Comparison of the effects of adrafinil, propentofylline, and nicergoline on behavior in aged dogs

Christina T. Siwak, HBSc; Philippe Gruet, DVM; Frédérique Woehrlé, DVM; Bruce A. Muggenburg, DVM, PhD; Heather L. Murphey, BA; Norton W. Milgram, PhD

Objective—To compare the efficacy of adrafinil, propentofylline, and nicergoline for enhancing behavior of aged dogs.

Animals—Thirty-six Beagles between 9 and 16 years old.

Procedure—Dogs were randomly assigned to receive adrafinil (20 mg/kg of body weight, PO, q 24 h; n = 12), propentofylline (5 mg/kg, PO, q 12 h; 12), or nicergoline (0.5 mg/kg, PO, q 24 h; 12) for 33 days. Baseline behaviors in an open field and in kennels (home cage) were recorded before treatment. After treatment, behaviors in the open field were recorded 2 hours after drug administration on days 2, 15, and 28, and 10 hours after administration on days 7, 20, and 33. Behaviors in the home cage were recorded 2 and 7 hours after drug administration on days 4, 17, and 30.

Results—Treatment with adrafinil resulted in a significant increase in locomotion in each of the open-field tests and an increase in locomotion in the home cage. This latter increase was smaller and more variable than that in the open field. Locomotion was not affected by treatment with propentofylline or nicergoline. In the open field, sniffing decreased over time in all 3 groups, but the largest decline was observed in the propentofylline group.

Conclusions and Clinical Relevance—Treatment with adrafinil may improve the quality of life of aged dogs by increasing exploratory behavior and alertness. (Am J Vet Res 2000;61:1410-1414)

The development of deprenyl for treatment of cognitive dysfunction in dogs has led to considerable interest in the possibility of using pharmaceuticals to enhance the quality of life in senescent companion animals. In particular, 3 pharmaceuticals, adrafinil, propentofylline, and nicergoline, are purported to increase activity of aged dogs.

Adrafinil is a novel stimulant that is used in Europe to improve vigilance, attention, memory, and mood problems associated with aging. Results of studies in laboratory animals have consistently indicated that locomotion increases after adrafinil treatment without development of stereotypy and sympathetic effects. Increased activity has been detected in mice, rats, and dogs. Similar locomotor-enhancing effects have been obtained with modafinil, an active metabolite of adrafinil. A previous study from our laboratory indicates that adrafinil increases locomotion in aged dogs, with the minimum effective dose being 20 mg/kg of body weight. This increase in activity lasted for at least 10 hours after dosing and was maintained for more than 14 days of drug administration. We have also found that adrafinil can enhance cognitive function in aged dogs. Dogs given adrafinil had an increased rate of discrimination learning, compared with dogs treated with a control substance. Adrafinil is believed to function as a central noradrenergic agonist, specifically affecting α1-adrenoceptors. Recent studies indicate that adrafinil also may act through inhibition of γ-aminobutyric acid nerve fibers or increases in cerebral metabolism.

Propentofylline is a xanthine derivative that inhibits adenosine uptake and reduces free-radical generation. Adenosine has direct effects on the vascular system and CNS. It acts as a vasodilator and may influence neurotransmitter release and neuronal firing. Propentofylline can reverse deficits in learning and memory caused by basal forebrain damage in rats. It also has been reported to enhance performance of an avoidance task in mice. Propentofylline is commercially available in the United Kingdom to improve the quality of life of aged dogs. Clinical trials with propentofylline also are underway to assess the efficacy of this drug for treatment of humans with Alzheimer’s disease.

Nicergoline, an ergoline derivative, is commercially available in Europe and reportedly improves the quality of life of aged dogs. Nicergoline functions as an α1-adrenoceptor antagonist. It induces vasodilation, increased acetylcholine release from the hippocampus, and improvement in learning and memory in rats. Nicergoline improves vigilance and memory in elderly, presenile, and hypoxic humans.

The objective of the study reported here was to compare the efficacy of adrafinil, propentofylline, and nicergoline for enhancing behavior of aged dogs. Behavior was observed in an open-field test described by Head and Milgram and a home-cage test specifically developed for this study. Drugs were administered daily for 33 consecutive days to allow for the possibility that repeated treatment was required before behavioral improvement could be observed.

Materials and Methods

Dogs—Thirty-six Beagles (18 males, 18 females) between 9 and 16 years old and weighing between 6.2 and 14.9 kg were included in the study. Dogs were housed in kennels.
period.

Experimental protocol—Each dog was observed during
2 open-field tests performed before treatment was initiated
(day 0). The mean locomotion score of these 2 tests consti-
tuted the baseline locomotion score. Dogs then were assigned
to 1 of 3 treatment groups, using a counterbalancing pro-
cedure that took into account sex and baseline locomotion
score. Each group had the same number of males and females,
and baseline locomotion score was equal among groups.

