A literature review on current practices, knowledge, and viewpoints on pentobarbital euthanasia performed by veterinarians and animal remains disposal in the United States

Nathaniel S. Kollias, DVM, MPH; Warren J. Hess, DVM; Cia L. Johnson, DVM, MSc; Mike Murphy, DVM, JD, PhD; Gail Golab, PhD, DVM, DACAW

1Animal Welfare Division, AVMA, Schaumburg, IL
2Division of Animal and Public Health, AVMA, Schaumburg, IL
3Public Policy Strategic Business Unit, AVMA, Schaumburg, IL
*Corresponding author: Dr. Kollias (nkollias@avma.org)

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ABSTRACT
Sodium pentobarbital and pentobarbital combination products are commonly used by veterinarians throughout the US for euthanasia of their animal patients. The AVMA Guidelines for the Euthanasia of Animals: 2020 Edition lists barbiturate acid derivatives (pentobarbital) and pentobarbital combination products as an acceptable method of euthanasia for all species when circumstances permit their use. When using pentobarbital products, a veterinarian must consider appropriate handling and disposal of animal remains to avoid the potential for environmental contamination, relay toxicosis in wildlife or domestic animals, and contamination of the animal food supply. Failure to appropriately consider these facets of pentobarbital euthanasia can result in legal and ethical consequences. Despite these concerns, to the authors’ knowledge no comprehensive literature review has been published concerning pentobarbital euthanasia or handling and disposal of animal remains following pentobarbital euthanasia. The literature review that follows aims to give a descriptive narrative of the most recent information available on the knowledge, use, challenges, and issues surrounding pentobarbital euthanasia and disposal of animal remains within the US.

Euthanasia of animals with pentobarbital agents occurs throughout the US, including in companion animals, livestock, research animals, and wildlife. Despite this, there are little data available to evaluate outcomes, including adverse events (eg, relay toxicosis [poisoning via consumption of pentobarbital-euthanized animals], environmental contamination, improper disposal of remains, failed euthanasia, etc), of using this euthanasia method by veterinarians.1,2 Veterinarians’ prima facie goals in carrying out euthanasia of animals include but are not limited to inducing death in a manner that is in accordance with an animal’s interest, because it is a matter of welfare, or both, and using humane techniques to induce the most rapid, painless, and distress-free death possible.3 End-of-life decisions present challenges for both the veterinarian and the client during the euthanasia process.4 The literature in physicians has shown that end-of-life decisions are often suboptimal due to lack of training; for example, training related to patient communication.5–7 Interpersonal skills have been noted in veterinary school alumni surveys as the most important skill in effective communication with clients.5,9 All of these variables can lead to challenges during the euthanasia process. This review addresses some of these challenges, focusing specifically on euthanasia with pentobarbital.

Overall, humane standards and options for euthanasia have improved over the last 50 years, but controlled rigorous studies regarding adverse events have been notably lacking, especially for pentobarbital euthanasia.2 This lack of studies results in gaps in understanding surrounding the use of pentobarbital in veterinary medicine, including appropriate dosing and administration, knowledge of laws and regulations, proper disposal of animal remains, and effective communication between the veterinarian and client.

The goal of this literature review is to evaluate current knowledge, practices, and viewpoints about pentobarbital euthanasia as performed by veterinarians in the US and subsequent disposal of animal remains.

Materials and Methods

Literature was reviewed using the following key words and phrases in the search criteria: euthanasia, animal disposal, carcass disposal, residues, pentobarbital, barbiturates, survey of, veterinarians, pre-
ferred method(s) of, laws and regulations, protocols, and alternatives. This review also encompassed several types of journals and databases, many of which were nonveterinary journals due to the lack of research on the use of pentobarbital for euthanasia in general. These journals included (but were not limited to) the following: Journal of the American Association for Laboratory Animal Science, Comparative Medicine, JAVMA, Veterinary Research, BMC Veterinary Research, Journal of Animal Science, Journal of Veterinary Diagnostics, as well as the databases PubMed, PLOS ONE, Elsevier, Multidisciplinary Digital Publishing Institute, National Center for Biotechnology Information, and Centre for Agriculture and Bioscience International. We also included relevant information from the current AVMA Guidelines for the Euthanasia of Animals: 2020 Edition. 3

This review did not include a meta-analysis because structured controlled studies on pentobarbital and, more broadly, euthanasia are lacking. Most of the information on this topic is derived from case studies, special reports, review articles, and guidance documents.

