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Controlled comparison of the efficacy and safety of four doses of suriclone, diazepam, and placebo in generalized anxiety disorder

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Abstract. The anxiolytic activity and tolerance of four doses of suriclone (0.1, 0.2, 0.3 and 0.4 mg tid), diazepam (5 mg tid), and placebo were compared in six parallel groups of 54–59 outpatients with generalized anxiety disorder (DSM III–R). After a 1-week placebo run-in period, the patients were treated for 4 weeks, with assessments at baseline and after 1, 2, and 4 weeks by the Hamilton anxiety scale and the Clinical Global Impressions. Results showed better improvement with active drugs as compared to placebo, without significant differences among the four different doses of suriclone and diazepam. The number of adverse events, particularly drowsiness, was significantly higher with diazepam than with suriclone, particularly 0.1 and 0.2 mg tid which did not differ from placebo. These results demonstrate that suriclone at daily doses ranging from 0.1 to 0.4 mg tid is an effective anxiolytic, better tolerated than diazepam.

Key words: Suriclone – Cyclopyrrolones – Anxiolytic – Generalized anxiety disorder – Diazepam – Benzodiazepines

Suriclone is a cyclopyrrolone derivative which differs chemically from the benzodiazepines. It binds with high affinity to a distinct site or to a special allosteric conformation of the GABA A/benzodiazepine/chloride ionophore receptor complex (Blanchard et al. 1979). Indeed, unlike classical benzodiazepines, suriclone binding is not enhanced by GABA, chloride, or barbiturates, and only minimally reduced by photo-affinity labelling of the benzodiazepine receptor (Blanchard et al. 1983; Blanchard and Julou 1983; Trifiletti and Snyder 1984; Zundel et al. 1985). In animals, the experimental profile of suriclone resembles benzodiazepines with anticonflict, anticonvulsant, antiaggressive, myorelaxant, and sedative-hypnotic activities (Sullivan et al. 1984; Julou et al. 1985; Ono et al. 1987). Several clinical studies have demonstrated the anxiolytic activity of suriclone in comparison to reference benzodiazepines such as lorazepam (Gotfryd 1984) and diazepam (Gerlach et al. 1987). In these studies, suriclone, which was used at daily doses ranging from 1.5 to 2.0 mg, exhibited an adverse events profile rather different from the benzodiazepines, with more dizziness and less sedation.

The purpose of the present study was to test if lower doses of suriclone would exhibit a better efficacy and safety profile in comparison with placebo and a standard benzodiazepine, diazepam. More precisely, we were interested in defining the optimal dosage of suriclone, i.e. with the best efficacy/safety ratio.

Subjects and methods

Design of the study. The study was performed between September 1987 and July 1988 by 50 Belgian and French psychiatrists. The trial used a double-blind design with six parallel groups of patients randomly allocated to suriclone 0.1 mg tid, 0.2 mg tid, 0.3 mg tid, 0.4 mg tid, diazepam 5 mg tid, or placebo. The active period was preceded by a 1-week drug-free period on placebo. The duration of the study was 4 weeks, with assessments at baseline and after 1, 2, and 4 weeks of treatment. The association of any psychotropic drug was not allowed throughout the study period. The study was monitored according to "Good clinical practices" (Ministère des Affaires Sociales et de l'Emploi 1987; Mathieu 1990).

Subjects. A total of 341 patients entered the simple-blind and 325 the double blind phase of the study. Of these, 323 were included in the analysis of efficacy, as two patients dropped out before the first week visit. All subjects were anxious outpatients, aged 18–65 years, who fulfilled DSM–III–R criteria for generalized anxiety disorder (American Psychiatric Association 1987) (except for the duration of illness which was reduced to at least 2 months), had a score of at least 20 on the Hamilton anxiety scale (Hamilton 1959) with a minimal score of 2 (moderate) on the two first items (anxious mood and tension) and a total score of at least 9 on the Covi anxiety scale (Covi et al. 1979). Moreover, in order to exclude predominantly depressed patients, their score on item 6 of the Hamilton anxiety

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Table 1. Demographic and clinical characteristics of the sample

