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Efficacy of alprazolam sublingual tablets in the treatment of the acute phase of panic disorders

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Background. Panic disorder affects 2-5% of the general population. In Argentina, one million people would be affected with a 91% rate of psychiatric comorbidity.

Aim. To compare efficacy parameters between sublingual (ALP-SL) and conventional (ALP-CT) tablets of alprazolam in the treatment of acute phase of panic disorder with and without agoraphobia.

Subjects and Methods. A comparative, multicenter (6 sites), double blind, randomized study was carried out. A total of 190 outpatients with (n=117) and without (n=73) agoraphobia were treated with ALP-SL or ALP-CT for 12 weeks. Outcome was assessed with the Clinical Global Impressions (CGI-S/CGI-I), Hamilton Rating Scale for Anxiety (HAM-A), Arizona Sexual Experiences Scale (ASEX), Patient Global Impression (PGI), Psychological General Well-Being Index (PGWBI), Panic Disorder Severity Scale (PDSS) also by the number of panic attacks and extension and intensity of panic attacks and anticipatory anxiety.

Results. Both treatments resulted in statistically significant clinical improvement in all measures. ASEX presented no changes during the study. The average dose of alprazolam for 12 weeks was 1.36 ± 0.70 mg/day (1.39 ± 0.77 ALP-CT and 1.33 ± 0.64 ALP-SL). With ALP-SL, panic attacks were shorter ($p < 0.05$) with shorter extension (p=0.16) and intensity of anticipatory anxiety (p=0.14). The treatment was well tolerated, there being no differences between both groups.

Conclusions. Alprazolam has been demonstrated to have efficacy, safety and good tolerability in the treatment of the acute phase of panic disorder, the sublingual tablets showing some comparative advantages.

Key words:
Alprazolam. Panic Disorders. Sublingual tablets. Panic attack.

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Eficacia del alprazolam en comprimidos sublinguales para el tratamiento de los trastornos de pánico en la fase aguda

Introducción. El trastorno de pánico afecta del 2 al 5% de la población general. En Argentina habría un millón de afectados con una tasa de comorbilidad psiquiátrica del 91%.

Objetivo. Comparar parámetros de eficacia entre comprimidos convencionales (CC) y sublinguales (CS) de alprazolam en el tratamiento de la fase aguda de los trastornos de pánico con o sin agorafobia.

Metodología. Estudio comparativo, multicéntrico (6 centros), doble ciego, aleatorizado. Se trataron 190 pacientes con (n=117) y sin (n=73) agorafobia, con CC o CS durante 12 semanas y se evaluaron con: Impresión Clínica Global (CGI), Escala de Ansiedad de Hamilton, Escala de Experiencia Sexual de Arizona (ASEX), Impresión General del Paciente (PGI), Índice de Bienestar Psicológico y General (PGWBI), Escala de Severidad del Trastorno de Pánico (PDSS) y por la cantidad de ataques de pánico, su duración, intensidad y ansiedad anticipatoria.

Resultados. Ambos tratamientos lograron una mejoría clínica estadísticamente significativa en todas las mediciones. El ASEX no presentó cambios durante el estudio. La dosis promedio de alprazolam durante las 12 semanas fue de 1,36 ± 0,70 mg/día (1,39 ± 0,77 CC y 1,33 ± 0,64 CS). Con CS los ataques de pánico fueron más breves ($p < 0,05$) así como menor la duración (p=0,16) e intensidad de la ansiedad anticipatoria (p=0,14). El tratamiento fue bien tolerado sin diferencias entre los dos grupos.

Conclusiones. el alprazolam demostró eficacia, seguridad y buena tolerabilidad en el tratamiento de la fase aguda de los trastornos de pánico. Los comprimidos sublinguales mostraron algunas ventajas comparativas.

Palabras clave:
Alprazolam. Trastornos de pánico. Comprimidos sublinguales. Ataque de pánico

INTRODUCTION

"Panic disorder" was officially introduced in the psychiatric nomenclature in 1980 by the American Psychiatric Association with the publication of the third edition of the Diagnostic and Statistical Manual Of Mental Disorders (DSM-III),[1] although its description was already known in the bibliography even before Sigmund Freud differentiated a specific picture of acute paroxysmal anxiety within the framework of anxiety neurosis in 1895.

