Evaluation of efficacy of heartworm preventive products at the FDA
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Abstract

The Center for Veterinary Medicine, U.S. Food and Drug Administration (FDA/CVM) has authority under the United States Code 21 under Section 514.80 to monitor for adverse experiences of approved animal products. Although veterinarians voluntarily report suspect drug-related events to manufacturers, firms that market FDA-approved animal products must report serious events to the FDA within 15 working days of the veterinarian or pet-owner’s call to them. Under the present regulations, canine heartworm preventatives are approved for 100% efficacy after testing in laboratory and field conditions. The report of lack of efficacy against heartworm larvae is a serious adverse drug event because the resulting condition or the treatment of the condition is life threatening. Information on lack of effect that are deemed possibly, probably, or definitely drug-related available for review under generic product on the FDA/CVM website Surveillance of these reports indicates there are some failures for virtually all heartworm prevention product categories. Most failures have been reported in heartworm-endemic states. At this time, it is unclear whether these are representative of the rare occurrences of failure that have been in existence for a long time, but not reported regularly or promptly, or whether there is a true increase in complaints of ineffectiveness and real variability between products. This paper discusses methods, personnel, and procedures in place in the Division of Surveillance that will aid the FDA to better assess heartworm preventive treatment failures. It discusses scoring paradigms presently utilized by FDA/CVM to assess severity of complaints of lack of efficacy against heartworms, and welcomes audience input as to how to improve existing processes. Results suggest that more comprehensive reporting will provide FDA/CVM more accurate surveillance information regarding efficacy problems. Such practices will permit FDA/CVM to better interpret both incidence and severity of in-effect and possible patterns of emerging resistance and to convey this in any necessary updated labeling. It also indicates that as part of that process, practitioners should return to a more conservative testing schedule.

Published by Elsevier B.V.

Keywords: Heartworm; Dirofilaria immitis; Preventative; Adverse event

1. Introduction

Adverse event reporting plays a formative role in post-market surveillance of the safe and efficacious use of drugs. The Center for Veterinary Medicine, Federal Food and Drug Administration (FDA/CVM) has employed six part-time clinical veterinarians to review adverse experience reports. These individuals have an average of 11 years of clinical experience each and still participate actively in either a companion or
large animal practice at least 20 h a week. The FDA/CVM managers feel this is important in understanding the context of use of the drugs FDA regulates.

Testing and review of the efficacy and safety of heartworm preventatives do not guarantee that the post-market history will be similar to results obtained pre-marketing because of inherent limitations imposed by testing the product in a relatively small population of animals and in limited or seasonally static environments.

Canine heartworm prevention products entered the market in 1977 with the launch of daily diethylcarbamazine. The monthly macrocyclic lactone products emerged a decade later and have since dominated the market. The millennium saw the launch of new choices for heartworm prevention, including topical and parenteral products. At the same time, testing that was previously recommended on an annual basis has, according to some reports, declined to less frequent periodicity. Additionally, in 1998, the first complaints of ineffectiveness began to arrive at the CVM. For the most part, these reports contained scant information. Most often it was assumed, but not verified, that owner compliance was responsible for the lack of (or reduced) efficacy.

In 2001, the number of complaints relating to product efficacy nearly doubled for some of the commercial products. Nonetheless, compared with the number of doses sold, the reports were few. By 2002, reports doubled again to over 1000 annual complaints. Initially, it appeared that these were principally related to topical product. An investigation into this matter led the FDA/CVM to understand that the requirement for reporting such events was not uniformly implemented across all manufacturers. A new regulation concerning the submission of adverse experience reports was published in the early spring of 2003 so that a combination of enhanced regulatory effort and rules of greater clarity led to filing of numerous other heartworm product complaints late in 2003. Some of these reports were quite old, and information provided was incomplete. Thus, the true incidence of product ineffectiveness is only just emerging. To complicate matters, the 2001 and 2002 Gulf Coast weather patterns changed in such a way as to shift concentrations and quantities of vectors. Thus, data presented here should be understood to be preliminary and will be useful as an aid in assisting practitioners, manufacturers, and regulators in determining best practices for testing, drug evaluation, and prevention of heartworm disease.

