J Neural Transm (1986) 67: 241–266

Journal of
Neural Transmission

On Central Effects of Serotonin Re-uptake Inhibitors: Quantitative EEG and Psychometric Studies with Sertraline and Zimelidine

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With 10 Figures

Received May 15, 1985; revised March 3, 1986

Summary

In a double-blind placebo-controlled cross-over study the encephalotropic and psychotropic properties of sertraline – a new potent and highly selective inhibitor of synaptosomal serotonin uptake – were studied along with blood levels of the parent drug and main metabolite in ten normal healthy volunteers. They received randomized at weekly intervals oral single doses of placebo, 100, 200 and 400 mg setraline and 100 mg zimelidine as reference drug. Blood sampling, EEG recordings, psychometric tests and evaluation of pulse, blood pressure and side-effects were carried out at the hours 0, 2, 4, 6, and 8. Blood level investigations demonstrated that sertraline is slowly absorbed with dose-dependent blood concentrations peaking in the 4th to 6th hour and remaining high thereafter, while the main metabolite, CP-53261 exhibited an even slower rise in plasma concentration up to the 8th hour. Computer-assisted spectral analysis of the EEG demonstrated slight effects of 100 mg zimelidine and 100 mg sertraline on human brain function, but moderate to marked effects after 200 and 400 mg sertraline as compared with placebo. Changes after 100 mg sertraline and the reference compound resembled the pharmaco-EEG profiles of antidepressants of the desipramine type and were indicative of some vigilance-improving properties while higher doses of sertraline induced alterations reminiscent of those after antidepressants of the imipramine type, thereby reflecting vigilance changes of the dissociative type. This neurophysiological conclusion was supported by the psycho-

metric and psychophysiological data showing partly after 100 mg sertraline and zimelidine an improvement in psychometric performance, while 200 and 400 mg sertraline induced a deterioration of noopsyche and thymopsyche of the normal volunteers. Psychophysiological variables exhibited a dose-dependent change in CNS activation and a widening of the pupillary size. Time-efficacy calculations based on pharmacodynamic changes demonstrated maximal encephalotropic effects after 100 mg zimelidine in the 2nd to 4th hour, and after setraline in the 4th to the 6th hour, which is in agreement with the blood level data. Pulse, systolic and diastolic blood pressure showed no clinically relevant findings. Side-effects were non-existent to minimal after 100 mg zimelidine and sertraline, but marked after 200 and 400 mg sertraline characterized by nausea, vomiting, diarrhea, giddiness, restlessness, tremor and trismus.

Key words: Antidepressants, serotonin re-uptake blocker, sertraline, zimelidine, pharmacodynamics, pharmaco-EEG, psychometry, encephalotropic effects, psychotropic effects, classification, human pharmacology.

Introduction

It has been suggested that there is at least a subgroup of depressed patients whose disorder is mainly seen in the serotonin system. Evidence supporting such a view stem from postmortem studies showing a decrease in 5-hydroxyindoleacetic acid (5-HIAA) in the brain of suicide victims (Bourne *et al.*, 1968) and from cerebral spinal fluid (CSF) data of patients with affective disorders (Ashcroft *et al.*, 1966; Dencker *et al.*, 1966; Shaw *et al.*, 1969; Coppen *et al.*, 1972). Asberg (1976) suggested that low 5-HIAA in CSF may be related to suicidal behaviour in depressives. Lloyd *et al.* (1974) described lower serotonin levels in the dorsal and inferior central raphe nuclei of the brain stem in suicide victims as compared with neurological controls, but levels of 5-HIAA were increased more rostrally, especially in the mamillary bodies. Birkmayer and Riederer (1975) observed a global decrease of serotonin in all brain areas of depressed patients, further a decrease of striatal dopamine levels and lower noradrenaline in the red nucleus. Oreland *et al.* (1981) described a bimodal distribution of CSF 5-HIAA in depressed patients, with the ones having lower values also showing greater suicidal behaviour. Banki *et al.* (1981) found an inverse correlation of CSF 5-HIAA with depressive symptoms, such as suicide, insomnia, anxiety and anorexia. They also showed a bimodal distribution of CSF 5-HIAA. A decrease in the serotonin-precursor L-tryptophan in the serum of depressed patients is further evidence of serotonin involvement in the pathogenesis of depression but the findings are not very consistent (Coppen *et al.*, 1972; Riley

and Shaw, 1976; Schmid-Burk *et al.*, 1981). The latter authors found free tryptophan reduced in neurotic-depressed as well as endogenous-depressed patients. If low baseline 5-HIAA values reflect reduced central nervous system (CNS) serotonin turnover, then administration of L-tryptophan or tricyclic antidepressants blocking serotonin re-uptake may be of therapeutic value in such selected patients. Indeed, some improvement in depression was seen with L-tryptophan as described by Dencker *et al.* (1966), Murphy *et al.* (1974), Farkas *et al.* (1976), Coppen and Wood (1978) and Shaw (1977). Positive therapeutic results have bee reported, moreover, after administration of selective serotonin re-uptake inhibitors such as zimelidine (Coppen *et al.*, 1979; Montgomery *et al.*, 1982; Claghorn *et al.*, 1983), fluvoxamine (Saletu *et al.*, 1977; Feldmann and Denber, 1982; Doogan, 1980) and fluoxetine (Lemberger, 1976; Feighner, 1983). However, zimelidine was withdrawn because of serious neurological side-effects.

The aim of the present double-blind placebo-controlled study was to investigate the encephalotropic and psychotropic effects of sertraline utilizing quantitative pharmaco-EEG and psychometric methods (Saletu, 1976, 1982 a; Grünberger and Saletu, 1980).

Sertraline* (CP-51,974) (15,4S-N-methyl-4-(3.4.dichlorophenyl)-1,2,3,4,-tetrahydro-1-naphthylamine) is a product of Pfizer Central Research. It has a novel chemical structure and is a potential antidepressant agent as it is potent inhibitor of serotonin uptake *in vivo* and *in vitro*. It does not alter the uptake processes of noradrenaline (NA) or dopamine (DA). It potentiates serotonin effects of 5-hydroxytryptophan (5-HTP). It is devoid of monamine oxidase inhibiting (MAOI), anticholinergic and amphetamine-like effects. There were no deleterious effects on the electrocardiogram. In the behavioural despair model sertraline showed similar effects to other known antidepressants (Koe *et al.*, 1984).

Animal toxicology studies showed no significant abnormal effects at the doses projected for human use.

Human volunteer studies have shown the compound to be slowly absorbed with peak plasma levels of sertraline being reached about 6 hours post dosing. The compound is extensively metabolised, and the main metabolite (CP-53,216) is formed by demethylation. The plasma half-life of sertraline is around 24 hours and around 80 hours for the metabolite which has similar but less potent effects on brain amine uptake.

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* Sertraline was kindly supplied by Pfizer-Munich, F.R.G.

Safety and tolerance studies in healthy volunteers given doses up to 400 mg sertraline showed typical side effects of gastrointestinal upset, tremor, headache and insomnia; but which did not in general prevent subjects continuing with dosing.

Methods

Ten normal healthy volunteers (5 males and 5 females) in the age between 19 and 31 years (mean 26 years) weighing from 50—80 kg (mean 62 kg) and ranging in height from 160—186 cm (mean 173 cm) were included in the double-blind, placebo-controlled crossover study. They were not allowed to take any psychoactive drugs 3 weeks before and/or during the period of the study. In random order (latin square design) they received in weekly intervals single oral doses of placebo, 100 mg, 200 mg and 400 mg sertraline as well as 100 mg zimelidine as reference drug. 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 and Washington. An informed written consent was obtained.

Blood sampling, EEG recordings, psychometric and psychophysiological testing and evaluation of blood pressure, pulse rate and side effects were carried out before as well as 2, 4, 6 and 8 hours after oral administration (9 a.m.).