In the fourth edition of the DSM (DSM IV),[2] *Panic Attack* was defined as "a discrete period of intense or discomfort fear," that is accompanied by at least four somatic or cognitive symptoms such as palpitations, tremors, shortness of breath, sweating, choking sensation or fear of dying, losing control or going crazy, among others.

In turn, *Anxiety Disorder or Panic Disorder* is characterized by the spontaneous unexpected presence of more than one panic attack, going from multiple attacks in one day to a single attack in one year, with the condition that one of them is followed by a period of at least one month in which the subject is worried about the consequences of the attack, by the possibility of suffering another one or there is a significant change in their behavior, as well as agoraphobia without any background of panic disorders.[3]

This disease is present in every culture, race and social economical level. Its symptoms initially occur at around 20 years of age (that is early adulthood, an epoch that implies transition to separation and independence). Less frequently, it debuts in puberty/adolescence or between 45-60 years and it is rare after 65 years.[4-11]

The alteration affects 2 to 5% of the general population and its incidence is increasing. This means that one out of every 30 persons suffers the disease, so that 1,000,000 persons would be affected in Argentina where, currently, it is a disease that is not always well diagnosed and consequently poorly treated.[4-11]

The rate of comorbidity with other psychiatric disorders reaches 91% of the patients with panic disorder and 84% of those with agoraphobia.[12, 13] The most frequent comorbid conditions are major depressive disorder, other anxiety disorders, personality disorders and substance-induced disorders. In general, half of the patients with panic disorder have agoraphobia.

The most effective treatments are pharmacological and cognitive behavioral psychotherapy.[14, 15] Benzodiazepines and selective serotonin reuptake inhibitors (SSRI) are the drugs used the most for the treatment of panic disorder and, to a lesser degree, serotonin norepinephrine reuptake inhibitor (SNRIs), tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs) are also used. Alprazolam has the advantage of producing a faster response against the anxiety attack and that it can be taken for long periods without developing tolerance to its anti-panic effects.[16] For some investigators, the concern about the prolonged use of benzodiazepines is in reference to a potential dependency on them.

The purposes of the pharmacotherapy are the following:

- To block the panic attack
- To decrease anticipatory anxiety and phobic avoidance
- To achieve remission and treat the residual symptoms
- To facilitate the associated therapies (cognitive-behavioral therapy)
- To recover self-esteem

In patients who experience panic attacks or acute anxiety, a rapid onset drug should be available.

In a three-sequence, single dose, crossover study, a study was made of the pharmacokinetics of alprazolam after the administration of a single dose of 0.5 in tablets, designed for sublingual administration compared with the oral and sublingual administration of 0.5 mg of alprazolam of a reference product, manufactured for standard oral administration. Its plasma concentrations were determined by high pressure liquid chromatography (HPLC). The results of the Area under the curve, Tmax and Cmax made it possible to establish that detectable plasma concentrations of the test product administered sublingually are achieved more rapidly than with the oral or sublingual administration of the standard reference preparation of alprazolam. This fact could have therapeutic advantages.[17]

In a clinical trial to evaluate the effect of sublingual alprazolam for acute anxiety disorders that included 78 patients with panic disorder, a significant improvement with an average daily dose of 1.5 mg/day of alprazolam was observed on the scales used to measure anxiety.[18]

Considering that the therapeutic guidelines of the American Psychiatric Association mention doses of 3 to 6 mg/day for the treatment of panic disorders, we would be seeing a pharmaceutical form that would make it possible to use lower doses of alprazolam and thus decrease the possibility of generating adverse events or some type of dependency.[19]

Therefore, the proposal of the present trial was to compare two groups affected by panic disorders with and without agoraphobia, who were randomly assigned to treatment with alprazolam in conventional tablets or alprazolam in sublingual tablets.

OBJECTIVE

To compare different efficacy parameters between alprazolam in conventional tablets (CT) of 0.5 mg and alprazolam in sublingual tablets (ST) of 0.5 mg for treatment in acute phase (90 days) of the panic disorders, with and without agoraphobia.

METHODOLOGY

A multicenter, comparative study with random allocation at a 1:1 ratio was performed.

Fifteen principal investigators, from 11 Psychiatric Care Centers known to have high academic level and distributed throughout the country, participated.

