

Lethargy Following use of ProMeris® Duo in Dogs – Myths and Facts

R. A. Pollet BS, MS, PhD
A. Boeckh DVM, PhD, DACVCP
R. Cobb BVSc (Hons), MACVSc

*Fort Dodge Animal Health
P.O.Box 5366
Princeton, NJ 08543-5366 USA*

KEY WORDS: ProMeris, metaflumizone, amitraz, lethargy, safety, dogs

ABSTRACT

ProMeris® Duo (or ProMeris for dogs) is a novel topical ectoparasiticide containing metaflumizone and amitraz to treat and prevent infestations of fleas and ticks and to treat lice and demodectic mange on dogs. The Internet is a valuable tool for accessing and disseminating information; however, this electronic medium has also become a means for the rapid spread and expansion of rumors which may or may not be based on accurate scientific information. Following the launch of ProMeris Duo, there was a low incidence of reports of transient sedation and lethargy from clients who used ProMeris Duo on their dogs. To evaluate and address this potential concern and other theories propagated by individuals through the Internet, Fort Dodge Animal Health (FDAH) conducted a series of post-registration studies. These studies included blood level and clinical evaluations on dogs in the laboratory and home settings. Conclusions based on the results of these studies are: 1) Lethargy and sedation are rare when ProMeris Duo is applied according to the label; most cases of lethargy are due to accidental oral ingestion of the product when the product is applied incorrectly, and not due to dermal absorption, 2) Application of ProMeris Duo to dogs that also had amitraz impregnated collars did

not lead to adverse events, 3) ProMeris Duo did not induce adverse events in dogs under treatment with a behavior modifying drug (i.e., fluoxetine HCL), and 4) Administration of the highly selective alpha-2 agonist dexmedetomidine to dogs treated with ProMeris Duo did not produce adverse side effects. These studies demonstrate that it is best to review product labels and results from well-controlled scientific studies when using new products rather than believe information posted on the Internet.

INTRODUCTION

When products are initially introduced to the marketplace, myths, theories and/or anecdotal evidence based on misinformation are propagated by individuals through the Internet. Multiple postings of a single comment can lead to a false impression of widespread issues. ProMeris Duo (ProMeris for Dogs in the USA) is a novel topical ectoparasiticide containing metaflumizone and amitraz to treat and prevent infestations of fleas and ticks and to treat lice and demodectic mange on dogs. The purpose of this article is to address some of the misinformation regarding ProMeris Duo and to provide veterinarians with facts and guidance in dealing with reports of lethargy in dogs following use of this product. It is well recognized that it is best to review the product label and results from well-controlled scientific studies when using new products.

The safety of ProMeris Duo has been established in puppies and adult dogs, with repeated doses as high as five times the label dose administered topically (Heaney and Lindahl 2007), and in pregnant and lactating dogs (EMEA 2009). The novel ProMeris Duo formulation, which is applied at a single spot at the base of the head or between the shoulder blades, rapidly spreads over the surface of the animal's body, providing highly therapeutic levels of the active ingredients on the surface of the skin and hair (Sabnis and others 2007). Both in a controlled laboratory study (DeLay and others 2007), and following application in a household situation, assays of plasma samples indicated very little, if any, amitraz or metaflumizone had been absorbed in individual animals following topical application of ProMeris Duo. This was expected, as the formulation is not designed for transdermal delivery. The results of prior animal studies, including evaluations in veterinary practices of approximately 400 client-owned dogs of various breeds, ages, and in single and multi-pet households (e.g., Hellmann and others 2007), indicated adverse events are rare when the product is properly applied.

Following the launch of ProMeris Duo, there was a low incidence of reports of transient sedation and lethargy from clients who used ProMeris Duo on their dogs. Typically, the clients described a reduction in normal activity that was mild and resolved within 24 hours without any medical treatment. Internet reports (often multiple reports of the same incident attributed to different postings) speculated that there was dermal absorption of amitraz accompanied by dire consequences and also conjectured on the potential for other therapeutic and/or drug-drug interactions. To address these potential concerns, Fort Dodge Animal Health (FDAH) conducted a series of post-registration evaluations.

MATERIALS, METHODS AND RESULTS

Lethargy Investigation

The first two studies evaluated the potential for oral exposure of the active ingredients

and excipients to induce lethargy. Various formulations with and without the active ingredients were evaluated in groups of six dogs each. The dogs were dosed orally with one-tenth of the label (topical) dose of ProMeris Duo or other test formulations. This one-tenth oral dose was thought to be a considerable over-dose compared to the amount a dog could orally ingest via licking following topical application, based on previously conducted dislodgement studies. After oral treatment, the dogs were observed and evaluated at defined intervals post-dosing for clinical and neurological signs (e.g., behavior, heart rate, body temperature), and blood samples were collected and assayed to determine if the components of ProMeris Duo could be detected and/or quantified in plasma.