For *plasma level* determination an indwelling catheter was placed in an antecubital vein and kept patent by a "saline-heparin lock". At the hours described above, 10 ml venous blood samples were collected in heparinized plastic tubes and immediately centrifuged. Thereafter, plasma was frozen and kept at −20 °C until analysis by a gaschromatograph fitted with 15 mci 63 Ni electron capture detector and fused silica column.

Quantitative EEG investigations included a 3 minutes vigilance-controlled EEG (V-EEG) and a 4 minutes resting EEG (R-EEG) by means of an 8-channel Beckman R-611 polygraph (high frequency response: 100 Hz; time constant: 0.3 sec; frequency range: 0.5—100 Hz) with the subjects lying relaxed with eyes closed in an electrically-shielded room. Electrodes were attached according to the international 10/20 system to the scalp. During the V-EEG recordings the technician tried to keep the subjects alert; as soon as drowsiness patterns appeared in the EEG, the subjects were aroused by the technician. 4 leads (02-Cz, 01-Cz, P 4-Cz, P 3-Cz) were recorded on a Hewlett-Packard 3968 tape recorder (cut-off frequency: 212 Hz; tape speed $1^7/_8$ in/sec). Analogously filtered signals (Kemo-Filter VBF/3: DC-40 Hz; 24 dB/oct.) were digitized off-line (sampling rate: 200 Hz) by an Intertechnique Plurimat S computer system utilizing Fast-Fourier-Transformation to calculate power spectral density smoothed by Hanning window. The latter permit analysis in 38 measurements: total power (T); the absolute and relative power in 13 different frequency bands; the dominant frequency (in

Hz), the relative (REL) and absolute (ABS) power of the dominant frequency; further, the center-of-gravity frequencies (centroids) (C) and their deviations (D) or the combined delta and theta (DT), alpha (A) and beta (B) bands as well as of the total activity (T). Each 20 sec epoch with muscle movements or eye artifacts was excluded from the analyses.

Psychometric and psychophysiological tests included the alphabetical cross-out test as paper/pencil version (AD-test = Alphabetischer Durchstreich-test) of Grünberger (1977) and the microprocessor-assisted alphabetical reaction test (Grünberger *et al.*, 1984) for the evaluation of the quantitative aspects (total score), qualitative aspects (errors in per cent of the total score or correct reactions) of attention and the attention variability (difference between extreme scores) as well as of the complex interaction of attention, motricity, reaction and mnestic function; numerical memory (short-term memory) (Grünberger, 1977); the Pauli test (correct calculations; errors %); the psychomotor activity (Feinmotoriktest) of Grünberger (1977); the reaction time (in msec) as determined on the Viennese reaction-apparatus and the errors occurring in the test; complex reaction as assessed on the Wiener Determinationsgerät of Schufried; the von Zerssen scale (von Zerssen *et al.*, 1970) for subjectively experienced well-being; a semantic differential polarity profile for changes in affectivity including the dimensions wakefulness, concentration, mood and extraversion (Osgood *et al.*, 1975); critical flicker frequency (CFF, descending threshold); the after-effect (Archimedean spiral); and microprocessor-assisted measurements of the pupillary diameter and skin conductance level (SCL, in μmhos) (Grünberger *et al.*, 1984).

Pulse, blood pressure and spontaneously reported complaints and *side-effects* were recorded at the hours 0, 2, 4, 6 and 8.

Exploratory statistical analyses included discriminant analysis, MANOVA, ANOVA, the Newman-Keuls test, Duncan test, the *t*-test, the Friedman and multiple Wilcoxon test. Confidence limits were set at $p < 0.05$; however, as the analyses have exploratory character, $p < 0.01$ limits are shown as well.

Results

I. Plasma Levels

Plasma concentrations demonstrated that sertraline was slowly absorbed, as peak concentrations were seen in the 4th hour after 100 mg sertraline and in the 6th hour after 200 and 400 mg sertraline. The respective mean peak concentrations and standard deviations were 54.50 (16.05), 105.40 (44.66) and 253.20 (112.29) ng/ml (Fig. 1). Plasma levels below 5 ng/ml were not detected.

Analysis of the main metabolite of sertraline (desmethylsertraline) demonstrated a continuous rise throughout 8 hours, with the most increase up to the 4th hour (Fig. 2).

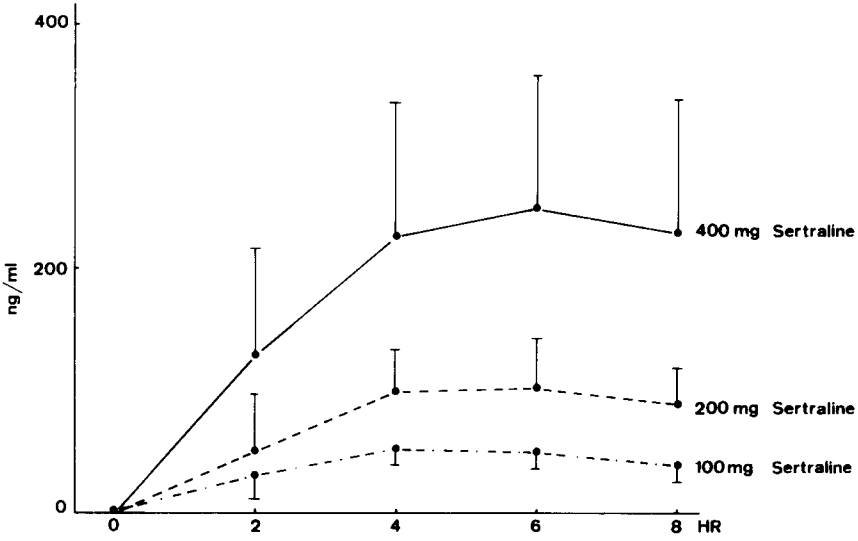

Fig. 1. Means and standard deviations of plasma concentrations of sertraline (CP-51974) (n: 10)

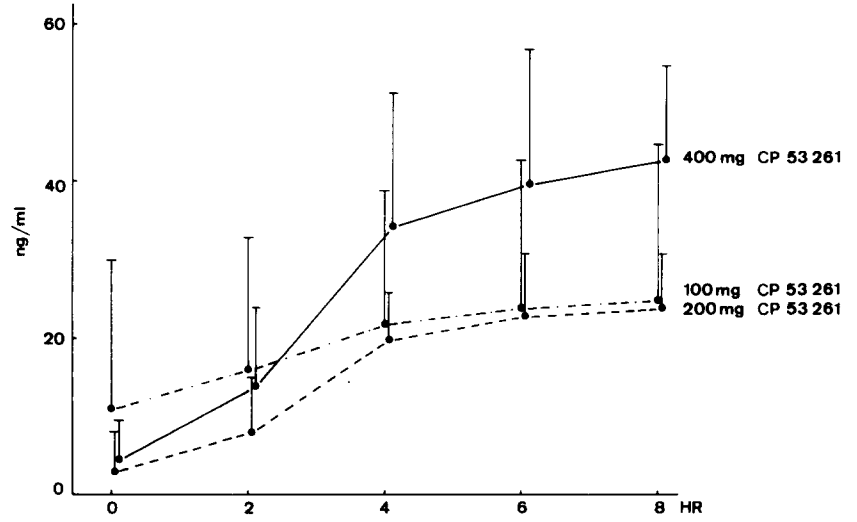

Fig. 2. Changes in plasma concentrations (means and standard deviations) of the main sertraline-metabolite, CP-53261 (n: 10)

II. Quantitative EEG Findings

Considering all 30 V- and R-EEG variables by means of a Friedman's test and multiple Wilcoxon test, it was found that sertraline could by significantly differentiated from placebo in doses of 200 and 400 mg ($p < 0.01$). Moreover, these two higher doses were also significantly different from the 100 mg dosage as well as 100 mg zimelidine ($p < 0.01$). The encephalotropic effect was clearly dose-related as the respective sums for placebo, 100 mg zimelidine, 100, 200 and 400 mg sertraline were 626, 626, 635.5, 806.5 and 906, respectively ($x_r^2 = 111.5$, $p < 0.01$). As can be seen in Table 1, 400 mg sertraline was significantly different from placebo at all times while 200 mg, was on the overall only in the second hour significantly different.