Results

A total of 50 journal articles, government documents, surveys, and guidance documents passed initial screening and were included in this review.

Pentobarbital as a euthanasia agent

Sodium pentobarbital (pentobarbital) is likely the most used barbiturate acid derivative for euthanasia of animals. Pentobarbital overdose is considered an “acceptable” method of euthanasia for a large array of species because it consistently produces a humane death when used as a sole means of euthanasia.3 Pentobarbital is a sedative-hypnotic agent4,5 with a narrow safety margin, which is good for an efficacious standpoint but contributes to the risk of secondary toxicosis from scavenging of carcasses that were euthanized via pentobarbital. It is potent, can be formulated as a concentrated solution so that relatively small volumes are needed, and has a rapid onset of action when given IV.5,11 Furthermore, pentobarbital has a long shelf life, is stable in solution, and is relatively inexpensive.3 Access and licensing requirements for pentobarbital purchases vary between countries; in the US, access is limited due to its listing as a schedule II and schedule III (when combined with phenytoin) controlled substance by the US Drug Enforcement Administration.11 The primary mode of action of pentobarbital is binding to and inhibiting the GABA complex receptor. The resulting effect is profound CNS depression (ataxia, marked obtundation, anesthesia, respiratory depression, and absent reflexes).12,13 When given as an intentional overdose to cause death, general anesthesia is induced, followed by depression of the respiratory and cardiovascular centers of the brain stem, leading to cardiorespiratory arrest.13,14

There are several pentobarbital euthanasia agents available for veterinary use for euthanasia. New applications containing pentobarbital may be approved by the FDA and some that are now approved may be withdrawn, so the examples may change over time. The agents currently available as of publication of this review include but are not limited to the following products: pentobarbital sodium 390 mg/mL and phenytoin sodium 50 mg/mL solutions for injection (eg, Euthasol and Euthanasia-III Solution), pentobarbital sodium powder for reconstitution and injection formulations (eg, Fatal-Plus Powder), and pentobarbital sodium solution for injection (eg, Fatal-Plus Solution).15,16 Many of these formulations and others are commonly utilized in veterinary practices and considered short-acting barbiturates with a rapid onset, high pKa values, high protein binding, high lipid solubility, and short duration of action, and they primarily undergo hepatic metabolism.15,17,18

Veterinary formulations of pentobarbital may also contain different chemicals that act as preservatives or additives to facilitate administration and a smooth and irreversible death.19 One such agent commonly added is phenytoin, a Vaughan-Williams Class-Ib antiarrhythmic,18 which behaves synergistically with pentobarbital and produces profound bradycardia. Other agents such as propylene glycol are added to help preserve the formulation and can add to residue considerations.19

Species considerations when utilizing pentobarbital

In general, pentobarbital given IV is the most commonly used route of administration for euthanasia in private practice when dealing with small animal species (dogs, cats, and other companion animals).17 In laboratory animal medicine, pentobarbital is an acceptable method chosen for euthanizing USDA-covered species (pigs, dogs, cats, nonhuman primates, sheep, cattle, and goats) as well as rodent (Mus musculus, Rattus norvegicus, etc) and avian species.3,20 Although pentobarbital is considered an acceptable method of euthanasia for rodents,3,20 it is more common to utilize CO2(e) euthanasia in laboratory rodent species due to ease of administration and the controlled substance status of pentobarbital,14,21-24 which makes it difficult to access, especially when those performing euthanasia in research settings may not be licensed veterinary professionals.