	Suriclone 0.1 mg tid $n=57$	Suriclone 0.2 mg tid $n=56$	Suriclone 0.3 mg tid $n=58$	Suriclone 0.4 mg tid $n=59$	Diazepam 5 mg tid $n=54$	Placebo $n=57$	F/χ^2	P
Age (SEM)	42.7 (1.7)	41.2 (1.7)	41.9 (1.6)	39.3 (1.5)	42.3 (1.6)	40.0 (1.4)	0.75	NS
M/F	19/38	21/35	19/39	26/33	22/32	26/31	0.12	NS
Weight (kg) (SEM)	70.0 (1.5)	64.5 (1.4)	65.0 (1.5)	63.8 (1.3)	66.9 (1.4)	64.9 (1.0)	1.92	NS
Height (cm) (SEM)	165.8 (1.0)	167.1 (0.9)	167.6 (2.0)	166.8 (0.9)	168.4 (1.2)	168.0 (1.5)	0.83	NS
History of BDZ intake (%)	84.2	67.3	65.5	78.0	79.6	68.4	0.40	NS
BDZ during last 3 wks (%)	18.7	27.8	30.6	32.6	37.2	30.8	0.06	NS
Alcohol intake (%)								
null	68.4	65.5	56.9	54.2	69.8	49.1	1.39	NS
moderate	29.8	32.7	39.7	45.8	28.3	49.1		
high	1.8	1.8	3.4	0.0	1.9	1.8		
Coffee intake (cups) (SEM)	2.4 (0.3)	2.9 (0.3)	2.3 (0.2)	2.7 (0.2)	2.5 (0.2)	2.3 (0.2)	0.93	NS
Duration of anxious episode (%)								
<2 months	38.6	44.6	42.1	33.9	35.2	35.1	0.67	NS
2–6 months	35.1	32.1	40.3	37.3	31.5	36.9		
6–12 months	8.8	7.1	3.5	11.9	13.0	10.5		
>12 months	17.6	16.1	14.0	16.9	20.4	17.5		
Previous therapy for the current episode (%)	32.1	30.4	28.1	35.6	33.3	34.0	0.03	NS
Baseline ratings (SD)								
Hamilton anxiety scale	29.0 (5.6)	28.6 (5.0)	30.1 (5.2)	30.0 (5.7)	29.9 (5.2)	29.4 (5.7)	0.97	NS
Covi anxiety scale	11.0 (1.3)	11.0 (1.4)	11.1 (1.3)	11.4 (1.5)	11.0 (1.2)	11.0 (1.4)	1.11	NS
Raskin depression scale	5.7 (1.2)	5.9 (1.0)	5.6 (1.1)	5.9 (1.0)	5.7 (1.1)	5.5 (1.1)	0.29	NS
CGI severity of illness	5.2 (0.7)	5.1 (0.7)	5.3 (0.6)	5.4 (0.8)	5.2 (0.6)	5.4 (0.7)	1.14	NS

scale (depressed mood) could not be higher than 2, with a lack of suicidal ideation, and their score on the Raskin scale for depression (Raskin et al. 1967) not higher than 8. Patients presenting any evidence of contra-indication for an anxiolytic benzodiazepine, or serious or uncontrolled medical illness, were excluded from the study. The characteristics and distribution of the patients in the six treatment groups are displayed in Table 1. No statistically significant differences existed among the treatment groups.

The study protocol was approved by the Ethical Committees of the University of Liège Medical School as well as the Sainte-Anne Hospital in Paris. All patients were fully informed of the purpose of the study and gave their consent.

Assessments. All assessments included the Hamilton anxiety scale, the Clinical Global Impressions (CGI) (Guy 1976), the Covi anxiety scale as well as two checklists of side-effects (DOTES and TWIS) (Guy 1976). Vital signs were recorded and a neurological examination was also included.

Data analysis. The homogeneity of the six treatment groups was controlled, using two-way analysis of variance (ANOVA) or the Cochran–Mantel-Haenszel Chi square statistics. No significant difference was present among the six treatment groups related to age, personal and family psychiatric and medical history, previous therapies, vital signs including blood pressure and pulse rate, medical and neurological examinations, alcohol and caffeine intake as well as the clinical characteristics of the current anxious episode.

All changes over time in rating were compared by one-way ANOVAs with repeated measures in an intent to treat analysis, using all data available from all patients having received the drugs (not only the complete cases). An endpoint analysis also compared the differences between baseline scores and scores of the last visit whenever it was of all patients (including all dropout patients). In the presence of a significant effect, pairwise comparisons used the Duncan test. The number of dropouts, adverse events, as well as treatment responders, defined as a decrease in Hamilton anxiety scores of at least 50% between baseline and last visit, was compared using the Cochran–Mantel–Haenszel Chi square statistics.

