

The Safety of a Plant-Based Nutraceutical for Behaviour in Cats and Dogs

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ABSTRACT

Two studies were conducted to determine the safety of PID 02027010 (Oystershell NV, Belgium), a nutraceutical for dogs and cats with behavior problems. The standard dose rate is 0.5 to 1 mL/kg body weight for ≥ 3 consecutive days. The tolerability in dogs was determined in a blinded, randomized study with 24 dogs (16 males and 8 females) divided into 4 groups of 6. The dogs were treated for 15 days with a placebo, 1 \times , 3 \times , or 5 \times the labeled dose rate (divided into 2 doses, morning and evening). Based on daily observations, body weight, clinical laboratory parameters, and clinical examinations, the product was well tolerated and did not cause any adverse events. Single high doses (5, 10, and 15 mL) were tested in 3 cats (average weight of 5 kg) to assess safety and determine if single high doses could have an impact on behavior. The 5-mL dose had no impact on behavior and there were no adverse events. The 10- and 15-mL doses resulted in a mild sedative effect for approximately 2 hours in 2 of the 3 cats, but there was no dose-linearity. One cat in the

10-mL group had diarrhea that was transient and slight.

INTRODUCTION

Behavioral issues in dogs and cats can be one of the reasons that owners decide to give away their pet. Treatments based on monoamine oxidase inhibitors (eg, selegiline), tricyclic antidepressants (eg, clomipramine), and serotonin selective reuptake inhibitors are effective control methods for many situations.^{1,2} Behavioral training normally is required along with chemical treatments to obtain the maximum benefit. However, in some cases, treatment is needed for especially stressful situations, such as car travel, veterinarian visits, celebration days with fireworks, etc. Sedatives can be used for many of these situations but there are many plant-based nutraceuticals marketed as alternatives to prescription-only medicines or as additional treatments for especially stressful situations. Few data are available on the efficacy and safety of these plant-based products. One such product is PID 02027010 (Oystershell NV, Belgium).

PID 02027010 contains magnesium (5% w/v) syrup (60% v/v), alcohol (<10% v/v), water (20% v/v), and water/alcohol extracts

of 6 plants and a homeopathic solution of lepidolite, glauconite, stramonium, selenium, *Ambra grisea*, *Ignatia amara*, and *Chamomile* (>5% v/v). The plants *Ballota nigra*,³⁻⁷ *Crataegus* spp.,⁸⁻¹² *Eschscholtzia californica*,¹³⁻¹⁵ *Humulus lupulus*,¹⁶⁻²⁰ and *Valeriana officinalis*^{4,21,22} all have documented use for altering behavior. Little is known about *Lotus corniculatus* beyond its use as a feed for livestock.

Research on the individual plants has shown that, in general, they are safe when used as described in the various herbal pharmacopeia (for humans). However, *Crataegus* spp can cause hypotension and sedation when taken in large quantities.^{8,12} *E californica* might potentiate monoamine oxidase inhibitor activity, and, theoretically, concomitant use with barbiturates and other drugs with sedative properties might cause additive effects and side effects.^{13,16} Also, *E californica* cannot be used when freshly harvested due to the presence of cyanogenic glycosides.⁴ *H lupulus* has been found to be non-toxic in small doses, but excessive use over a long period may cause dizziness.¹⁶ It is recommended to avoid using *E californica* and *H lupulus* during pregnancy and lactation.^{9,23}

PID 02027010 is marketed in several European countries as a feed supplement for dogs and cats with behavioral problems. The supplement is to be fed for at least 3 days at a rate of 0.5 to 1 mL/kg body weight (BW) before any effect occurs. One study designed to determine the efficacy of the product in the treatment of chronic behavioral disorders in 31 dogs (daily treatment for 1 month at an average dose of 0.95 mL/kg BW) showed a clear improvement in 56% of the dogs based on veterinarian and owner assessments. Another 8% and 24% of the dogs showed moderate and small improvement, respectively.²⁴

No studies have been published on the safety of PID 02027010. Also, little is known about its activity in cats. To increase the information available on the safety of this product, and on nutraceuticals in general, a tolerability study was conducted in

dogs comparing 3 dose rates of the product to a placebo when administered for 15 days. In addition, a mini-trial was done in cats to determine the safety of a single high dose and if a single high dose could have an immediate impact on behavior (versus the standard of 3 or more days of treatment).

MATERIALS AND METHODS

All animals used in the 2 studies belonged to the research facilities. The dog tolerability study was conducted to GLP standards and both studies were conducted at licensed research facilities with the approval of the incumbent animal ethics committee.

Dog tolerability

The dog tolerability study was randomized, blinded, and placebo-controlled. The placebo consisted of the syrup, water, and alcohol in the PID 02027010, but did not contain the water/alcohol plant extracts, the homeopathic solution, and the magnesium. A vanilla aroma was added to help mask the differences between the placebo and test product.