Conversely, when looking at production animal species (ie, livestock food and fiber animals), other AVMA guideline–described acceptable methods of euthanasia (eg, captive bolt or gunshot) tend to be selected due to ease of administration and little to no concern about residues in the animal remains.3,25 However, little is known about the relative frequency of pentobarbital use compared to physical methods in these species. Additionally, animals historically considered food animals are increasingly being kept as pets or on small hobby farms, especially small ruminant species such as goats and sheep. This creates potential for increased use of pentobarbital due to potential negative client perceptions of physical means (eg, captive bolt or gunshot) of humane killing. Proper disposal of these animal remains are vital, as failure can create a poten-
tal threat of pentobarbital relay toxicosis for wildlife and other domestic species.\textsuperscript{26,27–31}

**Pentobarbital euthanasia and relay toxicosis**

In general, the majority of readily available veterinary pentobarbital products for euthanasia are labeled to be administered IV at a dose of 1 mL/4.5 kg of body weight for small companion animals (eg, dogs and cats) and 10 to 15 mL/45.4 kg of body weight for large animals (eg, horses, goats, and llamas).\textsuperscript{15,16} Although IV is the preferred route of administration for pentobarbital in most species according to the current AVMA Guidelines for the Euthanasia of Animals, other routes discussed include intrahepatic, intracardiac, intrarenal, or intraperitoneal\textsuperscript{15,26} and are more frequently seen and allowed in laboratory animal species or animals deeply anesthetized prior to euthanasia.\textsuperscript{20–22} Some currently marketed pentobarbital products include “intrapeural” as an administration route on their label, but this route is not listed in the current AVMA Guidelines for the Euthanasia of Animals.\textsuperscript{3} Likewise, oral administration of pentobarbital is discouraged as it has several disadvantages when considered for administration, including lack of established dose, variability in bioavailability and rate of absorption, potential difficulty of administration (including potential for aspiration), and potential for loss of agent through vomiting or regurgitation (in species that are capable of these functions).\textsuperscript{2}

Relay, or secondary, toxicosis refers to the toxicity that occurs when one animal ingests or is otherwise exposed to another animal that has a toxic substance in its system. There are several published examples of relay toxicosis occurring in dogs associated with ingestion of animal remains contaminated with pentobarbital. In 1 instance, a dog ingested pentobarbital-containing blubber from a euthanized whale.\textsuperscript{2} In another report,\textsuperscript{26} 2 dogs fed on an improperly buried horse carcass that had been euthanized with pentobarbital 2 years previously, resulting in one of the dogs dying in transit to the veterinary clinic. Relay toxicosis of pentobarbital has also been reported as affecting zoo animals as well as wildlife.\textsuperscript{27,29,32} A recent study\textsuperscript{33} reported that in 79% of all pentobarbital-related relay toxicosis cases (wildlife and domestic animals), sheep, horses, and cattle were the most commonly implicated species. Additionally, another important factor to consider is the additional ingredients found in some pentobarbital-containing agents. These agents can induce cardiotoxicity (Vaughan-Williams Class Ia Ib 1b antiarrhythmics)\textsuperscript{34} and renal toxicity (propylene glycol),\textsuperscript{35} both presenting potential additional concerns for relay toxicosis.

These isolated yet reoccurring pentobarbital relay toxicosis cases could be attributed to dosing and means of disposal of animal remains. As mentioned earlier, the labeled dose for pentobarbital euthanasia in dogs is 1 mL/4.5 kg, and common drug formulators suggest a dose for euthanasia of small animals (eg, dogs and cats) of 1 mL/4.5 kg and 10 to 15 mL/45.4 kg body weight for euthanasia of large animals (eg, equids and bovids).\textsuperscript{15,16} Albeit this fact, case reports\textsuperscript{26,28,29} suggest that higher dosing is more likely to occur for large domestic and wildlife species. This inconsistent use of pentobarbital is suggested to occur from a lack of controlled studies establishing appropriate dosing in various species, which leads veterinarians to extrapolate from the dog and cat literature.\textsuperscript{15,16} Another aspect of overdosing to consider is that veterinarians want to ensure that the animal dies quickly without any apparent suffering for their own peace of mind and to meet client and societal expectations,\textsuperscript{1,33} which may also lead to a tendency toward overdosing. Altogether these actions can lead to a greater likelihood of residue issues with the remains of euthanized animals.