Table 1. *Dose/treatment efficacy relations after sertraline and zimelidine based on sign-free changes in all V+R-EEG variables*

Time	A sertraline 100 mg	B sertraline 200 mg	C sertraline 400 mg	D zimelidine 100 mg	E placebo	x_r^2	multiple Wilcoxon
							A:B,C**,B:D,E**
2 hrs	153	231	209,5	153	153,5	37,54	C:D**,C:E*
4 hrs	169,5	193	226,5	159	152	24,44	A,D,E:C**
							A,D:C**
6 hrs	159	195,5	227	145	173,5	27,72	B:D*,C:E*
8 hrs	154	187	243	169	147	39,36	A,D,E:C**,B:C*
							A:B,C**,B:C*
Total	635,5	806,5	906	626	626	111,48**	B:D,E**,C:D,E**

* $p < 0.05$
** $p < 0.01$

Time-efficacy calculations by means of sign-free, placebo-corrected changes in all 30 V- and R-EEG variables demonstrated the peak effect of sertraline in the 4th to the 6th hour as the rank sums for the combined three doses of sertraline were 431.5, 478.5, 500.5 and 389.5 for the 2nd, 4th, 6th and 8th hour, respectively ($x_r^2 = 24.55$, $p < 0.01$). The 8th hour was significantly different from the 4th and 6th hour based on the multiple Wilcoxon test ($p < 0.01$) but also the 2nd hour was different from the 6th hour ($p < 0.05$). However, one could not differentiate the 4th and the 6th hour. 100 mg zimelidine was most effective in the 4th hour. Detailed time-efficacy data after each compound can be seen in Table 2.

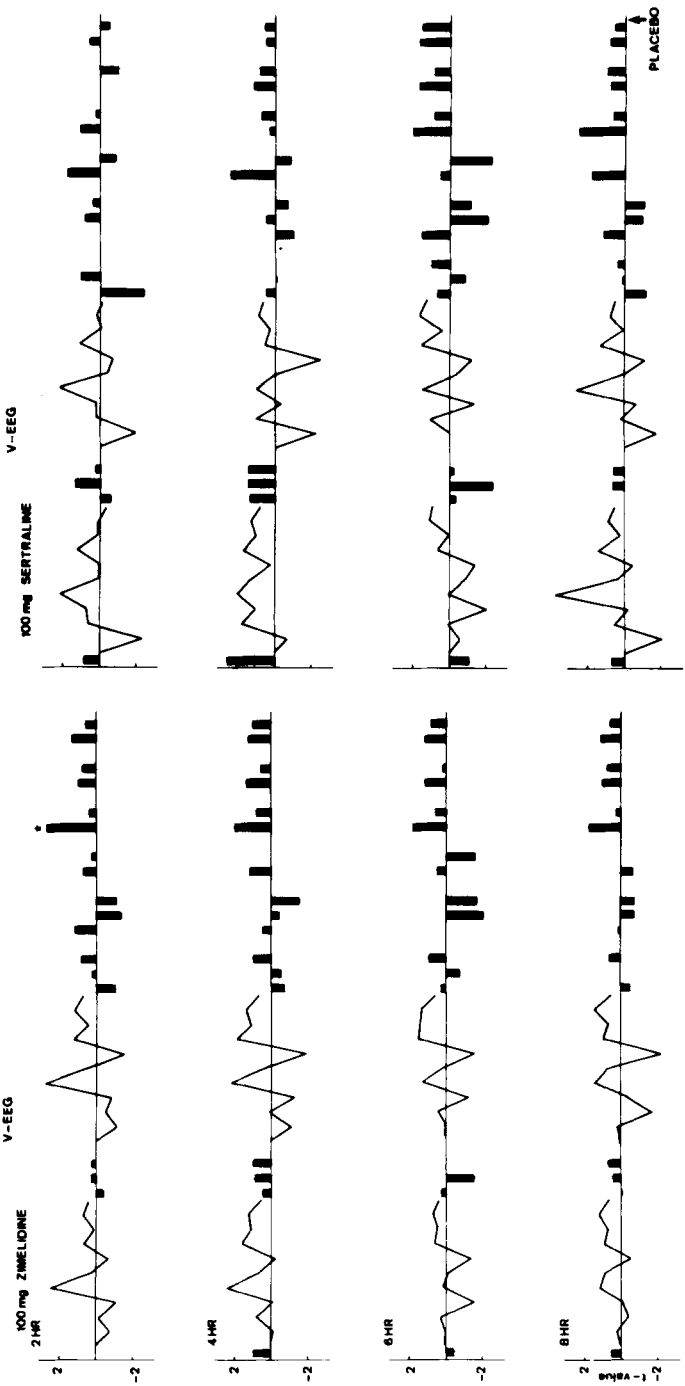

Fig. 3. Pharmaco-EEG profiles (V-EEG) of 100 mg sertraline and 100 mg zimelidine as compared with placebo (n: 10). 38 computer-assisted spectral-analyzed EEG variables are shown in the abscissas, differences between drug-induced and placebo-induced changes are indicated in the ordinates and expressed in terms of *t*-values. The 0 line represents changes after placebo. 100 mg sertraline and zimelidine increase alpha activity, accelerate the centroid of the alpha activity, attenuate delta activity and increase also the centroid of the combined delta and theta activity as compared with placebo

Table 2. *Time efficacy relations after sertraline and zimelidine based on placebo-corrected sign-free changes in all V+R-EEG variables*

Treatment	2 hrs	4 hrs	6 hrs	8 hrs	x_r^2	multiple Wilcoxon
A sertraline 100 mg	134	170	170	126	16,32**	4,6:8*
B sertraline 200 mg	171,5	144	161	123,5	13,21**	2:8**,6:8*
C sertraline 400 mg	126	164,5	169,5	140	12,66**	2:4,6*
D zimelidine 100 mg	162,5	167,5	143	127	10,40*	4:8*
A+B+C sertraline total	431,5	478,5	500,5	389,5	24,55**	2:6*,4:8**,6:8**

* $p < 0.05$
** $p < 0.01$

In detail we observed after *100 mg sertraline* as compared with placebo in the V-EEG an increase of total power, augmentation of alpha acitivity, acceleration of the centroid of the combined delta and theta activity in the 4th hour and of the centroid of alpha activity in the 8th hour ($p < 0.05$—0.01, *t*-test) (Fig. 3). Moreover there was a trend towards an attenuation of delta activity. In the resting recording the differences between 100 mg sertraline and placebo were less pronounced but reached the level of statistical significance in the 4th hour regarding the acceleration of the centroid of the total beta activity ($p < 0.05$), Newman-Keuls test).

200 mg sertraline induced in the V-EEG as compared with placebo a significant ($p < 0.05$, Newman-Keuls) acceleration of the centroid of the total beta activity (2nd hour) as well a decrease of relative power of the dominant frequency in the 6th hour (Fig. 4). There was a trend towards attenuation of the relative power of the combined delta and theta activity in the 2nd hour post drug, furthermore an augmentation of fast beta activity as well as acceleration of the total beta activity in the 6th hour ($p < 0.05$—0.01, *t*-test). In the resting condition the acceleration of the total beta activity reached the level of statistical significance ($p < 0.05$, Newman-Keuls test) in the 4th hour, while relative power of the 16—20 Hz beta activity was significantly attenuated in the 4th and 8th hour post drug. The centroid of the total beta activity was also increased in the 6th and 8th hour ($p < 0.05$, *t*-test) as was the relative power of the fast beta activity in the 4th and 6th hour. In the 8th hour there was an additional augmentation of theta activity ($p < 0.05$, *t*-test).

