Pharmacokinetic and -dynamic studies with a new anxiolytic, suriclone, utilizing EEG mapping and psychometry

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- 1 In a double-blind, placebo-controlled, cross-over study, acute pharmacokinetic, neurophysiological and psychotropic effects of suriclone, a new cyclopyrrolone derivative, were investigated and compared with alprazolam.
- 2 Fifteen normal young volunteers received randomized oral single doses of placebo, 0.1, 0.2 and 0.4 mg suriclone as well as 1 mg alprazolam as reference compound. Investigations were carried out before and 1, 2, 4, 6 and 8 h after drug administration.
- 3 Pharmacokinetic investigations by radioimmunoassay showed a dose-dependent fast rise of plasma concentrations with a peak at 1 h and a rapid decline thereafter. Both the $C_{\max}$ and the AUC values exhibited a linear relationship to dose.
- 4 EEG brain mapping demonstrated significant CNS effects of both compounds, characteristic for tranquillizers (increase of beta, decrease of alpha and increase of delta activity; attenuation of total power and acceleration of the centroid, i.e. centre of gravity frequency). When compared with alprazolam, suriclone exerted less sedative effects.
- 5 Time-efficacy calculations showed the pharmacodynamic peak effect of suriclone from the 2nd to the 4th hour, and of alprazolam in the 1st hour. Dose-efficacy calculations showed that the most pronounced CNS changes occurred after 1 mg alprazolam, followed by 0.4, 0.2 and 0.1 mg suriclone.
- 6 Psychometric investigations demonstrated no significant effects after the two lower doses of suriclone, while 0.4 mg and 1 mg alprazolam induced a decrement both in noopsyche and thymopsyche variables seen after higher doses of anxiolytic sedatives. Psychophysiology (critical flicker fusion, pupillometry, and skin conductance measures) pulse rate, systolic and diastolic blood pressure remained unchanged.
- 7 Psychophysiology (critical flicker fusion, pupillometry and skin conductance measures) showed differential dose-dependent effects. Pulse rate, systolic and diastolic blood pressure remained unchanged. Anxiolytic-characteristic side-effects (tiredness, drowsiness, etc.) occurred predominantly after the highest doses 0.4 mg suriclone and 1 mg alprazolam.

Keywords human psychopharmacology suriclone anxiolytic pharmacokinetics pharmacodynamics EEG mapping psychometry noopsyche thymopsyche psychophysiology tolerability

Introduction

Suriclone, [6-(7-chloro-1,8-naphthyridin-2-yl)-5-(4-methyl-piperazin-1-yl carbonyloxy)-2,3,6,7-tetrahydro-1,4-dithiino [2,3-c] pyrrol-7-one, RP 31264] is a new anxiolytic belonging to the cyclopyrrolone family. In psychopharmacological tests it exhibited the five main

types of activity which are considered to be characteristic for the benzodiazepine agonists in animals: anticonvulsant, myorelaxant, antiaggressive, sedative-hypnotic and anticonflict [1]. Inhibition of [^3H]-flunitrazepam binding was significantly more pronounced after

suriclone than diazepam. In contrast to classical benzodiazepine agonists suriclone binding sites are not enhanced by GABA, chloride or barbiturates, and only minimally reduced by photolabelling of benzodiazepine receptors with flunitrazepam [2, 3]. These data suggest that cyclopyrrolones and benzodiazepines bind to distinct sites or to different allosteric forms of the benzodiazepine receptor.

In animal experiments with five species the acute oral LD₅₀ of suriclone was higher than 45 mg kg⁻¹. Chronic toxicity studies showed little evidence of toxicity with exception of ataxia and sedation. Haematological and biological abnormalities were not reported. Human pharmacokinetic tests showed absorption times of 1–2 h. Hepatic biotransformation was extensive and elimination half-life ($t_{1/2}$) was about 2 h for suriclone and about 12 h for the active metabolites. The pharmacokinetic profile was not influenced by repeated administration and no accumulation-effect was produced [4].

Single oral doses up to 0.6 mg suriclone were well tolerated in healthy subjects [5]. Dose-dependent toxic effects were dizziness and ataxia. In comparative clinical trials with patients exhibiting generalized anxiety disorders suriclone (0.3–2 mg day⁻¹) proved to be as effective as diazepam (15–25 mg day⁻¹) [6, 7] and lorazepam (5 mg day⁻¹) [8]. The somatic complaints profile was different with suriclone compared with diazepam: alertness was less influenced but dizziness appeared to be more frequent after suriclone. The effect of suriclone on sleep and awakening quality was examined in healthy subjects [9, 10]. Higher doses showed some sleep-promoting properties but no hangover was noticed.

The aim of the present double-blind, placebo-controlled trial was to investigate pharmacokinetics as well as encephalotropic and psychotropic effects (i.e. effects on brain function and psyche) of suriclone compared with alprazolam utilizing pharmaco-EEG mapping, psychometric and psychophysiological techniques [11–13]. The latter have been shown to provide important information at an early stage of drug development about: 1) whether a drug will have an effect on the CNS compared with placebo; 2) what its clinical efficacy will eventually be like; 3) at what dosage it acts; and 4) at what time it acts on the target organ—the human brain.