Extrapolating doses from dogs to other species could be problematic as there are potentially vast differences in the pharmacodynamics and pharmacokinetics of pentobarbital among species. Available research of rodents shows that the metabolism and modes of action of pentobarbital can vary significantly,\textsuperscript{2} and intraspecies differences in response to euthanasia methods are observed within different strains of mice\textsuperscript{34,35} as well as among different age groups of mice.\textsuperscript{1,36} These issues highlight the need for standardization of euthanasia drug dosages and controlled studies on how pentobarbital is metabolized for the variety of species treated by veterinarians.\textsuperscript{1}

All of these factors can lead to administration of pentobarbital doses higher than the labeled dose. This higher dosing can then lead to increased tissue residue concentrations contributing to the risk of relay toxicosis\textsuperscript{26,28} and creating additional risk in disposal of the remains of animals euthanized with pentobarbital.\textsuperscript{25,31,37}

**Handling and disposal of animal remains**

To prevent relay toxicosis, disposal of animal remains following euthanasia is extremely important, especially when pentobarbital is used. Five methods for disposing of animal remains are burial, landfill, composting, incineration, and rendering. Rendering is virtually never appropriate for animals euthanized with a chemical method, such as pentobarbital.

A lesser used disposal method is biodigestion, which utilizes chemicals to break down the bodies of deceased animals into a sterile liquid slurry. Anecdotally, this method is used more often in institutions of higher education and research facilities, but biodigesters can be cost prohibitive and impractical for others. Not all of these disposal options are available in every locale and they are much less practical or affordable, but they are all preferable to leaving the carcass in a pasture, where scavengers can have access.

All of these methods have advantages and disadvantages. Socially, economically, and environmentally acceptable methods of disposing of animal remains are increasingly difficult to find.\textsuperscript{26,27} These difficulties may be amplified for animals euthanized with pentobarbital.

Rendering is 1 method of disposing of animal remains and has the advantage of “recycling” those
remains into useful products, such as animal feed ingredients and biofuel. However, rendering is an energy- and cost-intensive endeavor that is beholden to market fluctuations, consumer preferences, continued concerns of residues, and a growing concern of foreign animal diseases. Incidences of pentobarbital-contaminated pet food have led to specific investigations into the persistence or destruction of pentobarbital during rendering. Pentobarbital was found in meat, bone, and tallow fractions following rendering, resulting in a product unsuitable and unsafe for animal food. Thus, rendering for animal food is not a feasible option for clients to dispose of pentobarbital-euthanized animals, as foods containing pentobarbital are considered adulterated under the Federal Food, Drug, and Cosmetic Act.

Burial, landfills, and composting may be acceptable methods of disposing of pentobarbital-euthanized animals in some locales; however, challenges also exist when these methods are used. Pentobarbital may be detected in remains months to years after disposal, and the potential for leaching into groundwater and soil exists. Consumption by wildlife or domestic animals of carcass remains after disposal by 1 of these 3 methods may lead to relay toxicosis.

Incineration (ie, cremation) is another option for disposal of pentobarbital-euthanized animals. This method limits pentobarbital contamination risk but can be prohibitively expensive, especially for large animals, and it may not be accessible to some clients and veterinarians.

Each of the most common carcass disposal methods presents challenges that deserve consideration in each case. Outreach and additional research is needed regarding practical disposal of animal carcasses, particularly following pentobarbital euthanasia.

The veterinarian-client-patient relationship

Communication between the veterinarian and client is also an important consideration when evaluating the suitability of pentobarbital euthanasia. Communication is a critical part of establishing and maintaining a veterinarian-client-patient relationship, and breakdowns can precipitate issues mentioned earlier in this review, especially issues with handling and disposal of animal remains due to noncompliance with veterinarians’ direction or lack of understanding of animal remains after euthanasia.

The veterinarian’s perspective

Veterinarians have an ethical and moral obligation to relieve animal suffering, as conveyed in the Veterinarian’s Oath: “protection of animal health and welfare, the prevention and relief of animal suffering.” Relief of suffering may be achieved through euthanasia.