400 mg sertraline induced in the V-EEG as compared with placebo a significant increase in the centroid and its deviation of the beta activity specifically in the 2nd and 6th hour ($p < 0.05$, 0.01, Newman-Keuls test) (Fig. 4). Moreover, in the 6th hour there was also an

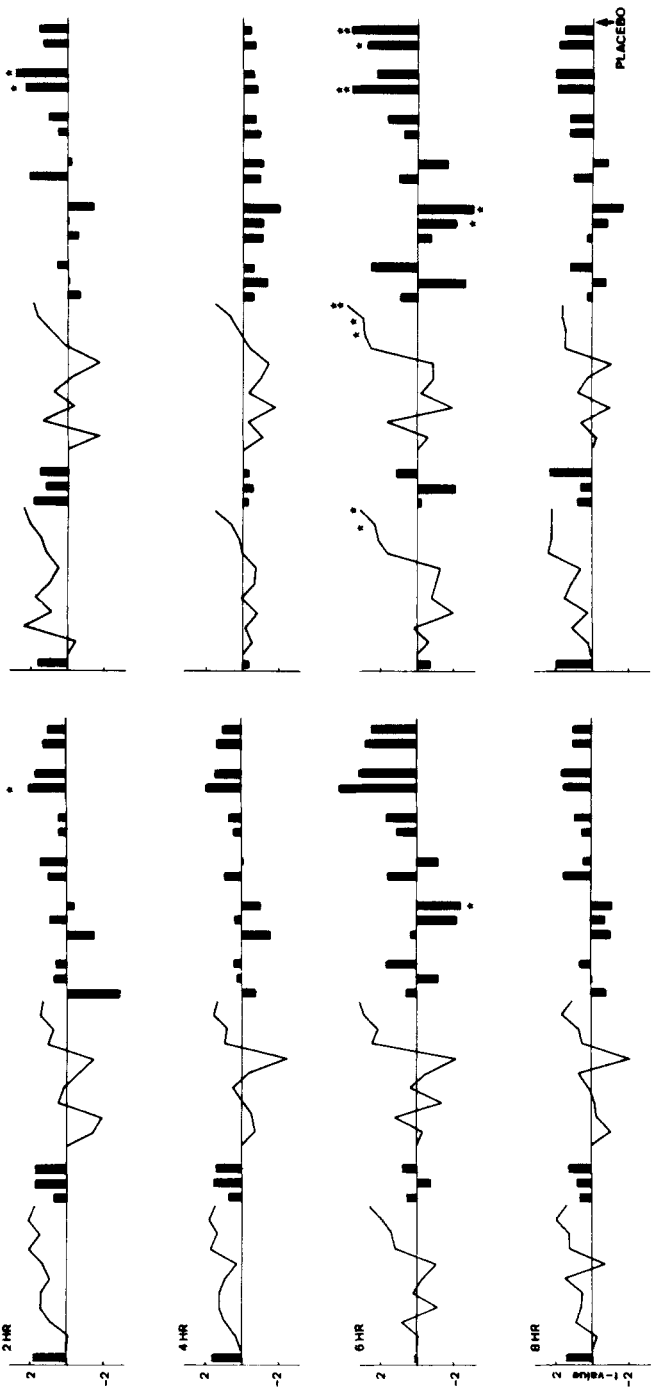

Fig. 4. Pharmaco-EEG profiles of 200 and 400 mg sertraline as compared with placebo (n: 10). For a description of the axes see Fig. 3. 200 and 400 mg sertraline produced especially in the 6th hour a decrease of alpha activity, an increase of fast beta activity, acceleration of the centroid of the beta and total activity as compared with placebo

increase of the absolute and relative power of the fast beta activity ($p < 0.05$–0.01, Newman-Keuls test) while the relative and absolute power of the dominant frequency declined significantly ($p < 0.05$, Newman-Keuls test). In the resting recording findings were similar. Again fast beta activity was increased in the 2nd, 4th and 8th hour at a level of statistical significance ($p < 0.05$–0.01, Newman-Keuls test) as was the increase in the centroid and its deviation in the 4th and 8th hour ($p < 0.05$, Newman-Keuls test).

100 mg zimelidine induced a significant acceleration of the centroid of the total alpha activity in the 2nd hour ($p < 0.05$, Newman-Keuls test) as well as an increase in absolute and total power of the alpha activity ($p < 0.05$, *t*-test) (Fig. 3). Similar findings were observed also in the resting condition with the attentuation of the delta and theta activity slightly more pronounced than in the V-EEG.

III. Psychometric and Psychophysiological Findings

Considering all 20 psychometric and physiological variables (described thereafter) by means of a Friedman's test and multiple Wilcoxon test, it was found that by means of the changes at all times 400 mg sertraline could be significantly differentiated from placebo ($p < 0.01$) as was the case for 100 mg zimelidine ($p < 0.05$). The respective rank sums for placebo, 100 mg zimelidine, 100 mg, 200 mg and 400 mg sertraline were 240, 191, 202, 269 and 298, respectively ($x_r^2 = 40.25$, $p < 0.01$). Both 100 mg zimelidine and 100 mg sertraline could be significantly differentiated from 200 and 400 mg sertraline ($p < 0.01$, multiple Wilcoxon). 400 mg sertraline was the most psychoactive drug at all times, 100 mg sertraline and 100 mg zimelidine induced the least changes. In the 4th and 6th the x_r^2 values were 12.4 and 14.7 ($p < 0.05$ and 0.01, respectively), with the difference between 400 mg sertraline and 100 mg zimelidine reaching the level of statistical significance in the multiple Wilcoxon test ($p < 0.05$). In the 8th hour the x_r^2 value was 13.16 ($p < 0.05$), with 400 mg being significantly different from 100 mg sertraline in the multiple Wilcoxon test ($p < 0.01$).

A multivariate statistical analysis by means of MANOVA and discriminant analysis considering changes in all 20 psychometric and psychophysiological variables at all times (2, 4, 6 and 8 hours) and after all drugs (placebo, 3 doses of sertraline and 100 mg zimelidine) demonstrated that 100 mg sertraline and 100 mg zimelidine produced a trend towards improvement of the psychometric variables, while 200 and 400 mg sertraline showed just the opposite (Fig. 5). Sub-

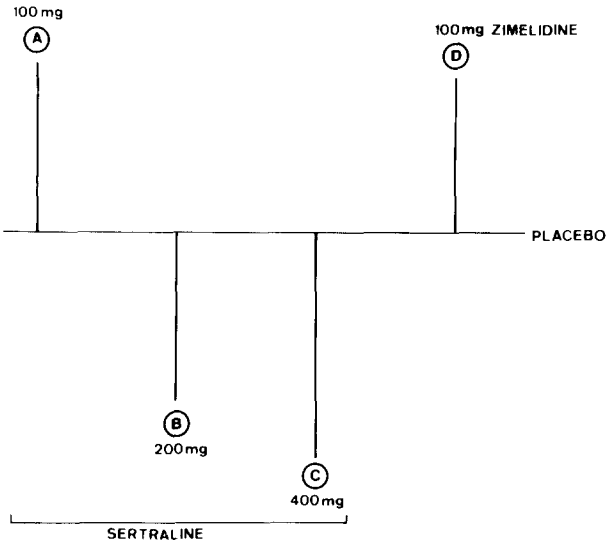

Fig. 5. Dose-treatment efficacy relationship based on discriminant function analysis of changes in all 20 psychometric and psychophysiological variables. While a trend towards an improvement may be seen after 100 mg sertraline and zimelidine as compared with placebo, a deterioration may be observed dose-dependently after the higher doses of sertraline in normals

dividing these variables into 13 noopsychic, 2 thymopsychic and 5 psychophysiological variables, no significant interdrug differences could be detected based on the noopsychic and psychophysiological variables, while highly significant differences were observed in the thymopsyche between all three doses of sertraline and placebo ($p < 0.05$–0.01) as well as between all three doses of sertraline and 100 mg zimelidine.

