Sleep laboratory studies on single dose effects of suriclone

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1 In a double-blind, placebo-controlled sleep laboratory study single doses of suriclone, a new non-benzodiazepine anxiolytic binding to benzodiazepine receptors, were investigated with respect to sleep and awakening.

2 Sixteen healthy young volunteers spent 10 nights in the sleep laboratory: 1 adaptation night, 1 baseline night and 4 drug nights (placebo; 0.2 mg, 0.4 mg suriclone; 2 mg lorazepam as reference drug) and 4 subsequent wash-out nights (drug-interval: 1 week). Somnopolygraphic investigations (22.30 h to 06.00 h) were commenced 0.5 h after drug-intake. A self-rating scale for sleep and awakening quality as well as psychometric tests were completed in the morning.

3 Hypnotic effects were most pronounced after lorazepam in regard to total sleep time and sleep efficiency. After lorazepam as well as after 0.4 mg suriclone nocturnal awakenings decreased significantly as compared with placebo, which was reflected in an improved subjective sleep quality after both dosages. Suriclone 0.2 mg did not induce any alterations in all night sleep.

4 In the morning, well-being, drowsiness and reaction time performance deteriorated after lorazepam as compared with placebo but not after suriclone. The latter was significantly superior to lorazepam with respect to subjective awakening quality, well-being, emotional rapport, drowsiness and attention.

5 Blood pressure and pulse remained unchanged after all of the drugs. Critical flicker frequency and muscle strength decreased only after lorazepam as compared with placebo.

Keywords human sleep awakening quality somnopolygraphy psychometry suriclone lorazepam sedative-hypnotic properties

Introduction

Suriclone belongs to the family of cyclopyrrolones, developed in the search for alternatives to the benzodiazepines with fewer sedative and addictive properties. Studies of suriclone in classical psychopharmacologic tests have shown that this compound possesses the five main types of activity which are considered as the characteristics of a benzodiazepine agonist profile in animals (anticonvulsant, myorelaxant, anti-aggressive, sedative-hypnotic and anticonflict)

(Garret *et al.*, 1983). Although chemically entirely different from the benzodiazepines, suriclone binds with high affinity to benzodiazepine receptors (Blanchard & Julou, 1983; Zundel *et al.*, 1985). It inhibited [³H]-flunitrazepam binding significantly more than diazepam and GABA-minergic systems are involved in the mechanism of action of both benzodiazepines and suriclone (Blanchard & Julou, 1983; Boireau *et al.*, 1984). Nevertheless, suriclone's mode of action differs

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from that of benzodiazepines. Unlike classical benzodiazepine agonists such as diazepam, suriclone binding sites were not enhanced by GABA, chloride or barbiturates, and only minimally reduced by photolabelling of benzodiazepine receptors with flunitrazepam (Blanchard *et al.*, 1983; Trifiletti & Snyder, 1984). These data suggest that cyclopyrrolones and benzodiazepines bind to distinct sites or to different allosteric forms of the benzodiazepine receptor.

The acute oral LD₅₀ in five different animal species was greater than 4.5 g kg⁻¹ suriclone p.o. Toxicity studies for up to 1 year in rats and dogs showed only limited evidence of drug toxicity, mainly ataxia and sedation. In these studies, oral doses of 20 mg kg⁻¹ day⁻¹ did not induce any significant haematological or biochemical abnormalities; the histopathology of suriclone-treated animals was unremarkable.

In human pharmacokinetic studies the absorption of suriclone was virtually complete 1 to 2 h after dosing. There was an extensive hepatic biotransformation and elimination half-life (*t*_{1/2}) was about 2 h for suriclone itself and about 12 h for the active metabolites. Repeated administration did not modify the pharmacokinetic profile, in particular no accumulation could be seen (Rhone Poulenc Sante, 1989).

Studies in healthy subjects resulted in a well tolerated single oral dose up to 0.6 mg suriclone (Shaw *et al.*, 1988). Toxic effects were dose dependent and mainly characterized by balance disorders (dizziness, ataxia).

