Safety Profile of Moxidectin (ProHeart 6) and Two Oral Heartworm Preventives in Dogs

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KEY WORDS: Adverse events, dogs, heartworm, moxidectin (ProHeart 6), pharmacovigilance, vaccines

ABSTRACT

Medical records of a nationwide veterinary practice (Banfield, the Pet Hospital) were evaluated to determine the incidence of adverse events and particular health problems following administration of the sustained-release injectable heartworm preventive moxidectin (ProHeart 6), 2 oral monthly heartworm preventives, and/or vaccines in dogs. Similar information was reviewed for dogs receiving neither heartworm preventives nor vaccines. The safety profile of these products was comparable. However, ProHeart 6 was associated with a 27% increased risk of mast cell tumor (2.1 per 10,000 exposures), while one of the oral heartworm preventives was associated with a 23% increased risk of death (22.0 per 10,000 exposures). This analysis of medical records for more than 7 million office visits and over 2 million dogs demonstrates the feasibility of using large electronic databases to test hypotheses generated by spontaneous adverse event reports to the United States Food and Drug Administration Center for Veterinary Medicine. In addition, information can be generated on baseline occurrences of certain conditions in a large population of dogs presented to veterinary hospitals across the United States.

Presented in part to the Veterinary Medicine Advisory Committee of the Food and Drug Administration, Center for Veterinary Medicine, Rockville, MD, at a public hearing on ProHeart 6, January 31, 2005.

INTRODUCTION

ProHeart 6 (moxidectin) was launched by Fort Dodge Animal Health (Overland Park, KS) in June 2001 with an indication to prevent canine heartworm disease caused by *Dirofilaria immitis* for 6 months and to treat existing larval and adult stages of the canine hookworm *Ancylostoma caninum*. Since ProHeart 6 was introduced to the market, the United States Food and Drug

Administration's (FDA) Center for Veterinary Medicine (CVM) has reported that they have received nearly 5,500 reports of serious adverse drug reactions attributed to ProHeart 6.[1] Of these adverse event reports, at least 1,900 were thought by CVM to be unrelated to the concurrent administration of other drugs or vaccines. Many of these events were judged by CVM to be severe, including more than 600 reports of death. Following discussions with CVM, Fort Dodge Animal Health announced on September 3, 2004, that it was voluntarily ceasing production and recalling ProHeart 6 from the market pending a review by an independent scientific panel.

Prelicensing studies of ProHeart 6 by Fort Dodge Animal Health did not reveal any serious adverse events. Healthy dogs treated with ProHeart 6 either 1, 3, or 5 times at the recommended dose of 0.17 mg/kg did not demonstrate any clinical signs, laboratory findings, or necropsy lesions associated with systemic or target organ toxicity.[2] In addition, when ProHeart 6 was administered to healthy 10-week old puppies at 3 or 5 times the recommended dosage or to genetic lines of Collie dogs sensitive to administration of ivermectin, no clinical or laboratory abnormalities were observed. Field studies of ProHeart 6 in 374 client-owned dogs treated twice at 6-month intervals at the recommended dose by veterinarians in 4 different states resulted in the following observed adverse events: vomiting (3 dogs), diarrhea (2 dogs), weight loss (2 dogs), listlessness (1 dog), injection site pruritus (1 dog), and elevated body temperature (1 dog). However, prelicensing safety and efficacy studies such as these typically involve fewer than 500 dogs and lack sufficient statistical power to identify relatively rare, though possibly serious, adverse events. As a result, rare drug-associated adverse events are not well characterized until after widespread marketing.[3]

Postmarketing surveillance of veterinary drug-associated adverse events currently depends on passive, spontaneous reporting by pet owners and veterinarians directly to the pharmaceutical company or CVM. When the number of spontaneous reports is sufficient to signal a potential safety problem, the same regulatory agency (CVM) that licensed the drug reviews the findings and may implement several decisions. These may range from no further action required, requesting changes to the approved labeling, requesting the drug be voluntarily withdrawn from the market, referring the matter to a CVM Advisory Committee for advice, or requesting that further studies be conducted to better understand the postmarketing observations. Spontaneous reporting of adverse events alone, whether to the pharmaceutical company or CVM, cannot by itself be used to calculate incidence rates of drug-associated adverse events, since the number of adverse events that actually occur and the number of dogs that received a drug (the population at risk) are both unknown. Following voluntary recall of ProHeart 6, Fort Dodge Animal Health asked one of the authors (LTG) to conduct an epidemiological study to determine the incidence of potential adverse events associated with ProHeart 6 and to compare these with the safety profile of 2 oral, monthly heartworm preventives and vaccines. This article reports the results of such a study utilizing the electronic medical records of Banfield, the Pet Hospital, a national veterinary hospital.

