The Efficacy of Cavain in Patients Suffering from Anxiety

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Summary

The therapeutical efficacy of Cavain should be proved in the treatment of patients suffering from abnormal anxiety, psychosomatic complaints and psychoreactive disorder. Thus two randomized groups of patients (26 each) were treated in double-blind technique with either 2 × 200 mg daily Cavain or placebo for a period of 28 days. Prior to the beginning of the investigations and within 14 days intervals the Hamilton Anxiety Scale (HAMA) and the Adjective Check List (Janke and Debus) were applied. The global therapeutical improvement and compatibility were documented after 14 and 28 days. A significant superiority of Cavain in comparison to placebo could be found. Cavain acted anxiolytically and promotive on the subjective vitality-related performance. Therapeutical conclusions are discussed.

Die Wirksamkeit von Cavain bei Angst-Patienten

Es sollte die therapeutische Wirksamkeit von Kavain bei der Behandlung von Patienten, die unter abnormer Angst, psychosomatischen Beschwerden oder erlebnisreaktiven Störungen leiden, geprüft werden. In Doppelblind-Anordnung wurden zwei Zufallsgruppen von Patienten gebildet, die 28 Tage lang entweder mit Kavain (2 × 200 mg/Tag) oder mit Plazebo behandelt wurden. Vor Beginn der Untersuchungen und in 14tägigen Intervallen wurden die Hamilton-Angst-Skala (HAMA) und die Eigenschaftswörterliste (*Janke* und *Debus*) angewandt. Die globale therapeutische Besserung und Verträglichkeit nach 14 und nach 28 Tagen wurden dokumentiert. Es konnte eine deutliche Überlegenheit von Kavain im Vergleich zu Plazebo festgestellt werden. Kavain wirkte angstlösend und verbesserte die subjektiv erlebte leistungsbezogene Aktivität. Therapeutische Schlußfolgerungen werden diskutiert.

Introduction

Patients suffering from abnormal anxiety, psychosomatic complaints or psychoreactive disorders are difficult patients. In general it is believed that a combination of the two main groups of procedures, psychotherapy and psychopharmacological therapy, is necessary for lasting success of treatment.

According to an idealized therapeutic plan the patient's complaints would be relieved by means of anxiolytics and improved continuously under psychotherapy.

In practice, patients with psychoneurotic disturbances primarily consult the family physician (*Laux*, 1981) and are mainly, often for many years, treated with psychopharmacological medication, as by reported in *Nervenarztpraxis* (*Heinrich* and *Lehmann*, 1988).

Catamnestic studies, which demonstrate the success or rather failure of psychotherapy in this respect over the years (*von Zerssen* et al., 1988), give no indication that there will be any fundamental change in due course. Psychopharmacological treatment will continue to play an important role in this field. Yet the widespread and long-term application of benzodiazepines will be questioned, especially because of the problem of addiction, and other side effects. It was for this reason that alternatives such as neurolept-anxiolysis (*Heinrich* and *Lehmann*, 1988) or anxiolysis by antidepressants (*Gastpar*, 1986) were closely investigated.

Searching for further alternatives, we examined the anxiolytic efficacy of Cavain. D, L-Cavain, which was derived from natural substances, corresponds to an ingredient of the root of the Cava bush (Piper methysticum Forst.) and on the basis of preliminary clinical-experimental investigations appears to produce the desired results. As expected, Cavain has an anxiolytic effect (*Krach*, 1986) without disturbing vigilance (*Krueger* and *Kell*, 1977; *Ambrozi*, 1979) and without involving addiction (*Kryspin-Exner*, 1974).

Method

In a double-blind trial two randomized groups of 26 patients were treated for a period of 28 days with either placebo or Cavain (2 × 200 mg/day = 2 × 1 capsule Neuronica*).

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* Neuronica is a registered trademark of Klinge Pharma GmbH

In accordance with the revised Helsinki declaration, male and female patients aged between 20 and 65 years (x = 39.6 years, s = 11.1) suffering from abnormal anxiety, psychoreactive disorders or psychosomatic complaints with anxiety, were included in the study. They agreed to participate after being thoroughly informed. The DSM-III diagnoses were: panic syndrome (N = 21), generalized anxiety syndrome (N = 17), disturbance of adaptability (N = 10), and phobic disturbances (N = 4).