A double-blind study could not be performed as two different pharmaceutical forms were being used (1 oral and another sublingual) and the Double-dummy or double simulation technique was not applied due to technical difficulties, such as achieving a similar flavoring in the sublingual tablets of the active drug and placebo.

Patients from 18 to 70 years, of both genders, with DSM-IV criteria for panic disorders with and without agoraphobia, who had a score of 20 or higher on the Hamilton Anxiety Scale and who had been without pharmacological treatment in the 30 days prior to their enrollment, were enrolled. The following evaluation methods were used: panic disorder severity scale (PDSS), duration and intensity of the episodes, percentage of daily time with anticipatory anxiety and its intensity on the visual analog scale, patient global impression (PGI), global clinical impression (GCI), Hamilton Anxiety Scale, Arizona Sexual Experience Scale (ASEX), quality of life test (PGWB) and chart of daily follow-up of the episodes (quanti- and qualitative analyses).

In order to achieve the primary objective of this study, the difference in efficacy between alprazolam in conventional tablets (CT) and alprazolam in sublingual tablets (ST), the primary parameter used was the difference in change between the baseline and final visit in the total score of the Hamilton Anxiety Scale (HAM-A). Controls were not made with this scale in each one of the visits because the efficacy of sublingual tablets of alprazolam in anxiety disorders had already been demonstrated in a previously published trial,[18] evaluating the Hamilton Anxiety Scale in seriated form.

The idea of incorporating the Arizona Sexual Experience Scale arose because even though some adverse events of alprazolam[20-22] had been described, we felt that it was of interest to demonstrate that the sexual dysfunctions caused by the study drug are of insignificant amount if they are compared with those caused by the SSRIs that are commonly used in panic disorders and which are a motive that affects treatment adherence by the patients.[23]

A-90 day follow-up was made with visits on days 0, 7, 30, 60, 70 and 90.

Each subject was instructed about the study characteristics and the possible adverse events and had to sign an informed consent before any procedure of the clinical trial was carried out. The protocol was approved by the respective teaching and research committees of the participating centers, by an independent ethics committee and by the ANMAT (Administración Nacional de Medicamentos, Alimentos y Tecnología Médica) [National Medicines, Food and Medical Technology Authority (ANMAT)]. Dossier No. 47-9421-05-0 of 15/06/2005.

RESULTS

The clinical trial began in June 2005 and ended in August 2007. One hundred and ninety patients were evaluable for efficacy and tolerability (94 with alprazolam ST and 96 with alprazolam CT). A total of 131 women and 59 men were enrolled. Median age was 37 years.

Table 1 shows the psychiatric comorbidities in the group studied with panic disorders and the corresponding

Table 1 Psychiatric comorbidity in Panic Disorders

Psychiatric comorbidity	Frequency	Percentage (%)
Depression	21	10.66
Generalized anxiety disorder	17	8.60
Personality disorders	15	7.62
Obsessive disorders	8	4.06
Stress disorders	2	1.02
Posttraumatic stress disorders	2	1.02
Phobic disorders	2	1.02
Psychosomatic disorders	2	1.02
Social phobia	1	0.51
Eating disorders	1	0.51
Without comorbidity	126	63.96
TOTAL	**197**	**100.00**

Table 2 Hamilton anxiety evaluation scale (X ± SD)

	Alprazolam CT	Alprazolam ST
Baseline	30.94 ± 6.16	30.92 ± 5.93
Day 60	12.47 ± 7.63	13.01 ± 7.01

Anova Test for paired data p< 0.01. Newman Keuls between CT and ST: nonsignificant p

Table 3 PGI (General Impression of the patient) DAY 90

	Alprazolam CT	Alprazolam ST
Much better	50 (55.56%)	41 (45.56%)
A lot better	29 (32.22%)	44 (48.89%)
A little better	11 (12.22%)	3 (3.33%)
Without changes		1 (1.11%)
A little worse		
A lot worse		1 (1.11%)
Much worse		

Anova Test for paired data p< 0.01. Newman Keuls between CT and ST: nonsignificant p

Table 4 CGI (Clinical Global Impression) baseline and end of treatment

	DAY 0	DAY 90	
		Alprazolam CT	Alprazolam ST
Not at all affected		34 (37.78%)	25 (27.78%)
Very little affected		43 (47.78%)	52 (57.78%)
A little affected	3 (3.19%)	8 (8.89%)	9 (10%)
Quite affected	19 (20.21%)	5 (5.56%)	4 (4.44%)
Very affected	39 (41.49%)		
Significantly affected	27 (28.72%)		
Extremely effective	6 (6.38%)		

Anova test for paired data p< 0.01. Newman Keuls between CT and ST: nonsignificant p

percentages. No psychiatric comorbidities occurred in 64% of the patients and 61.6% had agoraphobia.

