep in two studies with healthy volunteers [11,12]. These studies revealed a significant impact of tolterodine on REM sleep, in particular in volunteers aged 50 years and older.

The aim of the retrospective exploration presented here was to investigate whether tolterodine-related effects on sleep structure could be explained by a different CYP2D6 metabolizer status. For that purpose subjective sleep quality was assessed by questionnaire, objective sleep quality was assessed by polysomnography and cognitive functions were investigated by a psychophysiological test battery.

2. Methods

Data were drawn from two randomized, double-blind, placebo-controlled studies which were conducted in a cross-over design [11,12]. Volunteers underwent 4 two-night periods of polysomnography in a sleep laboratory using exactly the same design in both studies except for the recruitment of age groups. The first study group had a mean age of 28.1 ± 5.0 years, and the second study group had an age of 60.2 ± 4.2 years, being closer to potential users of the medication. Study medication was either a single dose of 4 mg of tolterodine (Detrusitol, Pharmacia GmbH, Germany) or placebo, which was administered two hours before the planned sleep onset on the second night. Both studies were approved by the Local Ethics Committee of the Charité University Hospital in Berlin.

Sleep was recorded by polysomnography in our sleep laboratory. Sleep stages were scored visually according to the criteria of Rechtschaffen and Kales [13]. Subjective quality of sleep was assessed using a structured questionnaire. Potential impairment of cognitive function was assessed one hour after administration of the study medication using a number combination test (ZVT) and the *d*2-test of attention [14,15].

Forty-four volunteers with complete polysomnographic, subjective and cognitive data gave their informed consent for genotyping. Analyses for the CYP2D6 alleles *3, *4, *5, *6 and the duplication were performed with the PCR–restriction fragment length polymorphism methods described earlier [16]. Within this population, we found 19 extensive metabolizers (EM) carrying two active alleles of CYP2D6, 20 intermediate metabolizers (IM) carrying one deficient allele, 4 poor metabolizers (PM) carrying two deficient alleles, and 1 ultrarapid metabolizer (UM) carrying a CYP2D6 gene duplication combined with a wild-type allele. This subject was not included in the subsequent analysis of sleep data. Demographic data including age did not differ significantly between EM, IM, and PM groups (age: $p = 0.310$, body mass index: $p = 0.662$).

An exploratory analysis was performed using the Wilcoxon Matched-Pairs Signed-Ranks Test. Objective sleep parameters, subjective sleep parameters, and parameters of psychometric tests under tolterodine and placebo in the EM group were compared to those in carriers of deficient alleles (IM + PM). All tests were interpreted on an explorative level.

3. Results

REM duration as a percentage of total sleep time (TST) showed a statistically significant reduction ($p = 0.019$) in the group carrying one or more deficient alleles (IM + PM), whereas no significant difference was found ($p = 0.658$) in the EM group. Eighteen out of 24 IM and PM subjects showed a reduction (Fig. 1, top). Of the PM subjects, all four showed a reduction;

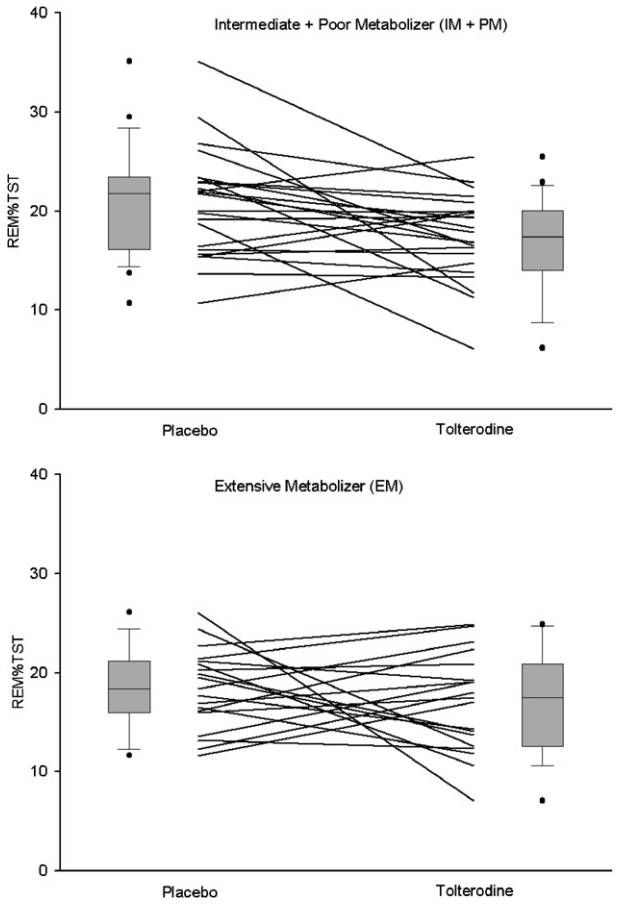

Fig. 1. REM sleep duration as calculated in percent of total sleep time was evaluated for tolterodine versus placebo. The reduction of REM sleep duration was found in subjects which were poor (PM) or intermediate metabolizers (IM) (top) and was not found in subjects which were extensive metabolizers (EM) (bottom). Data values are given as box plots with median and are also given as connected data points.