Double-blind clinical trials in patients with generalized anxiety disorders showed suriclone (1.5–2 mg day⁻¹) to be as effective as diazepam (25 mg day⁻¹) (Gerlach *et al.*, 1987) and lorazepam (5 mg day⁻¹) (Gotfryd, 1984) in the treatment of generalized anxiety disorders. The profile of somatic complaints with suriclone differed from that of the benzodiazepines. Decreased alertness was less frequent, but dizziness appeared to be more frequent with suriclone.

The aim of the present double-blind placebo-controlled sleep laboratory study was to examine the single dose effects of suriclone on objective and subjective sleep and awakening quality as compared with the classical benzodiazepine lorazepam (2 mg) in normal healthy volunteers.

Methods

Subjects and drug administration

Sixteen physically and mentally healthy volunteers (eight women, eight men), ranging in age

from 23 to 39 years (mean 26.8 years), weighing between 50 and 85 kg (mean 65.6 kg), and ranging in height from 160 to 199 cm (mean 174.8 cm) were included in the double-blind, placebo-controlled, cross-over design study. Subjects were not allowed to receive any psychotropic drugs 3 weeks prior to and/or during the trial. They spent 10 nights in the laboratory: 1 adaptation night, 1 baseline night, 4 treatment nights (placebo; 0.2 mg and 0.4 mg suriclone; 2 mg lorazepam as reference drug) and 4 respective wash-out nights. The drugs were administered in 1 week intervals in randomized fashion (Latin Square design) at 22.00 h, i.e. 30 min before bedtime. The study was performed in accordance with the requirements of the Declaration of Helsinki as revised in Tokyo (1975) and Venice (1983). Informed written consent was obtained.

Somnographic investigations

Polygraphic all-night recordings were performed between 22.30 h ('lights out') and 06.00 h ('buzzer') in two identically shielded rooms; thus the total time in bed was fixed. The electrodes were attached according to the international 10/20 system. In addition to the electroencephalographic (EEG) channels C4-A1, O2-A1 and Cz-O2, two electrooculographic (EOG) channels and the submental electromyogram (EMG) were recorded on 8-channel R611 Beckman polygraphs. Four channels (Cz-O2, EMG and two EOG) were also recorded on a Hewlett-Packard 3968 tape recorder. Thirty-second periods were scored according to the criteria of Rechtschaffen & Kales (1968). Sleep prints and variables were obtained by means of a Hewlett Packard Vectra Computer System.

Total sleep time is the amount of actual sleep time in the total sleep period (TSP). TSP is the period of time measured from sleep onset until final awakening. In addition to total sleep time, TSP includes wake time (awake/TSP) and movement time. The number of awakenings refers to the arousals to wakefulness during TSP. The sleep efficiency index is the proportion of sleep in the recorded period, and it is calculated by dividing total sleep time by the total time in bed multiplied by 100. Sleep stages 1, 2, 3, 4 and REM (rapid eye movement) are expressed in percentages of the total sleep time (S 1–S REM %). Latency to stage 1 describes the period of time measured from 'lights out' to the appearance of sleep stage 1. REM-latency describes the number of minutes of sleep from the appearance of stage 2 until the onset of the first REM period. Awake/early morning is the time spent awake from the final awakening until sounding of

'buzzer' at 06.00 h. Stage shifts refer to the number of shifts from one stage to another during the total time in bed.

Awakening quality and subjective sleep quality

At 06.00 h subjects were awakened by acoustic stimuli (1000 Hz tone, 1 s long), which started at 35 dB and increased stepwise (10 dB) at 1 min intervals to 94 dB until the subject awakened. The loudness of the tone that awakened the subject determined the awakening threshold.