METHODS

Data Source

Banfield, the Pet Hospital, was founded in 1955 in Portland, OR. By 2004 Banfield operated a national network of 403 full-service primary care animal hospitals in over 40 states with approximately 1.4 million active patients and 60,000 patient-visits per week. Banfield hospitals are paperless and utilize proprietary software (PetWare) to create electronic medical records that are uploaded weekly to a central data warehouse, where they are stored in Oracle (Redwood Shores, CA) format. Medical records for the period of time from January 1, 2002, to August 31, 2004, when ProHeart 6 was recalled, were

transferred to Purdue University as pipe-delimited ASCII files. The files included information on 7,075,250 encounters (office visits) for 2,047,809 dogs. The files were converted into data sets for analysis.

Data Analysis

Potential adverse events were categorized as liver related, neurological, ocular, immune mediated, allergic, anaphylaxis, cardiac, cancer, or death, based on a combination of clinical signs or laboratory findings (Table 1). The incidence of adverse events for each exposure group was calculated using SAS software (version 9.1.3, SAS Institute, Cary, NC, USA) and expressed as either the number of adverse events per 10,000 encounters or as the number of adverse events per 10,000 days at risk (for example, 10 days at risk could be 1 dog followed for 10 days postexposure or 10 dogs followed for one day each postexposure). Formal statistical analysis to evaluate differences between exposure types was generally not done due to the very large sample sizes. That is, the power to detect very small differences in adverse event rates for common outcomes between exposure groups was extremely high, even when such differences were unlikely to have any clinical significance. However, the same was not necessarily true for less common outcomes or when multivariate analyses were performed. Multivariate logistic regression models were developed using SAS version 9.1.3 software with the PROC LOGISTIC procedure. Results were expressed in terms of odds ratios, 95% confidence interval of the odds ratio, and P values. A P value < 0.05 was considered statistically significant.

Study Assumptions

It was assumed that oral, monthly heartworm preventives had been administered by owners to dogs on the same day of the encounter in which they appeared in the medical record. The potential impact of this assumption would be to *underestimate* the incidence rate of adverse events associated with the 2 oral, monthly heartworm preventive drugs, since some doses of oral heartworm drugs were either never given to their dog by owners or were given, but not at the beginning of the 30-day follow-up period.

RESULTS

From January 1, 2002, to August 31, 2004, there were 6,800,061 encounters for 1,983,162 individual dogs that met study eligibility criteria. These encounters or exposures were grouped as follows (number of encounters): ProHeart 6 with or without a vaccine (735,654), Heartworm preventive 1 with or without a vaccine (411,082), Heartworm preventive 2 with or without a vaccine (18,405), any vaccine without concurrent administration of a heartworm preventive (1,489,032), or none of these (4,144,984) (Table 2). The proportion of encounters associated with vaccination was 62.9% for ProHeart 6, 59.9% for Heartworm 1, and 65.1% for Heartworm 2. Vaccines were only administered during 26.4% of the encounters in which no heartworm preventive was given. This may be because many of these dogs presented with a health problem for which heartworm preventive drugs or vaccines were not indicated, and/or they may have already been on heartworm prophylaxis at the time of the visit. That is, these dogs were likely to be less healthy than dogs given a heartworm preventive or vaccine.

Univariate Analyses

The number of doses of ProHeart 6 administered monthly by Banfield veterinarians increased over time, with more being given during the peak of mosquito activity from March to September (Figure 1). The rate of any adverse event per 10,000 encounters was higher for dogs that received any of the heartworm preventives concurrent with vaccination compared with dogs that received any of the heartworm preventives without vaccination (Table 2). However, for dogs that did not receive any heartworm preventive, vaccination was associated with a lower rate of adverse events compared with dogs that were not vaccinated.