Results

Exclusions and drop-outs

From an initial total sample of 341 patients, 18 patients were not suitable for the statistical analysis of efficacy: 16 patients did not enter the double-blind phase of the study because they did not fulfil the inclusion criteria ($n=9$) or improved of more than 25% on the Hamilton anxiety scale during the placebo week ($n=7$); 2 patients dropped out the study before the first assessment of efficacy because of, respectively, intercurrent illness after 4 days of treatment and unknown reason.

A total of 61 patients left the study before completion: 4 in the diazepam group, 16 in the placebo group, 11 in the suriclone 0.1 mg tid group, 6 in the suriclone 0.2 mg tid group, 10 in the suriclone 0.3 mg tid group, and 14 in the suriclone 0.4 mg tid group ($\chi^2=0.98$, $P=$ NS). No significant differences were present in the distribution of the main reasons for dropout among the six groups (Table 2).

Efficacy

Hamilton anxiety scale. The comparison of changes over time on the Hamilton anxiety scale in the six treatment groups (Fig. 1) showed significant differences [$F(15,358)=11.90$, $P=0.0001$], with all active treatments being significantly better than placebo but without significant differences among them. The decrease in ratings from initial to last visit is presented in Table 3.

Table 2. Distribution of reasons for dropouts among the treatment groups

	Suriclone 0.1 mg tid $n=57$	Suriclone 0.2 mg tid $n=56$	Suriclone 0.3 mg tid $n=58$	Suriclone 0.4 mg tid $n=59$	Diazepam 5 mg tid $n=54$	Placebo $n=57$	χ^2	P
Lack of efficacy	6	4	3	6	0	12	1.30	NS
Adverse events	0	1	3	1	2	0	—	
Lack of efficacy +adverse events	2	0	3	3	0	3	—	
Lost to follow-up	2	1	1	2	1	1	—	
Other	1	0	0	2	1	0	—	
Total	11	6	10	14	4	16	0.98	NS

Table 3. Comparison of the mean decrease in ratings (%) between initial and final visit (endpoint scores) among the treatment groups

	Suriclone 0.1 mg tid $n=57$	Suriclone 0.2 mg tid $n=56$	Suriclone 0.3 mg tid $n=58$	Suriclone 0.4 mg tid $n=59$	Diazepam 5 mg tid $n=54$	Placebo $n=57$	F	P
Hamilton anxiety scale	51.0	52.5	57.1	51.6	62.1	29.6	11.90	0.0001
Covi anxiety scale	43.5	45.2	50.3	48.6	51.4	32.8	4.00	0.006
Raskin depression scale	23.5	25.6	26.5	22.3	16.9	11.1	2.38	NS
CGI: severity of illness	39.5	42.5	46.9	41.4	51.6	20.1	9.30	0.0001
global improvement	40.3	46.6	49.2	43.2	56.1	21.6	7.67	0.0001

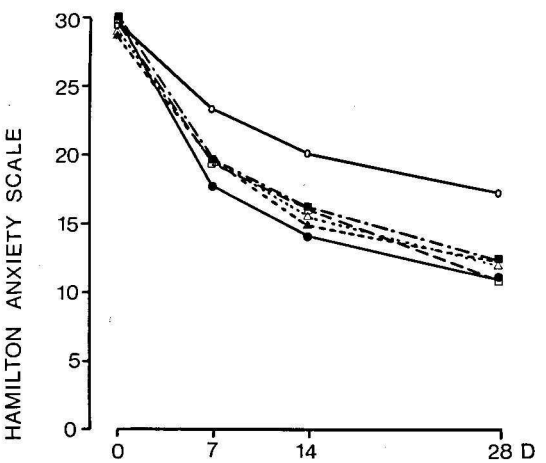

Fig. 1. Changes over time in mean Hamilton anxiety scores in outpatients with generalized anxiety treated by suriclone 0.1 mg tid (△- - -△), 0.2 mg tid (▲- - -▲), 0.3 mg tid (□- - -□), 0.4 mg tid (■- - -■), diazepam 5 mg tid (●——●), or placebo (○——○), (SD ranged from 5.07 to 11.09)

The percentage of treatment responders, as defined by endpoint scores, was significantly different among the treatment groups ($\chi^2=14.07$, $df=5$, $P=0.01$): respectively 32.7% in the placebo group, 64.6% in the diazepam group, 50.0% in the suriclone 0.1 mg tid group, 57.7% in the suriclone 0.2 mg tid group, 55.6% in the suriclone 0.3 mg tid group, and 50.0% in the suriclone 0.4 mg tid group.