After the morning toilet the volunteers completed a self-rating scale on their subjective quality of sleep and awakening (SSA) (Saletu *et al.*, 1987). The subscore of sleep quality includes the following assessments: 1) sleep comfort, 2) deep sleep, 3) early insomnia, 4) middle insomnia, 5) bad dreams, 6) difficulties returning to sleep after nocturnal awakenings, 7) late insomnia. The subscore of awakening quality assesses: 1) drowsiness after getting up, 2) disorientation, 3) tiredness, 4) good mood, 5) good emotional rapport, 6) retardation, 7) attention difficulties, 8) feeling of being refreshed. The subscore of somatic complaints assesses: 1) nausea, 2) headache, 3) dry mouth, 4) dizziness, 5) incoordination. The score of each individual item ranges from 1–4. Subjects participated in a series of psychometric tests, including the measurements of noopsychic variables (Stransky, 1909) such as the Grünberger Alphabetischer Durchstreicht (AD)-test (alphabetical cross-out test) for quantification of attention (AD/total score), concentration (AD/F % = errors in % of the total score) and attention variability (AD/SV = difference between extreme scores), the numerical memory test, as well as the Grünberger fine motor activity test (right and left hand) for evaluation of changes in psychomotor activity (Grünberger, 1977). Reaction time (ms; errors of omission and commission) was determined by the computer assisted Reaction Time Apparatus. Thymopsychic measurements (Stransky, 1909) included the von Zerssen Bf-scale (Zerssen *et al.*, 1970) for evaluation of well-being in the evening and in the morning. Drive, mood, emotional rapport and drowsiness were quantified by means of 100 mm visual analogue scales. Psychophysiological investigations included the critical flicker frequency (c.f.f., descending threshold), muscle strength of the right and left hand, as well as of the right and left index finger and thumb evaluated by a vigorimeter (kp cm^{-2}) (Fünfgeld, 1966). The evening and morning pulse rate and blood pressure were also recorded.

Statistics

Exploratory statistical analyses included the Friedman's test, the multiple Wilcoxon, and the Wilcoxon tests.

Results

Treatment nights

Objective sleep quality Lorazepam tended to shorten the latency to sleep stage 1 (Table 1) and significantly increased total sleep time and sleep efficiency as compared with baseline and placebo ($P < 0.01$ – 0.05 , multiple Wilcoxon). Only lorazepam could be distinguished from baseline when total sleep period was considered ($P < 0.05$, Wilcoxon test). Suriclone 0.4 mg caused an improvement in sleep efficiency as compared with baseline ($P < 0.05$, Wilcoxon test), but no interdrug differences were demonstrated by the multiple Wilcoxon. Wake time during TSP was significantly shorter after lorazepam and 0.4 mg suriclone than baseline ($P < 0.05$, multiple Wilcoxon). In addition, nocturnal arousals occurred less often after both lorazepam ($P < 0.01$, multiple Wilcoxon) and 0.4 mg suriclone ($P < 0.05$, multiple Wilcoxon) than after placebo. The time spent awake from the final awakening until the sounding of 'buzzer' remained unchanged.

Suriclone 0.4 mg caused a decrease of sleep stage 1 ($P < 0.01$; Wilcoxon test) and an increase of sleep stage 2 ($P < 0.05$; Wilcoxon test) as compared with baseline. Lorazepam augmented sleep stage 2 and produced a trend towards a decrease of stage REM and an increase of REM-latency. No changes occurred with respect to deep sleep (S 3, S 4), movement time and stage shifts.

Subjective sleep and awakening quality Self-assessment of the quality of sleep by the SSA-1 demonstrated a significant improvement after lorazepam as compared with baseline ($P < 0.05$, multiple Wilcoxon) and placebo ($P < 0.01$, multiple Wilcoxon). Suriclone 0.4 mg was also superior to baseline ($P < 0.05$, Wilcoxon test) and placebo ($P < 0.05$, multiple Wilcoxon) but to a lesser extent (Table 2). Awakening quality (SSA-2) deteriorated following lorazepam as compared with baseline ($P < 0.01$, Wilcoxon test). Interdrug comparison revealed a better quality of awakening after 0.4 mg suriclone, than after lorazepam ($P < 0.05$, multiple Wilcoxon). The evaluation of somatic complaints (SSA-3) did not exhibit any significant findings in the

Table 1 Objective sleep quality on baseline as well as after single oral doses of 0.2 and 0.4 mg suriclone, 2 mg lorazepam and placebo ($n = 16$). Mean (s.d.)