Table 1. Categorization of Potential Drug- and Vaccine-Associated Adverse Events Using Medical Records of Dogs Presented to Banfield, the Pet Hospital*

Disease Category	Adverse Event	Criteria
Liver disease	Liver: any diagnosis	Diagnosis: hepatopathy, hepatitis, hepatitis encephalopathy, hepatitis acute, hepatic disease
	Liver: elevated ALP	ALP ≥ 393 IU/L
	Liver: elevated ALT	ALT ≥ 236 IU/L
	Liver: elevated GGT	GGT ≥ 24 IU/L
	Liver: elevated total bilirubin	Total bilirubin ≥ 1.0 mg/dL
	Liver: any elevated enzyme	Any elevated enzyme (ALP, ALT, GGT, or total bilirubin)
	Liver: any diagnosis plus any elevated enzyme	Any liver disease diagnosis plus any elevated enzyme
	Liver: any diagnosis or any elevated enzyme	Any liver disease diagnosis or any elevated enzyme
Neurological disease	Neurological: any diagnosis or exam finding	Diagnosis: encephalopathy, meningitis, epilepsy, behavioral disorders of unknown origin, seizure-acquired, shock (cardiovascular); exam finding: paresis, paralysis, ataxia
Ocular disease	Ocular: any diagnosis or exam finding	Diagnosis: optic neuritis, retinal degeneration, anisocoria; exam finding: visual deficit, abnormal visual acuity
Immune-mediated disease	Thrombocytopenia	Diagnosis: thrombocytopenia; thrombocytopenia, immune mediated
	Immune-mediated disease	Diagnosis: Immune-mediated disease or AHA
	Immune-mediated disease plus abnormal laboratory value	Diagnosis: Immune-mediated disease or AHA with an abnormal reticulocyte count
	Immune-mediated disease: any	Any immune-mediated disease adverse event
Allergic reaction	Allergic reaction	Diagnosis: allergic reaction, drug reaction, drug induced disease, acute allergic reaction, vaccine reaction, urticaria, drug eruption
Cardiac disease	Cardiac murmur	Diagnosis: cardiac murmur
	Cardiac arrhythmia	Diagnosis: cardiac arrest, atrial fibrillation, atrial premature contractions, atrial tachycardia, bundle branch block, heart block 1st degree, heart block 2nd degree, heart block 3rd degree, cardiac arrhythmia, ventricular premature contractions, ventricular tachycardia
Cancer	Mast cell tumor	Diagnosis: mast cell tumor
	Lymphosarcoma	Diagnosis: lymphosarcoma
	Histiocytoma	Diagnosis: histiocytoma
	Cancer: any	Any cancer diagnosis (mast cell, lymphosarcoma, or histiocytoma)

*ALT indicates alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma glutamyltransferase; AHA, autoimmune hemolytic anemia.

Table 2. Incidence (per 10,000 Encounters) of Any Potential Adverse Event in Dogs Following Administration of ProHeart 6 or 2 Oral Heartworm Preventive Drugs, With or Without Coadministration of a Vaccine*

	ProHeart 6			Heartworm Preventive 1			Heartworm Preventive 2			No Heartworm Treatment		
Vaccine	**N**	**N_A**	**Rate**	**N**	**N_A**	**Rate**	**N**	**N_A**	**Rate**	**N**	**N_A**	**Rate**
Yes	483,064	6,292	130.3	246,131	2,804	113.9	11,975	120	100.2	1,489,032	17,406	116.9
No	252,590	2,253	89.2	164,951	1,469	89.1	6,430	45	70.0	4,144,984	120,529	290.8
Total	735,654	8,545	116.1	411,082	4,273	103.9	18,405	165	89.4	5,634,016	137,935	244.8

*Data from Banfield, the Pet Hospital. N indicates total number of encounters; N_A, total number of adverse events.

Table 3. Incidence (per 10,000 Encounters) of Potential Adverse Events in Dogs Following Administration of ProHeart 6 or 2 Oral Heartworm Preventive Drugs, With or Without Coadministration of a Vaccine*

Treatment Category					Potentially Associated Adverse Event Type									
ProHeart 6	**Heartworm Preventive 1**	**Heartworm Preventive 2**	**Any Vaccine**		**Liver Disease**		**Neurological Disease**		**Ocular Disease**		**Immune Mediated**		**Allergic Reaction**	
				N	N	Rate	N	Rate	N	Rate	N	Rate	N	Rate
				4,144,984	25,531	61.6	3,157	7.6	134	0.3	2,948	7.1	6,832	16.5
			Yes	1,489,032	5,207	35.0	522	3.5	27	0.2	265	1.8	6,598	44.3
		Yes		6,430	14	21.8	4	6.2	0	0.0	1	1.6	12	18.7
		Yes	Yes	11,975	24	20.0	2	1.7	0	0.0	2	1.7	62	51.8
	Yes			164,951	523	31.7	68	4.1	1	0.1	40	2.4	236	14.3
	Yes		Yes	246,131	671	27.3	94	3.8	2	0.1	22	0.9	1,336	54.3
Yes				252,590	880	34.8	123	4.9	4	0.2	59	2.3	465	18.4
Yes			Yes	483,064	2,011	41.6	178	3.7	7	0.1	98	2.0	2,581	53.4
Any				6,800,061	34,866	51.3	4,149	6.1	175	0.3	3,435	5.1	18,123	26.7

*Data from Banfield, the Pet Hospital. N indicates total number of encounters.