Methods

Design, subjects and drugs

Fifteen physically and mentally healthy volunteers (ten women and five men), ranging in age from 22 to 35 years (mean 27.3 years), in weight from 52 to 80 kg (mean 63.6 kg) and height from 163 to 192 cm (mean 171.3 cm) were included in this double-blind, placebo-controlled, cross-over-design study. They were not allowed to take any psychoactive drugs 3 weeks before and during the study period. Subjects received at weekly intervals in random order following single oral doses: placebo, 0.1 mg, 0.2 mg and 0.4 mg suriclone as well as 1 mg alprazolam. The study was performed in accordance with the rules and

regulations for the conduct of clinical trials stated in the Declaration of Helsinki, as revised by the World Medical Assembly at Tokyo (1975) and Venice (1983). Informed written consent was obtained from all subjects.

Blood sampling, EEG investigations, evaluations of blood pressure, pulse and side effects were carried out before as well as 1, 2, 4, 6 and 8 h post-drug administration. Psychometric tests were performed at the same time. Psychophysiological measures were also conducted at these times except at the first hour post-dose.

Pharmacokinetic investigations

The blood samples (10 ml) were taken into tubes containing dry heparin, and were immediately centrifuged at +4° C. Plasma was then separated and collected in another tube for freezing at –20° C, and stored at this temperature until assay.

TAP (total antigenic products) recognized by suriclone antibodies, was determined by radioimmunoassay. The direct radioimmunoassay method measures suriclone plus all the metabolites recognized by antibody (TAP) among them *N*-oxide, *S*-oxides, *N*-desmethyl and *N*-oxide-*S*-oxide of suriclone.

Neurophysiological investigations

Quantitative EEG investigations included a 4 min resting EEG (R-EEG) by means of a 21-channel Nihon Kohden 4321 F polygraph (time constant: 0.3 s; high frequency response: 35 Hz; frequency range: 0.5–35 Hz; amplification: approximately 1:20,000; maximal noise level: 2 µV peak-to-peak). For these investigations, the subjects were lying relaxed with their eyes closed in an electrically-shielded room. Electrodes were attached to the scalp according to the international 10/20 system. In addition to 19 EEG leads (F_p1, F_p2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1 and O2 referenced to averaged mastoids), vertical and horizontal EOG were digitized on-line by a Hewlett Packard Vectra system with a sampling frequency of 102.4 Hz [13, 14]. Spectral analysis was performed using the fast Fourier transform technique for 5 s epochs. The frequency resolution was 0.2 Hz. To maintain precision, power spectral density was calculated in floating-point arithmetic.

Artifact-free epochs were selected using a two step analysis for automatic minimization and rejection of artifacts [14–16].

The mean spectral curves contained data from 1.3–35 Hz quantified into 36 variables: total power (TP), the absolute and relative power in 12 different frequency bands, the dominant frequency in Hz (DF), the relative (RP) and absolute (AP) power of the dominant frequency, the centre-of-gravity frequencies [Centroids (C)] and their standard deviations (S) of the combined delta and theta (DT), alpha (A) and beta (B) bands as well as of the total activity (T). Nineteen numbers representing variables from the 19 electrodes are mapped in a 64 × 64 numerical matrix. Each interpolated value is based on the cubic distance from the values at the four nearest electrodes.

The differences in the distribution of particular EEG variables before and after drug administration were

displayed with the significance probability mapping [11, 15, 16]. Differences of the target variables at the 19 leads before and 1, 2, 4, 6 and 8 h after drug administration were compared. Results of this exploratory process were expressed in *t*-scores and displayed as SPMs. The same method was utilized to demonstrate differences between drug-induced and placebo-induced alterations ('pharmaco-EEG maps').

Psychometric and psychophysiological tests

Psychometric assessments included with regard to the noopsyche (i.e. the part of our psyche concerned with intellectual and mnemonic functions) the alphabetical cross-out test as paperpencil version (AD-Test = Alphabetischer Durchstreichtest) of Grünberger [19] for evaluation of the quantitative aspects (total score), qualitative aspects (errors in percent of the total score) of attention and the attention variability (difference between extreme scores); the Pauli-test (correct calculation and errors), numerical memory for the short term memory examination [19], the psychomotor activity (Feinmotoriktest) of Grünberger [19], the reaction time as determined on the Viennese reaction apparatus and the errors occurring in the test, as well as the complex reaction as assessed on the Wiener Determinationsgerät of Schuhfried, and a microprocessor-assisted rigidity and perseverence test [20].

Thymopsychic measurements (i.e. measures concerning mood, drive, affect, wakefulness) consisted of the von Zerssen Bf-S scale [21] for evaluation of subjective well-being; a semantic differential polarity profile for changes in affectivity including wakefulness, concentration, mood and extraversion [22] and also four 100 mm visual analogue scales for self-rating of mood, wakefulness, affectivity and drive.

Psychophysiological assessments included critical flicker fusion (CFF, descending threshold), microprocessor-assisted measurements of static and dynamic pupillometry (pupillary diameter under resting conditions (pupil size and number of spontaneous fluctuations) and after stimulation with a 300 ms light flash (baseline, latency, time until peak effect, maximal constriction, change in mm and % of baseline, recovery time in seconds)) and the skin conductance (SCL, in microsiemens and number of spontaneous fluctuations) [23].

