CHAPTER 24

Barbiturates Poisoning and its Therapeutic Trends in Veterinary Medicine

NAVEED RASOOL*, SYDA ZILLE HUMA NAQVI, AHMAD TARIQ, ATA UR REHMAN, NIMRA TARIQ

Faculty of Veterinary Science, University of Agriculture, Faisalabad-38040, Pakistan.
*Corresponding author: naveedrasool741@gmail.com

SUMMARY

Barbiturates are frequently used in practices due to their hypnotic, anticonvulsant, and anesthetic properties. However, it is critical to be aware of the risks they pose, such as addiction, overdose, and even death. Barbiturates' pharmacokinetics include administration, absorption, distribution within the body, metabolism, and excretion. These medications can be taken orally or via injection. Because of their lipid nature, they are easily absorbed into the bloodstream. They are distributed throughout the body's tissues after being absorbed. They are primarily metabolized by the liver, but this process can be influenced by factors such as age, liver function, drug interactions, and even the breed of animal being treated. The kidneys are responsible for the majority of excretion. Urine pH levels, renal function, drug half-life, age of the animal, dosage frequency, and other co-administered medications can all have an impact. Barbiturates are used in veterinary medicine for sedation, anesthesia induction, seizure management, premedication before surgery, and procedures requiring intubation. They are also frequently used for euthanasia. Barbiturate poisoning is a serious problem that can cause depression, coma, hypotension, seizures, and cardiac or respiratory distress. Poisoning treatment typically includes measures such as the administration of activated charcoal. In some cases, hemodialysis or hemoperfusion may be required. The chapter discusses remedies for poisoning, such as milk thistle, ginger, peppermint, nux vomica, burdock root, and dandelion. It emphasizes the significance of seeking assistance and consulting with healthcare professionals. To avoid complications, it is best to use barbiturates responsibly, store medicine properly, and dispose of them carefully.

INTRODUCTION

Barbiturates belong to a group of drugs that acts as central nervous system (CNS) depressants. In veterinary medicine, they are commonly used for their hypnotic, anticonvulsant, and anesthetic properties. These drugs became available in the early 20th century and were widely used as hypnotics and anticonvulsants until 1960, when benzodiazepines were introduced (López-Muoz et al., 2005) Nowadays barbiturates are mainly used for anesthesia and as anticonvulsants. Despite their numerous medical applications, it's crucial to handle them with caution as they can be highly dangerous and even fatal if misused. (Khantzian & McKenna 1979). They can lead to addiction and tolerance develops rapidly requiring higher doses to get desired effects. However, their excessive doses lead to severe respiratory depression coma, and death. (Peterson, 2013).

Furthermore, Barbiturates can potentially have interactions, with medications, which can result in drug reactions. They can cause birth abnormalities during pregnancy, making them inappropriate to use for pregnant ones. (Perucca, 2006). Despite their potential risks, they are widely used in veterinary medical situations including the sedation of animals, the induction of general anesthesia, the control of seizures, the administration of premedication before surgery, and the facilitation of endotracheal intubation. (Yoshikawa, 2007; Tranquilli et al., 2013).

Animals can come into contact with barbiturates accidentally or unintentionally. The most common way is through ingestion, which can occur when veterinary or human medicines are not properly stored. Animals may also be exposed to barbiturates by the carcasses of euthanized animals or simply curious pets attracted to the scent of human pills. In rare cases, contaminated food or water sources can be the source of poisoning. Regrettably, there are risks of exposure due to

How to Cite: Rasool N, SZH Naqvi, A Tariq, Au Rehman & N Tariq, 2023. Barbiturates poisoning and its therapeutic trends in veterinary medicine. In: Complementary and Alternative Medicine: One Health Perspective (Sindhu ZuD, B Aslam, U Uslu & M Mohsin, eds): FahumSci, Lahore, Pakistan, pp: 180-185. ISBN: 978-627-7745-01-1. https://doi.org/10.61748/CAM.2023/024

unintended injections by veterinary personnel. It's crucial to be aware of these routes of exposure to ensure the safety of our furry companions (Driscoll et al., 2000; Beck et al., 2020). Barbiturates have a negative impact not just on individual animals, but also on the natural environment. Improper disposal of poisonous scavengers contaminates water supplies and affects ecosystems across the food chain, risking widespread disease spread and ecological imbalances (Hamilton, 2016).

