Randomised, Double-Blind Study of the Effects of Oxybutynin, Tolterodine, Tros Titanum Chloride and Placebo on Sleep in Healthy Young Volunteers

Konstanze Diefenbach, Frank Donath, Agathe Maurer, Sabine Quispe Bravo, Klaus-Dieter Wernecke, Ulrich Schwantes, Julia Haselmann and Jörn Roots

1 Institute of Clinical Pharmacology, Charité University Medical Centre, Humboldt University of Berlin, Berlin, Germany
2 Institute of Medical Biometry, Charité University Medical Centre, Humboldt University of Berlin, Berlin, Germany
3 Department of Medical Science/Clinical Research, Dr R. Pfleger GmbH, Bamberg, Germany

Abstract

Objective: Central nervous effects of oral anticholinergics may limit the success of incontinence therapy and patient compliance. Only a few studies investigating this topic are available. This study was conducted to determine whether oral anticholinergics alter sleep and psychometric test parameters.

Design: Randomised, double-blind, crossover, placebo-controlled study.

Study participants: 24 healthy volunteers (age 22–36 years) without sleep-related problems.

Interventions: Polysomnographic recordings, sleep questionnaires and psychometric tests (the number combination test [Zahlen-Verbindungs Test; ZVT] and the d2 attention test) were performed following single doses of oxybutynin 15 mg, tolterodine 4 mg, tros Titanum chloride 45 mg or placebo, each separated by an 8-day washout period.

Results: Rapid eye movement (REM) sleep (relative to total sleep time) was the primary parameter of polysomnography. The REM sleep for oxybutynin was significantly lower than that for tros Titanum chloride (18.4% vs 20.2%; p < 0.05) and lower than that for placebo (20.1%; ns). The number combination test (ZVT), the primary parameter of cognitive function, and the d2 test did not reveal any differences in reaction time. With regard to the other sleep parameters, the REM latency for oxybutynin was clearly higher than that for placebo, tros Titanum chloride and tolterodine. Effects on non-REM sleep were observed only after administration of oxybutynin compared with placebo.

Conclusions: Oxybutynin influenced sleep structure, as was reflected by REM suppression and mild sedation, while subjective parameters and psychometric tests remained unaffected. The sleep and psychometric test values for tolterodine and tros Titanum chloride were comparable to those of placebo. The clinical relevance
of these effects is small in healthy young volunteers, but these results cannot be extended to the elderly.

Urinary incontinence is a common problem estimated to occur in 10–30% of all elderly women and in 2–3% of elderly men.\textsuperscript{[1]} Anticholinergic drugs such as trospium chloride, tolterodine and oxybutynin are widely used for treatment of detrusor hyperactivity and hyperreflexia of the urinary bladder. The success of therapy and patient compliance are often impaired by the typical adverse effects of these drugs, such as dry mouth, gastrointestinal disturbances and visual disorders.\textsuperscript{[2,3]} However, side effects in the central nervous system are more critical, especially in elderly individuals.\textsuperscript{[4]} Their incidence and intensity associated with different anticholinergic agents can vary: clinical studies revealed cognitive impairment\textsuperscript{[5–7]} and changes in central nervous electrical activity after treatment with oxybutynin, whereas trospium chloride did not cause any impairment.\textsuperscript{[8]} Neuropsychological adverse effects including psychosis, hallucination, confusion, cognitive impairment, impaired concentration and orientation,\textsuperscript{[9,10]} as well as drowsiness and disturbed sleep behaviour, have been observed in conjunction with oxybutynin.\textsuperscript{[11]} Tolterodine leads to central nervous adverse effects such as dizziness, sleepiness and nervousness,\textsuperscript{[12,13]} whereas no effects of this type have been observed with trospium chloride. The distinct pharmacodynamic and pharmacokinetic properties of the anticholinergic drugs seem to be responsible for these differences. The ability of a substance to cross the blood-brain barrier depends on its structure, i.e. on its lipophilicity, electrical charge and molecular size. Small, lipophilic, noncharged molecules and compounds containing a tertiary ammonium group pass the blood-brain barrier more readily than those containing a quaternary ammonium group or groups with opposing characteristics.\textsuperscript{[14,15]} Whereas oxybutynin and tolterodine are tertiary amines, trospium chloride is a quaternary ammonium compound.