Statistics

The dispersion of each of the kinetic parameter values was defined by the standard deviation (s.d.) and the coefficient of variation (C.V.%). This descriptive statistical analysis was performed using SIPHAR software (SIMED). The effects of doses on suriclone pharmacokinetic behaviour were assessed by comparing 0.1 mg vs 0.2 mg vs 0.4 mg pharmacokinetic parameters by linear regression.

Exploratory statistical analyses of pharmacodynamic data included discriminant analysis, multivariate analysis of variances (MANOVA), analysis of variances (ANOVA), the Newman-Keuls-Test, the Duncan-Test, the paired samples *t*-test, the Friedman-Test and the Wilcoxon-Wilcox-Test.

Results

Pharmacokinetic findings

Throughout the period of determination of TAP and suriclone in plasma samples, a quality control using samples spiked with suriclone was performed.

The mean plasma concentration-time curve is shown in Figure 1. There is a dose-dependent fast rise in plasma concentrations, with a peak at 1 h and a fast decrease thereafter.

The pharmacokinetic values derived from TAP included $t_{\max}$ (median 1.0 h for all three doses), $C_{\max}$ (0.91 ± 0.37 , 2.19 ± 0.74 and 4.36 ± 1.28 ng ml⁻¹ for 0.1, 0.2 and 0.4 mg suriclone, respectively) and the AUC (1.90 ± 1.60 , 6.12 ± 3.11 and 14.3 ± 5.80 ng ml⁻¹ h, respectively). There was a statistically significant ($P < 0.001$) proportionality between $C_{\max}$ and AUC with doses, according to the linear relationships ($r = 0.858$ ($n = 45$) and $r = 0.807$ ($n = 45$)).

Neurophysiological findings

Pharmaco-EEG maps—multivariate analysis In order to decide whether the investigational drugs exert significant effects on the human brain compared with placebo and at which times, MANOVAs were performed (for each of the 19 electrodes) considering groups (drugs, placebo), times (pre-, post-treatment) and relative power values in all nine R-EEG frequency bands. The relative power values were transformed ($\ln(\text{power\%}/(100 \cdot \text{power\%}))$) [24] to fulfil the conditions for the MANOVA (homogeneity of the variances and co-variances as well as the symmetric unimodal distribution). Hotelling's T^2 -values were used to avoid Type I errors with inflated df and were imaged in terms of brain maps (Figure 2).

As can be seen, 0.1 mg suriclone produced subtle changes in various locations in the 1st, 2nd and 6th hour

Figure 1 Plasma concentrations (ng ml⁻¹) of suriclone + metabolites after 0.1 mg (●), 0.2 mg (▲) and 0.4 mg (◆) ($n = 15$). There is a dose-dependent rise to a maximum plasma concentration in the 1st hour and a rapid decline thereafter.

and 0.2 mg suriclone slightly more changes at all times past the 2nd hour, mostly in central and temporo-occipital areas. More pronounced changes were induced by 0.4 mg suriclone at all times with the peak between the 2nd and 6th hour. The reference drug 1 mg alprazolam produced the most distinct and consistent CNS changes over all regions of the human brain, which reached statistical significance at all times.

Pharmaco-EEG maps—univariate analysis In order to demonstrate central effects after the four compounds in 28 EEG variables in detail, topographic brain maps were obtained showing drug-induced changes compared with placebo-induced alterations. The maps are based on R-EEG recordings obtained 2 h after drug intake, and are described in the following chapter. As was shown by multivariate analysis, this was the time of the pharmacodynamic peak effect, while in psychometric data the peak effect was between the 2nd and 4th hour.

Suriclone induced both in regard to absolute (Figure 3) and relative power (Figure 4) a dose-dependent increase of beta activity, decrease of alpha and theta activity and increase of delta activity (the latter in the higher doses range). Total power was attenuated, the centroid of the total spectrum accelerated (Figure 4). The centroid of the delta/theta activity slowed down, that of the alpha and beta activity was slightly accelerated. Such findings are typical for tranquilizers and were indeed seen also after the reference drug, 1 mg alprazolam. However, the latter produced in contrast to the former an increase of relative theta power (Figure 4), more

decrease of alpha activity (Figures 3 and 4) and a slowing of the beta centroid (Figure 5). Thus our findings reflect slightly more sedative effects of 1 mg alprazolam than the highest given dosage of suriclone (0.4 mg).

The location of greatest changes over time lay generally after both suriclone and alprazolam over the vertex, frontal, central and parietal areas.

Time efficacy relations were calculated utilizing the Friedman's and multiple Wilcoxon test of placebo-corrected changes in 27 R-EEG variables obtained in 19 derivations and demonstrated encephalotropic peak effects of suriclone in the 2nd to 4th hour and of 1 mg alprazolam in the 2nd hour.

Dose-efficacy relations calculated by the same method showed that placebo induced the least changes (rank sum 299.9), followed by 0.1, 0.2 and 0.4 mg suriclone (rank sums 322.4, 393.3 and 459.1, respectively). Alprazolam 1 mg induced the most CNS changes (rank sum 550.2).