Veterinarians often must navigate a complicated framework of laws, regulations, and stakeholder perspectives when discussing end-of-life decisions. This can lead to ethical conflicts for the veterinarian and potentially regulatory and other legal issues when dealing with clients whose animals are euthanized with pentobarbital. Research has shown that veterinarians’ perceptions of the needs of clients and their animals may differ significantly from what the client needs or expects. Demand for high-quality veterinary medical services is increasing, and along with this is a potential increase in the number of euthanasia events, which could magnify the possibility for communication challenges and resulting breakdowns of the veterinarian-client-patient relationship. As mentioned above, there is a general lack of rigorous controlled studies on euthanasia, and this includes communication surrounding end-of-life decisions, euthanasia, and disposal of animal remains. Such controlled studies could help illuminate how communication challenges might lead to unintended consequences following pentobarbital euthanasia (eg, issues related to relay toxicosis or adulterated food/feed) and would help inform guidance on best practices regarding pentobarbital euthanasia and disposal of animal remains.

End-of-life decisions

Veterinarians receive training in local, state, and federal laws and regulations related to veterinary medicine and are an important source of information on these topics for their clients. Despite this fact, end-of-life decisions may present challenges for veterinarians and clients, with multiple factors at play. Unfortunately, there are limited empirical studies on client communication in veterinary medicine generally and communications surrounding end-of-life decisions specifically. The client’s understanding and needs are also important to consider, especially in situations where they may be the one handling an animal that was euthanized with pentobarbital (eg, burying an animal on their own property). For example, local and regional regulations concerning euthanasia can vary substantively from one geographic location to another, and the client may require additional education on appropriate disposal methods. Thus, it is imperative that veterinarians discuss pertinent laws and regulations with their clients and be prepared to distribute written information to reinforce the message. This education could both make the client more comfortable and lead to better outcomes when disposing of animals euthanized with pentobarbital products, especially animals for which residues may be of particular concern (eg, cattle, sheep, goats, etc).

From the limited information available, animal owners appear to want clear and concise information, more options, and to feel like they are heard. Thoughtful conversations with veterinary clients in which information is freely shared and understood could help prevent some of the reported issues associated with improper disposal of animals euthanized with pentobarbital. These findings demonstrate a need for more rigorous studies focusing on end-of-life decisions to help further understand factors affecting decision-making around euthanasia and, specifically, decisions about the disposal of animal remains following the use of pentobarbital.
Conclusion

The purpose of this literature review was to identify and summarize current knowledge, practices, and risks of using pentobarbital for euthanasia in veterinary medicine. Controlled rigorous studies on pentobarbital (as well as euthanasia in general) appear to be lacking, contributing to more anecdotal than data-based evidence regarding how pentobarbital is used in euthanasia and what happens to remains of the animals for which it is used. Similarly, a lack of controlled studies prevented any quantitative statistical analysis. Most information available took the form of case reports, reviews, and surveys. While definitive conclusions are difficult to draw, our review did identify gaps in knowledge on pentobarbital dosing, evidence of relay toxicosis (particularly in wildlife), challenges with handling and disposing of remains of animals euthanized with pentobarbital, and how breakdowns in veterinarian-client communication associated with end-of-life decisions may contribute to these challenges. The purpose of this literature review was to identify and summarize current knowledge, practices, and risks of using pentobarbital for euthanasia in veterinary medicine. Controlled rigorous studies on pentobarbital (as well as euthanasia in general) appear to be lacking, contributing to more anecdotal than data-based evidence regarding how pentobarbital is used in euthanasia and what happens to remains of the animals for which it is used. Similarly, a lack of controlled studies prevented any quantitative statistical analysis. Most information available took the form of case reports, reviews, and surveys. While definitive conclusions are difficult to draw, our review did identify gaps in knowledge on pentobarbital dosing, evidence of relay toxicosis (particularly in wildlife), challenges with handling and disposing of remains of animals euthanized with pentobarbital, and how breakdowns in veterinarian-client communication associated with end-of-life decisions may contribute to these challenges.

Our review also pointed to a need to obtain quantitative information from veterinarians regarding pentobarbital euthanasia. Surveys are a tool that can provide a snapshot into current understanding and trends in euthanasia methods. Such information can then be used to design controlled studies to rigorously evaluate different aspects of pentobarbital euthanasia. The result will be a knowledge base that will enable veterinary organizations and regulatory bodies to establish sensible and reasonable recommendations as to how to best handle and administer pentobarbital euthanasia, properly dispose of animal remains, prevent contamination of the environment, safeguard wildlife and people’s pets, and, most importantly, maintain the highest level of animal welfare.

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