Treatment groups were as follows: adrafinil (20 mg/kg,
PO, q 24 h; n = 12), propentofylline (5 mg/kg, PO, q 12 h;
12), and nicergoline (0.5 mg/kg, PO, q 24 h, 12). Dogs were
weighed prior to baseline measurements; this weight was
used to determine amount of drug administered for the entire
study. Variations in body weight during the treatment period
may have resulted in the following dosage ranges: adrafinil,
18 to 25 mg/kg, PO, q 24 h; propentofylline, 4 to 7.5 mg/kg,
PO, q 12 h; and nicergoline, 0.4 to 0.65 mg/kg, PO, q 24 h.

The dosage of adrafinil used was based on the results of
a previous study6 indicating that 20 mg of adrafinil/kg/d was
the minimum effective dosage required to observe a consist-
ten increase in locomotion. Dosages of propentofylline and
nicergoline used were recommended by the manufacturer.

Drugs were administered for 33 days. Baseline open-field
tests were performed 10 and 6 days before the treatment
phase. Open-field tests during the treatment phase were per-
formed 2 and 10 hours after the morning administration of
drugs. The 2-hour open-field tests were done on days 2, 15,
and 28 of treatment, whereas the 10-hour tests were done on
days 7, 20, and 33. Baseline home-cage tests were performed
8 and 4 days before the treatment phase. Home-cage tests dur-
ing the treatment phase were performed 2 and 7 hours after
the morning administration of drugs on days 4, 17, and 30.

On test days, drug administration began at 7 AM, and
subsequent dogs were administered their drugs at 15-minute
intervals until all dogs had been tested that day had received
their treatment. Open-field testing started at 9 AM on days 2, 15,
and 28 and proceeded at 15-minute intervals. On days 7, 20,
and 33, open-field testing started at 5 PM prior to the second
daily administration of propentofylline and proceeded at 15-
minute intervals. Home-cage testing started at 9 AM and 2 PM
on days 4, 17, and 30 and proceeded at 10-minute intervals.
Because some dogs were housed in pairs, home-cage testing
could be completed in less time than open-field testing. The
dogs were arbitrarily assigned to 2 groups of 18 dogs to facili-
tate testing. Treatment was identical in all respects except
that group 2 began treatment 1 day later than group 1.

Preparation of drugs—Adrafinil was obtained as a raw
powder.7 Propentofylline8 and nicergoline9 were obtained in
prepackaged tablets, which were crushed into a powder.
Correct doses of all 3 drugs were measured for each dog and
placed into capsules. To ensure that persons involved with
treatment and behavioral testing were not aware of treatment
group, body weights were not associated with dog identifica-
tion numbers. Capsules were placed into balls of commer-
cially available canned food,1 which were then fed to the
dogs. All 3 drugs were administered in the morning at least 4
hours before the dogs were fed. The second daily dose of
propentofylline was administered in the afternoon, approxi-
mately 12 hours after the morning dose and at least 1 hour
after feeding. Dogs in the other 2 treatment groups received
a second ball of canned food without drugs at the same time.

Behavioral testing procedures—Open-field testing was
performed in a 3.81 × 2.35-m test arena. The arena was erect-
ed within a larger room, using a wooden barrier bolted to the
floor. A hinged door was installed to provide access to the
arena. The floor of the arena was marked into 36 rectangles
(61.6 × 36.2 cm) with black electrical tape to simplify tracing
of behavior patterns. Prior to each test, the floor was cleaned
with a disinfectant solution to prevent disruptive effects of
odor cues from other dogs.

Test sessions lasted 10 minutes. Each dog was placed in
the arena immediately inside the hinged door and was
observed by an investigator who recorded the animal’s behav-
ior with a video camera. Videotapes were analyzed, using
dedicated computer software2 that provided quantitative
measures of locomotion, directed sniffing, urination, inactiv-
ity, grooming, rearing, vocalization, and jumping. For loco-
motion, grooming, and inactivity, the program provided a
measure of total distance (locomotion) or duration (groom-
ing, inactivity). Number of times each of the other behaviors
was observed (ie, frequency of that behavior) was recorded.
For grooming, we obtained frequency and duration. To min-
imize variability and bias, all of the behavioral observations
were analyzed by the same person (CTS) who was not aware
of the respective treatment groups.

Home-cage testing was performed in each dog’s kennel.
A video camera was placed on a tripod in front of the kennel,
and behavior was recorded for 10 minutes. The videotape
then was analyzed, using the same computer program as that
used for the open-field tests. Grooming behavior was not
recorded for dogs housed in pairs. Instead, interaction dura-
tion and frequency were recorded.