Psychometric and psychophysiological findings

Noopsyche changes—multivariate analysis Multivariate statistical analysis considering changes in nine noopsyche variables at all times post drug (1, 2, 4, 6, 8 h) after all five substances demonstrated after placebo a slight deterioration in noopsyche performance which was statistically significant compared with pretreatment in the 2nd hour (Figure 6). Suriclone induced after 0.1 mg a noopsyche deterioration in the 2nd and 6th hour, after 0.2 mg no significant changes at all, while after 0.4 mg a

Figure 2 Brain maps showing differences between drug-induced and placebo-induced central effects after 0.1 mg, 0.2 mg and 0.4 mg suriclone and 1 mg alprazolam (left to right column, respectively) at hours 1, 2, 3, 6 and 8 (top to bottom row). The vertex view shows nose on the top, occiput on the bottom, left ear to the left and right ear to the right. Electrode positions are indicated by white dots. Maps are based on Hotelling's T^2 obtained from multivariate tests in repeated measures ANOVA on the relative power of the nine frequency bands [$\ln(\text{power}\%/100 - \text{power}\%)$ transformations] for each electrode (R-EEG, $n = 15$). The colour key shows T^2 values with hot/red colour indicating significant differences: larger than 2.96 = $P < 0.10$, larger than 4.1 = $P < 0.05$ and larger than 7.98 = $P < 0.01$. With increasing doses, suriclone exerts an increasing effect on the human brain compared with placebo, which may be observed topographically first over the vertex, right parietal and temporal regions. The encephalotropic effects of the single oral doses start as early as in the 1st hour and reach up to the 8th hour. The reference compound, 1 mg alprazolam, induces most CNS effects.

Figure 3 Maps of topographic pharmaco-EEG changes in absolute power of the delta (1.3–3.5 Hz), theta (3.5–7.5 Hz), slow alpha (7.5–10.5 Hz), fast alpha (10.5–13 Hz) and beta (13–35 Hz) activities (top to bottom rows, respectively) after 0.1 mg, 0.2 mg, 0.4 mg suriclone and 1 mg alprazolam (left to right column, respectively) compared with placebo in the 2nd hour post-drug (R-EEG, $n = 15$). Eight-colour scales represent drug-induced changes expressed in t -values. Orange, red and purple colours represent significant ($P < 0.10$, 0.05 and 0.01, respectively) increases; dark green, light blue and dark blue indicate significant ($P < 0.10$, 0.05 and 0.01, respectively) decreases compared with placebo. With increasing doses, suriclone increases delta power and beta power and attenuates slow and fast alpha power. The same type of changes, though more pronounced, can be seen after 1 mg alprazolam.

Figure 4 Maps of topographic pharmaco-EEG changes in relative power of the delta (1.3–3.5 Hz), theta (3.5–7.5 Hz) slow alpha (7.5–10.5 Hz), fast alpha (10.5–13 Hz) and beta (13–35 Hz) activities (top to bottom row) after 0.1 mg, 0.2 mg, 0.4 mg suriclone and 1 mg alprazolam (left to right column, respectively) compared with placebo in the 2nd hour post-drug (R-EEG, $n = 15$). For technical description of the colour scale, see Figure 3. Suriclone induces with increasing doses an augmentation of relative delta and beta power as well as decrease of relative theta, slow and fast alpha power. 1 mg alprazolam increases delta and theta activity (reflecting sedative properties), attenuates alpha activity and increases beta activity.

Figure 5 Maps of topographic pharmaco-EEG changes in total power (1.3–35 Hz), centroid of the total activity (1.3–35 Hz) as well as the centroid of the combined delta/theta, alpha and beta frequencies after 0.1 mg, 0.2 mg, 0.4 mg suriclone and 1 mg alprazolam (left to right column) compared with placebo in the 2nd hour post-drug (R-EEG, $n = 15$). For technical description of the colour scale, see Figure 3. Suriclone attenuates dose-dependently absolute power, accelerates the centroid of the total activity, slows the centroid of the delta/theta frequency bands and accelerates the centroid of the alpha frequency band. The same type of changes are seen after the reference compound, 1 mg alprazolam, although the centroid of the alpha band is slowed over the occipital region and the centroid of the beta frequency band is slowed almost over the whole brain.

Figure 6 Effect of suriclone on the noopsyche (multivariate analysis considering changes in 9 noopsychic variables at 1, 2, 4, 6 and 8 h after placebo (—, D), 0.1 mg (····, A), 0.2 mg (---, B), 0.4 mg (-·-·, C) suriclone and 1 mg alprazolam (- - - - , E); $n = 15$). Time is represented in the abscissa, changes from the pre-treatment (expressed in Euclid's distances) are shown in the ordinate. Euclid's distances are calculated based on the centroids of discriminant analysis of changes in nine noopsychic variables and subjected subsequently to a three-way ANOVA (overall 3.631**, F_T 10.789**, F_D 33.67). While 0.4 mg suriclone and the reference compound, 1 mg alprazolam, induce a significant performance decrement, compared with placebo in the 4th and 8th hour as well as in the 1st to the 4th hour, respectively, 0.2 mg suriclone produces an improvement (2nd hour). * $P < 0.05$, ** $P < 0.01$, Newman Keuls test.

performance decrement was found at all times. The latter was also the case for the reference compound, except for the 8th hour.

