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RESEARCH

Effect of alpha-casozepine (Zylkene) on anxiety in cats

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stress

Abstract The putative effects of a tryptic bovine αs1-casein hydrolysate on anxious disorders in cats was investigated. This product is known as alpha-casozepine and patented under the name of Zylkene (Ingredia, Arras, France). Within veterinary practices, 34 cats were recruited by certified behaviorist surgeons. This 56-day trial against placebo showed the statistically positive effect of this product in the management of anxious disorders such as social phobias in cats. Global score, as well as different items (fear of strangers, contact with familiars, general fears, fear-related aggressions, autonomic disorders), were all significantly improved by the use of this natural decapeptide.

Introduction

Feline medicine is a growing field in which behavioral disorders are becoming better known every day. Cats are sometimes described as more territorial animals than social ones (Beata, 2005). Other authors postulate that cats have complex social interactions (Crowell-Davis et al., 2004; Curtis et al., 2003). Inadequate contact with unfamiliar people and uncontrolled access to other cats have been postulated as a classical factor of stress for this species (Carlstead et al., 1993).

Cats can exhibit many different signs related to their anxious state. Urine spraying, compulsive licking, and aggressive behaviors are some of the most obvious signs of stress and anxiety in cats (Pryor et al., 2001). Cat owners are often very sensitive to these behaviors and may wish to treat these cats, but they do not wish to use psychotropic drugs. If a nonpharmaceutical, natural biological compound were available, many owners would choose to use it.

Cow's milk has long been considered a beverage with natural "tranquillizing" properties. Research has shown that some of the peptides present in the milk may have a calming effect (Brezinova and Oswald, 1972). This calming effect has been observed in babies and has been hypothesized to be associated with the specific way in which milk is digested by babies. Trypsin is more common in babies' digestions, whereas pepsin is more active in adults.

Alpha-S1 casein is one of the major proteins in cows' milk. Preliminary studies have demonstrated that many of the peptides that make up this protein have strong biological

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properties, including effects on opioid and immunologic systems (Morley et al., 1985; Biziulevicius et al., 2003; Sakaguchi, et al., 2003). The tryptic hydrolysis of the alpha-S1 casein produces a decapeptide whose spatial structure is known. This structure allows the decapeptide to fit into a segment of the GABA-B receptor thought to be responsible for anxiolytic activity (Lecouvey et al.,1997a; Lecouvey et al.,1997b).

First Evidence of the Anxiolytic Effect

In Rats

The conditioned defensive burying paradigm (CDB) is a classic test to screen drugs for potential anxiolytic activity in rodents. Rats bury aversive stimuli, and burying activity can be linked with anxiety response (Pinel and Treit, 1978). Rats bury the electrode when they are under stress, and treatment with anxiolytics prevents burying behavior. This test is sensitive, as it allows for discrimination between any anxiolytic effect and an effect on general activity. The CDB paradigm has been validated as a test for clinical effects of anxiolytics (Treit et al., 1981). The strength of the response to the electrode can also be measured (Rohmer et al., 1990).

Alpha-casozepine was first tested in male Wistar rats (*Rattus norvegicus*). Using the CDB model, treatment with alpha-casozepine has been shown to be as effective as the reference molecule, diazepam. Neither an increase in aggression to cagemates nor a loss of working memory was seen with treatment with alpha-casozepine, but these effects have been noted for benzodiazepines (Schroeder et al., 2003). Similar results were found for rodents tested with the elevated-plus maze paradigm, another test used to evaluate putative anxiolytic effects of drugs (Violle et al., 2006).

In Human Beings

Alpha-casozepine has been used in people with acute and chronic anxiety models. All studies were conducted according to Good Clinical Practices (GCP), and the designs of these studies were approved by an ethical committee (CCP-PRB), as would be true for a drug trial. In both the cold pressure test and the Stroop test, 2 old but consistent anxiety tests in human beings, treatment with alpha-casozepine showed statistically significant effects (Lanoir et al., 2002; Messaoudi et al., 2002; Messaoudi et al., 2005). Based on these results, it seemed logical to test this product on companion animals (e.g., dogs and cats) experiencing stressful conditions.