	Baseline (A)	Suriclone 0.2 mg (B)	Suriclone 0.4 mg (C)	Lorazepam 2 mg (D)	Placebo (E)	Interdrug differences
Latency to stage 1 (min)	17.19 (18.76)	23.69 (40.35)	19.00 (19.38)	9.81 (9.65)	14.13 (10.67)	
Total sleep period (min)	426.50 (19.41)	419.44 (40.19)	425.31 (19.97)	436.06 (11.21)*	427.19 (18.73)	
Total sleep time (min)	385.66 (78.55)	401.75 (53.32)	410.69 (30.14)	422.16 (20.14)**	397.53 (34.07)	D : A, E‡
Sleep efficiency (%)	86.54 (17.49)	90.58 (12.09)	92.42 (6.69)*	94.67 (4.37)**	89.73 (7.39)	D : A‡, E†
Awake/TSP	36.44 (73.47)	13.53 (18.27)	10.00 (20.80)*	8.81 (12.93)*	25.03 (33.85)	C : A†; D : A†
Awake/Early morning	1.75 (7.00)	0.44 (1.75)	0.03 (0.13)	0.00 (0.00)	1.50 (6.00)	
Number of awakenings/TSP	3.38 (2.50)	3.13 (4.29)	2.44 (3.18)	1.69 (1.99)*	4.19 (3.27)	C : E†; D : E‡
S 1 (%)	4.45 (5.92)	3.71 (2.97)	2.67 (2.65)**	2.77 (1.47)	4.31 (3.25)	
S 2 (%)	58.21 (9.61)	60.64 (8.84)	63.00 (9.07)*	63.36 (6.55)*	59.58 (6.99)	
S 3 (%)	9.58 (5.19)	10.24 (6.54)	8.33 (3.97)	10.12 (3.81)	8.81 (4.85)	
S 4 (%)	12.17 (8.35)	9.45 (7.15)	10.31 (5.87)	11.14 (7.56)	9.96 (7.15)	
S REM (%)	15.61 (6.01)	15.98 (5.08)	15.67 (4.57)	12.58 (4.28)	17.33 (2.78)	
REM-Latency	102.91 (68.26)	117.28 (78.93)	121.09 (71.88)	140.41 (79.19)	102.06 (65.29)	
Number of REM-periods	3.63 (1.20)	3.44 (1.09)	3.69 (1.20)	3.31 (0.95)	3.63 (0.96)	
Stage shifts/time in bed	51.50 (13.76)	49.88 (14.91)	47.19 (8.56)	45.81 (10.03)	53.44 (13.93)	
Movement time (min)	4.41 (3.03)	4.16 (2.29)	4.63 (2.66)	5.09 (2.89)	4.63 (2.49)	

* $P < 0.05$, ** $P < 0.01$ compared with baseline (Wilcoxon test).† $P < 0.05$, ‡ $P < 0.01$ Multiple Wilcoxon test.

morning after drug administration. The worst score of morning well-being (Zerssen Bf-scale) after awakening was obtained after lorazepam, and this differed significantly from baseline, placebo and both doses of suriclone ($P < 0.05$, multiple Wilcoxon). Statistical analysis of the 100 mm analogue scales showed significant inter-drug differences. Drive was diminished by lorazepam as compared with baseline ($P < 0.05$, multiple Wilcoxon), emotional rapport decreased after lorazepam as compared with 0.2 mg suriclone ($P < 0.05$, multiple Wilcoxon), and drowsiness increased after lorazepam when compared with baseline ($P < 0.05$, multiple Wilcoxon), placebo ($P < 0.05$, multiple Wilcoxon) and 0.4 mg suriclone ($P < 0.01$, multiple Wilcoxon) as well.