Inter-drug comparison showed a significantly more pronounced noopsychic decrement after 1 mg alprazolam than placebo and suriclone in the 1st and 2nd hour. In contrast, 0.4 mg suriclone induced, in comparison with all other substances, a significant deterioration between the 4th and the 8th hour. Suriclone 0.2 mg was significantly superior to 0.4 mg suriclone from the 2nd to the 8th hour, to alprazolam from the 1st to the 4th hour, to placebo and 0.1 mg suriclone only in the 2nd hour.

Noopsychic changes—univariate analysis (Table 1) Attention as evaluated by means of the total score in the alphabetical cross-out test of Grünberger [19] showed in the three-way ANOVA significant changes over time ($F_T = 6.3$, $P < 0.01$), as well as significant inter-drug differences ($F_D = 12.9$, $P < 0.01$). Detailed analysis by the Newman Keuls Test demonstrated after 0.4 mg suriclone, compared with placebo, significant deteriorations in the 2nd and 4th hour, while after the reference substance between the 1st and the 4th hour. The other two suriclone doses did not induce any changes in attention. Thus, inter-drug comparison by means of the Newman-Keuls-Test demonstrated a superiority of 0.1 mg and 0.2 mg suriclone from the 1st to the 4th hour over alprazolam and over 0.4 mg suriclone in the 1st hour. Beginning with the 6th hour, there were no differences between the five substances in attention.

Concentration as evaluated by means of errors in % of the total score of the alphabetical cross-out test of

Grünberger demonstrated no significant changes compared with placebo. In the 2nd hour there was a significant superiority of 0.4 mg suriclone over the reference substance.

Attention variability did not demonstrate any significant findings.

Fine motor activity test of Grünberger [19] showed, compared with placebo, significant deterioration after 0.4 mg suriclone in the 4th and 6th hour and after 1 mg alprazolam in the 1st throughout the 4th hour. The other substances did not induce any significant changes over time. Inter-drug comparison proved that the reference substance was significantly inferior to placebo until the 4th hour and to the three suriclone doses in the 1st hour.

Reaction time as measured by means of the Viennese reaction time apparatus demonstrated, compared with placebo, a significant deterioration in the 4th hour after 1 mg alprazolam. In contrast, 0.2 mg suriclone shortened reaction time in the 2nd and 4th hour. Inter-drug comparison showed all three suriclone doses superior to 1 mg alprazolam.

Errors in the reaction time task showed an increase only at 4 h after 0.4 mg suriclone compared with placebo.

Complex reaction measured by the 'Wiener Determinationsgerät' showed a deterioration 1–4 h after 0.4 mg suriclone and 1 mg alprazolam, compared with placebo. Inter-drug comparison by means of the Newman Keuls test demonstrated a superiority of the lower doses over 0.4 mg suriclone and the reference compound between the 2nd and the 6th hour.

Correct calculations in the Pauli-test decreased after 0.4 mg suriclone between the 2nd and the 8th hour as well as after 1 mg alprazolam between the 1st and the 8th hour, compared with placebo. Inter-drug comparison showed a significant superiority of all doses of suriclone over the reference compound up to the 2nd hour.

Errors in per cent of the total score in the Pauli-test showed a significant superiority of 0.2 mg suriclone (decreasing errors) in the 4th hour over placebo (increasing errors). In the 2nd hour 0.1 and 0.2 mg suriclone were superior to the reference compound.

Short term memory as evaluated by the numerical memory test of Grünberger [19] demonstrated deterioration in the 4th hour after 0.4 mg suriclone and in the 2nd hour after 1 mg alprazolam, compared with placebo. Inter-drug comparison demonstrated a significant superiority of all three doses of suriclone over the reference compound in the 2nd hour.

Evaluation of rigidity and perserverance by means of a computer-assisted technique demonstrated, based on a multivariate analysis of five test variables (right hand), a significant deterioration after 1 mg alprazolam in the 2nd and 4th hour in comparison with pretreatment. Inter-drug comparison revealed significantly more increase of rigidity after 1 mg alprazolam at all times, compared with placebo, but also compared with 0.1 and 0.2 mg suriclone. Similar results were obtained with the left hand.

Thymopsychic changes—multivariate analysis A multivariate analysis considering changes in four thymopsychic variables at all times after drug administration (1, 2, 4, 6, 8 h) and after all five substances demonstrated a significant deterioration from the 1st to the 8th hour after

Table 1 Change in noopsyche variables after a single dose of 0.1 mg, 0.2 mg and 0.4 mg suriclone compared with 1 mg alprazolam and placebo respectively ($n = 15$; 1, 2, 4, 6, 8 h post-drug)