Covi anxiety scale. Changes over time on the Covi anxiety scale paralleled those on the Hamilton scale, with all active compounds being more effective than placebo [$F(5,334)=4.00$, $P=0.006$]. Changes from initial scores are presented in Table 3.

CGI. Changes over time in the severity of anxiety (CGI–1) also showed significantly better results with active compounds as compared to placebo [$F(5,385)=9.30$, $P=0.0001$]. The changes over time in the global improvement (CGI–2) showed similar results [$F(5,358)=7.67$, $P=0.0001$]. Changes from initial scores are presented in Table 3. The mean endpoint efficacy indexes (CGI–3) (SD) were significantly different: respectively 2.59 (1.35) with suriclone 0.1 mg tid, 2.55 (1.39) with suriclone 0.2 mg tid, 2.67 (1.25) with suriclone 0.3 mg tid, 2.29 (1.27) with suriclone 0.4 mg tid, 2.40 (1.19) with diazepam, and 1.99 (1.26) with placebo [$F(5,385)=6.31$, $P=0.0001$]. The efficacy index in the placebo group was significantly worse than in all other groups.

Adverse events. The frequency of patients exhibiting at least one adverse event during the 4 weeks of treatment was significantly different among the treatment groups ($\chi^2=15.13$, $df=5$, $P=0.01$): 59.3% with diazepam, 47.5% with suriclone 0.4 mg tid, 46.5% with suriclone 0.3 mg tid, 33.9% with suriclone 0.2 mg tid, 31.6% with placebo, and 29.8% with suriclone 0.1 mg tid. The comparison of the frequency of the individual adverse events in the six treatment groups is presented in Table 4. Drowsiness was significantly more frequent with diazepam.

The neurological examination did not exhibit significant differences except for the Romberg test which was more frequently disturbed after 2 ($\chi^2=14.00$, $df=5$, $P=0.02$) and 4 weeks ($\chi^2=11.57$, $df=5$, $P=0.04$) of treatment with suriclone 0.4 mg tid (in, respectively, 7.5 and 6.8% of the patients) as compared to placebo (in respectively 4.1% and 2.6% of the patients) and all other suriclone doses as well as diazepam (0% and 0%). Blood

Table 4. Frequency (%) of adverse events among the treatment groups

	Suriclone 0.1 mg tid $n=57$	Suriclone 0.2 mg tid $n=56$	Suriclone 0.3 mg tid $n=58$	Suriclone 0.4 mg tid $n=59$	Diazepam 5 mg tid $n=54$	Placebo $n=57$	χ^2	P
Drowsiness	8.8	10.7	17.2	20.3	38.9	10.5	23.99	0.001
Restlessness	7.0	5.4	13.8	8.5	13.0	8.8	3.89	NS
Depression	0.0	1.8	1.7	3.4	1.8	3.5	2.34	NS
Tremor	5.3	1.8	6.9	5.0	1.8	3.5	3.06	NS
Hypertonia	0.0	0.0	1.7	3.4	0.0	1.7	4.71	NS
Digestive symptoms	8.8	3.6	17.2	8.5	13.0	8.8	6.88	NS
Autonomic disturbances	12.3	7.1	15.5	8.5	18.5	7.0	6.36	NS
Dizziness	10.5	7.1	10.3	13.6	9.3	3.5	4.05	NS
Cardiovascular symptoms	1.7	0.0	6.9	5.0	9.3	5.3	7.06	NS
Headaches	7.0	3.6	13.8	3.4	9.3	3.5	7.94	NS
Visual symptoms	0.0	1.8	1.7	0.0	3.7	1.7	3.67	NS

pressure, pulse rate, and weight did not exhibit any significant change throughout the study.

Discussion

The results of the present study show significantly better anxiolytic activity for four daily doses of suriclone (0.1, 0.2, 0.3, and 0.4 mg tid) and diazepam as compared to placebo but a lack of significant differences among the four doses of suriclone and diazepam.