Cat Trial

The role of anxiety in behavioral disorders of cats has been discussed (Houpt, 1998; Horwitz and Landsberg, 1998; Overall, 1997). Composition of social groups within any given environment has been shown to be important to cats (Turner and Bateson, 2000; Curtis et al, 2003; Crowell-Davis et al., 2004). Any modification to their living area and social environment can be stressful for cats and has been associated with various anxiety-related conditions, including obsessive-compulsive disorders (Overall and Dunham, 2002). Cats also have strong relationships with people (Beata, 2001), and separation anxiety has been described in this species (Schwartz, 2002, 2003). We define social phobia in cats as the situation where the cat disappears when a human or another cat enters the territory occupied by the cat, and during which the cat exhibits aggression or signs associated with autonomic activity. Social phobia, as defined here, is one of the main complaints of cat owners.

Subjects, Materials, and Methods

A European multicentric, randomized, double-blind, placebo-controlled trial conducted according to GCP was designed to evaluate the efficacy of alpha-casozepine as an anxiolytic in cats. Cats were selected from general or specialist practices. Investigators ensured that cats were not subjected to inadequate living conditions. Inclusion criteria were based on a behavioral scale validated among the investigators, who were all behaviorist veterinary surgeons (Table 1).

Prior to including the first cats, investigators tested the scale in their practice on cats with or without social phobia diagnosis. This first evaluation of the behavioral scale led to an agreement between investigators that the scale was robust but not very sensitive. In other words, we could miss slightly anxious cats, but there were no false positives; if a cat was identified as anxious, it was. We decided not to evaluate elimination and marking behaviors because of our focus on interspecific relationships and because of false positives related to medical conditions such as crystalluria. To be included in the study, the cat had to have a score of < 15 on the behavioral scale or to have one of the 5 categories with a score of 0. Only 2 of 34 cats tested were enrolled using this second criterion.

Cats were randomly assigned to each treatment. Randomization was done by the sponsor and remained unknown to the client, the investigator, and the monitor until the trial was finished.

Over 56 days, cats received capsules of either alpha-casozepine at 15 mg/kg or placebo p.o. q. 24 hours. Practitioners were also allowed to implement classical behavior modification. The interventions involving behavior modification were not fully standardized but included the standard principles of stopping any physical punishment, increasing positive reinforcement, and providing the cat with an adequate environment.

All cats were evaluated 5 times. They had a physical consultation at days 0 (visit 1), 28 (visit 2), and 56 (visit 3) and a phone follow-up at days 14 (T1) and 42 (T2).

Table 1 Cat emotional scale

	Contact tolerance with familiar people
0	Can't be touched
1	Allows only short contact with humans when the cat initiates it
2	Does not tolerate long, provoked or spontaneous, contact
3	Variable acceptance and seeking of contact
4	The cat regularly seeks and accepts contacts – seldom refuses
5	Easily manipulated
	Contact tolerance with non –familiar people
0	Disappears or is aggressive in the presence of people
1	Comes to observe but can't be touched
2	Initiates contact after awhile but does not accept being touched
3	Initiates contact after awhile and accepts being touched
4	Accepts most, but not all human contact
5	Tolerant, friendly and playful with non-familiar and with familiar people
	Aggression
0	Aggressive to familiar and non-familiar people, causing injury
1	Aggressive to familiar and non-familiar people except for one person, causing injury
2	Possible but infrequent aggression that causes injury
3	Threatens without fleeing
4	Threatens and flees
5	Never aggressive
	Other fears
0	Frightened by the slightest noise or any new stimulus
1	Unwilling to explore, responds in a fearful way to numerous stimuli
2	Exhibits fearful behavior, but explores after a while
3	Frightened only by specific, known stimuli
4	Seldom frightened – Calms down quickly
5	Never afraid
	Organic signs
0	Systematic stress-related autonomic signs (+/- displacement activities)
1	Frequent stress-related autonomic signs (+/- displacement activities)
2	Displacement activities with severe consequences (+/- autonomic signs)
3	Displacement activities with medium consequences (+/- autonomic signs)
4	Displacement activities with mild consequences (without autonomic signs)
5	Nothing