In Spain, from 2004 to 2020 about 3210 suspected wildlife and domestic animal poisoning cases were reported. Barbiturate intoxication was seen in 3.4% (45/1334) of the total number of confirmed intoxicated animals (Herrero et al., 2021). Similarly in Europe, 330 calves, aged between 2 and 4 weeks, showed severe depression, sternal to lateral recumbency, tremor, and headshaking, and 13.6% died due to barbiturates poisoning which demonstrates the possible effects of this on animal health (Caloni et al., 2018). Even though they have therapeutic benefits, they may be harmful to many patients due to their tendency for addiction and overdose risk. People must follow advice from a healthcare expert who can monitor their effect and ensure efficient administration (Wells et al., 2020).

PHARMACOKINETICS OF BARBITURATES

The pharmacokinetics of barbiturates (Fig 1) include administration, absorption, distribution, metabolism, and excretion. (Gopinath & Wilson 2020).

Administration

Barbiturates can be administered orally or parenterally. However, the parenteral route has a quicker onset of action (Mathur & Malik 2021).

Absorption

Barbiturates are lipid-soluble weak acids that are easily absorbed by the gastrointestinal tract, lungs, and mucosal membranes. The rate of absorption is affected by the barbiturate used, solubility, formulation, and pKa value (Avdeef, 2012). Short-acting barbiturates such as secobarbital or pentobarbital are more lipid soluble and easily absorbed than long-acting such as phenobarbital (Greydanus et al., 2023).

Distribution

Barbiturates have a high degree of lipid solubility, and once they are in the bloodstream, they are readily distributed throughout the body, including the brain, liver, and adipose tissues. (Levine & LeBeau 2020). They can cross the blood-brain barrier in the brain where they attach themselves to GABA receptors and increase the inhibitory actions of GABA. This action induces a feeling of calmness, resulting in the hypnotic and sedative effects of barbiturates. However, some factors can affect the distribution of barbiturates in the body, such as tissue perfusion, blood flow, and protein binding (Deighton, 2022).

Metabolism

Barbiturates are mostly metabolized in the liver through a process called conjugation and oxidation. The liver has a primary role in metabolizing barbiturates. However, Other organs, like the kidneys, also play a part in metabolism (Remmer, 1970). Various factors can influence the metabolism of barbiturates, such as liver function, age, drug interactions, and breed and species of animal which are explained below.

Age: Barbiturates metabolize slowly in older adults due to low metabolic capacity and impaired liver function, thus increasing the risk of toxicity (Campbell et al., 2021).

Liver function: The effectiveness of barbiturate metabolism depends on liver function. Individuals with liver diseases have compromised drug metabolism, which increases risks of drug toxicity and may require dose adjustments. (Richards & Appel 1941).

Drug interactions: Barbiturates can interact with other medications and can affect their metabolism. For instance, medications like phenytoin and carbamazepine, which stimulate liver enzymes, can speed up the breakdown of barbiturates. Consequently, the duration of action is reduced (Milner, 1970).

Species and breed of animals: The impact of barbiturates on pet and dairy animals can vary depending on factors such as species, size, and specific health conditions (Halevy & Frumin 1973). Certain pet breeds, like greyhounds, are more susceptible to barbiturates due to their effective liver metabolism (Stafford, 2006). It is also recommended to avoid using barbiturates on dairy animals such as cows and goats to prevent contamination of milk and meat products (Cook & Wilson 1971).

Excretion

Barbiturates are excreted from the body as by-products through the kidneys. When they are metabolized in the liver, they are converted into water-soluble compounds that can be eliminated from the body through urine in a healthy individual. (Sim, 2015). Factors like urine acidity, kidney performance, barbiturate life, age, and gender can influence how quickly they are eliminated from the body. These are explained below.

Urine pH: The excretion of barbiturates may be influenced by the pH of the urine. They are weak acids and are more easily eliminated in acidic urine. Alkaline urine, on the other hand, may increase reabsorption while lowering the elimination of

barbiturates, resulting in higher drug concentrations in the body (Roberts & Buckley 2011)

Renal clearance: The kidneys play an important role in the excretion of drugs and metabolites. Barbiturate excretion may be reduced by renal dysfunction. As a result, individuals with impaired renal function may have extended elimination of barbiturates resulting in higher concentrations of drugs within the body.