Oxybutynin, tolterodine and trospium chloride do not appear to selectively block muscarinic recep-
tor subtypes M\textsubscript{1} to M\textsubscript{5}, although functional differences in the affinity to muscarinic receptors in different organs may be an explanation for the different qualities of their anticholinergic effects.\textsuperscript{[16,17]} There is strong evidence that anticholinergic compounds influence sleep structure and sleep quality. Five case reports of pavor nocturnus ("night terror") after administration of oxybutynin have been described.\textsuperscript{[11]} Neuropsychological adverse effects have been reported in conjunction with several anticholinergic drugs and other substances with anticholinergic properties.\textsuperscript{[18–21]} Distinct changes in sleep structure were observed after treatment with the nonselective cholinergic antagonist scopolamine. These changes along with an up to 130% increase in rapid eye movement (REM) latency and a 20–60% reduction in REM duration are more pronounced in REM sleep than in non-REM sleep.\textsuperscript{[22–25]} The aim of the present study was to compare the effects of oxybutynin, tolterodine and trospium chloride versus placebo on sleep parameters in healthy individuals. Subjective assessments of sleep and cognitive behaviour were analysed in addition to the usual polysomnographic parameters of sleep structure.

**Study Participants and Methods**

**Subjects**

A total of 28 healthy young volunteers were recruited in the study. Twenty-four of them (6 female, 18 male) aged 22–36 years (mean ± SD 28.5 ± 5 years) completed the study; four participants dropped out. All volunteers were in good health for their age group. Exclusion criteria were sleep disturbances and organic or psychiatric diseases that could cause sleep disturbances or were contraindications to one of the study medications. Such diseases were excluded by investigating each volunteer's current clinical status, laboratory parameters and polysomnographic findings before carol-
ment into the study. Starting 2 months before the study until its conclusion, the volunteers were not allowed to smoke or to take drugs with cholinergic or anticholinergic effects, substances that alter sleep structure, daytime vigilance or gastrointestinal motility, or drugs metabolised by cytochrome P450 2D6 or 3A4.

Participants had to abstain from alcohol on the day before the nightly measurements, and to abstain from caffeine after 4pm on all days of testing in the sleep laboratory. Compliance tests showed that none of the participants had consumed drugs or large amounts of alcohol or caffeine prior to the study or had a history of drug abuse.

The volunteers gave their written informed consent to participate after receiving full written and verbal information. The study was approved by the local ethics committee of the Charité University Medical Centre.

Study Protocol

This randomised, double-blind, placebo-controlled study was conducted in a crossover design according to the European Guidelines of Good Clinical Practice and the Declaration of Helsinki. The participants spent 9 nights in the sleep laboratory: 1 night prior to the study to exclude sleep disturbances such as sleep apnoea syndrome, periodic leg movements or restless legs, and four trial periods on two consecutive nights separated by an 8-day washout period. Cognitive tests and polysomnographic recordings were done during the nights at the sleep laboratory. The first night of every trial served as a period of adaptation; the second night was considered the treatment night during which the effects of the medication on sleep were studied.

The volunteers arrived at the sleep laboratory at about 7.30pm. All were screened for nicotine and drugs (amphetamine, barbiturates, benzodiazepines, cannabinoids, cocaine, ethanol, opiates); the women were additionally tested for pregnancy. They then filled out the sleep questionnaire, and the electrodes for polysomnographic recording were put in place. On the nights of treatment, a single dose of the study medication was administered at 8.30pm (2 hours before polysomnography). Cognitive testing was performed every night at 9.30pm (1 hour before polysomnography). Polysomnography was performed between lights out (10.30pm) and lights on (after spontaneous awakening but by 6.30am at the latest). The volunteers then filled out another sleep questionnaire and were asked to report adverse events. The volunteers were allowed to leave the sleep laboratory after breakfast.