Patients suffering from neurological or severe organic diseases, with acute intoxication by alcohol, soporifics, analgetics or other psychoactive drugs, and with psychosis, and female patients during pregnancy or lactation were excluded. Also excluded were patients who habitually used psychoactive drugs. As the only psychotropic accompanying medication the administration of Chloraldurate for sleeping problems was permitted, a possibility which was used only in two cases.

The timetable and procedure of the study are listed in Table 1.

The personal history questionnaire (*Lazarus*, 1973) and the Minnesota Multiphasic Personality Inventory MMPI (*Greene*, 1980) was intended to provide a differential description of the patients and to diagnose their condition. In addition, the MMPI served to estimate the validity of the patients' statements. Only patients who were able and willing to describe themselves, were included in the study.

The main variables for evaluating efficacy were the total score on the Hamilton Anxiety Scale HAMA (*Hamilton*, 1976) and the global therapeutic efficacy rated at the end of the study.

The subscales of the HAMA, the scales of the adjective check list EWL (*Janke* and *Debus*, 1977), the global therapeutic efficacy rating after 14 days, the global compatibility ratings, and the free report on side-effects were evaluated exploratively.

There were 56 patients included in the study, 29 of whom were randomly assigned to the Cavain group and 27 to the placebo group.

Four of the 56 patients dropped out of the study within the first two weeks of treatment. Three of them belonged to the verum and one to the placebo group. There were no apparent study-related reasons for this discontinuation. Fifty-two patients (26 in each group) remained for testing the efficacy and making a descriptive analysis of the drug. Homogeneity of both random samples was established for the variables age, duration of illness, the clinical standard scales of the MMPI, as well as for the initial scores of the HAMA and EWL scales, by means of the t-test for independent random samples (double-sided questioning).

In respect of sex, the DSM-III diagnosis, pretreatment and the dynamics of the disease during the week prior to the beginning of the study, homogeneity was controlled by means of the Chi^2 test. For not one of the variables could a statistically significant difference be proved ($P < 0.05$). It may thus be assumed that the randomized assignment did not cause any unequal distribution.

Results

The efficacy of Cavain was proved by the two main variables under conditions of dosage and indication. Since both main variables are correlated closely to each other, we dispensed with an alpha adjustment. Yet it can easily be stated that the placebo – verum differences also exist after alpha adjustment.

The total HAMA score was significantly lower under Cavain than under placebo.

Table 2 showes the group structure, the difference from the initial values, the standard deviations, and the analysis of variance for the HAMA total score.

As Table 2 shows, the reduction under Cavain after 28 days was 11.54 points (49.9% of the initial value), whereas the reduction in the HAMA total score under placebo was only 2.81 points (12.8% of the initial value). This difference is statistically significant in the evaluation of the variance analysis ($P < 0.001$).

Table 3 shows the individual raw scores of the HAMA total score at the beginning and end of the study. The raw scores were not computed for the statistical evaluation of the verum-placebo differences. We had planned a priori to use the differences from the initial state instead.

However, Table 3 shows that the placebo – verum differences between the centers obviously do not differ essentially. The significant Cavain – placebo difference in efficacy was also proved for the second main variable, global therapeutic efficacy in the physician's assessment.

Table 4 contains the frequency of grades of improvement and their statistical evaluation.

Under Cavain 13 patients showed a marked improvement; only four remained unchanged. Under placebo only two patients were markedly improved and 13 remained

Table 1 Timetable of Study.

	Weeks 0	2	4
Investigation by a Physician	x		
Questionnaire Personal History	x		
MMPI	x		
HAMA	x	x	x
EWL	x	x	x
Physician's global impression			
- therapeutic effectiveness		x	x
- compatibility		x	x
Free report on side-effects		x	x

Table 2 Mean Values, Standard Deviations (SD) and Variance Analysis for the Changes in the HAMA Total Value.

	Cavain (N = 26) Mean	SD	Placebo (N = 26) Mean	SD
Day 14-0	- 8.15	7.42	-2.31	5.17
Day 28-0	-11.54	8.16	-2.81	7.18

HAMA Total Values

Source	Sum of squares	Degrees of freedom	Mean square	F	Tail prob.
Mean	4000	1	4000	46.84	0.000
Group	1381	1	1381	16.17	0.000
Error	4270	50	85		
Time	98	1	98	6.72	0.012
TG	54	1	54	3.71	0.060
Error	729	50	15		

Table 3 Total HAMA value at beginning of study and after 28 days.