Half-life: Barbiturates have distinct half-lives based on their lipid composition, structure, and metabolism. The half-life of a drug is the time it takes for half of it to be removed from the body. (Hayes, 1982) The half-lives of short-acting barbiturates are often only a few hours. such as thiopental, with a half-life of 3–18 hours, and pentobarbital with 15–50 hours, while the effects of long-acting barbiturates might last for several days at a time like phenobarbital with a half-life of 24–96 h. The half-life of a drug influences its duration of action and possible side effects (Choo et al., 2023; Bauerschmidt et al., 2023).

Age: Age is another factor that can influence barbiturate excretion. In elderly animals, the elimination half-life is extended due to decreased renal function and metabolic activity (Jusko et al., 1979).

Active dose and frequency: Excretion of barbiturates may also be affected by dose and frequency of administration. Larger dosages and more frequent administration may result in delayed elimination, whereas smaller doses and less frequent administration may result in rapid elimination (Owen & Tyrer 1983).

Co-administration with other drugs: The presence of other drugs in the body can affect barbiturate excretion. These medicines may either increase or reduce the excretion of barbiturates (Corrie & Hardman 2011).

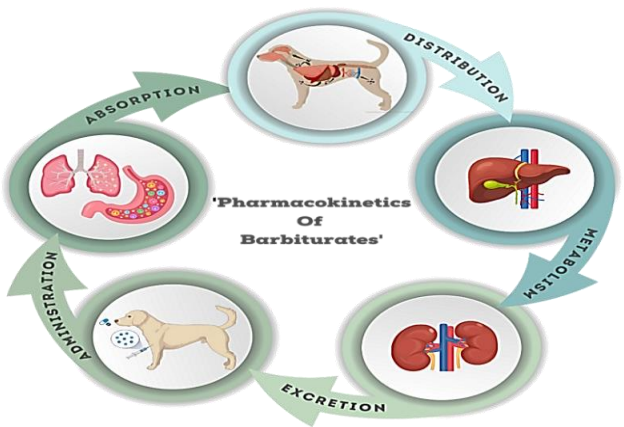

Fig 1. Pharmacokinetics of barbiturate

BENEFITS AND CLINICAL USES OF BARBITURATES

Barbiturates are a class of drugs that act as CNS depressants. Once these were widely used in both human and veterinary medicine Fig 2. However, its use in the veterinary field has declined significantly due to the availability of more effective and safer drugs. Nonetheless, there are still uses for barbiturates in veterinary medicine. These are potent sedatives that are frequently used to calm anxious or aggressive animals. Depending on the desired duration and intensity of sedation, they may be given intravenously, intramuscularly, or orally (Donaldson et al., 2007). Moreover, these are extensively utilized as anesthetic agents in veterinary medicine. They can be used either alone or in combination with other drugs to induce and maintain general anesthesia during prolonged surgical procedures. Barbiturates typically used for this purpose include methohexital, thiopental, and pentobarbital (Tranquilli et al., 2013).

Barbiturates are potent anticonvulsant drugs frequently used to treat epilepsy and other seizure disorders in dogs. These drugs reduce the overall excitability of neurons in the brain, lowering the frequency and severity of seizures. Phenobarbital is one such barbiturate that is often recommended for dogs that have seizures (Shah & Eddleston 2010). Likewise, these are used as premedication before surgery to mitigate animal anxiety and reduce the amount of anesthesia required. This can help to reduce the possibility of complications during and after surgery (Dyson, 1990). Barbiturates can aid in endotracheal intubation, which is required for animals while administering general anesthesia. They induce sedation, which aids in the relaxation of the animal's airways. Thus making it easier to insert an endotracheal tube (Sivilotti et al., 2003).

In veterinary medicine, one of the well-known uses of barbiturates is euthanasia. When an animal is in terrible pain due to a disease or suffering with little hope of recovery, veterinarians may choose to deliver a controlled overdose of barbiturates to ensure a quick and painless end-of-life solution. Veterinarians commonly use sodium pentobarbital and pentobarbital combination products for the euthanasia of their animal patients (Kollias et al., 2023).