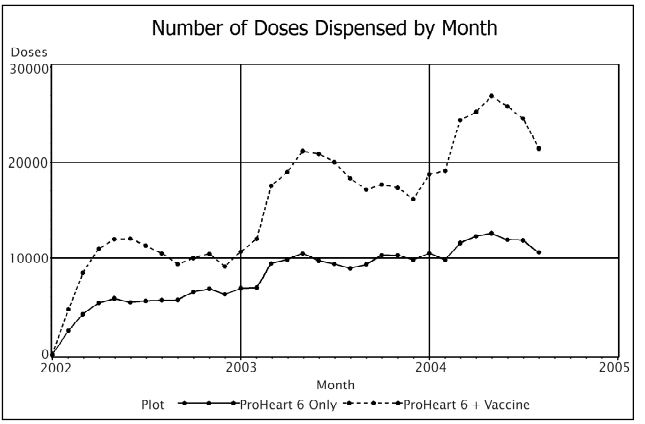

Figure 1. Number of doses of ProHeart 6 administered to dogs by veterinarians at Banfield, the Pet Hospital, from January 1, 2002, to August 31, 2004.

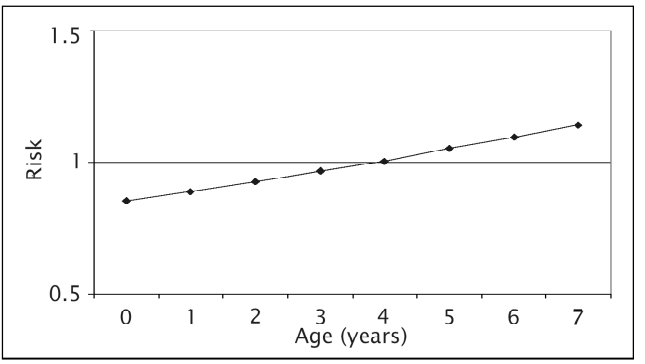

Figure 2. Risk of potential liver-related adverse events in dogs as a function of age following administration of ProHeart 6 by veterinarians at Banfield, the Pet Hospital. Risk was based on results of multivariate logistic regression.*

*Using the odds ratios (OR) for age and for the interaction of age x ProHeart 6 administration, respectively, from the multivariate logistic model, the following equations compute the risk of potential liver-related adverse events:
Risk (for a 1-year old) = 0.854 x 1.043 = 0.89
Risk (for a 7-year old) = (0.853 x 1.043)7 = 1.14

The incidence of any liver-related adverse event per 10,000 encounters was higher for dogs receiving ProHeart 6 than for dogs receiving either of the 2 oral, monthly heartworm preventives, regardless of whether a vaccine was administered or not (Table 3). However, the incidence of liver-related adverse events was not as high as for dogs in the group that received no heartworm preventive drug or vaccine. When the incidence of liver-associated adverse events was measured per 10,000 days at risk, the rates were comparable for dogs that received Heartworm 1 only (1.15), ProHeart 6 only (1.17), or vaccine only (1.27). The mean number of days at risk for dogs receiving ProHeart 6 alone was 29.2 compared with 27.2 and 27.4 for dogs receiving Heartworm 1 or Heartworm 2, respectively. This same pattern of risk persisted when liver-related adverse events were evaluated separately for any laboratory abnormality or any clinical diagnosis consistent with liver dysfunction (data not shown).

The incidence of allergic reactions was similar for dogs that received ProHeart 6, any of the oral, monthly heartworm preventives, or vaccine alone. However, the incidence of allergic reactions was consistently higher for vaccinated compared with unvaccinated dogs, regardless of the heartworm preventive they received. In addition, the incidence of allergic reactions per 10,000 days at risk was 0.52 for dogs that received Heartworm 1 only, 0.68 for those receiving Heartworm 2 only, and 0.62 for the ProHeart 6 only dogs, versus 1.65 for dogs that received a vaccine only. More than 95% of all allergic reactions occurred in the first 3 days following an exposure, while liver-associated adverse events were more evenly distributed over the 30-day follow-up period. The rate of anaphylaxis was lower than for any of the other adverse events studied. The highest rate of anaphylaxis was observed in the group of dogs that received Heartworm 2 plus vaccine, but this rate was based on only 2 observed anaphylactic events.