Twenty-four dogs of mixed breed (16 males and 8 females, age >3 months) were divided into 4 groups of 6 (balanced by gender and weight): placebo at 5× the labeled dose rate of the product; and 1×, 3×, and 5× the labeled dose rate of the product. The labeled daily dose rate (1×), divided into 2 doses (morning and evening) added to the feed (a mixture of wet and dry food), was ≤7.5 kg, 5 mL; >7.5 to <15 kg, 7.5 mL; 15 to <20 kg, 10 mL; and ≥20 kg, 15 mL. Dogs were weighed on Study Day -7 to determine dose and for allocation to group. All groups were treated in parallel for 15 days (Study Day 0 to end of Day 14).

During the study, dogs were maintained in their normal housing at the facility. Dogs were conditioned for 7 days (Study Day -7 to -1) to the twice daily feeding; no other acclimatization was required. If a dog refused to consume all of the food (dry biscuits and wet food), the ratio of dry:wet was altered.

Safety was assessed by: 1) twice-daily observations of the dogs' behavior and feed

intake; 2) comparing body weight pretreatment (Study Day -7) to Study Days 7 and 20; and 3) clinical laboratory parameters and results of clinical examinations on Study Days -1, 7, and 15. In addition, dogs were observed from Study Day 15 through 21, after treatment was discontinued, to determine if any other adverse events occurred.

Clinical laboratory parameters included hematology and biochemistry parameters: white blood cells, lymphocytes, monocytes, granulocytes, red blood cells, mean corpuscular volume, hematocrit, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), hemoglobin, platelets, mean platelet volume, platelet distribution width, albumin, alkaline phosphatase, alanine aminotransferase (ALT), amylase, calcium (Ca), cholesterol (Chol), creatinine, globulin, glucose, total protein, total bilirubin, potassium, and blood urea nitrogen (BUN). Blood samples were analyzed on the day of collection.

Means and standard deviations were calculated on all response variables for each group and each sample. Groups were compared using analysis of variance (ANOVA) methods, if normal distribution assumptions could be met. A repeated-measurements model was used with the observed values on Study Days 7 and 15 being dependent variables; treatment group, Study Day -1 values, sex, day, and interaction group*day as independent variables; and the day effect modeled as a repeated-measures effect. In the reduction of the model, an effect was removed only if it had a P -value >0.2 . Day and group were always retained in the model. When assumptions of normality could not be met, analysis was done on observed values for each Study Day and differences to Study Day -1 values using Kruskal-Wallis and Mann-Whitney U tests. Significance was set at the 5% level.

Cat mini-trial

Two cat mini-trials were conducted. In Trial 1, 3 cats (European shorthair, age 4-5 years, weight approximately 5 kg) were

used to test 2 doses (5 and 10 mL/cat; 1 and 2 mL/kg BW). On Day 1, each cat was administered orally (via a syringe) 10 mL of the formulated product. On Day 2, each cat was administered 5 mL of the formulated product. In Trial 2, 3 cats (ages 2 to 5 years, weight approximately 5 kg) were used to test a single dose of 15 mL/cat (3 mL/kg BW). In Trial 2 (conducted the day following Trial 1), 2 of the cats used were from Trial 1; 1 cat had been removed for another study. In both trials, cats were observed and examined 0.5, 1, 2, 3, 6, and 8 hours post-treatment. Respiratory and cardiac functions were examined and the general behavior of the cats and reaction to stimuli were observed. Cats were maintained in a group pen with the standard daily diet and water ad libitum.

RESULTS

Dog tolerability

During the administration period of the product and the 7-day post-observation period, no dog was observed to have an adverse event related to the product. None of the dogs behaved abnormally and no digestive upsets such as diarrhea or vomiting were observed. Two dogs required adjustment of the ratio of dry:wet food during Study Days 1 and 2; otherwise, all dogs consumed the treatment in the feed. Physical examinations, body weight, and the blood analyses showed that the dogs maintained good health throughout the study.

While the group means of all hematology and biochemistry parameters remained within the normal range, some possible group differences were found (Table 1):

1. MCHC: There was a dose-linear increase with group 4 (5 \times) being significantly higher than group 1 (placebo) ($P = 0.0141$); however, group 2 (1 \times) was higher than group 3 (3 \times), though not significantly different.
2. RDW: There was a dose-linear increase with group 4 being significantly higher than group 1 ($P = 0.0041$).
3. ALT: There was a dose-linear decrease with group 4 being significantly lower than group 1 ($P = 0.0091$), especially in light of higher baseline values for group 4.

4. BUN: There was a dose-linear decrease with groups 3 ($P = 0.0341$) and 4 ($P = 0.0186$) being significantly lower than group 1 (in the non-parametric test, this appears only in group 3 ($P = 0.0238$); however, baseline values are reduced in these groups as well).
5. Ca and Chol: group differences were found but were not believed to be real differences, especially since none of the groups could be shown to be different from the control group in a pairwise comparison.