POISONING OF BARBITURATES

Barbiturate poisoning, a severe medical condition, can result from the misuse or prolonged use of barbiturates. Barbiturates are effective for sedation and hypnosis because they act on the central nervous system; however, excessive doses can cause respiratory depression, low blood pressure, coma, and seizures in the most severe cases. Moreover, an excessive intake of barbiturates can cause cardiac or respiratory distress, which leads to death (Hargrove et al., 1952).

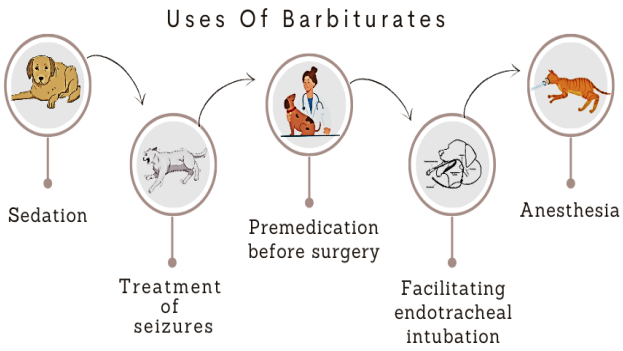

Fig 2. Barbiturates uses in animals.

In veterinary medicine, barbiturate poisoning is one of the most common toxicities in animals, particularly cats and dogs. In Spain, between 2004 and 2020, barbiturates accounted for approximately 3.4% of documented poisoning cases involving these animals, making this the second most prevalent toxin (Herrero-Villar et al., 2021).

The most common symptom of barbiturate poisoning is respiratory depression. Other symptoms include coma, hypotension, and seizures (Arena, 1970). The intensity of the symptoms is determined by the duration of exposure and the amount of drug used. Various factors, such as co-use with other sedatives, and underlying medical conditions such as liver and kidney disease, increase the likelihood of barbiturate poisoning in animals (Hadden et al., 1969: Jones et al., 2012). Very young or old animals are at a greater risk of developing toxicity (Otten & Blomkalns 1998). Barbiturate overdose is a common cause of poisoning in animals, particularly in cats and dogs (Romano et al., 2020). Other factors, such as pre-existing respiratory patterns, dryness, cardiovascular abnormalities, and a subnormal body temperature can all aggravate the condition (Smith, 1989).

Chronic use of barbiturates leads to the development of tolerance and physical dependence, which increases the possibility of additional dosage intake along with the appearance of withdrawal symptoms (Michelini et al., 1996). In addition to their hypnotic and sedative effects, they induce behavioral changes, like aggression or hyperactivity, particularly in cats (Meyer & Fish 2008). Other side effects include diminished appetite, sleepiness or drowsiness, and impaired coordination resulting in sluggish movements (Golubovic & Rossmeisl 2017).

CONVENTIONAL TREATMENTS FOR BARBITURATE POISONING

An overabundance of barbiturates can result in potentially fatal consequences such as respiratory failure. It is a medical emergency, since there is no known cure for overdosing, supportive care for barbiturate toxicity is of primary importance. Multiple doses of activated charcoal are an effective remedy for barbiturate poisoning because they can absorb the drug from the gastrointestinal tract and reduce its absorption into the bloodstream. However, the administration of charcoal should be done immediately after ingestion, ideally within a few hours (Roberts & Buckley 2011). Hemodialysis or hemoperfusion may be required in severe cases of barbiturate poisoning to remove the drug from the bloodstream (Mactier et al., 2014). Supportive measures such as airway management, ventilation, gastric lavage, and intravenous fluids can be applied to stabilize the animal and maintain vital functions. Mechanical ventilation may be required in case of severe respiratory depression or apnea (Sharma & Bangar 2005).

