Pharmacology Biochemistry & Behavior, Vol. 29, pp. 803–806. © Pergamon Press plc, 1988. Printed in the U.S.A. 0091-3057/88 $3.00 + .00

Clinical Studies With the New Anxiolytic Alpidem in Anxious Patients: An Overview of the European Experiences

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MUSCH, B., P. L. MORSELLI AND P. PRIORE. *Clinical studies with the new anxiolytic alpidem in anxious patients: An overview of the European experiences.* PHARMACOL BIOCHEM BEHAV **29**(4) 803–806, 1988.—Alpidem is a new imidazopyridine compound which has been selected in animal pharmacology for its anxiolytic and anticonvulsant activity, and for its high therapeutic index. In healthy volunteers, alpidem was well tolerated up to doses of 300 mg and appeared to be devoid of CNS toxic effects. An extensive clinical development plan has been carried out in Europe to test its efficacy and safety in anxious patients. In a series of 5 double-blind placebo controlled parallel group studies, alpidem was administered as a single dose in a situation of stress induced anxiety where the stress was represented by diagnostic investigations such as gastroscopy, cardiac catheterisation or minor surgical operations. In these studies, 188 patients received placebo and 188 received alpidem; their anxiety was assessed before and after the drug administration by means of visual analogue scales and state anxiety inventories. Alpidem at 50 and 75 mg was significantly better than placebo in reducing stress induced anxiety. Alpidem was then administered to patients suffering from severe generalized anxiety in doses from 50 to 150 mg/day for 3–4 weeks in 3 double-blind placebo controlled studies: 127 patients received alpidem and 80 received placebo. Patients were assessed by means of rating scales and visual analogue scales. Alpidem did show an anxiolytic activity in this patient population and was well tolerated especially with regard to CNS side-effects. In 3 other double-blind parallel group studies alpidem was compared to reference drugs, lorazepam, diazepam and clorazepate: 103 patients were treated with alpidem and 105 patients with the reference drugs; in these studies, the anxiolytic effect of alpidem was comparable to that of reference drugs. The effect of alpidem on long-term treatment in a population of 300 patients suffering from anxiety are also presented with particular emphasis on the lack of tolerance and withdrawal effects together with a general overview of its safety profile.

Alpidem Anxiolytic Anxious patients Clinical trials

ALPIDEM is an imidazo-1,2a-pyridine molecule synthesized by L.E.R.S.

In animal tests predictive of anxiolytic activity, alpidem produces effects comparable to chlordiazepoxide and diazepam. In addition to its anxiolytic activity, alpidem also has anticonvulsant properties, which are similar to that of chlordiazepoxide.

In tests predictive of a myorelaxant and sedative action as well as in tests related to memory in animals, alpidem has been shown to have a very weak effect leading to a favourable therapeutic index with respect to benzodiazepines anxiolytics.

Studies in healthy volunteers have shown [7, 13, 14] that alpidem in single or repeated administrations does not affect cognitive functions and psychomotor performances at therapeutic anxiolytic doses (25, 50, 75 mg single dose).

In 8 pilot open studies in severely anxious patients, alpidem showed an anxiolytic effect in 64% of the cases, at daily doses from 50 to 250 mg. An extensive clinical development plan has been carried out in Europe to test its efficacy and safety in anxious patients.

SINGLE DOSE STUDIES IN LIFE-STRESS INDUCED ANXIETY

Patients undergoing dental surgery, surgical operations and patients admitted to coronary care unit have been shown to represent a suitable population to test the anxiolytic effect of a drug [10] because of their level of anxiety necessitating a drug treatment with an anxiolytic.

Five studies [1, 2, 6, 12] were carried out with alpidem, as single dose, parallel groups, placebo controlled trials, in patients suffering from reactive anxiety induced by a life-stress. Three studies were performed in a cardiovascular unit in patients prior to undergoing a cardiovascular examination (mainly cardiac catheterism), one study was performed in a surgical unit in patients prior to undergoing a minor surgical operation under general anesthesia and the remaining study was carried out in patients prior to undergoing a gastroscopy.

The instruments chosen to assess efficacy were: two visual analogue scales where the patients had to score their level of "anxiety" and of "physical tension," and 2 four point scales assessing the same variables by the investigator; moreover both patient and investigator had to assess sedation: the patient by means of a visual analogue scale, the investigator on a four point scale.

Patients were assessed before the administration of a single dose of alpidem and after 2 hours.

In all studies the investigator had to assess the therapeutic response on a four point scale (no response, slight, good, excellent) and patients indicated the degree of anxiety on a visual analogue scale.

Four hundred patients were included: 200 received alpidem and 200 placebo. Alpidem was administered at the single dose of 50 mg in 3 studies and at 75 mg in the other 2 studies.

Both patient and investigator judged alpidem to be statistically better than placebo in all studies. On the contrary, no difference with placebo was found with respect to sedation in both studies where alpidem was administered at 50 mg. In 2 out of 3 studies with 75 mg administration, a higher incidence of sedation was observed with respect to placebo.