Treatment

The volunteers were randomly assigned to one of the four possible treatment sequences using the Latin square technique. Each test medication was administered as a single dose consisting of three capsules (wafer capsules) corresponding to the usual daily dosage specified in the monograph for trosplem chloride (45mg, Spasmox® 15, Dr R. Pfieger GmbH, Germany), tolterodine (4mg, Detrusitol®, Pharmacia & Upjohn GmbH, Germany) or oxybutynin (15mg, Dridase®, Pharmacia & Upjohn GmbH, Germany). All of the test medications were identical in appearance and taste. Randomisation was carried out in blocks (Latin square) and a possible dropout rate of 24 subjects was considered.

Polysomnographic Recordings

Sleep recordings were made using the Alice3® computerised polysomnographic system (Healthdyne Technologies, Respironics). Standard sleep electrodes for tests including the electroencephalogram (EEG), electro-occulogram (EOG), electromyogram (EMG) and electrocardiogram (ECG) were used. Four EEG leads (C4-A1, O2-A1, C3-A2, O1-A2), two EOG leads, two EMG leads (chin, leg) and one ECG lead were used on each adaptation and treatment night at the sleep laboratory. Respiratory parameters such as microphone monitoring, nasal flow, thoracic/abdominal effort and O2 saturation were recorded on the night prior to the study to exclude sleep disturbances. Sleep stages were

1 The use of tradenames is for product identification only and does not imply endorsement.
scored visually according to the criteria of Rechtschaffen and Kales\textsuperscript{[27]} by two separate monitors. The interindividual agreement for scoring sleep among the two raters, as reflected by the kappa index, was excellent (kappa = 0.80).

The following parameters were used to describe objective changes in sleep structure. The primary parameter was REM sleep as a percentage of total sleep time. The secondary parameters were sleep efficiency (total sleep time/time in bed × 100), duration of different stages of sleep as a percentage of total sleep time: stage 1, stage 2, slow-wave sleep (SWS, stages 3 and 4 combined), duration of wake as a percentage of sleep period time, and the latencies of sleep onset, SWS and REM.

Sleep Questionnaires

To assess the subjective quality of sleep, the volunteers filled out structured questionnaires designed by the German Society of Sleep Medicine in the evening before and the morning after each polysomnographic recording. The questionnaires contained visual analogue scales for the variables ‘sleep quality’, ‘morning well-being’ and ‘daytime performance’ and asked for the subjectively perceived duration of sleep latency and total sleep time. These variables were investigated as secondary parameters in the study.

Furthermore, questions about dreams, subjective sleep disturbances, daytime activities, use of drugs, caffeine and nicotine during the day and time of application were included in the questionnaire. The responses were used to assess volunteer compliance and exclusion criteria.

Cognitive Testing

To evaluate cognitive impairment, the d2 attention test (d2 test) and a number combination test (the Zahlen-Verbindungs Test; ZVT) were performed 1 hour after administration of each study medication.

The ZVT measures information-processing and working velocity.\textsuperscript{[28]} The results are expressed as reaction time. This parameter was chosen as the primary target variable.

The d2 test measures processing speed, rule compliance and quality of performance, allowing a neuropsychological evaluation of individual sustained attention and concentration performance.\textsuperscript{[29]} Results are expressed as ‘N’ (number of items completed) and ‘M’ (mistakes/missed target items plus commissions). Mistakes should be interpreted with care, as they could be based on accommodation disturbances. The d2 test scores were used as secondary parameters.