ALTERNATIVE AND COMPLEMENTARY APPROACHES TO MANAGE BARBITURATE POISONING

Barbiturate poisoning is a medical emergency that necessitates prompt intervention from conventional medical services. However, certain herbal remedies may provide supportive benefits in the detoxification and liver support process. It's crucial to remember that these herbal treatments should not be used as a substitute for standard medical care but they can be considered as supplementary measures when under the supervision of healthcare providers. Milk thistle also known as silymarin, is well-known for its ability to protect the liver and may be able to assist when liver function has been affected by barbiturate poisoning. According to studies, silymarin has the ability to flush toxins from the body because it dramatically lowers serum ALT and AST levels when given to dogs prior to CCl_4 injection (Paulova et al., 1990). Ginger (*Zingiber officinale*) and peppermint are often recommended to alleviate symptoms such as nausea and vomiting caused by barbiturate toxicity. However, they are typically used more for managing symptoms than directly counteracting the effects of barbiturates (Bhowmik et al., 2010). Nux Vomica is another remedy often used to treat symptoms such as nausea, vomiting, and gastrointestinal disturbances which are common in cases of poisoning (Katiyar et al., 2010). Burdock root (*Arctium lappa*) is believed to have detoxifying properties, support liver and kidney function, and is thought to be effective in barbiturates poisoning (Mahboubi, 2021). Finally, dandelion (*Taraxacum officinale*) has traditionally been used to promote liver health. Its potential diuretic effects may aid in eliminating toxins from the body (Al-Malki et al., 2013).

The effectiveness of these herbal medications may vary in different species. It is important to consult healthcare professionals before starting any herbal regimen, taking into account the patient's overall health condition. Seeking prompt

medical attention should be the top priority in cases of barbiturate poisoning (Roberts & Buckley 2011).

COMPLICATIONS AND PREVENTION OF BARBITURATE POISONING

Barbiturate poisoning in animals can have serious consequences, so it's important to be extra cautious around them. Possible side effects of this drug on the cardiovascular and respiratory systems include hypotension, electrolyte imbalances, and metabolic acidosis (Plumb, 2018). To completely avoid cases of barbiturate poisoning, one must use barbiturates as prescribed and under a veterinarian's supervision (Boullata & Nace 2000). Additionally, unused medications should be kept in the proper containers and disposed of properly to avoid accidental poisoning of pets and wildlife.

CONCLUSION

Barbiturates have a wide range of applications in veterinary medicine because of their sedative, hypnotic, anticonvulsant, and anesthetic properties, which makes them an important class of drugs. However, it's important to understand that mishandling or taking barbiturates can have grave outcomes resulting in severe harm, illness, or even death. That's why veterinarians must assess the use of barbiturates in medicine carefully. They should familiarize themselves with the characteristics of these drugs, including how they act in the body, potential side effects, and appropriate treatment including conventional and complementary approaches. Additionally, Veterinarians are required to carefully observe animals who receive treatment for any indications of toxicity or adverse reactions.

REFERENCES

Al-Malki AL, MK Abo-Golayel, G Abo-Elnaga & H Al-Beshri, 2013. Hepatoprotective effect of dandelion (*Taraxacum officinale*) against induced chronic liver cirrhosis. Journal of Medicinal Plants Research 7:1494-505.

Arena JM, 1970. The clinical diagnosis of poisoning. Pediatric Clinics of North America 17(3):477-494.

Avdeef A, 2012. Absorption and drug development: solubility, permeability, and charge state. John Wiley and Sons.

Bauerschmidt A, T Al-Bermani, S Ali, B Bass, J Dorilio, J Rosenberg & F Al-Mufti, 2023. Modern sedation and analgesia strategies in neurocritical care. Current Neurology and Neuroscience Reports 23(4):149-158.

Beck AC, EM Lash & JB Hack, 2020. Environmental toxic exposures using companion animals as an indicator of human toxicity: a case report and discussion. The journal of emergency medicine 59(1):1-7.

Bhowmik D, KK Tripathi, MR Chandira & KP Kumar, 2010. *Zingiber officinale* the herbal and traditional medicine and its therapeutically importance. Research Journal of Pharmacognosy and Phytochemistry 2(2):102-110.

Golubovic BS & JH Rossmeisl, 2017. Status epilepticus in dogs and cats, part 2: treatment, monitoring, and prognosis. Journal of veterinary emergency and critical care 27(3):288-300.

Boullata JI & AM Nace, 2000. Safety issues with herbal medicine. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy 20(3):257-269.

Caloni F, P Berny, S Croubels, M Sachana & R Guitart, 2018. Epidemiology of animal poisonings in Europe. In Veterinary toxicology, Academic Press pp: 45-56.

Campbell G, S Darke, E Zahra, J Duflou, F Shand & J Lappin, 2021. Trends and characteristics in barbiturate deaths Australia 2000–2019: a national retrospective study. Clinical toxicology 59(3):224-230.

Choo YH, Seo Y & Oh HJ, 2023. Deep sedation in traumatic brain injury patients. Korean Journal of Neurotrauma,19(2):185-194.