The incidence of neurological, ocular, or immune-mediated events were all relatively low and there was no obvious association with respect to exposure group, except for

the dogs that received no heartworm preventive or vaccine; these dogs had the highest risk. There was no apparent association between the incidence of cardiovascular disease and exposure group except for dogs that received no heartworm preventive or vaccine, which had the highest risk.

The death rate per 10,000 encounters was higher for Heartworm 1 alone than it was for Heartworm 2 or ProHeart 6, whether administered alone or with a vaccine, or for dogs in the vaccine-only group (Table 4). A similar pattern was observed when the death rate was measured per 10,000 days at risk (data not shown). The higher death rate for dogs in the group that neither received a heartworm preventive nor were vaccinated is indicative of the fact that these dogs probably presented for a medical condition rather than for preventive medicine or a wellness program (Table 4).

The incidence of cancer was higher for dogs that received ProHeart 6 alone or with vaccine than it was for dogs in the other exposure groups, with the exception of dogs that did not receive either a heartworm preventive or vaccine. The incidence of mast cell tumor per 10,000 encounters was higher for dogs that received ProHeart 6 either with or without a vaccine, compared with dogs that received either of the 2 oral, monthly heartworm preventives, or vaccine alone (Table 5). In contrast, no such association with ProHeart 6 was observed for lymphosarcoma or histiocytoma. The incidence of mast cell tumor per 10,000 days at risk was 0.024 for dogs that received Heartworm 1 only, 0.0 for Heartworm 2 only, 0.072 for ProHeart 6 only, and 0.043 for dogs that received a vaccine only. The incidence of mast cell tumor per 10,000 encounters for dogs that had received 1, 2, 3, 4, or 5 or more doses of ProHeart 6 was 1.91, 2.01, 1.39, 3.31, and 3.35, respectively, showing no statistically significant dose-response relationship with subsequent treatments. The clinical significance of a diagnosis of mast cell tumor within 30 days of treatment is not known. In addition, it was not known if these dogs had ever been given ProHeart 6 by a non-Banfield veterinarian.

Multivariate Analyses

Separate multivariate logistic regression models were developed for the risk of adverse events including liver disease, allergic reactions, cancer, and death, in order to control for potential confounding effects and to identify interactions between independent variables. The independent variables included in each model were exposure group (ProHeart 6, Heartworm 1, Heartworm 2, and vaccine), ProHeart 6 dose number, age, weight, use of nonsteroidal anti-inflammatory drugs (NSAIDs), or steroid drugs. All possible 2-way interactions of these independent variables were also evaluated.

In the liver disease model (Table 6), steroid use was associated with a 25% increased risk, while ProHeart 6 was associated with a 15% reduction in risk. Each additional dose of ProHeart 6 resulted in an 8% reduction in the risk of liver-associated adverse events. However, there was evidence of a significant interaction (effect modification) between age and ProHeart 6. Using the best-fit equation from the logistic regression model, the relationship between the risk of liver-associated adverse events and ProHeart 6 administration was graphed as a function of age (Figure 2). The risk of a liver-associated adverse event in dogs receiving ProHeart 6 increased with increasing age. ProHeart 6 was associated with a decreased risk of liver disease in dogs less than 4 years of age and an increased risk of liver disease in dogs greater than 4 years of age.

In the allergic reaction model (Table 6), ProHeart 6, Heartworm 1, vaccines, NSAIDs, and steroid use were all associated with increased risk, with vaccines having the strongest effect. However, each additional dose of ProHeart 6 was associated with a significant 7% reduction in the risk of allergic events. In the model for death (Table 6), Heartworm 1 was associated with a significant 23% increased risk, whereas

Table 4. Incidence (per 10,000 Encounters) of Potential Adverse Events in Dogs Following Administration of ProHeart 6 or 2 Oral Heartworm Preventive Drugs, With or Without Coadministration of a Vaccine*

Treatment Category											
ProHeart 6	Heartworm Preventive 1	Heartworm Preventive 2	Any Vaccine	N	Death		Cancer		Cardiovascular Disease		Anaphylaxis	
					N	Rate	N	Rate	N	Rate	N	Rate
				4,144,984	74,470	179.7	3,724	9.0	8,089	19.5	139	0.3
			Yes	1,489,032	2,690	18.1	562	3.8	1,804	12.1	108	0.7
		Yes		6,430	11	17.1	0	0.0	4	6.2	0	0.0
		Yes	Yes	11,975	17	14.2	2	1.7	10	8.4	2	1.7
	Yes			164,951	363	22.0	67	4.1	219	13.3	4	0.2
	Yes		Yes	246,131	354	14.4	75	3.0	261	10.6	18	0.7
Yes				252,590	392	15.5	155	6.1	250	9.9	13	0.5
Yes			Yes	483,064	709	14.7	205	4.2	635	13.1	34	0.7
Any				6,800,061	79,006	116.2	4,790	7.0	11,274	16.6	318	0.5

*Data from Banfield, the Pet Hospital. N indicates total number of encounters.