Variable		Three-way ANOVA		As compared with placebo		
		F_{Time}	F_{Drug}	0.1 mg suriclone	0.2 mg suriclone	0.4 mg suriclone 1 mg alprazolam
Attention (total score)	↑	6.3**	12.9**			--2, -4
Concentration (errors %)	↓	NS	4.9**			
Attention variability	↓	NS	3.3*			
Fine motor activity	↑	2.4*	11.8**			--4, -6
Reaction time (ms)	↓	3.7**	22.6**		--2, -4	-1, 2, --4
Reaction time task (errors)	↓	NS	3.7**			+4
Complex reaction (determination)	↑	8.8**	48.2**			--1, 2, 4, -6
Pauli-Test (correct)	↑	4.3**	47.1**			--2, 4, 6, 8
Pauli-Test (errors)	↓	NS	7.4**		-4	--1, 2, 4, 6, -8
Numerical memory	↑	2.5*	5.3**			-4
As compared with alprazolam						
Variable		0.1 mg suriclone	0.2 mg suriclone	0.4 mg suriclone		
Attention (total score)	↑	+1, ++2, ++4	+1, ++2, +4	+1		
Concentration (errors %)	↓			-2		
Attention variability	↓					
Fine motor activity	↑	++1	++1, +4	+1		
Reaction time (ms)	↓	-1, --4	--1, 2, 4, -6	--1		
Reaction time task (errors)	↓					
Complex reaction (determination)	↑	++2, 4, 6	++2, 4, 6	-6, 8		
Pauli-Test (correct)	↑	++1, 2, 4, 6	++1, 2, 4, 6, +8	++1, +2		
Pauli-Test (errors)	↓	-2	-2, 4			
Numerical memory	↑	+2	+1, 2	+1, 2		

↓ ↑ Direction of improvement.

+ Increase at $P < 0.05$; ++ increase at $P < 0.01$; - decrease at $P < 0.05$; -- decrease at $P < 0.01$ (Newman Keuls).

0.4 mg suriclone and 1 mg alprazolam, compared with pretreatment (Figure 7), while after placebo and the lower doses of suriclone, no changes occurred. Thus, inter-drug comparison demonstrated significant differences between the three latter and two former substances.

Thymopsychic changes—univariate analysis (Table 2) Well-being as evaluated by means of the von Zerssen Bf-Scale demonstrated, compared with placebo, after 0.4 mg suriclone a deterioration between the 2nd and

6th hour, and after 1 mg alprazolam in the 2nd, 4th and 8th hour. These two drugs differed also from the lower doses of suriclone.

The total score of the semantic differential polarity profile, reflecting changes in mood, affect, extraversion and wakefulness, showed a significant deterioration. Inter-drug comparison demonstrated improvement after 0.1 mg and 0.2 mg suriclone, compared with placebo, while after 0.4 mg suriclone and 1 mg alprazolam a deterioration. Thus, the lower doses of suriclone were

Figure 7 Effect of suriclone on the thymopsychic (multivariate analysis considering changes in four thymopsychic variables at 1, 2, 4, 6 and 8 h after placebo (—D), 0.1 mg (····, A), 0.2 mg (---, B), 0.4 mg (—, C) suriclone and 1 mg alprazolam (---, E); $n = 15$). For the description of the axes, see Figure 6. Suriclone induces dose-dependently a thymopsychic deterioration reflecting sedative properties, which are also shared by the reference compound, 1 mg alprazolam. * $P < 0.05$, ** $P < 0.01$, Newman Keuls test. Three-way ANOVA, $F_T 14.524^{**}$, $F_D 122.534^{**}$.

significantly superior to the reference compound.

Drive as evaluated by a 100 mm visual analogue scale (VAS) showed, compared with placebo, after 0.4 mg suriclone and 1 mg alprazolam a decrease between the 2nd and 6th hour, while there were no changes after 0.1 mg and 0.2 mg suriclone.

Mood as evaluated by a 100 mm visual analogue scale (VAS) demonstrated a significant deterioration in mood 2–4 h after 0.4 mg suriclone and 2 h after 1 mg alprazolam, compared with placebo. There were no significant changes with the two lower doses of suriclone.

Affectivity (affective resonance) as evaluated by a 100 mm visual analogue scale (VAS) showed a significant decrease in the 2nd to the 6th hour after 0.4 mg suriclone and in the 1st to the 4th hour after 1 mg alprazolam, compared with placebo, while there were no significant changes after the lower doses of suriclone.

Sedation as rated by the subjects themselves by means of a 100 mm visual analogue scale (VAS) demonstrated a significant increase in the 2nd to 6th hour after 0.4 mg suriclone and 1 mg alprazolam, compared with placebo, while there were no changes with the lower doses of suriclone.

Psychophysiological changes—multivariate analysis A multivariate statistical analysis by means of the MANOVA concerning changes in seven psychophysiological variables obtained at 2, 4, 6, 8 h after administration of all five treatments demonstrated no significant changes over time. Inter-drug comparison showed only in the 4th hour a significant difference of 1 mg alprazolam compared with placebo in the sense of a deactivation.

Psychophysiological changes—univariate analysis (Table 3) Critical flicker frequency (CFF; descending threshold) showed, compared with placebo, a decrease at all times after 1 mg alprazolam, a decrease in the 2nd–4th hour after 0.1 and 0.2 mg suriclone, while it increased

in the 6th and 8th hour after 0.4 mg suriclone. Inter-drug comparison showed a greater decrease after the reference compound than after all three suriclone doses.

Pupillary diameter as measured by means of a micro-processor-assisted pupillometer demonstrated significant dilation over time after 0.1 mg suriclone in the 4th to the 8th hour, compared with placebo. This dose induced also a significant widening of pupil diameter, compared with the other drugs in the 4th and 8th hour and with placebo between 4th hour and the 8th hour.