Objective awakening quality The awakening threshold increased following lorazepam as compared with baseline ($P < 0.05$, Wilcoxon test) (Table 3).

Attention (Alphabetischer Durchstreichtest (AD)/total score) improved significantly after 0.2 mg suriclone as compared with baseline and lorazepam ($P < 0.01$, multiple Wilcoxon). Concentration (AD/errors in % of the total score) and attention variability (AD/difference between extreme scores) appeared to be better with placebo, than on baseline-conditions ($P < 0.05$, Wilcoxon test). Numerical memory remained unchanged after all dosages. The Grünberger fine motor activity test revealed significant deterioration of the left hand after lorazepam as

Table 2 Subjective sleep and awakening quality on baseline as well as after single oral doses of 0.2 and 0.4 mg suriclone, 2 mg lorazepam and placebo ($n = 16$). Mean (s.d.)

		Baseline (A)	Suriclone 0.2 mg (B)	Suriclone 0.4 mg (C)	Lorazepam 2 mg (D)	Placebo (E)	Interdrug differences
Sleep quality (SSA-1)	↓	11.94 (4.82)	10.00 (3.81)	9.19 (3.31)*	8.13 (2.09)**	12.31 (3.93)	C : E†; D : E‡, A†
Awakening quality (SSA-2)	↓	13.56 (3.61)	14.13 (3.42)	13.44 (4.32)	17.31 (4.70)**	14.19 (3.82)	C : D†
Somatic complaints (SSA-3)	↓	6.25 (1.29)	6.31 (1.85)	6.06 (1.39)	6.87 (2.39)	6.50 (1.55)	
Total score (SSA)	↓	31.75 (8.26)	30.44 (6.42)	28.63 (7.41)	32.31 (7.58)	33.00 (7.81)	
Well-being (Bf-s) Evening	↓	8.69 (5.25)	8.75 (6.17)	9.63 (5.20)	12.06 (10.34)	7.31 (5.30)	
Well-being (Bf-s) Morning	↓	9.94 (8.14)	10.56 (8.30)	9.63 (8.38)	18.13 (9.69)**	10.88 (8.65)	D : A, B, C, E†
Drive	↓	36.94 (24.00)	37.88 (25.12)	37.88 (22.34)	53.94 (25.20)**	35.00 (21.20)	D : A†
Mood	↑	71.44 (14.81)	76.63 (14.24)	71.44 (13.91)	62.88 (20.87)	70.00 (13.33)	
Emotional rapport	↑	72.63 (16.36)	74.69 (16.95)	61.56 (24.20)*	57.94 (24.60)**	68.19 (19.99)	D : B†
Drowsiness	↓	45.19 (29.87)	42.94 (26.72)	40.37 (24.06)	62.00 (25.38)*	42.75 (25.01)	D : C‡, A, E†

↓ ↑ Direction of improvement.

* $P < 0.05$, ** $P < 0.01$ compared with baseline (Wilcoxon test).† $P < 0.05$, ‡ $P < 0.01$ Multiple Wilcoxon test.

compared with baseline ($P < 0.05$, multiple Wilcoxon). Reaction time did not exhibit any results of statistical relevance, but the errors of commission increased after lorazepam as compared with baseline ($P < 0.05$, Wilcoxon test) and placebo ($P < 0.01$, multiple Wilcoxon).

There was a decrease in morning c.f.f. after the four treatment nights when compared with the baseline-night ($P < 0.01$, Wilcoxon test) (Table 3). The decrease was most pronounced after lorazepam, which could be distinguished from placebo also ($P < 0.05$, multiple Wilcoxon). Muscle strength of the right hand deteriorated significantly after lorazepam as compared with baseline ($P < 0.01$, multiple Wilcoxon) and placebo ($P < 0.05$, multiple Wilcoxon), while it remained unchanged in the left hand as well as in left and right fingers. Evening and morning blood pressure and pulse was unaffected.