Time-efficacy calculations based on the Friedman's and multiple Wilcoxon tests of sign-free placebo-corrected changes in all psychometric and psychophysiological variables demonstrated the peak effect of sertraline in the 4th to 6th hour, as the rank sums for the 2nd, 4th, 6th and 8th hour were 129.5, 172.5, 156.5 and 141.5, respectively (x_r^2 is 10.41, $p < 0.05$). Based on the multiple Wilcoxon test the 4th hour was significantly different from the 2nd hour ($p < 0.01$). The respective rank sums for 100 mg zimelidine were 41.5, 48.5, 56 and 54 ($x_r^2 = 3.8$, n.s.).

A. Noopsychic Changes

1. *Attention* as evaluated by means of the total score in the AD-test demonstrated in the 3-way ANOVA significant changes over

time ($Fb = 3.75$, $p < 0.05$) as well as significant interdrug differences ($Fc = 21.41$, $p < 0.01$). Analysis of each drug separately showed significant deterioration of attention in the 4th to the 8th hour after 400 mg sertraline ($p < 0.05$, 0.01, Newman-Keuls test) (Fig. 6). 200 mg sertraline produced a trend towards a deterioration, 100 mg sertraline and placebo showed inconsistent changes while after 100 mg zimelidine a trend towards improvement was observed. Interdrug comparisons by means of the Newman-Keuls test demonstrated significant differences between the 5 substances at each time point, which may be seen in Fig. 6.

2. *Concentration* as evaluated by means of errors in % of the total score in the AD-test demonstrated significant interdrug differences ($Fc = 18.44$, $p < 0.01$) in the 3-way ANOVA (Table 3). This was due to the fact that after 200 mg sertraline and 100 mg zimelidine a decrease of errors occurred while the other active substances induced oppositional changes. 100 mg and 400 mg sertraline differed thus between the 6th and 8th hour from placebo, as did zimelidine in the 2nd hour. The latter drug was significantly superior to both 100 and 400 mg sertraline.

3. *Attention variability* also showed significant interdrug differences in the 3-way ANOVA ($Fc = 5.97$, $p < 0.01$) (Table 3). While 200

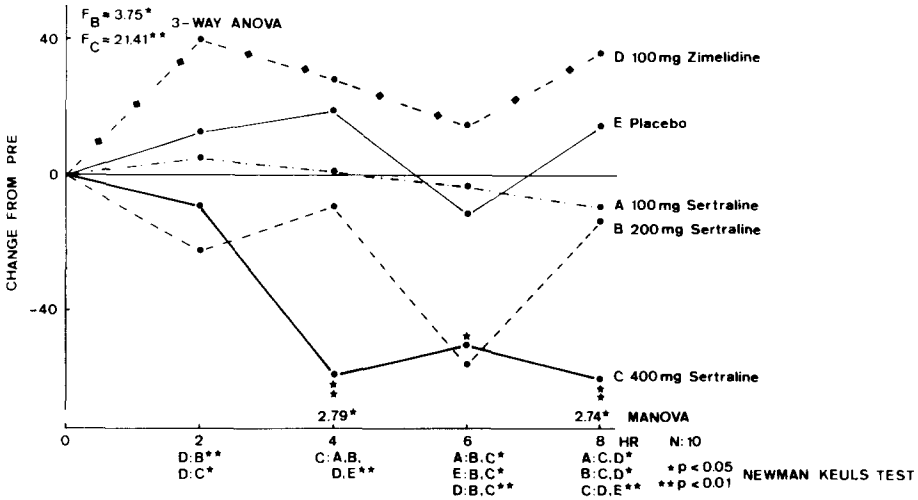

Fig. 6. Changes in attention as evaluated by means of the total score in the AD-test after sertraline, zimelidine and placebo (n: 10). Time is shown in the abscissa, changes from pretreatment are indicated in the ordinate. While after 200 and 400 mg sertraline attention deteriorates, only minimal alterations are observed after 100 mg sertraline and placebo. 100 mg zimelidine tends to improve attention

Table 3. *Changes in psychometric and psychophysiological variables after single doses of sertraline and zimelidine as compared with placebo (N:10)*

Variable	3-way ANOVA F-time	3-way ANOVA F-drugs	Sertraline 100 mg	Sertraline 200 mg	Sertraline 400 mg	Zimelidine 100 mg	Newman Keuls-test S 100 versus placebo	Newman Keuls-test S 200 versus placebo	Newman Keuls-test S 400 versus placebo
			as compared with placebo						
Attention (total score)	3,7*	21,4**			=4–8 hrs		–	=	=
Concentration (errors %)		16,4**	++8 hrs		++6–8 hrs	–2 hrs	++		++
Attention variability		6,0**		+2–4 hrs	+4 hrs			++	
Alphabetical reaction test (total score)		7,3**	+4 hrs	+4 hrs		++2–4 hrs	=	–	=
Alphabetical reaction test (errors %)									
Alphabetical reaction test (range)	2,7*	6,6**	=2–4 hrs	–4 hrs		=2–4 hrs			+
Pauli-test (total score)	2,8*	15,2**	=2–4 hrs	=8 hrs	=4–8 hrs	=4 hrs	=		–
Pauli-test (errors %)		3,8**	+4 hrs	+4 hrs	+4 hrs	+2–4 hrs			
Numerical memory		6,7**				+4 hrs			
Psychomotor activity	3,7*	18,7*			=2–8 hrs	=2 hrs	++	+	–
Reaction time (msec)		2,5*							
Reaction time task (errors)		7,7**	–2–8 hrs	=2 hrs	–2 hrs				
Complex reaction		8,2**		–4 hrs	–4–6 hrs			–	–
After effect		26,6**		=4–8 hrs	=4–8 hrs			–	–
Well-being (BF-S)	5,8**	31,7**	++4–6 hrs	++4–8 hrs	++4–8 hrs			++	++
CFF		14,4*	+		++2–		–	–	–
Semantic differential polarity profile	5,4**	18,4**		++4–8 hrs	++4–6 hrs			++	++
Pupillary diameter pre-stimulus	10,9**	49,0**	++4–8 hrs	++4–8 hrs	++4–8 hrs	+6 hrs	++	++	++
Pupillary diameter post-stimulus	5,6**	31,3**	++4,8 hrs	++4–8 hrs	++4–8 hrs	+6 hrs		++	++
SCL	5,5**	2,9*					+	+	+

* $p < 0,05$.
** $p < 0,01$.

\+ increase or – decrease at $p < 0,05$.
++ increase or = decrease at $p < 0,01$. Newman Keuls-test.

and 400 mg sertraline tended to increase attention variability, a decrease occurred in the initial hours after 100 mg zimelidine and placebo. Thus, 200 and 400 mg differed from placebo in the 2nd to the 4th hour; moreover, 200 mg sertraline was different from the reference compound as well.