Pat.-Nr.	Condition 1 = Cavain 2 = Placebo	Center	Total HAMA Value Day 0	Day 28
1	2	D	20	15
2	2	D	37	35
3	1	D	22	19
4	1	D	26	19
5	1	D	10	15
6	2	D	24	24
7	2	D	19	12
8	2	D	18	20
9	2	D	20	13
10	2	D	29	29
11	1	D	28	17
12	1	D	17	7
13	1	D	37	8
14	1	D	26	26
15	2	D	17	19
16	1	D	13	11
17	2	D	17	27
18	2	D	23	14
19	2	D	30	31
20	1	D	11	4
21	2	D	26	39
22	1	D	21	5
23	1	D	31	6
24	2	D	19	28
25	1	D	24	12
26	2	D	23	4
27	2	D	14	7
28	2	U	13	9
29	1	U	29	19
30	2	U	22	22
31	1	U	19	7
32	1	U	32	26
33	1	U	32	6
34	2	U	28	24
35	2	U	7	0
36	1	U	32	25
37	2	U	25	21
38	2	U	27	27
39	2	U	33	29
40	1	U	31	24
41	1	U	10	0
42	1	U	29	7
43	2	U	34	31
44	2	T	2	2
45	1	T	14	0
46	1	T	23	6
47	1	T	10	2
48	2	T	27	14
49	1	T	19	5
50	1	T	27	18
51	2	T	20	5
52	1	T	37	16

D = Düsseldorf, U = Ulm, T = Bad Tölz

Table 4 Therapeutic Improvement after 4 Weeks.

	markedly improved	improved	slightly improved	unchanged	impaired	
Cavain	13	8	1	4		26
Placebo	2	5	6	10	3	26
Total	15	13	7	14	3	52

Chi^2 (df : 4) = 17.9, $P < 0.01$

Table 5 Mean values, Standard Deviations (SD) and Variance Analysis of the Changes on the HAMA Scales "Psychic Anxiety" (PA) and "Somatic Anxiety" (SA).

		Cavain (N = 26) Mean	SD	Placebo (N = 26) Mean	SD
Day 14-0	PA	-5.12	4.92	-1.77	3.54
	SA	-3.04	3.65	-0.54	2.30
Day 28-0	PA	-7.04	5.39	-2.15	4.63
	SA	-4.50	3.59	-0.65	3.67
Effects (PA):		Prep. = $P < 0.01$		Time = $P < 0.05$	
Effects (SA):		Prep. = $P < 0.001$		Time = $P < 0.1$	

unchanged or impaired. The difference between the two preparation groups is too significant ($P < 0.01$) to be ascribed nearly to coincidence.

As expected, due to the very distinct effect on the HAMA total score, the explorative analysis resulted in an obvious influence of Cavain on the HAMA subscales "Psychic Anxiety" and "Somatic Anxiety". Table 5 contains the mean differences from the initial values, with standard deviations and variance analysis of the effects for these variables.

For both preparations there was a significantly greater reduction under Cavain than under placebo. Psychic anxiety was reduced on average by 7.04 points (49.9% of the initial value) under Cavain after four weeks; under placebo there was a reduction of only 2.15 points (16.2% of the initial value).

The reduction in somatic anxiety under Cavain over the same period of time was 4.50 points (49.8% of the initial value), while under placebo it was only 0.65 points (7.6% of the initial value).

As shown in the analysis of the EWL scales, the efficacy of Cavain as stated by the physician by means of the HAMA and the global impression correspond to the patients' own descriptions.

Six EWL scales were established, namely vitality-related activity, general inactivity, extro-/introversion, general comfortableness, emotional irritation, and anxiety/depression.

Cavain and placebo differed as far as the scales vitality-related activity and anxiety/depression were concerned.

Vitality-related activity improved under Cavain by 3.29 points (39% of the initial value), while under placebo the improvement was only 0.08 points (0.9% of the initial value).

Whereas Cavain therapy led to an improvement in "vitality-related activity" in the subjective view of the patients, it resulted in diminished values on the EWL scale "anxiety/depression".