Cook RM & K Wilson, 1971. Removal of pesticide residues from dairy cattle. Journal of Dairy Science 54(5):712-718.

Corrie K & JG Hardman, 2011. Mechanisms of drug interactions: pharmacodynamics and pharmacokinetics. Anaesthesia and Intensive Care Medicine 12(4):156-159.

Deighton JC, 2022. Physician assisted dying (PAD): an investigation into the mechanistic action of opioid, benzodiazepine, and barbiturate administration as an alternative measure to forgoing life-sustaining treatment and aggressive palliation.

Donaldson M, G Gizzarelli & B Chanpong, 2007. Oral sedation: a primer on anxiolysis for the adult patient. Anesthesia Progress 54(3):118-129.

Driscoll KE, DL Costa, G Hatch, R Henderson, G Oberdorster, H Salem & RB Schlesinger, 2000. Intratracheal instillation as an exposure technique for the evaluation of respiratory tract toxicity: uses and limitations. Toxicological Sciences 55(1):24-35.

Dyson DH, 1990. Update on butorphanol tartrate: use in small animals: the Canadian Veterinary Journal 31(2):120.

Gopinath A & M Wilson, 2020. Factors affecting drug absorption and distribution. Anaesthesia and Intensive Care Medicine 21(5):223-228.

Greydanus DE, P Kukreti & HK Pemde, 2023. Substance use and abuse in adolescents: An overview. International Journal of Child and Adolescent Health 16(1):21-51.

Griffin CE, AM Kaye, FR Bueno & AD Kaye, 2013. Benzodiazepine pharmacology and central nervous system–mediated effects. Ochsner Journal 13(2):214-223.

Hadden J, K Johnson, S Smith, L Price & E Giardina, 1969. Acute barbiturate intoxication: concepts of management. The Journal of American Medical Association 209(6):893-900.

Halevy S, & MJ Frumin, 1973. Genetic control of barbiturate depression: strain and sex variation. BJA: British Journal of Anaesthesia 45(10):999-1004.

Hamilton PB, IG Cowx, MF Oleksiak, AM Griffiths, M Grahn, JR Stevens & CR Tyler, 2016. Population-level consequences for wild fish exposed to sublethal concentrations of chemicals–a critical review. Fish and Fisheries 17(3):545-566.

Hargrove EA, AE Bennett & FR Ford, 1952. Acute and chronic barbiturate intoxication—recent advances in therapeutic management. California Medicine 77(6):383.

Hayes JE, 1982. Normal changes in aging and nursing implications of drug therapy. Nursing Clinics of North America 17(2):253-262.

Herrero-Villar M, IS Sánchez-Barbudo, PR Camarero, MA Taggart & R Mateo, 2021. Increasing incidence of barbiturate intoxication in avian scavengers and mammals in Spain. Environmental Pollution 284:117452.

Jones JD, S Mogali & SD Comer, 2012. Polydrug abuse: a review of opioid and benzodiazepine combination use. Drug and Alcohol Dependence 125(1-2):8-18.

Jusko WJ, MJ Gardner, A Mangione, JJ Schentag, JR Koup & JW Vance, 1979. Factors affecting theophylline clearances: age, tobacco, marijuana, cirrhosis, congestive heart failure, obesity, oral contraceptives, benzodiazepines, barbiturates, and ethanol. Journal of Pharmaceutical Sciences 68(11):1358-1366.

Katiyar C, A Kumar, SK Bhattacharya & RS Singh, 2010. Ayurvedic processed seeds of nux-vomica: neuropharmacological and chemical evaluation. Fitoterapia 81(3):190-195.

Khantzian EJ & GJ McKenna, 1979. Acute toxic and withdrawal reactions associated with drug use and abuse. Annals of Internal Medicine 90(3):361-372.

Kollias NS, WJ Hess, CL Johnson, M Murphy & G Golab, 2023. A literature review on current practices, knowledge, and viewpoints on pentobarbital

euthanasia performed by veterinarians and animal remains disposal in the United States. Journal of the American Veterinary Medical Association :1-6.

Levine BS & M LeBeau, 2020. Miscellaneous central nervous system depressants. Principles of Forensic Toxicology 333-346.