2. FDA/CVM methods for evaluating complaints of ineffectiveness

The FDA/CVM uses a modified scoring system based on the methods of Kramer et al. (1979), and modified by Bataller and Keller (1999). This system has been further modified for heartworm product efficacy failure scoring by the author and colleagues at the FDA/CVM. The unmodified algorithm provides component scoring for ranking the probability of causation when drug safety is in question, but it is inappropriately used for efficacy. To modify this scoring algorithm for heartworm testing, the FDA/CVM uses decision analysis to assign a single score based primarily on timing, owner compliance, region of incidence, and test history using information provided by the American Heartworm Society (AHS). This decision analysis is described the following way:

2.1. Ineffectiveness score of 0–1 (remotely possible)

- Previous use of heartworm prevention, but no test performed before administration.
- No previous heartworm prevention used, and negative test before administration.
- A negative heartworm antigen test following adult heartworm treatment; now positive after starting treatment.
- In the case of dogs under 1 year of age:
  - If the dog started on heartworm prevention at 6 weeks or older, was born during transmission season, and had no 6–7-month antigen test, a pre-patent infection is possible; the FDA usually scores it 0.
  - If the dog was born outside of the transmission season and there was no 6–7-month antigen test; the FDA usually scores it 1.

2.2. Ineffectiveness score 1 or 3 (possible)

Dogs meeting the following criteria generally received a score of 1:
The dog has been on heartworm prevention since it was a puppy or was previously on a different heartworm preventative and then switched to the preventative under scrutiny.

- It had a negative heartworm antigen test before initiation of the new product, but had no test 6–7 months inside the treatment period with the new product.
- The dog was consistently given seasonal preventive treatment, then became positive in the spring (depending on location, seasonal temperature, and time between last dose and positive test).
- If the dog is under 1 year of age, was started on heartworm prevention at 6 weeks, was not born or started on the preventative during the transmission season, and there was no 6- or 7-month antigen test, a pre-patent infection is unlikely, and the FDA would score this 3.

2.3. Ineffectiveness score 4–6

A score of 4–6 is assigned if the dog has been on heartworm prevention consistently and has had one or more years of negative testing starting after the first 7 months of product administration and repeated annually. This includes puppies if started between 6 and 8 weeks and a negative antigen test starting at 6–7 months and thereafter.

2.4. Remotely possible, lacking information

A score of 9 is given when there is a remote possibility of drug ineffectiveness. The numbers of reports in this category do not appear in the public domain, and there are presently very few cases in this category.

The information contained in the reports was randomly verified by the reviewers by contacting the veterinarian and the owner. These reports are listed by frequency on the FDA/CVM adverse drug event website at http://www.fda.gov/cvm/index/ade/ade_cum.htm (FDA, 2005a). More specific reports are available by Freedom of Information requests to the agency (FDA, 2005b).

3. Results

Ineffectiveness reports for heartworm preventatives have no detectable breed, sex, or age distribution pattern. Initially, reports were variable in the amount of information contained in regarding previous heartworm prevention product administration and test history. By mid 2004 this variability was decreased as CVM attempted to clarify what information was necessary in order to fairly evaluate them. Reports are concentrated in regions where heavy endemic infections exist. Over one-third of all reports originated from south Texas followed by Florida, North Carolina, and the Mississippi River, southern Ohio River, and lake state regions (Fig. 1).