Wash-out nights

Objective sleep quality The only significant interdrug finding in sleep initiation and maintenance was a decreased number of awakenings in the wash-out nights after placebo as compared with wash-out nights after 0.4 mg suriclone ($P < 0.05$, multiple Wilcoxon) and baseline ($P < 0.05$,

Wilcoxon test). There were no changes in non-REM stages in wash-out nights, while REM stages decreased significantly after lorazepam when compared with placebo ($P < 0.05$, multiple Wilcoxon) and 0.4 mg suriclone ($P < 0.05$, multiple Wilcoxon).

Awakening quality The only significant wash-out findings on self-rating scales and psychometric tests were of attention, where both doses of suriclone as well as placebo were superior to baseline ($P < 0.05$, multiple Wilcoxon).

Discussion

In this single-dose sleep laboratory investigation the classical 1,4-benzodiazepine lorazepam showed sedative-hypnotic effects, characterized by an increase in total sleep time and sleep efficiency as well as by a decrease in nocturnal arousal as compared with placebo. In parallel with these objective results healthy volunteers reported a better subjective sleep quality after lorazepam. The cyclopyrrolone derivative suriclone lacked significant effects after the 0.2 mg dose, while both subjective and objective data demonstrated that the 0.4 mg dose was effective

Table 3 Objective awakening quality on baseline as well as after single oral doses of 0.2 and 0.4 mg suriclone, 2 mg lorazepam and placebo ($n = 16$). Mean (s.d.)

	Baseline (A)	Suriclone 0.2 mg (B)	Suriclone 0.4 mg (C)	Lorazepam 2 mg (D)	Placebo (E)	Interdrug differences
Awakening threshold (dB)	53.13 (16.64)	53.81 (21.33)	54.44 (21.17)	71.06 (24.12)*	43.44 (15.89)	
Attention (AD/Total score)	422.50 (142.36)	478.44 (119.91)**	453.75 (114.04)	416.44 (111.25)	451.81 (122.30)	B : A,D‡
Concentration (AD/F%)	4.35 (3.49)	2.65 (1.94)	3.56 (2.89)	4.18 (3.49)	2.50 (1.26)*	
Attention variability (AD/SV)	15.31 (4.01)	14.88 (4.81)	13.44 (2.83)	14.75 (5.09)	12.44 (3.12)*	
Numerical memory	6.87 (2.06)	7.69 (1.85)	7.27 (2.22)	7.50 (1.90)	7.44 (1.59)	
Fine motor activity (right)	50.31 (9.29)	53.06 (9.92)	52.75 (9.79)	49.44 (9.05)	51.81 (10.24)	
Fine motor activity (left)	46.25 (14.44)	42.13 (9.09)	43.31 (9.96)	37.63 (9.95)**	42.75 (12.44)	D : A†
Fine motor activity (total)	90.69 (21.65)	94.56 (16.09)	96.06 (15.93)	86.94 (15.42)	94.56 (18.81)	
Reaction time (ms)	420.94 (119.33)	419.44 (85.44)	403.06 (78.32)	389.67 (82.55)	399.94 (84.04)	
Reaction-errors of omission	0.25 (1.00)	0.13 (0.50)	0.06 (0.25)	0.50 (0.97)	0.00 (0.00)	
Reaction-errors of commission	0.94 (1.24)	1.38 (1.09)	1.75 (1.06)	2.06 (1.39)*	0.69 (0.79)	D : E‡
C.f.f. (Hz)	42.75 (3.12)	40.72 (2.25)**	40.55 (2.54)**	38.71 (2.42)**	40.05 (4.44)**	D : A‡,E†
Vigorimeter right hand	0.79 (0.16)	0.73 (0.15)*	0.75 (0.16)	0.68 (0.18)**	0.75 (0.19)	D : A‡,E†
Vigorimeter left hand	0.73 (0.20)	0.68 (0.16)	0.69 (0.15)	0.64 (0.18)	0.71 (0.16)	