Adverse Events

The volunteers were questioned about adverse events during each visit to the sleep laboratory. All adverse events were documented according to type, intensity (mild, tolerable, severe), onset, duration and causal relationship to the study medication (unrelated, unlikely, possible or probable).

Statistical Analysis

The primary aims of the study were to evaluate the effects of the tested anticholinergic drugs on REM duration as a percentage of total sleep time and reaction time as scored in the number combination test (ZVT). The required sample size was estimated on the basis of an expected 20% reduction in REM sleep, which has been observed in healthy volunteers after administration of various anticholinergic drugs.\textsuperscript{[22,23,29]} A 20% change in REM sleep was defined as clinically relevant, and a required sample size of 23 was calculated with an α level of 0.05 and a β level of 0.2. The study was therefore carried out with a total of 24 volunteers; substitutes for dropouts were assigned according to the randomisation scheme.

For primary parameters of the study, Friedman's nonparametric analysis of variance (ANOVA) was used to test overall differences. Wilcoxon-Wilcoxon rank sum tests for multiple testing were performed to assess statistically significant differences between the treatment groups in the post hoc analyses (p < 0.05).\textsuperscript{[30,31]}

In addition, the distribution of all objective and subjective sleep parameters as well as parameters of psychometric testing were described as median and
first and third quartile values for each treatment night and exploratory analyses were performed using Wilcoxon matched-pair tests. All tests except the primary parameters had to be interpreted on an explorative level.

The kappa index for multiple ratings was used to measure interindividual agreement among the raters. Values from 0 to 0.40 indicate poor agreement, from 0.40 to 0.75 fair to good, and values from 0.75 to 1.00 indicate excellent agreement.

Results

Polysomnographic Recording

REM sleep (percentage of REM relative to total sleep time) was used as the primary parameter of polysomnographic recording. The REM sleep tended to differ between treatments ($p = 0.06$), as was demonstrated by Friedman’s ANOVA test. The Wilcoxon-Wilcoxon rank sum test for multiple testing showed that the REM sleep for oxybutynin (18.4%) was significantly lower ($p < 0.05$) than that of trosium chloride (20.2%). REM sleep after oxybutynin was shorter than that after placebo (20.1%) and that after tolterodine (19.1%), but did not reach statistical significance (table I, figure 1).

In a secondary exploratory analysis REM latency (time between sleep onset and first period of REM) for oxybutynin was 25 minutes longer than that of placebo ($p = 0.03$) and trosium chloride ($p = 0.001$) and 20 minutes longer than that of tolterodine ($p = 0.045$). No differences could be found between trosium chloride and placebo. The REM latency for tolterodine tended to be longer than that for placebo and trosium chloride (table I, figure 1). Other differences between sleep parameters for oxybutynin and placebo were observed: objective sleep onset latency decreased by 5.8 minutes ($p = 0.01$), stage I increased by 2.5% ($p = 0.017$), and sleep efficiency increased by 1.6% with oxybutynin ($p = 0.002$). The measured total sleep time, subjective sleep duration, wakefulness after sleep onset, and deeper sleep stages (stage 2, SWS) were not affected. Trosium chloride and tolterodine did not differ from placebo with respect to these parameters (table I).

Sleep Questionnaire

Data provided by the sleep questionnaire were described and analysed as secondary study parameters. Compared with placebo, the subjective sleep latency decreased by 5 minutes after oxybutynin treatment ($p = 0.031$), but none of the groups differed with respect to subjective sleep time (table I).

The visual analogue scales revealed better ‘sleep quality’ with trosium chloride (75.7%) than tolterodine (72.0%), placebo (72.7%) and oxybutynin (74.7%). Differences did not reach statistical significance. The different groups did not differ with respect to ‘morning well-being’ and ‘daytime performance’ (table I).

Cognitive Testing

The reaction time measured in the number combination test (ZVT) was used as the primary parameter for cognitive testing. Analysis of this parameter using Friedman’s ANOVA did not reveal any significant differences between placebo and the three anticholinergic drugs (table I, figure 2). The d2 attention test also did not reveal any significant differences between the different groups (table I, figure 2).