Pupillary fluctuations showed no significant differences over time. There was a tendency to a lower frequency of spontaneous fluctuations after 0.1 mg and 0.2 mg suriclone in the 2nd hour, while after the other substances the opposite trend occurred. Thus, the difference between two groups reached the level of statistical significance.

The latency of the pupillary reaction as well as the relative change in diameter were not altered by any of the compounds.

Skin conductance level (SCL in μmhos) showed significant inter-drug differences in the 4th hour which was due to the fact that after placebo skin conductance increased, compared with all other drugs. At the other times there were no significant inter-drug differences.

Number of SCL-fluctuations decreased in the 2nd, 6th and 8th hour after 0.4 mg suriclone and in the 2nd hour after 1 mg alprazolam.

Clinical findings

Pulse rate, systolic and diastolic blood pressure did not exhibit any clinically relevant changes after any of the five substances.

Side-effects were observed in 5, 11, 15, 8 and 15 out of 15 subjects after 0.1 mg, 0.2 mg, 0.4 mg suriclone, placebo and 1 mg alprazolam, respectively. Specifically, tiredness and drowsiness were reported by 5, 7, 12, 6, 15 subjects after the five doses, respectively; dizziness or giddiness in 1, 5, 12, 1, 8; sickness or nausea in 0, 0, 1, 1, 2 subjects, while two subjects experienced a decrease in concentration after 0.4 mg suriclone. Headache was observed in one subject after 0.4 mg suriclone and in three subjects after placebo. Activation was reported by one subject after 0.1 mg suriclone and placebo each. Loss of appetite was reported once after placebo, blurred vision once after 0.2 mg suriclone and hiccup once after 1 mg alprazolam.

Discussion

Pharmacokinetic investigations demonstrated that suriclone was rapidly absorbed as plasma peaks were seen 1 h after oral drug administration. There was a rapid decline thereafter in blood concentrations. Mean TAP C_{max} were 0.91, 2.19 and 4.36 ng ml^{-1} after the administration of 0.1, 0.2 and 0.4 mg, respectively, showing a linear relationship between the dose administered and the plasma concentration in the 15 subjects. Areas under the plasma concentration curve (AUC_{0-t}) increased slightly more rapidly than doses. This is a consequence of the limit of detection of the assays: 8 h after administration of 0.1 mg suriclone, only two plasma

Table 2 Change in thymopsychic variables after a single dose of 0.1 mg, 0.2 mg and 0.4 mg suriclone compared with 1 mg alprazolam and placebo respectively ($n = 15$; 2, 4, 6, 8 h post-drug)

Variable		Three-way ANOVA		As compared with placebo			
		F _{Time}	F _{Drug}	0.1 mg suriclone	0.2 mg suriclone	0.4 mg suriclone	1 mg alprazolam
Well being (Bf-S scale)	↓	8.6**	28.8**			++2, 4, 6	++2, 4 +8
Semantic difference polarity profile	↓	3.9**	43.9**	−2, 4	−4, 8	++2, 4, 6	++2, 4
(n = 15; 1, 2, 4, 6, 8 h post-drug)							
VAS drive	↓	3.0*	34.2**			++2, 4, 6	++2, 4, 6
VAS sedation	↓	5.0**	24.3**			++2, 4, 6	+1, ++2, 4
VAS mood	↑	9.8**	NS			−−2, 4	−−2
VAS affectivity	↑	NS	30.3**			−−2, 4, 6	−−1, 2, 4
As compared with alprazolam							
Variable		0.1 mg suriclone	0.2 mg suriclone	0.4 mg suriclone			
Well being (Bf-S scale)	↓	−−2, 4, 6	−−2, 4	++6, +8			
Semantic difference polarity profile	↓	−−2, 4, 6	−−2, 4, −6, 8	+6			
(n = 15; 1, 2, 4, 6, 8 h post-drug)							
VAS drive	↓	−−2, 4, 6	−−2, 4, 6				
VAS sedation	↓	−−2, 4	−−1, 2, 4				
VAS mood	↑						
VAS affectivity	↑	+1, ++2, 4, 6	++1, 2, 4	+1, 2			

↓ ↑ Direction of improvement.

+ Increase at $P < 0.05$; ++ increase at $P < 0.01$; - decrease at $P < 0.05$; -- decrease at $P < 0.01$ (Newman Keuls).

levels of TAP over 15 were higher than the limit of detection (0.2 ng ml^{-1}). At the same time, this ratio was 5/15 and 14/15 after administration of 0.2 and 0.4 mg, respectively. As a consequence, the AUC_{0-t} values are underestimated for the lowest doses (0.1 and 0.2 mg).

Pharmacodynamic studies utilizing EEG mapping demonstrated a significant effect of both the new cyclopyrrolone, suriclone, and the triazolobenzodiazepine, alprazolam, on human brain function, compared with placebo. These changes were characterized by a dose-dependent increase of beta activity, decrease of alpha and theta activity and increase of delta activity. Total power was attenuated, the centroid of the total spectrum accelerated. The centroid of the delta/theta activity slowed down, that of the alpha was slightly accelerated. Such findings are typical for anxiolytic benzodiazepines [11–13, 25–32] and have also been described after suriclone [33].