4. In the microprocessor-assisted *alphabetical reaction test* we observed in the 3-way ANOVA also significant interdrug differences regarding the total score ($Fc = 7.34$, $p < 0.01$) (Table 3). Analysis of each drug separately revealed a significant deterioration of performance in the 4th hour after placebo while, contrarily, significant improvements occurred in the 2nd and 4th hour after 100 mg zimelidine ($p < 0.05$, 0.01, Newman-Keuls test); sertraline was inbetween. Interdrug comparison demonstrated a significant superiority of 100 and 200 mg sertraline over placebo in the 4th hour as well as of 100 mg zimelidine in the 2nd and 4th hour. The reference compound differed also significantly from sertraline. There were no significant findings concerning the errors in per cent of the total score in this test.

However, the *range between extreme scores* changed significantly over time ($Fb = 2.7$, $p < 0.05$) and demonstrated significant interdrug differences ($Fc = 6.62$, $p < 0.01$) in the 3-way ANOVA (Table 3). Specifically there was a significant improvement in the 2nd hour after 100 mg zimelidine which was also superior to placebo ($p < 0.01$, Newman-Keuls test). However, 100 mg sertraline were significantly superior to placebo too in the 2nd and 4th hour ($p < 0.05$, 0.01). Also 200 mg sertraline differed significantly from placebo in the 4th hour (inducing an improvement). On the other hand, 400 mg sertraline were inferior to 100 mg in the 8th hour.

5. *Cognitive functions* evaluated by means of *correct calculations* in the Pauli test demonstrated in the 3-way ANOVA significant changes over time ($Fb = 2.79$, $p < 0.05$) as well as significant interdrug differences ($Fc = 15.17$, $p < 0.01$) (Table 3). This was largely due to the fact that an improvement occurred after placebo which was attenuated by the active compound. Evaluations of *errors* (in per cent of the total score) in the Pauli test showed significant interdrug differences ($Fc = 3.81$, $p < 0.01$) (Table 3). While errors tended to decrease after placebo, they increased after 100 mg zimelidine and slightly less after sertraline, with the differences reaching of statistical significance in the 4th hour.

6. *Numerical memory* showed in the 3-way ANOVA interdrug differences at the level of statistical significance ($Fc = 6.71$, $p < 0.01$) (Fig. 7). While numerical memory declined during the placebo day and significantly so in the 4th hour, this was attenuated by the active

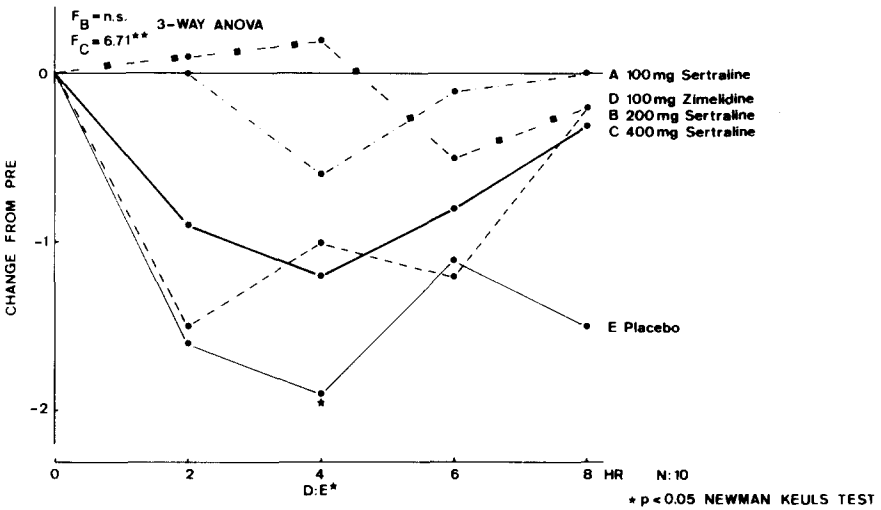

Fig. 7. Changes in numerical memory after sertraline, zimelidine and placebo (n: 10). A deterioration of numerical memory occurs during the recording day after placebo administration which is dose-dependently attenuated by sertraline but also by 100 mg zimelidine

compounds and mostly so with 100 mg sertraline and zimelidine. Based on the Newman-Keuls test, 100 mg zimelidine was significantly superior to placebo in the 4th hour.

7. *Psychomotor activity* showed in the 3-way ANOVA significant changes over time ($Fb = 3.67$, $p < 0.05$) and significant interdrug differences ($Fc = 18.91$, $p < 0.01$) (Table 3). While there was a slight trend toward improvement after placebo and 2 hours after 100 mg and 200 mg sertraline, a trend towards a deterioration occurred after 100 mg zimelidine and significantly so in the 4th to the 8th hour post drug ($p < 0.05$, 0.01, Newman-Keuls test). Interdrug comparison by means of the Newman-Keuls test showed that 400 mg sertraline and 100 mg zimelidine differed significantly from placebo while on the other hand 100 and 200 mg sertraline were significantly superior to the reference compound.

8. *Reaction time (in msec)* revealed in the 3-way ANOVA only a barely significant F value concerning interdrug differences ($Fc = 2.53$, $p < 0.05$) (Table 3). However, based on the Newman-Keuls test at each single time period, no significant differences emerged. This was the case, though, with *errors* in the reaction time task (Table 3). In the 3-way ANOVA the Fc value was 7.66 ($p < 0.01$). While errors increased under placebo, a decrease occurred with all active substances in the 2nd hour post drug, so that they all differed from pla-

cebo at that time. In the 4th hour 200 mg sertraline were significantly superior to 400 mg, while in the 6th and 8th hour 100 mg sertraline were superior to placebo.

9. *Complex reaction* as determined by means of the Viennese Determinationsapparatus showed significant interdrug differences in the 3-way ANOVA ($Fc = 8.17$, $p < 0.01$) (Table 3). This was largely due to the fact that the slight deterioration after 200 and 400 mg sertraline differed from the improvement after 100 mg sertraline and zimelidine as well as placebo in the 4th hour. In the 6th hour there was still a difference between 400 mg sertraline and placebo.

B. Thymopsychic Changes

1. *Subjectively experienced well-being* evaluated by means of the von Zerssen score demonstrated in the 3-way ANOVA significant changes over time ($Fb = 5.8$, $p < 0.01$) as well as significant interdrug differences ($Fc = 31.7$, $p < 0.01$) (Fig. 8). 100 mg sertraline and zimelidine produced no changes at all. While a trend towards improvement was seen after placebo, a significant deterioration occurred in the 4th to the 8th hour after 200 and 400 mg sertraline ($p < 0.01$, Newman-Keuls test). Thus, interdrug comparison by means of the Newman-Keuls test showed significant interdrug

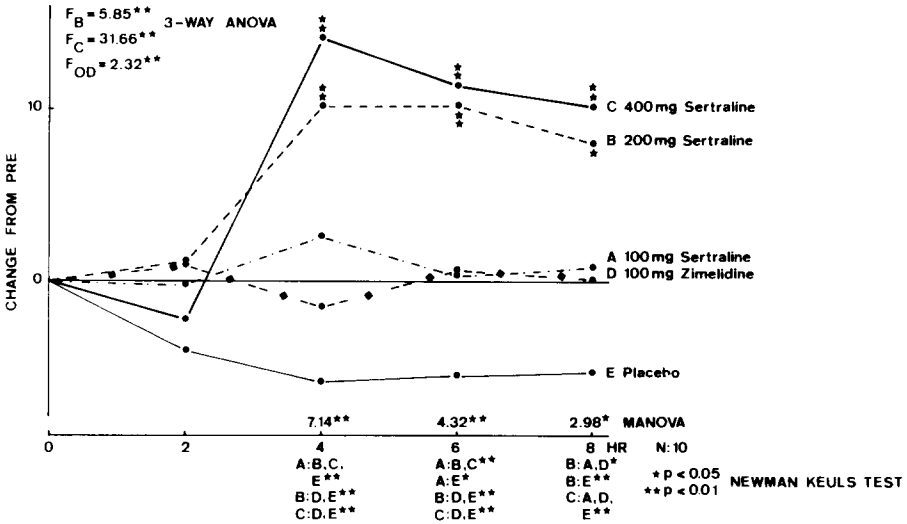

Fig. 8. Changes in subjectivity experienced well-being (von Zerssen score) after sertraline, zimelidine and placebo (n: 10). While high doses of sertraline deteriorate significantly subjectively experienced well-being, no changes occur after 100 mg sertraline and the reference compound