Adverse Events

Twenty of the 28 recruited volunteers reported a total of 40 adverse events (table II). The majority of these events occurred with oxybutynin, whereas trosium chloride and tolterodine did not differ from placebo with respect to the number and quality of adverse events. The causal relationship of adverse events to the study medication was assessed as probable in 17 cases and possible in 4 cases (trosium chloride 4, tolterodine 1, oxybutynin 16). Thirteen events were judged as unlikely to be related or unrelated to the study medication. A further six adverse events occurred with placebo (table II). In the oxybutynin group, reports of dry mouth were more frequent (8 reports) than with placebo (1).
Table I. Objective and subjective parameters of sleep structure and cognitive testing; median values (first and third quartiles) are listed

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Tröspium chloride</th>
<th>Tolterodine</th>
<th>Oxybutynin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>REM (%)</td>
<td>20.1</td>
<td>(16.1–22.2)</td>
<td>20.2</td>
<td>(17.0–23.0)</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>94.7</td>
<td>(92.3–96.5)</td>
<td>95.6</td>
<td>(92.4–97.6)</td>
</tr>
<tr>
<td>Stage 1 (%)</td>
<td>6.1</td>
<td>(5.0–8.4)</td>
<td>6.7</td>
<td>(5.5–8.1)</td>
</tr>
<tr>
<td>Stage 2 (%)</td>
<td>57.8</td>
<td>(54.9–60.1)</td>
<td>58.4</td>
<td>(53.5–60.6)</td>
</tr>
<tr>
<td>SWS (%)</td>
<td>14.5</td>
<td>(13.7–15.8)</td>
<td>14.6</td>
<td>(10.5–16.7)</td>
</tr>
<tr>
<td>Wake (% sleep period time)</td>
<td>1.7</td>
<td>(0.6–5.4)</td>
<td>1.4</td>
<td>(0.7–2.9)</td>
</tr>
<tr>
<td>Sleep onset latency (min)</td>
<td>16.8</td>
<td>(8.0–33.4)</td>
<td>13.4</td>
<td>(7.0–22.6)</td>
</tr>
<tr>
<td>SWS latency (min)</td>
<td>12.4</td>
<td>(9.8–15.8)</td>
<td>11.9</td>
<td>(11.5–13.7)</td>
</tr>
<tr>
<td>REM latency (min)</td>
<td>55.0</td>
<td>(53.0–97.4)</td>
<td>94.6</td>
<td>(53.9–82.5)</td>
</tr>
<tr>
<td><strong>Cognitive testing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reaction time (sec), ZVT</td>
<td>46.4</td>
<td>(41.8–65.3)</td>
<td>48.4</td>
<td>(40.8–66.6)</td>
</tr>
<tr>
<td>N value, d2 test</td>
<td>463</td>
<td>(405–514)</td>
<td>434</td>
<td>(377–542)</td>
</tr>
<tr>
<td>M value, d2 test</td>
<td>5</td>
<td>(4.0–10.3)</td>
<td>5</td>
<td>(2.9–12.8)</td>
</tr>
<tr>
<td><strong>Subjective parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjective sleep latency (min)</td>
<td>15.0</td>
<td>(10.5–30.0)</td>
<td>13.5</td>
<td>(10.0–27.5)</td>
</tr>
<tr>
<td>Subjective sleep time (min)</td>
<td>440</td>
<td>(420–450)</td>
<td>440</td>
<td>(408.9–460)</td>
</tr>
<tr>
<td>Subjective sleep quality (% VAS)</td>
<td>72.7</td>
<td>(43.8–88.0)</td>
<td>75.7</td>
<td>(49.2–90.5)</td>
</tr>
<tr>
<td>Morning well-being (% VAS)</td>
<td>68.3</td>
<td>(69.1–92.7)</td>
<td>81.7</td>
<td>(68.2–96.4)</td>
</tr>
<tr>
<td>Daytime performance (% VAS)</td>
<td>75.0</td>
<td>(48.7–84.3)</td>
<td>71.0</td>
<td>(56.0–88.2)</td>
</tr>
</tbody>
</table>