We tracked 3 items: (1) the overall score; (2) the number of items scoring 0; and (3) the owner's evaluation of any change. For the treatment to be assessed as successful, 3 conditions had to be met: (1) overall score equal to or greater than 16; (2) number of items evaluated as 0 by the owner equal to 0; and (3) owner's evaluation mark equal to or greater than 6/10.

Statview software was used to evaluate the data using an *a priori* level of significance set at $P \leq 0.05$. Mann-Whitney U tests were used to compare the product and the placebo effect at each step. Analysis of variance (ANOVA) was performed to evaluate the effect of each product along the test period.

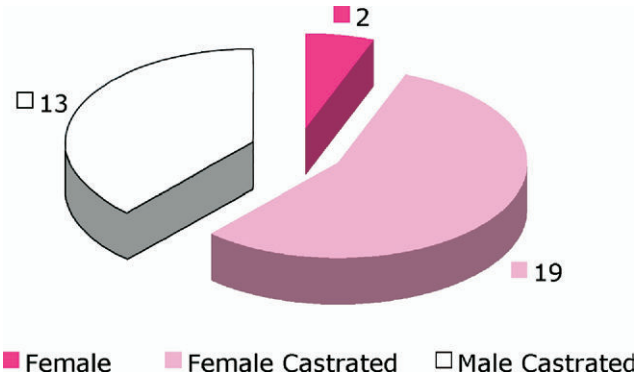

Figure 1 Sex ratio of the population of the study.

Results

Thirty-four (34) cats were enrolled in and completed the trial. Accordingly, random assignment of cats resulted in 17 cats in each treatment group (placebo and alpha-casozepine).

Population

The majority of the participants included were European cats (common cats). Only 4 of 34 were of purebred cats (1 High-Strait, 1 Siamese, 1 Birman, 1 Persian). The sex ratio favored females; 21 of the 34 cats tested were female, and only 2 were not spayed. All males in the study population were castrated (Figure 1). This pattern of enrollment may be consistent with the clinical impression and literature for the human species showing that females seem more vulnerable to stress and anxiety (Cameron and Hill, 1989; Longstreth and Wolde-Tsadik, 1993; Olie et al., 2002; Silver et al., 2002).

Homogeneity of the Groups

At day 0, there were no significant differences between the scores of cats in the placebo group and in the alpha-casozepine group, or between the number of items scored 0 at day 0 (D0) (Table 2).

"Successful treatment" was defined as an increase in the behavioral score (objective) *and* an owner evaluation indicating improvement (subjective). Of the 34 test subjects, 14 cats met the criteria for successful treatment. Of these 14 cats, 10 were treated with alpha-casozepine and 4 with placebo. The results are summarized in Table 3. These results were statistically significant (chi-square test, 1 d.f, $P = 0.02$).

Detailed Results

We compared the scores, the number of items scored 0, and the owners' evaluations using the Mann-Whitney U test to see if there was any significant difference for each eval-