* $P < 0.05$, ** $P < 0.01$ compared with baseline (Wilcoxon test).† $P < 0.05$, ‡ $P < 0.01$ Multiple Wilcoxon test.

in maintaining sleep, but to a lesser extent than 2 mg lorazepam. The statistical analyses of sleep latency did not reveal interdrug differences, although subjects fell asleep after lorazepam about twice as fast as after placebo or suriclone. Sleep architecture was influenced by the benzodiazepine, as sleep stage 2 was slightly augmented as compared with baseline and stage REM tended to be attenuated. Suriclone 0.4 mg caused rather subtle changes in light sleep, namely a decrease of sleep stage 1 and an increase of stage 2.

The awakening threshold and awakening quality suggested a morning hang-over after lorazepam, but not after suriclone. If one compares lorazepam with suriclone, the cyclopyrrolone derivate is superior with regard to well-being, emotional rapport, drowsiness and attention. Drive, psychomotor activity, muscle strength and critical flicker frequency only decreased after the benzodiazepine. Short-term

memory was unaffected by all of the drugs. Deterioration in awakening quality is to be expected with lorazepam. Previous pharmac-EEG and psychometric studies revealed sedative-hypnotic properties of lorazepam as late as 8 h after a 2 mg oral dosage (Grünberger *et al.*, 1988; Saletu *et al.*, 1985, 1988). Topographic pharmac-EEG and psychometric investigations are ongoing to evaluate time and dose/treatment efficacy relations of suriclone (Saletu *et al.*, in preparation). Suriclone's pharmacodynamic effects in the present sleep study appear to last less than 7–8 h, since 0.4 mg suriclone caused some effects on sleep, but no changes in early morning behaviour. In clinical use suriclone tended to be better tolerated than equipotent anxiolytic doses of benzodiazepines, particularly in regard to drowsiness and sedation (Gerlach *et al.*, 1987). The present sleep laboratory data in young healthy volunteers confirm this clinical observa-

tion, since sleep initiation and maintenance as well as awakening quality were less influenced by 0.4 mg suriclone than by 2 mg lorazepam. The low 0.2 mg dose did not exhibit any sedative properties. Previous investigations demonstrated an improvement in psychometric tests after low doses of certain anxiolytics (Grünberger *et al.*, 1978; Saletu *et al.*, 1980). Indeed, in the present study we observed an improvement in attention after the low dose (0.2 mg) of suriclone as well.

Suriclone is chemically entirely different from any existing anxiolytic. It was developed to obtain an alternative to the benzodiazepines with both fewer sedative and addictive properties. Tranquillizers with marked rebound phenomena, such as rebound insomnia and anxiety, may reinforce drug-taking behaviour and thus contribute to the development of drug dependency. Rebound phenomena have been demonstrated after withdrawal of zopiclone, the first cyclopyrrolone, which is utilized as a short half-life hypnotic (for review see Goa & Heel, 1986). Nocturnal awakenings appeared more often in the wash-out nights after 0.4 mg suriclone than in those after placebo. As the increase was

small and non-significant after 0.4 mg suriclone as compared to baseline, the difference to placebo appeared mainly due to the fact that a decrease occurred after placebo as compared with baseline. Thus, the increase of the nocturnal arousals in the wash-out nights after 0.4 mg suriclone may not be a genuine rebound phenomenon. REM-sleep decreased in the wash-out nights after lorazepam as compared with placebo and 0.4 mg suriclone, which is opposite to what one would expect.

In conclusion, the effects of suriclone on sleep and early morning behaviour were rather subtle in healthy volunteers, with higher doses exerting some sleep-promoting properties but no hang-over signs in the morning. Evaluation of somatic complaints, pulse rate and blood pressure confirmed the good tolerability of the new compound.

The authors would like to express their thanks to Rhone Poulenc Sante, Antony, France, for supplying the drugs; and to the entire staff of the Section of Pharmacopsychiatry and the Sleep Laboratory of the Psychiatric University of Vienna for their valuable assistance in this project.

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(Received 12 October 1989,
accepted 11 June 1990)