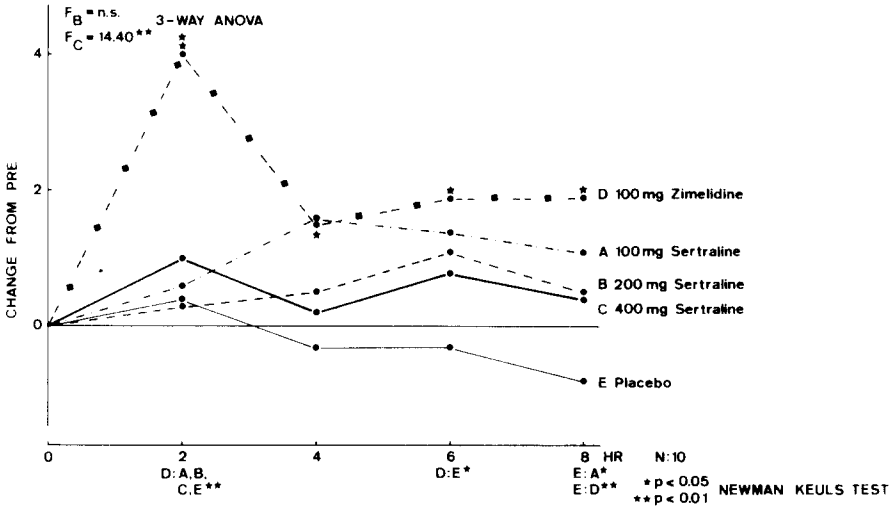

Fig. 9. Changes in critical flicker frequency (CFF) after sertraline, zimelidine and placebo (n:10). An increase of CFF especially after low doses of sertraline and zimelidine suggests CNS activation as compared with placebo

differences between the 4th and the 8th hour which may be seen in Fig. 8.

2. *Affectivity* as evaluated by means of the semantic differential polarity profile (including the dimensions wakefulness, mood, extraversion and concentration) demonstrated in the 3-way ANOVA highly significant changes over time ($Fb = 5.36$, $p < 0.01$) and interdrug differences ($Fc = 18.4$, $p < 0.01$) (Table 3). While placebo, 100 mg sertraline and zimelidine produced only minimal changes over time, 200 and 400 mg sertraline induced a deterioration ($p < 0.05$, 0.01, Newman-Keuls test). These two higher doses of sertraline differed also from the other three substances in the 4th through the 8th hour.

C. Psychophysiological Findings

1. *Critical flicker frequency (CFF)* showed in the 3-way ANOVA significant interdrug differences ($Fc = 14.4$, $p < 0.01$) (Fig. 9). This was due to the fact that only a slight trend towards a decrease occurred after placebo while sertraline induced a dosedependent but small increase (the lower the dose the more the increase). The reference compound 100 mg zimelidine, however, induced a marked and significant increase in CFF ($p < 0.05$, 0.01) especially in the 2nd hour post drug administration. At that time the reference compound was also significantly different from all the other substances

($p < 0.01$, Newman-Keuls test). Furthermore, 100 mg zimelidine differed in the 6th and 8th hour from placebo. In the 8th hour also 100 mg sertraline produced an increase in CFF as compared with placebo ($p < 0.05$, Newman-Keuls test).

2. The *after-effect* as evaluated by means of the *Archimedean* spiral showed also highly significant interdrug differences in the 3-way ANOVA ($Fc = 26.61$, $p < 0.01$) (Table 3). While a trend toward a lenghthening of the after-effect (reflecting CNS activation) was observed after 100 mg sertraline, 100 mg zimelidine and placebo, oppositional changes were seen after 200 mg sertraline, while a significant decrease (disactivation) occurred in the 4th and 8th hour after 400 mg sertraline ($p < 0.05$, 0.01, Newman-Keuls test). Interdrug comparison by means of the Newman-Keuls test showed in the second hour 400 mg sertraline to be different from 100 and 200 mg as well as the reference compound. In the 4th hour 200 and 400 mg sertraline were significantly different from placebo as well as 100 mg zimelidine; but also 100 mg sertraline were different from 200 mg. In the 6th hour 200 mg sertraline differed from 100 mg sertraline and zimelidine and placebo, as did 400 mg from placebo and the reference compound. Finally, in the 8th hour the same differences were observed as in the 4th hour.

3. *Pupillary diameter* showed in the 3-way ANOVA significant changes over time ($Fb = 10.87$, $p < 0.01$) as well as highly significant interdrug differences ($Fc = 49.02$, $p < 0.01$) (Fig. 10). Also the overall

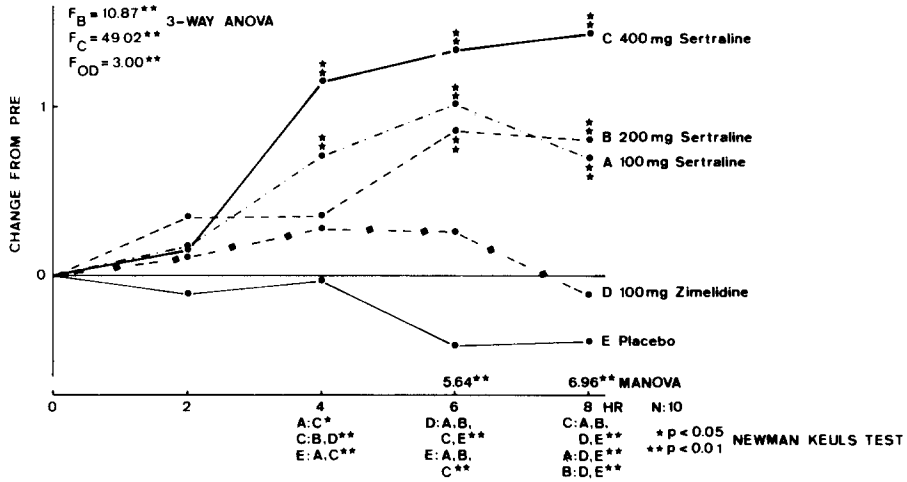

Fig. 10. Changes in pupillary diameter after sertraline, zimelidine and placebo (n: 10). A dose-dependent widening of the pupils can be seen after sertraline

discrimination by means of the discriminant function analysis reached the level of statistical significance (FOD = 3.0, $p < 0.01$). While a slight trend towards a decrease in pupillary diameter was observed after placebo, 100 mg zimelidine produced an oppositional trend. There was a highly statistically significant and marked dose-dependent widening of the pupil after all three doses of sertraline. Interdrug comparison by the Newman-Keuls test demonstrated all three doses of sertraline to be different from placebo as well as from 100 mg zimelidine in the 6th and 8th hour. In the 4th hour, 100 and 400 mg sertraline were different from placebo; but also 400 mg differed from 100 mg as was the case in the 6th and the 8th hour. In the 6th hour also 100 mg zimelidine were different from placebo. After stimulation with a flash, the interdrug differences remained the same (Table 3).