The superiority of suriclone over placebo was already demonstrated in two studies (Basset et al. 1983; Vadrot et al. 1986). The first study was a cross-over comparison of suriclone 0.9 mg/day and placebo in two 2-week periods in 140 outpatients suffering from neurotic anxiety; the second study compared three single doses of suriclone (0.15, 0.20, and 0.30 mg), placebo, and clorazepate 5 mg in anxiety associated with dental procedures and found better results with suriclone 0.20 and 0.30 mg and clorazepate than placebo. Two negative trials were, however, recently published. The first one did not find any significant difference between five dosages of suriclone (0.4, 0.8, 1.2, 1.6, and 1.8 mg/day) and placebo (Falk et al. 1987). Due to difficulties with recruitment, the number of subjects included in the four dose groups (respectively 6, 4, 4, and 1) was so small that a lack of statistical power could be expected. The second study was unable over a 4-week period to differentiate suriclone at a daily dose of 1.5–2.25 mg, lorazepam at a daily dose of 5–7.5 mg, and placebo over a 4-week period (De Jonghe et al. 1989). The lack of difference between lorazepam, particularly at this rather high dose, and placebo shows the low discriminative power of this study, probably due, on the one hand, to the small number of patients included and, on the other hand, to a high placebo response.

Our study also demonstrates that the anxiolytic activity of the four doses of suriclone and the reference benzodiazepine do not differ. This confirms previous studies using diazepam (Gerlach et al. 1987), lorazepam (Gotfryd 1984), and clorazepate (Hakim 1984) as reference benzodiazepines. Most previous studies have used suriclone daily doses of 1.2 mg or higher (Gotfryd 1984; Hakim 1984; Gerlach et al. 1987). In a single blind study in nine patients, Lapierre and Oyewiumi (1983) did not find that suriclone (0.6 mg/day) was effective, and suggested that a therapeutic response never occurred with less that 1.2 mg/day. Our study demonstrates that suriclone exhibits significant anxiolytic activity even with a daily dose as low as 0.3 mg/day.

In this study, the mean improvement rate on the Hamilton anxiety scale was 54.9% for all active compounds taken together and 29.6% for placebo. These relatively low figures deserve comments. First, these rates, which represent differences between baseline and final scores, include all patients who left the study before completion, mainly for reasons of inefficacy. The corresponding figures using only the patients who completed the 4-week study period are respectively 61.7% for active drugs and 42.5% for placebo. Second, this study includes only patients seen by psychiatrists, who exhibit more severe and more chronic symptomatology than patients seen by general practitioners and are much less responsive to placebo as well as to active drugs (Ansseau et al. 1985). The mean baseline Hamilton anxiety score in this study was as high as 29.5 despite a 1-week placebo period. In contrast, the placebo effect for an anxiolytic drug in general practice can often be so significant that it makes it practically impossible to differentiate placebo from active compounds (Ansseau and von Frenckell 1991).

The present study also shows fewer adverse events with suriclone than with diazepam, particularly with the lower doses which did not differ at all from placebo. Previous studies have already noted the less sedative properties of suriclone as compared to benzodiazepines (Gotfryd 1984; Gerlach et al. 1987). In the study by Gerlach et al. (1987), suriclone used at much higher doses than in our study induced more dizziness. In the comparison of neurologic effects in normal volunteers, single doses of suriclone 0.2 mg did not differ from placebo while suriclone 0.4 and 0.6 mg were equivalent with diazepam 10 mg. Only suriclone 0.8 mg caused significantly more decrement than diazepam 10 mg (Shaw et al. 1988). Suriclone 0.8 mg caused nausea, clumsiness, and loss of balance more frequently than diazepam 10 mg. Our study does not confirm this profile of adverse events of suriclone with the lower doses used, although the

highest dose of suriclone (1.2 mg/day) was responsible for disturbances in the Romberg test in 7% of patients. These problems never appeared, however, with the three lower doses. Therefore, suriclone should preferentially be used at doses lower than 1.2 mg/day which exhibit the best efficacy/safety ratio.

The difference in the profile of adverse events between diazepam and suriclone lends support to animal data suggesting that suriclone binds to distinct sites within the GABA A/benzodiazepine/chloride ionophore receptor complex or to different allosteric forms of this complex. These biochemical differences could explain why suriclone might involve less risk of misuse and development of tolerance, as suggested by animal data showing that, in contrast to benzodiazepines, chronically administered suriclone does not induce physical dependence in mice (Blanchard et al. 1990). However, an actual comparison of the withdrawal symptomatology following abrupt discontinuation of suriclone and a reference benzodiazepine in anxious subjects is clearly needed in order to confirm this important characteristic.

In conclusion, this study demonstrates that suriclone, in the dose range 0.1–0.4 mg tid, is an effective anxiolytic with fewer sedative effects than diazepam.

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