Dogs that were treated with the ProMeris Duo vehicle (i.e., the formulation without the active ingredients) or the vehicle with metaflumizone only did not display sedation or lethargy. The majority of dogs treated with oral doses of formulations containing amitraz displayed a small decrease in body temperature and about half showed signs of sedation or lethargy approximately 0.5 to 2 hours after treatment, and lasting up to 12 hours. The signs were mild and transient and were consistent with mild amitraz toxicity (Hugnet and others 1996). There was no apparent correlation between the occurrence of sedation or lethargy and plasma concentrations of the excipients, amitraz or metaflumizone. The concentrations of amitraz and amitraz metabolites were extremely low and there was no threshold level of amitraz that correlated with sedation or lethargy, confirming that sensitivity varied among individual dogs.

In a subsequent study, 18 dogs, most of which had previously showed signs of sedation or lethargy when treated orally at a one-tenth topical dose, did not show any adverse signs (including sedation or lethargy) when treated topically between the shoulder blades with a full label dose of ProMeris Duo. In addition, there was no change in body temperature. The outcome of these

three laboratory studies demonstrates that the pattern and timing of sedation and lethargy after oral administration is similar to that seen in reports from the field of lethargy and sedation. Therefore, the suspicion that the reported lethargy was most likely due to accidental oral ingestion of the product and not dermal absorption was confirmed.

Further investigations were undertaken to determine if there could be differences in laboratory dogs compared to dogs in the home use setting. Volunteers were recruited to treat their dogs according to the product label. The 263 dogs that were treated with ProMeris included a variety of breeds, ranged in weight from 1.4 to 68 kg, and were from 8 weeks to 15 years of age. Volunteers were given verbal directions on how to apply the product correctly and provided with the product label. They were also educated on the signs of lethargy and sedation and asked to return to local veterinarians for evaluation and collection of blood samples for analysis if adverse signs occurred. During the recruitment process, we were surprised to learn that many of the owners had previously treated their animals incorrectly, either by emulating instructions from other products or even by instruction from their own veterinarians. Incorrect application of ProMeris Duo included using multiple spots or a stripe along the back. The product label instructions indicate ProMeris Duo should be applied as a single spot between the shoulders or at the base of the head. Clearly, applying ProMeris Duo to the lower portion of the back would allow dogs to reach the treatment site and ingest a portion of the product while it was still wet.

Of the 263 dogs that were treated according to the ProMeris Duo label, only one animal was reported as being “not herself” by the owner. This dog did not seem to be sedated or lethargic when examined by the veterinarian approximately 8 hours after treatment and did not show a decreased body temperature. This dog had a reported history of lethargy on two prior occasions when ProMeris Duo had been applied in

multiple spots. Thus, when a large number of dogs were treated by their owners in normal household settings in accordance with the label directions, lethargy following treatment was rare. The results of this evaluation emphasize the importance of proper product application and for veterinarians and clients to adhere to the product label instructions.

Investigation of ProMeris Duo in Conjunction with Collars Containing Amitraz

Another potential concern that was raised involved treatment of dogs with ProMeris Duo in conjunction with collars impregnated with amitraz. Individuals propagated the theory that amitraz overdose could occur when both treatments are given simultaneously, despite already published information confirming the lack of significant absorption of amitraz from topically applied ProMeris Duo (DeLay and others 2007). While it is unlikely that co-administration of two highly effective tickicides would be necessary or even recommended by veterinarians, the over-the-counter availability of some flea and tick control products could not preclude this possibility. We therefore conducted a study to investigate this concern. Sixteen dogs ranging in weight from 4.6 to 40 kg, were treated with ProMeris Duo spot-on on Days 0 and 14. On the same day (Day 0) the first ProMeris Duo treatment was given, a commercial collar impregnated with amitraz (Preventic® 2 Months Tick Collar; Virbac) was applied to eight of the dogs. Even with the amitraz collar and two ProMeris Duo treatments within 14 days, there were no differences in the clinical parameters, clinical chemistry or hematology when compared to the control group treated with ProMeris Duo only. Application of ProMeris Duo to dogs that also had amitraz impregnated collars did not lead to adverse events.