With respect to the investigator's global evaluation of efficacy, pooling together the results of the five studies, 53.5% of patients treated with alpidem were considered as responders (good or excellent response) against only 30.5% of patients in the placebo group; this difference was statistically significant ($p<0.001$).

In conclusion, these five placebo controlled studies showed that single dose of alpidem, 50 and 75 mg, exerts an anxiolytic effect in life-stress induced anxiety; this anxiolytic effect is not accompanied by sedation when alpidem is administered at the dose of 50 mg.

COMPARATIVE TRIALS VERSUS PLACEBO (REPEATED DOSE)

Alpidem was compared to placebo in 3 double-blind parallel group studies: two studies were carried out in patients suffering from anxiety disorders, the third study in psychotic patients suffering from anxiety. The 3 studies will be described separately.

Double-Blind Study Comparing Alpidem 50 mg t.i.d. Versus Placebo in Anxious Patients [9]

In this study, alpidem administered at a fixed dose of 50 mg t.i.d. for 3 weeks was compared to placebo: 30 patients received alpidem and 30 received placebo after a one week placebo run-in period. Most of the patients were suffering from generalized anxiety (24 in the alpidem group, 21 in the placebo group).

At the end of the treatment period, 60% of the patients in the alpidem group were considered to have responded to treatment (good or excellent therapeutic response according to the CGI) against only 23.3% of the placebo treated patients ($p<0.02$).

The anxiolytic effect of alpidem shown by the CGI was also evident in the decrease of the rating scale total scores. At the HARS, the mean total score dropped from 28.3±3.4 18.7±9.2 at the end of the study period in the alpidem group, which represented a 34.1% decrease with respect to the pretreatment score, this decrease was only 11.3% in the placebo group (from 28±4.5 to 24.8±6.4 mean total score): this difference between alpidem and placebo was highly significant ($p<0.0001$). The same difference between alpidem and placebo was observed at the STAI-X1. According to the patient's visual analogue scale assessing anxiety, alpidem was significantly better than placebo ($p<0.0003$).

Considering the results of the digit symbol substitution test, the anxiolytic effect of alpidem was not accompanied by any reduction of the vigilance-attention level of the patient.

Double-Blind Placebo Controlled Study Comparing Three Doses of Alpidem (50, 100 mg/day) in Anxious Patients [10]

In this study, three doses of alpidem were compared to placebo over 3 week administration.

One hundred patients, mainly suffering from generalized anxiety, participated to the study: 24 patients received alpidem 25 mg b.i.d., 25 patients 50 mg b.i.d and 26 patients received placebo.

The following results were in favour of the anxiolytic activity of alpidem:

—Drop-out rate for inefficacy was in favour of alpidem (34.6% in the placebo group, 18.9% in the alpidem groups).

—The percentage of responders according to the CGI was higher in the alpidem group (47.2% all doses together) than in the placebo group (40%) and especially in the 50 mg/day group (58.3%).

—The onset of action was significantly shorter in the alpidem groups (3.2 days to 5.8 days according to the dose) than in the placebo group (6.9 days).

—Differences between alpidem and placebo at the different rating scales were in favour of alpidem but reached the statistical significance ($p<0.006$) at the Zung rating scale only.

Again in this study the incidence of side-effect was low and close to the incidence in the placebo group.

Double-Blind Placebo Controlled Trial in Psychotic Patients Suffering From Anxiety [8]

Minor tranquilizers are employed in the treatment of psychotic patients, eventually in association with neuroleptics, to provide relief of the symptoms such as anxiety, tension, somatic conversion, irritability and excitement; the aim of this study was the evaluation of the possible anxiolytic activity of alpidem in this particular form of anxiety at doses higher than those administered in generalized anxiety.

Sixty-six patients were included in the study: 33 received alpidem, 33 placebo for 3 weeks. Alpidem was administered at the daily dose of 300 mg in 3 divided administrations.

All patients were suffering from schizophrenia mainly of paranoid type (DSM III: 295.3) and were selected while on a phase of remission or stability of their psychotic symptoms but still suffering from anxiety of a certain severity (HARS total score >18). All patients completed the trial period. Alpidem was very effective in releaving anxiety as shown by a highly significant decrease of the rating scale total scores, HARS and BPRS, in comparison to placebo ($p<0.0001$).

At the CGI, 31 out of 33 patients in the alpidem group showed a moderate to marked improvement, against only 3 out of 33 patients in the placebo group. Notwithstanding the high doses, alpidem was remarkably well tolerated.

COMPARATIVE STUDIES VERSUS REFERENCE DRUGS

Alpidem was compared to reference anxiolytic drugs in 3 double-blind parallel group studies of 3 week duration.