López-Muñoz F, R Ucha-Udabe & C Alamo, 2005. The history of barbiturates a century after their clinical introduction. Neuropsychiatric disease and treatment 1(4):329-343.

Mactier R, M Laliberté, J Mardini, M Ghannoum, V Lavergne & S Gosselin, 2014. Extracorporeal treatment for barbiturate poisoning: recommendations from the EXTRIP Workgroup. American Journal of Kidney Diseases 64(3):347-358.

Mahboubi M, 2021. *Arctium Lappa* and management of liver functions to detoxify the bloodstream. The Natural Products Journal 11(5):609-616.

Mathur M & MT Malik, 2021. Benzodiazepines and barbiturates: sedation and analgesia for the Pediatric Intensivist: A Clinical Guide 401-410.

Meyer RE & R Fish, 2008. Pharmacology of injectable anesthetics, sedatives, and tranquillizers. In book: Anesthesia and Analgesia in Laboratory Animals. Academia pp: 27-82.

Michelini S, GB Cassano, F Frare & G Perugi, 1996. Long-term use of benzodiazepines: tolerance, dependence and clinical problems in anxiety and mood disorders. Pharmacopsychiatry 29(04):127-134.

Milner G, 1970. Interaction between barbiturates, alcohol and some psychotropic drugs. Medical Journal of Australia 1(24):1204-1207.

Otten EJ & AL Blomkalns, 1998. Venomous animal injuries. Emergency medicine concepts and clinical practices. New York: Mosby pp. 924-40.

Owen RT & P Tyrer, 1983. Benzodiazepine dependence: a review of the evidence. Drugs 25:385-398.

Paulova J, M Dvorak, F Kolouch, L Vanova & L Janeckova, 1990. Verification of the hepatoprotective and therapeutic effect of silymarin in experimental liver injury with tetrachloromethane in dogs. Veterinary Medicine 1990(35):629–35.

Perucca E, 2006. Clinically relevant drug interactions with antiepileptic drugs. British Journal of Clinical Pharmacology 61(3):246-255.

Peterson JM, 2013. The truth about barbiturates. The Rosen Publishing Group, Inc.

Plumb DC, 2018. Plumb's veterinary drug handbook. John Wiley and Sons.

Remmer H, 1970. The role of the liver in drug metabolism. The American journal of medicine 49(5):617-629.

Richards RK & M Appel, 1941. The Barbiturates and the liver. Anesthesia and Analgesia 20(2):64-77.

Roberts DM & NA Buckley, 2011. Enhanced elimination in acute barbiturate poisoning–a systematic review. Clinical Toxicology 49(1):2-12.

Romano MC, DC Dorman & CL Gaskill, 2020. Postmortem veterinary toxicology: Animal death investigation and the veterinary diagnostic laboratory. Wiley Interdisciplinary Reviews: Forensic Science 2(5):e1375.

Shah AS & M Eddleston, 2010. Should phenytoin or barbiturates be used as second-line anticonvulsant therapy for toxicological seizures? Clinical toxicology 48(8):800-805.

Sharma BR & S Bangar, 2005. Management of common poisoning: changing trends & challenges. Indian Congress of Forensic Medicine and Toxicology.

Sim DSM, 2015. Drug elimination. Pharmacological Basis of Acute Care, pp:37-47.

Sivilotti ML, MR Filbin, HE Murray, P Slasor & RM Walls, 2003. Does the sedative agent facilitate emergency rapid sequence intubation? Academic Emergency Medicine 10(6):612-620.

Smith JA, 1989. Noninfectious diseases, metabolic diseases, toxicities, and neoplastic diseases of South American camelids. Veterinary Clinics of North America: Food Animal Practice 5(1):101-143.

Stafford K, 2006. The welfare of the athletes; greyhounds and sled dogs. In: The Welfare of Dogs. Animal Welfare: Vol 2: Springer pp:143-160.

Tranquilli WJ, JC Thurmon & KA Grimm, 2013. Lumb and Jones' veterinary anesthesia and analgesia. John Wiley and Sons.

Wells K, A Butterworth & N Richards, 2020. A review of secondary pentobarbital poisoning in scavenging wildlife, companion animals and captive carnivores. Journal of Veterinary Forensic Sciences 1(1):1-15.

Yoshikawa H, 2007. First-line therapy for theophylline-associated seizures. Acta Neurologica Scandinavica 115:57-61.