Table 2 Summary results for the 34 cats enrolled in the study

			Age					Score					Evaluation				Nbr Items 0						
	Breed	Weight	Mo.	S	Environment	Origin	V1	T1	V2	T2	V3	T1	V2	T2	V3	V1	T1	V2	T2	V3	Result	Treatment
1	European	4,0	15	FC	House	House	8	9	8	9	9	4	3	4	4	1	0	1	1	1	**Failure**	**alpha-casozepine**
2	European	4,0	67	FC	House	Humane Soc.	9	9	9	9	9	1	3	5	6	2	2	2	1	1	**Failure**	placebo
3	European	6,0	55	FC	House	House	9	11	12	13	16	5	7	7	7	3	1	0	0	0	**Success**	**alpha-casozepine**
4	European	3,5	78	MC	House	House	9	9	9	9	9	3	4	4	4	2	2	2	2	2	**Failure**	placebo
5	Highland Strait	6,2	50	FC	Apartment	Marketplace	10	10	10	10	10	5	6	6	6	2	2	2	2	2	**Failure**	**alpha-casozepine**
6	European	2,0	10	MC	Apartment	Barn	6	6	6	6	6	3	3,5	4	4	3	3	3	3	3	**Failure**	placebo
7	European	3,5	9	FC	Apartment	Street	14	15	17	18	21	6	7,0	8	9	1	1	0	0	0	**Success**	**alpha-casozepine**
8	European	3,7	54	FC	Apartment	Street	13	13	13	13	13	0	0,0	0	0	2	2	2	2	2	**Failure**	**alpha-casozepine**
9	European	6,0	64	FC	Apartment	Street	12	14	17	19	19	6	6,5	7	8	0	0	0	0	0	**Success**	**alpha-casozepine**
10	European	4,0	30	MC	Apartment	Barn	5	12	14	15	17	5	6,0	6	6	2	0	0	0	0	**Success**	**alpha-casozepine**
11	European	6,0	36	FC	House	House	10	12	13	14	14	3	4,0	5	5	0	0	0	0	0	**Failure**	**alpha-casozepine**
12	Persian	5,0	74	FC	House	Breeder	8	12	16	16	16	7	8,0	8	8	0	0	0	0	0	**Success**	placebo
13	European	7,8	56	MC	Apartment	Barn	9	17	18	19	19	7	8,0	8	9	1	0	0	0	0	**Success**	placebo
14	European	5,0	47	MC	Apartment	Street	9	9	9	9	9	0	0	0	0	1	1	1	1	1	**Failure**	placebo
15	European	6,0	44	MC	Apartment	House	7	7	11	11	11	2	4	4	5	1	1	0	0	0	**Failure**	placebo
16	European	7,0	44	FC	House	House	14	14	14	14	14	0	0	0	0	0	0	0	0	0	**Failure**	**alpha-casozepine**
17	European	4,7	143	FC	Apartment	Street	13	13	13	13	13	0	0	0	0	2	2	2	2	2	**Failure**	placebo
18	European	4,5	20	MC	House	House	13	14	16	18	18	6	8	8	8	0	0	0	0	0	**Success**	**alpha-casozepine**
19	European	3,4	12	F	House	House		14	14	14	15	2	3	3	3	0	0	0	0	0	**Failure**	placebo
20	European	3,8	34	FC	Apartment	Humane Soc.	11	9	16	19	19	2	5	7	7	0	1	0	0	0	**Success**	**alpha-casozepine**
21	European	5,0	140	FC	House	Humane Soc.	13	13	13	13	12	0	0	0	0	0	0	0	0	1	**Failure**	**alpha-casozepine**
22	European	3,9	118	FC	House	House	6	10	10	9	9	1	1	0	0	2	0	0	0	0	**Failure**	placebo
23	European	4,3	86	MC	House	Street	14	14	19	21	21	0	6	7	8	2	2	0	0	0	**Success**	**alpha-casozepine**
24	European	4,5	129	FC	Apartment	House	2	2	2	2	2	0	0	0	0	3	3	3	3	3	**Failure**	placebo
25	European	6,4	66	MC	Apartment	Apartment	8	8	9	12	17	0	1	3	6	1	1	1	0	0	**Success**	**alpha-casozepine**
26	Siamese	6,0	46	MC	House	House	12	13	14	16	17	2	2	4	6	0	1	1	0	0	**Success**	placebo
27	European	4,9	44	MC	House	House	11	11	11	11	11	0	0	0	0	2	2	2	2	2	**Failure**	placebo
28	European	6,4	27	MC	Apartment	Humane Soc.	15	15	15	15	15	0	0	0	0	1	1	1	1	1	**Failure**	placebo
29	European	5,5	34	MC	Apartment	Street	13	15	14	21	19	1	3	7	8	1	1	1	0	0	**Success**	placebo
30	European	4,3	48	FC	House	Street	7	9	8	13	14	1	1	0	0	2	1	1	1	0	**Failure**	**alpha-casozepine**
31	Birman	3,1	90	FC	Apartment	Breeder	17	18	19	23	23	1	4,0	9	9	1	1	1	0	0	**Success**	**alpha-casozepine**
32	European	4,0	56	FC	House	House	8	11	13	14	17	4	4,0	6	7	2	1	1	1	0	**Success**	**alpha-casozepine**
33	European	4,0	14	F	Apartment	Street	5	5	4	4	4	-1	-3,0	-3,0	-3,0	3	3	3	3	3	**Failure**	placebo
34	European	3,5	72	FC	Apartment	Street	6	6	10	10	10	4	5,0	5	5	3	3	1	1	1	**Failure**	placebo