Table 5. Incidence (per 10,000 Encounters) of 3 Potential Cancer-Related Events in Dogs Following Administration of ProHeart 6 or 2 Oral Heartworm Preventive Drugs, With or Without Coadministration of a Vaccine*

Treatment Category										
ProHeart 6	Heartworm Preventive 1	Heartworm Preventive 2	Any Vaccine	N	Mast Cell Tumor		Lympho-sarcoma		Histiocytoma	
					N	Rate	N	Rate	N	Rate
				4,144,984	1,285	3.1	1,021	2.5	1,434	3.5
			Yes	1,489,032	172	1.2	36	0.2	359	2.4
		Yes		6,430	0	0.0	0	0.0	0	0.0
		Yes	Yes	11,975	0	0.0	0	0.0	2	1.7
	Yes			164,951	10	0.6	12	0.7	45	2.7
	Yes		Yes	246,131	13	0.5	0	0.0	62	2.5
Yes				252,590	54	2.1	13	0.5	89	3.5
Yes			Yes	483,064	90	1.9	14	0.3	101	2.1
Any				6,800,061	1,624	2.4	1,096	1.6	2,092	3.1

*Data from Banfield, the Pet Hospital. N indicates total number of encounters.

ProHeart 6 was associated with a 71% decreased risk. However, age significantly modified the effect of ProHeart 6 such that the protective effect of ProHeart 6 for death applies primarily to low-weight, low-age dogs without concurrent vaccine. Each additional dose of ProHeart 6 further reduced the risk of death by 9%.

In the mast cell tumor model (Table 6), ProHeart 6 was associated with a 26% increased risk, whereas the 2 oral, monthly heartworm preventives and vaccines were unassociated with mast cell tumor risk. NSAIDs also were associated with a 422% increased risk of mast cell tumor. Steroid administration was associated with a 182% increased risk of lymphosarcoma, which can be explained by the fact that Banfield veterinarians administer long-term steroids as part of the lymphosarcoma treatment protocol. None of the exposure groups was associated with an increased risk of histiocytoma, but vaccines were protective.

DISCUSSION

Mosquito-transmitted canine heartworm infection has been diagnosed in dogs in many parts of the world and is endemic in the 48 contiguous states in the United States.[4] While the prevalence of heartworm infection in dogs and the length of the mosquito season varies from state to state, the peak heartworm transmission generally occurs in July and August and may last for 6 months above the 37th parallel. Despite widespread availability of monthly heartworm preventives, the infection rate increased in the 1990s, while the use of heartworm preventives declined.[5] Surveys have shown that compliance (reliable monthly treatment by owners) is problematic and is a limiting factor in the control of heartworm in the dog population.[6] In June 2001 moxidectin in the form of ProHeart 6 was approved and launched in the United States by Fort Dodge Animal Health to prevent canine heartworm infection for 6 months and to treat existing larval and adult stages of the canine hookworm. In addition to its duration of action, the major advantage of this product is the fact that it does not depend on dog owners to administer it on a monthly basis. This product provides an avenue for continuous protection against heartworm infection while decreasing dependence on owner compliance compared with monthly preventives. Since experimental studies have shown that ProHeart 6 has similar efficacy to the commonly used oral, monthly heartworm preventives, and since compliance with an injectable drug like ProHeart 6 is greater than for heartworm preventives that depend on administration by dog owners, ProHeart 6 is likely to be more effective for pet dogs than oral, monthly heartworm preventives. The results of this study indicate that the incidence of adverse events following administration of ProHeart 6 is indeed comparable to 2 oral, monthly heartworm preventives, despite the fact that nearly 5,500 reports of adverse events following the use of ProHeart 6 have been submitted to the CVM at the time of this study.

By the third quarter of 2004, ProHeart 6 was the number-two product sold in the United States for heartworm prevention, with a 24% market share. ProHeart products have also been registered in a number of international markets since 2001, including Australia, Canada, the European Union (France, Greece, Italy, Portugal, and Spain), Korea, and Japan. The length of activity claims and active ingredient concentration vary depending on the market. For example, ProHeart 12 has gained a 47% market share in Australia, where it offers 12 months of protection and contains 3 times the amount of moxidectin as ProHeart 6. In Italy, the same product (trade name GUARDIAN SR) is expected to achieve a 35% market share by the end of 2004. Shortly after the US launch of ProHeart 6, CVM expressed concern about a number of reports of allergic-type reactions after administration, ranging from mild and self-limiting to severe anaphylactoid reactions.