Table 2 shows the pre- and post-Hamilton Anxiety Scale.

Table 5 PDSS (Panic Disorder Severity Scale) (X ± $\overline{SD}$)

	Alprazolam CT	Alprazolam ST
Baseline	16.80 ± 3.67	16.99 ± 3.87
Day 90	4.41 ± 4.81	3.81 ± 3.00

The higher the score the greater the severity
Anova test for paired data p< 0.01. Newman Keuls between CT and ST: nonsignificant p

Table 6 PGWB (Psychological General Well-being Index) X ± $\overline{SD}$

	Alprazolam CT	Alprazolam ST
Baseline	45.41 ± 13.41	45.53 ± 13.20
Day 60	74.3 ± 17.52	73.85 ± 14.33

Score between 0 and 110 points, the higher score corresponding to "better well-being."
Anova test for paired data p< 0.01. Newman Keuls between CT and ST: nonsignificant p.

Table 7 ASEX (Arizona Sexual Experience Scale) X ± $\overline{SD}$

	Alprazolam CT	Alprazolam ST
Baseline	19.28 ± 5.07	17.98 ± 4.88
Day 60	17.23 ± 5.59	16.00 ± 4.75

Student's t-test for paired data: nonsignificant p

Alprazolam in both pharmaceutical forms was effective in statistically significant terms and 90% of the cases, in accordance with the results of the different efficacy evaluations: PDSS, GCI and PGI as shown in Tables 3, 4 and 5.

The quality of life test used (PGWB) evidenced a significant improvement as shown in Table 6, fulfilling one of the principal proposals in the treatment of this condition.

As shown in Table 7, alprazolam in both pharmaceutical forms did not modify the sexual behavior guidelines evaluated with the ASEX test.

Although the duration of the panic attacks showed a considerable reduction with both pharmaceutical forms, a clear tendency towards greater decrease was observed with the use of sublingual tablets of alprazolam, as shown in Table 8.

Table 8 Duration of the panic attacks (minutes)

	Alprazolam CT	Alprazolam ST
Baseline	18.99 ± 9.23	21.14 ± 12.72
Day 30	13.01 ± 9.53	14.13 ± 10.12
Day 60	13.32 ± 15.07	9.87 ± 6.62
Day 90	15.07 ± 13.29	8.84 ± 6.44

Anova test for paired data p< 0.01. Newman Keuls between CT and ST: p < 0.03

Table 9 Intensity of the panic attacks Visual Analog Scale

	Alprazolam CT	Alprazolam ST
Baseline	7.31 ± 1.14	7.15 ± 1.33
Day 30	5.67 ± 6.91	4.90 ± 1.65
Day 60	3.82 ± 2.19	3.44 ± 1.66
Day 90	3.22 ± 2.02	2.63 ± 1.67

Anova test for paired data p< 0.01. Newman Keuls between CT and ST: p < 0.24

Table 10 Percentage of daily time with anticipatory anxiety

	Alprazolam CT	Alprazolam ST
Baseline	62.54 ± 16.24	60.36 ± 20.11
Day 30	35.77 ± 18.71	35.16 ± 18.24
Day 60	25.09 ± 20.24	25.63 ± 16.03
Day 90	18.09 ± 17.35	14.82 ± 11.18

Anova test for paired data p< 0.01. Newman Keuls between CT and ST: p < 0.16

Table 11 Intensity of the anticipatory anxiety

	Alprazolam CT	Alprazolam ST
Baseline	6.87 ± 1.37	6.81 ± 1.72
Day 30	4.35 ± 2.19	4.24 ± 1.81
Day 60	3.11 ± 2.27	3.09 ± 1.83
Day 90	2.24 ± 2.03	1.83 ± 1.44

Anova test for paired data p< 0.01. Newman Keuls between CT and ST: p < 0.14

The intensity of the episodes, shown in Table 9, was lower with the alprazolam ST with a P value without statistical significance.