Investigation of ProMeris Duo with Behavior Modifying Drugs

A third possible concern that gained credence through Internet sites involved the possible interaction of amitraz with monoamine oxidase (MAO) inhibitors. While no actual published report of such

interaction was found by these authors, the theory presented on the Internet postings was that dogs receiving behavior modifying drugs, such as the serotonin reuptake inhibitors clomipramine HCl (Clomicalm®; Novartis) or fluoxetine HCl (Reconcile®; Lilly), could experience adverse events with ProMeris Duo. To address this concern, six Beagles were treated daily for 35 days with the label dose of fluoxetine. A control group of six dogs was not pre-treated with fluoxetine. Following this pre-treatment, both groups were administered a topical commercial dose of ProMeris Duo. Several of the fluoxetine-treated dogs had dilated pupils and slow pupillary reflexes prior to treatment with ProMeris Duo. The administration of ProMeris Duo did not alter the condition of the dogs. ProMeris Duo did not induce adverse events in dogs under treatment with a behavior modifying drug.

Investigation of ProMeris Duo with Alpha-2 Adrenergic Agonists

The final potential concern that will be discussed in this article involves the mechanism of action of amitraz. It was theorized by some clinicians that due to the similarity between octopaminergic receptors in invertebrates and alpha-2 adrenergic receptors in mammals, amitraz could potentially interact with compounds that have alpha-2 adrenergic agonist activity if amitraz was systemically absorbed following application to the skin. However, no actual report of interaction of the metaflumizone and amitraz combination with alpha-2 adrenergic agonists is known or can be found in the published literature. Although prior work indicates amitraz is very poorly absorbed following topical administration of ProMeris Duo, the potential interaction remained a question in the minds of some individuals.

To address this concern, a study was conducted in seven healthy Beagle dogs previously fitted with telemetry devices for monitoring cardiopulmonary parameters. Each dog was sedated with the alpha-2 adrenergic agonist dexmedetomidine HCl (Dexdormitor®; Pfizer) twice (3 days apart)

according to the product label, first without any pre-treatment (control, Day 0), and subsequently on Day 3, approximately 24 hours after treatment with ProMeris Duo. The timing was such that it allowed ProMeris Duo to spread across the skin and hair before the second dexmedetomidine treatment. Temperature, heart rate, respiratory rate, and blood pressure were monitored prior to induction of sedation, and subsequently, every 10 minutes until reversal with atipamezole (Antisedan®; Pfizer) 60 minutes after induction.

There were no adverse signs and values for temperature, heart rate, respiratory rate. Mean systolic and diastolic arterial blood pressures were not different after the administration of dexmedetomidine to dogs that had not been pre-treated or had been pre-treated with ProMeris Duo. These results are not surprising since very little amitraz is absorbed following topical administration. Administration of the highly selective alpha-2 agonist dexmedetomidine to dogs treated with ProMeris Duo did not produce adverse side effects.

DISCUSSION

When new products are introduced to the market it is appropriate to consider potential concerns based on the mechanism of action and concurrent therapies. However, the examples presented in this article document that it is critically important to replace theories, rumors and Internet chatter with actual data from scientific studies. If in any doubt, veterinarians can obtain factual information from technical support personnel employed by the company that manufactures and/markets the product in question. It is equally important for clinicians to carefully read and adhere to product labels, including directions as to how the product should be administered. Label directions are written after completion of extensive studies and are the best specific guidance for the safe and effective use of any product.

REFERENCES

1. DeLay, R.L., Lacoste, E., Mezzasalma, T., & Blond-Riou, F: Pharmacokinetics of metaflu-

- mizone and amitraz in the plasma and hair of dogs following topical application. *Veterinary Parasitology* 150: 251-257, 2007.
2. EMEA (2009) ProMeris Duo European Public Assessment Report. <http://www.emea.europa.eu/vetdocs/vets/epar/promerisduo/promerisduo.htm>. Additional data on file.
 3. Heaney, K. & Lindahl R.G: Safety of a topically applied spot-on formulation of metaflumizone plus amitraz for flea and tick control in dogs. *Veterinary Parasitology* 150: 225-232, 2007.
 4. Hellmann, K., Adler, K., Parker, L., Pfister, K., DeLay, R.L. & Rugg, D: Evaluation of the efficacy and safety of a novel formulation of metaflumizone plus amitraz in dogs naturally infested with fleas and ticks in Europe. *Veterinary Parasitology* 150: 239-245, 2007.
 5. Hugnet, C., Buronfosse, F., Pineau, X., Cadoré, J.-L., Lorgue, G., Berny, P.J: Toxicology and kinetics of amitraz in dogs. *American Journal of Veterinary Research* 57(10): 1506-1510, 1996.
 6. Sabnis, S., Zupan, J. & Gliddon, M: Topical formulations of metaflumizone plus amitraz to treat flea and tick infestations on dogs. *Veterinary Parasitology* 150, 196-202, 2007.