Table 3 Number of successes and failures in each treatment group

	Alpha-casozepine	placebo
Successes	10	4
failures	7	13

uation period. We also used ANOVA to compare the patterns of change across products.

Score

The score at D0 is represented as V1S (V stands for Visit, 1 for the rank of the visit, S for Score). Figure 2 compares the results at each visit or phone follow-up. The behavioral score at V3 (V3S) is significantly different between the placebo and alpha-casozepine groups. Looking at the rate of change, or slope, we also found a significant difference between placebo group and alpha-casozepine group, in favor of the treatment by alpha-casozepine (ANOVA, $F_{(4,32)} = 4.097$; $P = 0.003$).

Number of Items Quoted 0

The difference in the number of items scored 0 at D56 is statistically significant between the alpha-casozepine group and the placebo group, in favor of alpha-casozepine (Mann-Whitney U test $P = 0.04$).

Cats Included with a 0 Quote in only 1 Category

Two cats were included with a 0 quote in 1 category as the only element of inclusion. One was treated with placebo, and his score did not change; the item quoted 0 remained stable. The other was treated with alpha-casozepine, and the score jumped from 17 to 23, with the item quoted 0 at visit 1 changing to 3 at the end of the trial.

Owner Evaluations

Difference in owner evaluations at V3 were not statistically significant (Mann-Whitney U test $P = 0.07$) between treatment groups. The owner evaluations showed an average score of just under 6 for alpha-casozepine and just above 3 for placebo.

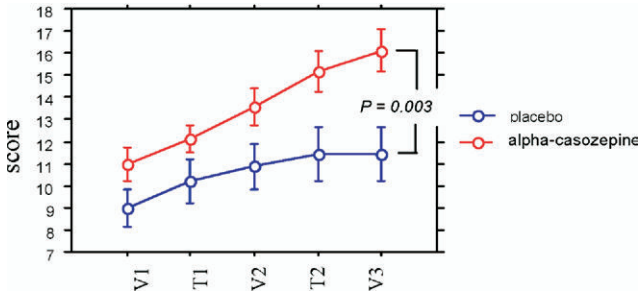

Figure 2 Comparison of global scores.