Heartworm product complaints relating to lack of effectiveness began in 1998 and occurred rarely across all products until 2000. The numbers increased dramatically between 2000 ($n = 405$) and 2002 ($n = 951$), a 57% increase. The number of reports rose again to 1503 (57%) between 2002 and 2003 then dropped slightly to 881 (41%) in the last quarter of 2003. Reports dropped sharply to 393 (as of May 12, 2004) for the first quarter 2004 compared with the 506 reports received for the first quarter of 2003 (Fig. 2). Data capture is incomplete for spring 2004 at this time.

4. Discussion

In trying to understand possible reasons for reported heartworm product failures, the agency must constantly compare the present conditions of use with those under which the product was approved. This requires soliciting opinions from experts within industry as well as from independent sources.

Inter-product variability cannot be discussed or interpreted at this time, except to say that recent compliance in reporting has brought this issue under close scrutiny. The issue of specific product failures is part of ongoing deliberative processes in a dynamic discussion with product sponsors. Any changes in recommendation and post-experience adverse events for specific products, including failures, will appear in product labeling.

The slight decline in reports of ineffectiveness observed for 2003, despite regulatory effort to closely monitor these reports, is of interest. Rationales for this downward trend include a possible actual decrease in incidence, shifts in specific product use, decreases in testing frequency among veterinary clinics, or perhaps ongoing variable reporting frequency among veter-
inarians and manufacturers. The apparent further decline in 2004 may also be related to delayed reporting of findings from spring testing or it may indicate that fewer veterinarians are testing their patients on an annual basis. Reports of ineffectiveness for heartworm preventatives continue and are concerning to the FDA. High drug association (causality or score) occurs in 20–35% of reports and is similar among all products. This is a strong indication the problem is real and not just a perception.

Environmental trends are also interesting features. Mosquito species of the genera *Psorophora*, *Aedes* and *Anopheles* are most commonly described as vectors for *Dirofilaria immitis*. Because of consistent strict regional prevalence, factors other than owner compliance and specific product efficacy seemed important to investigate. Regional mosquito trapping data in south Texas was provided to the FDA. This county authority has counted species of mosquito caught in carbon dioxide traps covering a 2400 mile² sampling area near the Texas Gulf. Information from regional authorities in south Texas indicates that of the heartworm vectors, *Psorophora* have been most
 prevalent followed by Aedes vexans. Interestingly, A. aegypti were rarely found, and it is theorized that the storm activity in the Gulf in 2000 and 2001 brought with it more competitive salt water species such as Ochlerotatus taeniorhynchus, which drove Aedes species away. Data from this source also indicates Psorophora species were also roughly sevenfold higher in the sampling region in 2002 versus 2003 (Weldon Sheard, personal communication). Thus, this information indicates trends that might explain peak ineffectiveness complaints arising, even in older and seemingly reliable oral products in 2002 and a slight decline in late 2003 and early 2004, despite aggressive regulatory measures.

5. Conclusions

The information presented represents a period of enhanced regulatory activity in surveillance at the FDA/CVM. Preliminary investigations into complaints of heartworm product ineffectiveness underscore to the FDA that more thoughtful discussion should take place between regulators and manufacturers regarding potential changes in vector challenge, bioavailability, and the possibility of emerging resistance. Heartworm disease has certain natural elements associated with its transmission and these elements may present moving targets as our biosphere changes. More dialogue with the American Heartworm Society (AHS) is also paramount. The FDA has opened this channel of discussion by appealing to the AHS to return to a more conservative recommendation for heartworm testing; at least in endemic regions. Fundamental to the ability to evaluate and interpret product efficacy complaints is the need for practitioners to report such events to the manufacturer or to FDA. Finally, it is extremely important that veterinary practitioners stay informed of product updates by reading literature from product manufacturers carefully. Envelopes labeled “Important Drug Information” should not be mistaken for promotional advertising. These notices usually accompany changes in product labeling and could highlight improved dosing schedules and administration routines for heartworm preventatives.

References

Weldon Sheard, 2005. Personal Communication. Fort Bend County Road and Bridge, Needville, TX 77461.