M = mistakes/misused target items plus commissions; N = number of items completed; REM = rapid eye movement; SWS = slow-wave sleep; VAS = visual analogue scale; ZVT = Zahlen-Verbindungs Test.
Effects of Anticholinergics on Sleep

Trospium chloride (2) and tolterodine (0). All groups were similar with respect to the number of other typical peripheral adverse events, such as gastrointestinal complaints and retention of urine.

Four volunteers dropped out of the study prematurely. None of the reasons for dropout was related to the study medication. One volunteer developed an acute attack of itching skin eczema due to contact allergy 2 weeks before the first night of treatment. Another volunteer had an acute attack of gouty arthritis starting at the end of the second washout period. Both volunteers had previously experienced similar health problems. Two volunteers were excluded because of a suspicious result in the drug screening.

Discussion

The objective of the study was to investigate the central nervous adverse effects of various anticholinergic drugs (oxybutynin, tolterodine, trospium chloride) used to treat incontinence. Objective and subjective parameters of sleep structure as well as cognitive function were studied as indicators of central nervous effects after single doses of these anticholinergics. Different authors have shown that relevant neuropsychological adverse effects occur during regular treatment with tertiary anticholinergic

Fig. 1. Effects of placebo, trospium chloride, tolterodine and oxybutynin on rapid eye movement (REM) sleep as a percentage of total sleep time (TST) and REM latency. Median and first and third quartile values are shown.

Fig. 2. Effects of placebo, trospium chloride, tolterodine and oxybutynin on reaction time in the number combination test (Zahlen-Verbindungs Test; ZVT) and on the number of items completed in the d2 attention test. Median and first and third quartile values are shown.
Table II. Summary of adverse events observed during the study: number of events (corresponding number of events possibly or probably related to the study medication in parentheses)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Placebo</th>
<th>Trosium chloride</th>
<th>Tolterodine</th>
<th>Oxybutynin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry mouth</td>
<td>1</td>
<td>2 (2)</td>
<td>-</td>
<td>8 (3)</td>
</tr>
<tr>
<td>Sleep disturbances with or without dry mouth</td>
<td>2 with dry mouth</td>
<td>1 with dry mouth</td>
<td>-</td>
<td>1 with dry mouth</td>
</tr>
<tr>
<td>Orthostatic dysregulation</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Urine retention</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>1</td>
<td>1 (1)</td>
<td>-</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>5 (1)</td>
<td>-</td>
<td>8 (3)</td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
<td>11 (4)</td>
<td>1 (1)</td>
<td>22 (16)</td>
</tr>
</tbody>
</table>

compounds, and cases of pavor nocturnus have been reported following treatment with oxybutynin. The present study was carried out in a double-blind, placebo-controlled, crossover design to minimise the influence of interindividual variance of sleep parameters as well as of external factors on test statistics. As the crossover design required a long study period and multiple recordings, volunteers were randomised to one of four treatment sequences with six participants each. Single application of the total normal recommended daily dose (oxybutynin 3 × 5mg, tolterodine 2 × 2mg, trosium chloride 3 × 15mg) was chosen to minimise the treatment period for the participants. Foregoing studies have shown that this course of action is suitable to demonstrate significant changes in quantitative EEGs of healthy volunteers.