In the first study [11], alpidem was compared to lorazepam at flexible increasing doses (mean doses: alpidem

TABLE 1

STUDIES VERSUS REFERENCE DRUGS: EFFICACY VARIABLES

Study	Variables	Alpidem		Reference		% D21–D0		No. of Patients	
		Day 0	Day 21	Day 0	Day 21	ALP	REF	ALP	REF
Ropert (versus lorazepam)	HARS	26.7 ± 0.7	11.7 ± 1.3	25.8 ± 0.7	11 ± 1.3	56.1	57.3	40	45
	VAS (100=very anxious)	81.1 ± 2.4	40 ± 4	77 ± 2.3	38.9 ± 3.8	50.6	49.8		
Guibert (versus lorazepate)	HARS	32.62 ± 0.9	14.28 ± 1.3	33.45 ± 0.8	15.4 ± 1.4	56.2	53.9	50	51
	VAS (0=very anxious)*	20.75 ± 1.5 (79.25)	60.46 ± 3.7 (39.54)	21.1 ± 1.6 (78.9)	55.23 ± 3.6 (44.77)	(50.1)	(43.3)		
Pancheri (versus diazepam)	HARS	30.7 ± 0.8	13.6 ± 2.9	32.1 ± 0.6	13.8 ± 2.1	55.7	57	15	15
	VAS (100=very anxious)	77.3 ± 5.4	45.8 ± 8.5	77.2 ± 4.9	46 ± 6.6	40.7	40		
	STAI-X_1	58.9 ± 1.7	48 ± 3.6	57.5 ± 2.6	50 ± 2.7	18.5	13		
	STAI-X_2	56.5 ± 2.1	47.8 ± 2.7	55.1 ± 2.2	48.5 ± 2.7	15.4	12		

*In order to calculate the VAS in the same direction as in the other 2 studies, the extremes have been inverted in this table.

227.5±11.2 mg/day, lorazepam 4.3±0.2 mg/day), in the second study [5], a fixed daily dose of 50 mg t.i.d. of alpidem was compared to 10 mg t.i.d. of clorazepate and in the third study [9], a fixed dose of 50 mg b.i.d. of alpidem was compared to 5 mg b.i.d. of diazepam.

A total of 216 patients suffering from generalized anxiety participated to the studies: 105 received alpidem, 111 received the reference drugs (45 lorazepam, 51 clorazepate, 15 diazepam).

As shown in Table 1, the anxiolytic effect of alpidem was comparable to that of the reference anxiolytics: a more than 50% reduction with respect to the pre-treatment score was observed both with alpidem and with the reference drugs at the HARS and at the patient's VAS; the results with the STAI were consistent with a significant decrease of anxiety both with alpidem and the reference drugs.

According to the CGI at the end of the study, 67% of the patients treated with alpidem and 71.8% of patients treated with reference drugs (all groups together) responded to the treatment; the comparison between alpidem and the reference drugs is not statistically significant.

Considering the safety profile of alpidem with respect to the reference drugs, the incidence of sedation (somnolence or drowsiness) was equal between alpidem and the reference drug in each study. On the contrary, in the alpidem groups, there was a much lower incidence of fatigue and depression with respect to the reference drugs.

LONG-TERM STUDY IN ANXIOUS PATIENTS

An extensive open long-term multicenter study assessing the efficacy and safety of alpidem over a 6 to 12 months treatment in anxious patients is going on in 23 centers in Europe.

Up to now, 374 patients suffering from anxiety disorders have been included; among them 84 reached one year treatment.

Data collected so far show that: alpidem is well tolerated as side-effect profile does not differ from the one observed in short-term trials; alpidem maintains its anxiolytic efficacy on long-term and no dose increase is observed over time suggesting no development of tolerance phenomena; in patients who discontinued the treatment for full recovery, no withdrawal symptoms were observed nor rebound anxiety. These data are in favour of the safety of alpidem when administered on long-term and of the lack of tolerance and dependance liability.

CONCLUSIONS

Alpidem is an imidazopyridine compound which has been developed because of its activity in animal tests predictive of an anxiolytic effect in patients.

The high therapeutic index of alpidem in animals and its lack of sedative effect in healthy volunteers at therapeutic doses suggested that alpidem can be a new anxiolytic with advantages over the existing benzodiazepines and deserves to be studied in anxious patients.

Clinical data presented in this paper concerning 11 double-blind studies and one open long-term study, show that alpidem is an effective anxiolytic in patients suffering from anxiety disorders. The safety profile of alpidem was particularly favourable confirming the low incidence of a sedative effect at therapeutic doses as shown in healthy volunteer studies. When administered on long-term up to 1 year, alpidem appeared to be well tolerated and its anxiolytic effect did not show any tolerance phenomena; upon discontinuation of alpidem patients did not show any withdrawal symptons or rebound anxiety.

In conclusion, clinical data show that alpidem is an effective anxiolytic which can represent an alternative to the existing drugs because of its selective effect on anxiety and its safety profile in short- and long-term treatment.

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