The percentage of daily time with anticipatory anxiety and its intensity showed a clear tendency to greater improvement with ST, as shown in Tables 10 and 11.

The final dose of alprazolam was less than 1.5 mg/day for all of the sample (1.36 ± 0.7), 1.39 ± 0.77 for CT and 1.33 ± 0.64 for ST. Somnolence and sedation were the principal adverse events (25%), without differences between both pharmaceutical forms.

DISCUSSION

Controlled studies have shown the efficacy of tricyclic antidepressants, of the MAOIs, of the SSRIs, of the SNRIs and of the high-potency benzodiazepines in the treatment of panic disorder. The pharmacotherapy includes a first acute or attack treatment phase, in which the use of high potency benzodiazepines either alone or combined with an antidepressant is common. If the patient does not have an elevated level of anxiety or frequent panic attacks and agoraphobia prevails, treatment can be begun with SSRI unless there are contraindications. After this first period, which may last for months, a second maintenance phase is begun. This is aimed at stabilizing the improvement. Because the course of the disease is chronic and fluctuating, it is difficult to determine when treatment will be completed.

In the case of the present clinical trial conducted with alprazolam in different pharmaceutical forms for 90 days, patients who were seriously affected by the panic disorder were incorporated since the anxiety levels were high (> 20 on the Hamilton Anxiety Scale) and more than 60% reported some form of agoraphobia. Depression occurred with comorbidity in 11% of them and 64% of the patients enrolled had no psychiatric comorbidity.

In this population sample, it could be observed that alprazolam was effective in statistically significant terms in 90% of the cases, in accordance with the results of the different efficacy evaluations: PDSS, GCI and PGI. It was also seen that the final dose of alprazolam used was less than 1.5 mg per day for all of the sample (1.36 ± 0.7). This is not an insignificant fact, since alprazolam could be a useful therapeutic tool not only in those patients receiving SSRIs who manifest intolerances or sexual dysfunctions secondary to them but also as an alternative of choice for the first episode of the disorder since once the symptoms are contained during the acute stage with this benzodiazepine and additional psychotherapy techniques of proven efficacy,

the picture could remit without needing prolonged treatments with antidepressants, also avoiding high costs and adverse events.

In the first place, it can be stressed that there were no significant differences between both pharmaceutical forms of alprazolam, even though the sublingual form seemed to have some comparative advantages, above all on the duration and intensity of both the panic attack as well as the anticipatory anxiety. Although statistical significance was not achieved in these points evaluated, if the sample size had been increase, a $p<0.05$ could have been obtained since a power under 80% had already been reached.

The fact observed during this study that the medication did not affect the patients in their sexual sphere makes it possible to observe an additional comparative advantage versus the SSRIs in addition to its lower cost.

The average dose of alprazolam at 7 days of beginning the treatment was 3.4 mg/day. On the other hand, the lower dose of 1.5 mg of alprazolam per day at 3 months of beginning the treatment makes it possible to suppose that the incorporation of other therapeutic measures such as psychotherapy and psychoeducation would make it possible to achieve a gradual dose reduction, with scant risks of dependence and/or abstinence symptoms at the time of discontinuing the benzodiazepines.

CONCLUSIONS

Alprazolam in both pharmaceutical forms was effective in more than 90% of the patients during the acute phase of panic disorder.

The final dose was less than 1.5 mg/ day in both groups.

The Hamilton Anxiety and Panic Disorder Severity scales showed improvement regarding baseline with $p<0.01$ before and after both treatments.

The ASEX score did not show statistically significant differences before and after both treatments. This made it possible to infer that alprazolam does not affect the sexual sphere.

The quality of life scale (PGWB) showed improvement compared to its baseline values with $p< 0.01$ before and after both treatments.

Somnolence and sedation were the principal adverse events (25%), without differences between both pharmaceutical forms.

There were no significant differences between alprazolam CT and ST, even though the sublingual form seems to have some comparative advantages, above all in the duration and intensity of the panic episodes and anticipatory anxiety.

The study has limitations that are especially linked to the fact that it was not designed as a double-blind study for technical reasons and the fact that the sample size did not make it possible to elucidate if the comparative advantages of the sublingual form may reach statistical significance.

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CONFLICTS OF INTEREST

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