The studied changes in sleep structure after administration of anticholinergic agents were mainly related to REM sleep and are reflected as an increase in REM latency and a reduction in REM duration. REM sleep as a percentage of total sleep time was used as the primary target variable in our polysomnographic recordings. This parameter extends throughout the night and is better suited for comparison of compounds with different pharmacokinetic properties than REM latency, which represents only the beginning of the night. Analysis of the results of polysomnography revealed that REM sleep was suppressed only after oxybutynin treatment. REM as percentage of total sleep was 1–2% lower with oxybutynin than with the other two drugs and placebo. REM latency in the oxybutynin group was longer (more than 20 minutes) than in the placebo, tolterodine and trosium chloride groups. These results indicate that REM suppression occurs mainly at the beginning of the night, whereas subsequent REM periods are probably influenced to a lesser extent. Effects on REM at the beginning of the night are of little consequence, as the duration of REM periods increases during the night. None of the anticholinergic drugs used in this single-dose study in young healthy volunteers was found to diminish REM sleep to a pathological extent.

As observed in other studies, non-REM sleep was affected to a lesser extent by the anticholinergic drugs. In our study, oxybutynin differed from placebo with respect to its effect on non-REM sleep. Wakefulness before sleep onset decreased in favour of lighter sleep (stage 1), which was reflected as a reduction in objective sleep onset, a reduction in subjective sleep latency and an increase in stage 1, whereas the measured total sleep time, subjective sleep duration, wakefulness after sleep onset and deeper sleep stages (stage 2, SWS) were not affected. These changes suggest that oxybutynin leads to mild sedation, while sedation was negligible after tolterodine and trosium chloride administration. The test substances did not differ with respect to "morning well-being" and "daytime performance".

The clinical relevance of the observed effects on sleep structure is minimal in healthy young volunteers. Thus, no loss of cognitive function or concentration due to disturbed sleep structure was expected. Potential impairment of cognitive function was assessed using a number combination test (ZVT) for evaluation of information processing capacity and working velocity (primary parameter)
and by the d2 attention test for assessment of individual sustained attention and concentration performance (secondary parameter). In contrast to others, we did not observe any effect of oxybutynin, tolterodine and trospium chloride on the measured cognitive parameters.

The effects of the tested drugs on sleep structure and on cognitive function may be different in elderly individuals or in individuals with impaired REM sleep behaviour due to various psychological diseases (e.g., depression) and sleep disturbances. Pharmacokinetic and pharmacodynamic properties can vary in the elderly. The pharmacokinetic differences can result from changes in body composition and the function of drug-eliminating organs. Physiological changes in the elderly may lead to a higher frequency of central drug effects and increased susceptibility to unwanted effects, even if dosage is properly adjusted to account for age-related pharmacokinetic changes.

Most of the adverse events possibly related to the test medications used in this study were typical anticholinergic effects (dry mouth and gastrointestinal disturbances). The trospium chloride, tolterodine and placebo groups did not differ with respect to the number and quality of adverse events between the treatment periods, whereas differences between oxybutynin and placebo were observed. These findings correlate well with those of therapeutic studies.

Conclusion

This study showed that oxybutynin influences sleep structure by suppressing REM sleep and by causing mild sedation, while subjective parameters and psychometric tests remained unaffected. The investigated polysomnographic parameters, subjective criteria and psychometric test results for tolterodine and trospium chloride were comparable to those for placebo. The clinical relevance of all the observed effects is minimal in healthy young volunteers, but the findings cannot be extended to the elderly, which is the population with the highest frequency of urinary incontinence. Further studies must be performed to determine the effects of the tested anticholinergic drugs in elderly individuals and for example neurological patients, in order to detect potential differences in the pharmacodynamic and pharmacokinetic properties of these compounds in such cohorts.

Acknowledgements

The authors are grateful to Suzyn O’Neal Wondrey, Berlin for proofreading the manuscript. This trial was funded by the Dr R. Pfleger GmbH as part of its clinical development programme for trospium chloride.

Dr Haselmann and Dr Schwantes are with Dr R Pfleger GmbH working on concept, planning, administrative and organisational matters and monitoring of clinical trials.

References