The average reduction after four weeks of Cavain therapy was 5.04 points (38.1% of the initial value); under placebo it was 1.81 points (13.9% of the initial value), as shown in Table 6.

The proof of the anxiolytic efficacy of Cavain, which can be derived from the direct comparison of Cavain and placebo, is also expressed in differential correlations.

Between the initial values of all three HAMA scales and the success criterion "reduction in the HAMA total score after four weeks of treatment" significant correlative connections were found. The greater "psychic anxiety", the greater "somatic anxiety", and the greater the initial total HAMA score, the greater was the success of treatment. Under placebo no significant correlations were found, i. e., changes occurring under placebo were, in contrast to Cavain, independent of the grade of the target variable "anxiety".

The compatibility of Cavain did not differ from that of placebo on any of the measuring dates in our study. Both preparations were accepted mainly very well or well. The very occasional side-effects were not distinguishable from symptoms of illness.

Discussion

A valid experiment was conducted. Initially, the randomized groups did not differ from each other in any of the investigated variables. The variables "reduction in total HAMA score" and "physician's global impression of therapeutic effect" prove equally that Cavain, as opposed to placebo, had a significant anxiolytic effect. This effect was achieved without any difference in tolerance between Cavain and placebo. The explorative analysis showed that the physical effectiveness as perceived by the patient himself was actually improved under Cavain. At the same time Cavain noticeably promoted sound sleep and physical relaxation. Finally, the efficacy of Cavain as an anxiolytic medication can be deduced from the differential correlations, according to which Cavain was especially active, depending on the grade of anxiety, at the beginning of therapy.

Proof of these effects was established in mainly long-term disturbed patients who showed minor tendencies to spontaneous remission or response to placebo. Under placebo only two of 26 patients were markedly improved. These patients will have to be assigned to long-term therapy. Considering this it is useful to have Cavain as another effective very alternative in addition to psychotherapy, whose effectiveness in this indication is somewhat limited (*v. Zerssen*, 1988), besides the benzodiazepines, the low-dosage neuroleptics, and antidepressants in anxiolytic dosage.

The overall compatibility of the applied dosage was very good or good, as also was the acceptance of placebo. There were no traces of potential addiction. Nor was there any tendency to increase the dosage, or any traces of withdrawal symptoms upon termination of medication.

Though there is as yet no clinical investigation available which compares the efficacy of Cavain directly with other anxiolytics, Cavain seems to be as effective as low-dosed neuroleptics (*Lehmann*, 1987), while the applied dosage was well tolerated without any severe side-effects. Thus Cavain may be useful in the treatment of mild and moderate states of anxiety states, especially if there are accompanying symptoms such as sleep disturbance and psychovegetative complaints. It may be used as a supportive medication to complement non-psychopharmacological strategies such as psychotherapy.

If further invstigations confirm the clinical impression (*Kryspin-Exner*, 1974) that there are no clinical or subjective complaints after withdrawal or signs of addiction, Cavain could be recommended in many cases in which, usually, benzodiazepines may be indicated.

Our results confirm – as far as comparable – former results (*Krach*, 1986) and are in good agreement with the results of a study carried out at the same time (*Möller* and *Heuberger*, 1988).

Table 6 Mean Values, Standard Deviation (SD) and Variance Analysis of the Changes on the EWL scales "Vitality Related Acitivty" (VA) and "Anxiety/Depression" (AD).

		Cavain (N = 26) Mean	SD	Placebo (N = 26) Mean	SD
Day 14-0	VA	1.96	3.28	0.44	3.71
	AD	–4.29	4.44	-1.92	3.92
Day 28-0	VA	3.29	4.21	0.08	5.13
	AD	–5.04	5.00	-1.81	6.82
Effects (VA)		Prep. = $P < 0.05$		Time = n.s.	
Effects (AD)		Prep. = $P < 0.05$		Time = n.s.	

Table 7 Correlations of the Reduction in the HAMA Total Score after 4 Weeks and the Initial Values of the HAMA Scales.

		Psychic Anxiety Day 0	Somatic Anxiety Day 0	Total Value Day 0
Total Value Day 28-0	Cavain	-.49 ($P < 0.01$)	.40 ($P < 0.05$)	-.51 ($P < 0.01$)
	Placebo	.07	.05	.00

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