Despite the fact that the type of CNS changes were very much alike after both suriclone and alprazolam, some slight differences could be observed. While after suriclone, an attenuation was observed in regard to relative theta power, an augmentation occurred in this

variable after 1 mg alprazolam. As also the attenuation of the total power, the decrease of alpha activity and the slowing of the centroid of the beta frequency band was more pronounced after the reference compound than suriclone, it may be hypothesized that the investigated doses of 0.1–0.4 mg suriclone are less sedative than 1 mg alprazolam. Indeed, in a recent sleep study concerning the acute effects of single doses of 0.2 mg and 0.4 mg suriclone, compared with 2 mg lorazepam, we noted that 0.2 mg suriclone did not induce any alterations in the all-night sleep, while after 0.4 mg suriclone and 2 mg lorazepam nocturnal awakenings decreased significantly, compared with placebo, which was reflected in an improved subjective sleep quality [9]. In the morning, well-being, drowsiness and reaction time performance deteriorated after 2 mg lorazepam, 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. In a much earlier sleep laboratory study alprazolam given in doses of 0.5 1.0 and 2.0 mg was identified as an anti-anxiety drug with hypnotic effects in the higher dosage range [11, 34].

Table 3 Change in psychophysiological variables after a single dose of 0.1 mg, 0.2 mg and 0.4 mg suriclone compared with 1 mg alprazolam and placebo respectively ($n = 15$; 2, 4, 6, 8 h post-drug)

Variable	Three-way ANOVA		As compared with placebo			
	F_{Time}	F_{Drug}	0.1 mg suriclone	0.2 mg suriclone	0.4 mg suriclone	1 mg alprazolam
Critical flicker frequency (CFF)	2.3**	55.5**	-2, 4	-2, 4	+6, ++8	--2, 4, 8, -6
Pupillary (diameter)	4.4**	10.8**	++4, 8, +6			
Pupillary (fluctuations)	NS	4.6**	-2	-2		
Pupillary (latency time)	NS	3.2**				
Pupillary (relative change)	NS	NS				
SCL (μ mhos)	4.8**	9.4**	--4	-4	--4	--4
SCL (fluctuations)	NS	9.9**			-2, 6, --8	-2

Variable	As compared with alprazolam		
	0.1 mg suriclone	0.2 mg suriclone	0.4 mg suriclone
Critical flicker frequency (CFF)	++2, 4, 8, +6	++2, 4, 8	++2, 4, 6, 8
Pupillary (diameter)	+4, ++8		
Pupillary (fluctuations)	-2	-2	
Pupillary (latency time)			
Pupillary (relative change)			
SCL (μ mhos)			
SCL (fluctuations)	+2	++2	

+ Increase at $P < 0.05$; ++ increase at $P < 0.01$; - decrease at $P < 0.05$; -- decrease at $P < 0.01$ (Newman Keuls).

As far as the time-course of the encephalotropic effect was concerned, we observed after suriclone initial changes already in the 1st hour, a plateau effect between the 2nd and 6th hour with a slight decrease thereafter. After the reference substance, CNS changes were much more pronounced already in the 1st hour and remained marked from the 2nd throughout the 8th hour.

Psychometric investigations demonstrated both after suriclone and alprazolam changes typical for anxiolytic sedatives [28, 29, 32–40]. While the two lower doses of suriclone induced no significant deterioration in the noopsyche, 0.4 mg suriclone and 1.0 mg alprazolam decreased noopsychic performance. After 0.2 mg suriclone we observed even an improvement in complex reaction, a shortening of reaction time, a decrease of errors in the reaction time task, an increase of correct calculations in the Pauli test, as well as an improvement in the psychomotor activity. Indeed, an improvement in noopsychic functions as measured in attention was described in our sleep laboratory studies when we

measured objective awakening qualities in the morning after bedtime medication of suriclone [9].

The thymopsyche was also differentially influenced by different suriclone doses as well as the two compounds. While there were no changes in the thymopsyche after lower doses of suriclone, 0.4 mg and 1.0 mg alprazolam produced a deterioration. The 0.1 mg and 0.2 mg suriclone did not exhibit any sedative properties. Our present results are in agreement with previous investigations of differential effects of low and high doses of certain anxiolytics [9, 40, 41]. Psychophysiological investigations showed inconsistent changes in CFF (decrease after 0.1, 0.2 mg suriclone and 1 mg alprazolam; increase after 0.4 mg suriclone), a widening of the pupillary diameter and decrease of pupillary fluctuations with the lower dose of suriclone, a decrease in skin conductance with all drugs and a decrease in skin fluctuations only with higher doses of suriclone and the reference compound. In regard to CFF, Allen & Lader [33] reported in normal volunteers after 7 days of suri-

clone (0.2 and 0.4 mg three times daily) an increase in CFF (suggesting some improvement in sensory perception), while a decrease after 5 mg diazepam three times daily. There were neither clinically nor statistically significant changes in pulse rate and blood pressure. As is known, tranquillizers induce only little autonomous nervous system reactions. Somatic complaints and side-effects such as tiredness, drowsiness, dizziness, etc., usually seen after anxiolytics in normal volunteers, occurred predominantly after higher doses of suriclone (0.4 mg) and the reference compound, 1 mg alprazolam.

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