When Fort Dodge Animal Health announced that it was voluntarily ceasing production and recalling ProHeart 6 from the US market until resolution of CVM

Table 6. Stepwise Multivariate Logistic Regression Risk Analysis for Potential Adverse Events Following Administration of ProHeart 6, 2 Oral Heartworm Preventive Drugs, Steroids, NSAIDs, or Vaccines.*

Adverse Event	Odds Ratio	95% Confidence Limits		Statistical Significance
Liver				
Age	1.16	1.16	1.17	<.0001
Weight	0.99	0.99	0.99	<.0001
ProHeart 6	0.85	0.79	0.92	<.0001
Steroid	1.24	1.04	1.49	0.015
ProHeart 6 each additional dose	0.92	0.88	0.95	<.0001
Age x ProHeart 6	1.04	1.03	1.05	<.0001
Weight x steroid	1.00	1.00	1.00	0.024
Allergic reaction				
Heartworm preventive 1	1.11	1.03	1.20	0.005
ProHeart 6	1.48	1.37	1.60	<.0001
ProHeart 6 each additional dose	0.93	0.90	0.97	0.002
Age	0.84	0.81	0.88	<.0001
Vaccine	2.90	2.51	3.36	<.0001
NSAID	1.64	1.23	2.20	0.001
Steroid	2.11	1.71	2.61	<.0001
Heartworm preventive 1 x age	1.04	1.01	1.07	0.001
Heartworm preventive 1 x weight	0.99	0.99	1.00	0.029
Vaccine x NSAID	0.41	0.30	0.58	<.0001
Age x vaccine	1.11	1.06	1.15	<.0001
Weight x vaccine	0.99	0.99	0.99	0.005
Age x steroid	0.89	0.84	0.94	<.0001
Weight x steroid	0.99	0.98	0.99	0.011
Mast cell tumor				
Age	1.27	1.23	1.30	<.0001
Weight	1.01	1.01	1.01	<.0001
ProHeart 6	1.26	1.01	1.59	0.044
NSAID	5.22	2.80	9.73	<.0001
Age x NSAID	0.92	0.85	0.99	0.038
Lymphosarcoma				
Age	1.36	1.28	1.44	<.0001
Weight	1.01	1.00	1.02	0.001
Vaccine	0.36	0.21	0.63	0.001
Steroid	2.82	1.12	7.06	0.027
Histiocytoma				
Age	0.72	0.69	0.75	<.0001
Weight	1.01	1.01	1.01	<.0001
Vaccine	0.62	0.50	0.77	<.0001

*Only factors significant in each model at $P < 0.05$ are shown.

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Table 6. continued

Adverse Event	Odds Ratio	95% Confidence Limits		Statistical Significance
Death				
Heartworm preventive 1	1.23	1.05	1.42	0.008
ProHeart 6	0.29	0.22	0.38	<.0001
ProHeart 6 each additional dose	0.91	0.85	0.97	0.005
Vaccine	0.55	0.44	0.68	<.0001
Age	1.21	1.17	1.24	<.0001
Weight	0.99	0.99	0.99	<.0001
ProHeart 6 x vaccine	2.06	1.61	2.64	<.0001
Age x Heartworm preventive 1	0.96	0.94	0.99	0.021
Age x ProHeart 6	1.03	1.01	1.05	0.001
Age x vaccine	0.96	0.93	0.98	0.002
Age x steroid	1.05	1.01	1.09	0.019
Age x NSAID	1.03	1.01	1.05	0.021
Weight x Heartworm preventive 1	0.99	0.99	1.00	0.037
Weight x ProHeart 6	1.01	1.00	1.01	0.001
Weight x NSAID	1.01	1.01	1.01	<.0001

*Only factors significant in each model at $P < 0.05$ are shown.

safety concerns based on adverse event reports it had received, regulatory agencies in other countries also reviewed the safety record of ProHeart in dogs. To date, no regulatory agency outside of the United States has found ProHeart to present a clear and present danger to dogs, and with the exception of Korea, have not taken any action to recall the product. For example, based on a review of suspected adverse reactions, the Canadian Veterinary Drugs Directorate determined that "an immediate recall is not warranted for ProHeart 6 in Canada."[7]