4. *Skin conductance* (SCL, in μmhos) demonstrated in the 3-way ANOVA significant changes over time (Fb = 5.54, $p < 0.01$) as well as significant interdrug differences (Fc = 2.92, $p < 0.05$) (Table 3). While sertraline produced mostly in the 6th hour a trend towards an increase in skin conductance, no changes or even a small decrease

Table 4. *Side effects: No. of subjects reporting*

	Placebo	Zimelidine	Sertraline		
		100 mg	100 mg	200 mg	400 mg
Nausea	–	–	2	5	10
Dizziness	1	–	2	5	4
Restlessness	2	–	–	3	5
Tremor	–	–	1	2	4
Dry mouth	–	–	–	4	2
Yawning	–	–	2	2	3
Vomiting	–	–	–	3	2
Headache	1	–	–	3	1
Trismus	–	–	–	–	3
Masseter cramp/tremor	–	–	–	1	2
Diarrhoea	–	–	–	2	1
Feeling of coldness	1	–	–	1	2
Tiredness	–	–	1	3	3
Loss of appetite	–	–	1	1	–
Mydriasis	–	–	–	1	1
Paraesthesia	–	–	–	2	–
Muscle tension/weakness/twitching	–	–	–	1	2
Sweating	–	–	–	1	–
Euphoria	–	–	–	1	1
Hyperkinesia	–	–	–	–	1
Photophobia	1	–	–	–	1
Pollakiuria	–	–	–	–	1

were seen after placebo as well as 100 mg zimelidine. Thus, the latter reference compound differed from sertraline in the 6th hour at the level of statistical significance and in the 8th hour from 200 mg sertraline.

5. *Pulse, blood pressure* did not show any clinically relevant findings.

6. Sertraline appeared to produce dose related side effects, zimelidine produced no side effects (see Table 4). Notably all ten subjects receiving sertraline 400 mg experienced nausea. The other most frequent side effects encountered were restlessness, dizziness, tremor and dry mouth. Both the 200 and 400 mg dose of sertraline could be considered poorly tolerated in these volunteers.

Discussion

Our blood level investigations demonstrated that sertraline was slowly absorbed as peak plasma concentrations were observed in the 4th to the 6th hour and were clearly dose-dependent. Thereafter plasma levels remained high. As far as the main metabolite CP-53261 is concerned, there was a steady increase over the recording day up to the 8th hour. Later data were not obtained.

Computer-assisted spectral analysis of the EEG demonstrated after 100 mg sertraline and zimelidine slight, after 200 and 400 mg moderate to marked effects on human brain function as compared with placebo. Changes after 100 mg sertraline but also of the reference compound 100 mg zimelidine were characterized by an increase of total power, augmentation and acceleration of alpha activity as well as by an attenuation and acceleration of delta activity. Such changes have been previously observed by us after antidepressants of the desipramine type (Saletu, 1982 a) and are indicative of vigilance-improving properties of such compounds as they are seen also after psychostimulatory and nootropic/antihypoxidotic drugs (Saletu, 1982 b; Herrmann, 1982). In the higher dosage range the type of sertraline-induced changes became different as alpha activity and alpha adjacent beta activity decreased, while fast beta activity and under resting condition also theta activity increased as compared with placebo. Such alterations have been described by us and other investigators after antidepressants of the imipramine type (Fink, 1969; Itil, 1974; Saletu, 1976, 1982; Hermann, 1982) and are indicative of alterations in vigilance of the disassociative type, thereby reflecting also sedative properties. Our present pharmaco-EEG data are in good agreement with our own previous findings concerning quanti-

tative EEG effects of serotonin-reuptake inhibiting antidepressants such as fluvoxamine (Saletu *et al.*, 1980) and fluoxetine (Saletu *et al.*, 1984), as the latter two compounds exhibited pharmaco-EEG profile remniscent of desipramine and imipramine type antidepressants. Measuring vigilance fluctuations based on EEG spetra after administration of different psychotropic agents such as beta blockers, antidepressants and neuroleptics, Matousek *et al.* (1984) described the following values for the mean vigilance level, presented in arbitrary units (where "100" corresponds to full alertness) throughout a 5-minute examination period: zimelidine 96, placebo 93–96, propranolol 90, maprotilin 87, metroprolol 84 and thioridazine 81. Zimelidine thus had a slight excitatory effect compared to placebo. Evaluating the effects of 25–200 mg zimelidine in normal volunteers by digital computer period analysis, Saito *et al.* (1982) concluded that zimelidine had antidepressant properties resembling imipramine rather than amitriptyline (the latter producing more slow activities than the former, as was described by us, Saletu, 1982 a) and that the action lasts a little longer than imipramine but disappears between 6 and 12 hours after single dose administration. This is also in accordance with our present zimelidine data showing a maximal encephalotrophic effect in the 2nd to the 4th hour and thereafter a steep decline. In contrast, after sertraline we observed maximal CNS effects in the 4th to the 6th hour, which is in agreement with the blood level data of the parent drug.

Our psychometric data support the aforementioned interpretation of our neurophysiological data in as much as 100 mg sertraline and 100 mg zimelidine tended to improve the overall psychometric performance, while 200 and 400 mg sertraline dosedependently produced a deterioration. In detail, 100 mg sertraline improved performance in the alphabetical reaction test but also in the reaction time task, decreased attention variability, although errors in the AD and Pauli test increased as well. Concerning the thymopsyche we found a deterioration of subjectively experienced well-being, which was previously described by us as frequent behavioral change after administration of many antidepressants in normals (Grünberger and Saletu, 1980). In psychophysiological variables we noted an increase in CFF and pupillary size reflecting activation in the central and autonomous nervous system. Similarly, 100 mg zimelidine increased the CFF and pupil size; regarding noopsychic variables, we saw an improvement in attention, concentration, attention variability, numerical memory on the one hand, but deterioration in psychomotor activity and in the Pauli test. Thymopsychic variables did not exhibit significant changes as compared with placebo. Higher doses

of sertraline 200 and 400 mg produced in our normal volunteers a deterioration in both noopsychic and thymopsychic variables and demonstrated sedation in the after-effect as measured by means of the Archimedean spiral. Pupil size increased dosedependently. Again this is what we would expect from administration of higher doses of antidepressants in normals (Grünberger and Saletu, 1980; Spiegel and Aebi, 1981).

Our present neurophysiological and behavioural findings with sertraline are of interest in connection with the recently proposed hypothesis of Koe *et al.* (1983) attempting to reconcile the pronounced selectivity of 5-HT uptake blockers like sertraline, with the evidence that implicates both noradrenaline and serotonin in depression as well as the action of existing antidepressant drugs. Serotoninergic neurons in the raphe exerting inhibitory control over noradrenergic neurons of the locus coeruleus (Pujol *et al.*, 1978) are depressed by serotonin uptake blockers, MAO inhibitors and serotonin precursors, such as tryptophan and 5-hydroxytryptophan (Aghajanian and Wang, 1978). Shutdown of firing of these serotoninenergic neurons by 5-HT uptake inhibitors could activate noradrenergic neurons and thereby elicit subsequent desensitization of postsynaptic beta and presynaptic alpha-2-adrenergic receptor systems and, ultimately, an antidepressant response.

Evaluation of pulse, systolic and diastolic blood pressure revealed no clinically relevant changes after sertraline and zimelidine. Side-effects did not exist or were minimal after 100 mg zimelidine and 100 mg sertraline and were characterized only by slight transient nausea, yawning, giddiness and tremor. However, after administration of higher doses of sertraline (200 and 400 mg) all volunteers experienced marked side effects such as nausea, vomiting, diarrhea, giddiness, restlessness, muscle weakness and tremor as well as trismus of the jaw muscles. These somatic complaints and side-effects lasted sometimes up to 48 hours which is in agreement with the long half-life of the biologically active main metabolite.

Acknowledgements

The authors would like to express their thanks to Dr. H. Melzer of Pfizer Clinical Research, Munich for supplying the drugs; to Dipl.-Ing. P. Anderer, biotechnician; Hebe Jeffrey, secretary and to the entire staff of the Section of Pharmocopsychiatry of the Psychiatric University Clinic of Vienna for their valuable assistance in this project.

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