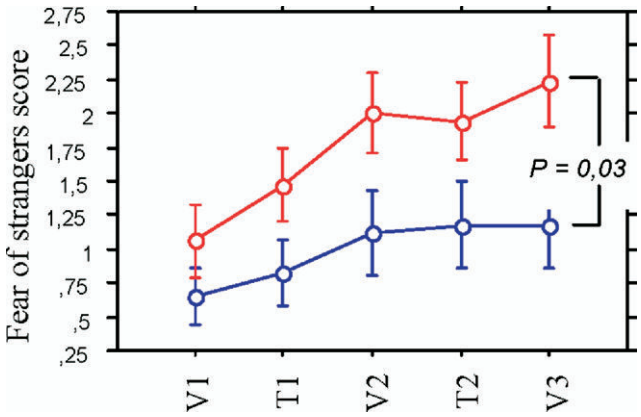

Figure 3 Comparison of scores for the item "Fear of strangers."

Relationships with Familiar and Nonfamiliar People

Both categories show an improvement with alpha-casozepine treatment when focusing on the social behavior of cats with human beings. This was the first aim of the study, and it is important to underline that, although there was no significant difference between groups at D0, we found a significant difference at D56 for familiar people (Mann-Whitney U test $P = 0.04$) and for nonfamiliar ones (Mann-Whitney U test $P = 0.03$) (Figure 3).

Fear

Even though there is no statistically significant difference at V3 regarding fear (Mann-Whitney U test $P = 0.09$), there is a difference in the rate of change, or slope, in favor of alpha-casozepine (ANOVA, $F_{(4,32)} = 3.34$; $P = 0.01$).

Autonomic Signs

For the assessment of autonomic signs, the difference at V3 is not significant, but the difference in the rate of change, or slope, is statistically significant (ANOVA, $F_{(4,32)} = 2.508$; $P = 0.04$). This finding is relevant, and many owners provided descriptions of quick relief of autonomic signs (Figure 4).

Summary

In looking through each of the 5 categories of items, we found no difference between treatment groups with respect

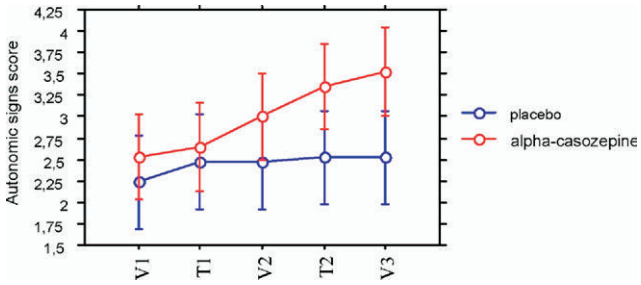

Figure 4 Comparison of scores for the item "Autonomic signs."

Table 4 Summary of detailed results

	Score	Nbr 0	Eval	Familiar humans	Unfamiliar humans	Fears	Autonomic signs	Aggression
Mann-Withney U Test	<0.01	0.04	0.09	0.04	0.03	0.09	0.16	0.70
	**	*	t	*	*	t	N.S	N.S
Anova	0.003	0.88	0.19	0.67	0.18	0.01	0.04	0.46
	**	N.S	N.S	N.S	N.S	*	*	N.S

to aggression. For all other items, as summarized in Table 4, either the difference between V1 and V3 or the rate of change is significantly different, always with alpha-casozepine treatment producing a greater effect.

Discussion

This study provides evidence for the efficacy of alpha-casozepine in the management of cats exhibiting anxiety in socially stressful conditions. Cats treated with alpha-casozepine sought contact with both familiar and unfamiliar people and showed improvement in fearful behaviors and in their associated autonomic signs.

No differences were seen in aggressive behaviors, but the study was relatively small. Behavior modification seemed to help manage or avoid the aggression, based on the data from both treatment groups.

Alpha-casozepine is a dairy ingredient that is lactose free. It has a GRAS (Generally Recognized As Safe) status and, as a natural product, it is not considered a drug in Europe. This is a desirable profile for many owners. None of the side effects occasionally reported for benzodiazepines, such as disinhibition of aggression, was seen in this study.

Conclusion

Alpha-casozepine, patented under the name of Zylkene (Ingredia, Arras, France), is a very interesting alternative in the management of anxiety in cats. In preclinical studies, it appears safe, and it is lactose free, making it suitable for most cats.

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