Since ProHeart products are all manufactured at one site by the same method, using the same ingredients, one may speculate that dogs in the United States somehow react differently to ProHeart 6 than dogs in other countries. A more likely explanation however, is that the CVM in the United States interpreted adverse event reports to ProHeart 6 differently than regulatory agencies in other countries, or that US pet owners are more inclined to report adverse reactions. An analysis of Banfield data in this study showed that allergic reaction rates following ProHeart 6 administration were comparable overall to those for 2 oral heartworm preventives and far less than the incidence when any of the heartworm preventives studied were administered with a vaccine, or when vaccine alone was administered. Also, the incidence of allergic events following ProHeart 6 administration by Banfield veterinarians decreased by 26.4% from the first quarter of 2002 to the third quarter of 2004, when ProHeart 6 was recalled (data not shown).

The major finding from this epidemiological postmarketing study involving almost 2 million dogs seen by Banfield hospitals over a 2-year period was similarity in the safety profiles of ProHeart 6 and two oral heartworm preventives. While ProHeart 6 was associated with an increased incidence of liver-related adverse events in univariate analysis, this same increase was not found in either the days-at-risk analysis or when controlling for confounding factors such as age in multivariate analyses. Another important finding was that ProHeart 6, the 2 monthly heartworm preventive drugs, and vaccines were all associated with a clinically significant increase in the incidence of allergic reactions, especially during the first few days

post-exposure. In addition, one of the oral heartworm preventive drugs (Heartworm 1) was associated with a clinically significant increased risk of death within 30 days following administration.

The only potential adverse event studied that was independently associated with an increased incidence following administration of ProHeart 6 was mast cell tumor. However, the absolute magnitude of the increased risk of mast cell tumor associated with ProHeart 6 alone (2.1 per 10,000 doses administered) or ProHeart 6 plus vaccine (1.9 per 10,000 doses administered) was small. For example, it would require a prospective study of 600,000 dogs receiving ProHeart 6 alone and 600,000 dogs receiving ProHeart 6 plus a vaccine to detect this small difference in mast cell tumor incidence 90% of the time with a Type I error of 0.05%. Also no significant dose-response relationship was observed between the number of ProHeart 6 doses a dog had received and the risk of developing mast cell tumor. Two-year studies in mice[8] and rats[9] did not find any evidence of moxidectin-related target organ toxicity or tumorigenicity. Furthermore, a plausible mechanism has not been proposed whereby moxidectin or similar chemical compounds can induce or promote cancer formation, especially within 30 days of administration.

This epidemiologic study also demonstrates the advantage of using electronic medical records from a large primary care veterinary practice rather than relying on the current pharmacovigilance system of passive or spontaneous reporting of drug-associated adverse events in animals to CVM and drug companies. The latter depends on veterinarians or dog owners deciding what constitutes an adverse event and requires them to report such events either by telephone or in writing. It is well known that passive systems are plagued by a varying degree of underreporting.[10] In addition, news releases or Internet postings about adverse events associated with a product may bias people to report adverse events, whereas Internet reports are less likely to influence the occurrence of potential adverse events gleaned directly from medical records. Other advantages to the use of medical records over spontaneous reporting are that it facilitates calculation of drug-associated adverse event rates (absolute risk) based on the population at risk or number of doses administered and allows adjustment of these rates for potential confounding factors (age, breed, weight) and for concurrent administration of other drugs or vaccines.

Epidemiological studies are not intended to replace passive surveillance following marketing of new veterinary products. Rather, they are most useful for testing hypotheses or alarms raised through passive postmarketing surveillance. Epidemiological studies of this type will be facilitated in the future by the trend toward computerization of veterinary medical records and the growth of large corporate and private veterinary practices. The results of the epidemiological study described in this report do not indicate major safety concerns regarding ProHeart 6, which affords 6 months of continuous protection against heartworm prevention and reduces dependence on owner compliance for its effectiveness. Since no drug is completely safe, veterinarians can use the results of this study to select the most appropriate heartworm preventive strategy for individual dogs. The practice of evidence-based veterinary medicine ultimately depends on the availability of unbiased findings from controlled population-based studies.

ACKNOWLEDGMENTS

This study was funded in part by grant RO1 CI 000093 from the US Centers for Disease Control and Prevention, and by a contract with Fort Dodge Animal Health.

We appreciate the help of the Banfield veterinarians who generated the medical records reviewed in this study and Dr. Scott Campbell, Chairman and Chief Executive Officer of Banfield, the Pet Hospital, for making this valuable resource available to Purdue University at no cost.

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