Statistical analyses—All statistical analyses were per-
formed, using commercially available software.3 Significance
was set at P < 0.05. Locomotion and sniffing were the only 2
behaviors observed during every test (Fig 1). Accordingly,
statistical analyses focused on locomotion and sniffing.
Locomotion and sniffing were compared over time by use of
a repeated-measures ANCOVA. Mean baseline was the
covariate, and drug treatment was a between-subjects factor.
Duration of treatment and the drug-test interval served as
repeated-measures factors. Results of home-cage tests were
analyzed by use of a repeated-measures ANCOVA. Duration
and interval served as within-subject factors, and treatment
group was a between-subjects factor. The respective baseline
scores served as covariates for each interval. Where appro-

FIG 1—Number of dogs for which each class of behavior was observed during baseline open-field (OF) and home-cage (HC) tests. AM = tests in AM; PM = tests in PM.
appropriate, the Tukey HSD test was used for multiple comparisons. Other behaviors were recorded, and effect of drug treatment on each behavior was assessed with the same statistical tests.

**Results**

**Open-field testing**—Compared with the pretreatment value, locomotion increased significantly after treatment with adrafinil (Fig 2). This increase was sustained throughout the treatment period. Locomotion was not affected by treatment with the other 2 drugs. Overall, locomotion in the adrafinil group was greater 2 hours after drug administration than it was 10 hours after administration (Fig 3). A separate analysis of the data collected 10 hours after administration revealed that locomotion remained higher in the adrafinil group, compared with the other 2 groups, but the difference among groups was not significant. The pattern of behavioral activity was idiosyncratic, and we did not find evidence that any of the drugs affected the pattern.

Sniffing frequency decreased significantly over time in all 3 groups. We also detected a significant drug-by-duration interaction attributable to the largest decrease in sniffing frequency over time in the propentofylline group.

All other behaviors measured were not affected by drug treatment.

**Home-cage testing**—A significant main effect of drug on locomotion was detected (Fig 4); locomotion increased after treatment with adrafinil. This effect persisted for the duration of the treatment phase. Drug-test interval also significantly affected locomotion. Locomotion was greater during the 2-hour test, compared with the 7-hour test. There was a significant effect of treatment duration on sniffing frequency during the 2-hour test but not during the 7-hour test. Overall, there was a significant drug effect, because there was less sniffing observed in the adrafinil group than the other 2 groups.

All other behaviors measured were not affected by drug treatment.

Behavioral activity patterns for each dog in the home cage were more variable than in the open field. The pattern depended, in part, on the weather (part of the home cage was outside) and, in part, on time of day. We did not detect evidence of any drug effect.

**Discussion**

![Figure 2](image_url)  
**Figure 2**—Mean ± SEM locomotion score (distance, in meters) determined during open-field testing of aged dogs before (day 0) and after daily treatment with adrafinil (n = 12), nicergoline (12), or propentofylline (12). *Value significantly (P < 0.05) different from baseline value determined for the same group. **Value significantly (P < 0.05) different from values determined for the other 2 groups at the same time.*

![Figure 3](image_url)  
**Figure 3**—Computer-generated activity patterns determined during open-field testing of aged dogs before (baseline) and 2 and 10 hours after administration of adrafinil (ADR; n = 12), propentofylline (PRO; 12), or nicergoline (NIC; 12). Each pattern is a representative activity pattern of 1 dog from each drug group. Lines represent the path of each dog around the test room.
Adrafinil was the only 1 of the 3 drugs tested that was effective in enhancing behavior (ie, locomotion) of aged dogs. This result supports and extends results of a previous study by indicating that the activity-enhancing effect of adrafinil persisted during daily treatment for >28 days. The increase in locomotion induced by adrafinil is also consistent with findings in other species. The failure to find any effect of the other 2 drugs was surprising in light of the claims made for these drugs. This failure was not attributable to dosage used; we used the prescribed dosages for both drugs. It is not likely that the effectiveness of either of these drugs would have changed if the study had been prolonged. Results of 1 study that evaluated nicergoline are consistent with results of the study reported here. In that study, nicergoline did not modify locomotion in aged rats.

The home-cage results were similar to the open-field results, because adrafinil was the only drug to induce a significant increase in locomotion. The magnitude of this increase, however, was considerably smaller in the home-cage test than in the open-field test. This difference is probably related to environmental familiarity. We previously found that the open-field effect of adrafinil is diminished in dogs that are familiar with the open-field test room. Similar results also have been reported for rats treated with amphetamine; familiar environments appear to attenuate the activity-enhancing effects of some drugs. On the other hand, amphetamine-like effects also result in increased stereotypy, which may be represented in activity patterns. Each dog has a characteristic pattern of behavior in the open field, which is identifiable with repeated testing. The general pattern detected in the study reported here and our previous study was unchanged by treatment with adrafinil.

The only other behavior that changed significantly during the study was directed sniffing. Sniffing frequency decreased during the treatment period, particularly in the open-field test and in the propentofylline group. Although sniffing scores were lowest in dogs treated with adrafinil, the difference among groups was not significant.

Results of the study reported here, coupled with results of a previous study indicating that adrafinil enhanced performance on a discrimination learning task, suggest that adrafinil may enhance the quality of life of aged dogs. In addition, our results provide justification for testing adrafinil in clinical trials with aged inactive dogs.

References