During the study, 2 dogs (1 pre-treatment and 1 on Study Days 20 and 21) were given antibiotics due to injuries incurred while playing with other dogs. These treatments were not believed to have an impact on the study outcome.

Cat mini-trial

In Trial 1, the 10-mL dose resulted in mild sedation (resting on side in cage, not responding to stimuli, reluctant to move) of 2 of the 3 cats, which lasted for approximately 2 hours. One of these cats, in which the sedative effect lasted slightly longer, developed slight diarrhea within 1.5 hours of treatment. In the third cat, there was no effect. At the 5-mL dose, there was no effect in any of the cats and no adverse events in any of the cats. In Trial 2, the 15-mL dose resulted in mild signs of sedation (resting on side in cage, not responding to stimuli, reluctant to move) in 2 cats 0.5 and 1 hour post-treatment. There was no effect on the other cat. There were no adverse events in any of the cats. There were no temperature changes or changes to the respiratory or cardiac rate in any of the cats in either trial.

DISCUSSION

Based on the dog tolerability study, the product is safe at up to $5\times$ the labeled dose rate and up to 3 times the standard length of treatment if used as a short-term treatment for expected stressful events (5 days treatment: 3 pre-event for the product to work and 2 during the event [eg, car trip]). No explanation for the dose-linear changes in some blood parameters could be identified. The 2 parameters of most concern were ALT and BUN. ALT increases are normally due

to liver damage or disease. However, in this case, ALT levels decreased. BUN decreases can be caused by liver failure, malnutrition, and/or over-hydration. There were no other symptoms of liver failure, the dogs were on a well-balanced diet, and none of the dogs were observed to be drinking or urinating excessively. Given that all values were within the normal range, it is believed that the results could be coincidental and of no importance. However, if the product were to be used at high doses for extended periods of time, further investigation might be required to confirm that these results were coincidental.

In the cat mini-trial, the high dose was difficult to administer. The doses of 10 and 15 mL did not seem to result in significant differences. However, this could have been caused by the stress induced when trying to administer the large quantity. There did not appear to be any carryover effect between treatments, since the 5 mL dose was administered after the 10 mL dose, and the 5 mL dose had no impact. It was concluded that a concentrated formula would be preferable if a high dose was to be used to obtain an immediate effect on behavior and that the level of compounds in the 10-mL level could be the basis for a re-formulation. In addition, a concentrated formula, with less syrup could decrease the side effect of diarrhea.

CONCLUSION

Based on these studies and previously published literature on PID 02027010, the product does have some impact on behavior and is safe at the recommended application rate. A new formulation would be required if a quick-acting, short-term effect is desired for unplanned stressful events. Also, additional studies are needed to evaluate the safety of long-term use of the product and to determine if the product can be used at the same time as other products. Lastly, studies such as these need to be conducted on more of the nutraceuticals available for cats and dogs to ensure the safety of the products and to make consumers more aware of some of the potential side effects.

Table 1. Means and Standard Deviations for Hematology and Biochemistry Parameters for Which Possible Differences Were Seen.

Parameter	Group	Study Day -1		Study Day 7		Study Day 15	
		Mean	SD	Mean	SD	Mean	SD
Mean corpuscular haemoglobin concentration (g/dL)	1	31.52	1.52	33.07	1.47	31.20	1.17
	2	32.60	2.55	33.65	1.81	32.72	1.68
	3	32.08	1.87	33.03	1.45	32.20	1.92
	4	32.67	2.17	34.12	0.90	34.23	1.85
Red cell distribution width	1	8.32	0.26	8.35	0.36	8.65	0.21
	2	7.95	0.25	8.23	0.31	8.58	0.21
	3	8.25	0.26	8.23	0.26	8.97	0.39
	4	8.35	0.32	8.53	0.10	9.13	0.35
Alanine aminotransferase (U/L)	1	43.7	17.6	48.8	27.5	48.8	28.7
	2	44.5	9.4	42.3	6.2	44.3	9.1
	3	44.5	15.9	48.5	24.5	51.5	29.6
	4	49.2	20.1	43.2	15.3	45.0	15.9
Blood urea nitrogen (mmol/L)	1	4.75	0.75	5.05	0.71	5.05	0.52
	2	5.15	1.21	4.98	1.21	4.90	1.29
	3	4.20	1.08	4.25	0.70	4.05	0.58
	4	4.62	1.09	4.35	1.10	4.37	0.81
Calcium (mmol/L)	1	2.900	0.272	2.970	0.312	2.588	0.205
	2	3.083	0.449	3.232	0.939	2.470	0.099
	3	3.113	0.364	2.818	0.193	2.743	0.155
	4	3.000	0.282	3.108	0.774	2.640	0.172
Cholesterol (mmol/L)	1	5.97	0.96	6.07	0.90	6.22	0.79
	2	6.57	1.10	6.32	0.77	6.28	0.62
	3	7.08	1.02	6.80	0.86	6.93	1.01
	4	6.45	0.95	6.78	1.37	6.75	1.07

SD = standard deviation.

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