REVIEW ARTICLE

SUDDEN DEATH RELATED TO ACUTE IATROGENIC CONDITIONS IN DOMESTIC RUMINANTS AND HORSES: A REVIEW

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Original Submission:
06 June 2024
Revised Submission:
27 June 2024
Accepted:
02 July 2024

How to cite this article: Benchohra M. 2024. Sudden death related to acute iatrogenic conditions in domestic ruminants and horses: A Review. Veterinaria, 73(2), 105-19.

ABSTRACT

Drug poisoning in animals is generally due to adverse drug reactions (ADRs), drug-drug interactions (DDIs) or iatrogenesis. No drug is exempt from the risk of adverse reactions or side effects. Acute drug poisoning can lead to unexpected animals death, with anaphylaxis being the most common and harmful pathophysiological phenomenon among ADRs. Antibiotics are primarily involved, either through an individual effect or through interaction with another drug. Furthermore, self-medication, a widespread practice in veterinary medicine, amplifies the risk of iatrogenesis. ADRs, DDIs, and iatrogenesis are all potentially serious risks that can lead to sudden death (SD) in ruminants and horses. In such situations, forensic medicine is needed to determine the cause of death, and veterinary forensic analyses may be necessary in spite of the lack of toxicological drugs references in veterinary toxicology laboratories. Thus, it seems appropriate to consider iatrogenic factors as a hypothetical cause in the differential diagnosis of sudden death syndrome (SDS).

Keywords: Adverse drug reaction, drug-drug interactions, iatrogenesis, sudden death, ruminants, horse

doi.org/10.51607/22331360.2024.73.2.105

INTRODUCTION

The complexity of veterinary pharmacology and toxicology lies in the multiplicity of animal species, as well as diversity among breed, age, sex, and pathophysiological state, all of which may react differently to certain drugs (Anadon, 2016). In addition, a lack of information about the safe and appropriate use of veterinary medicines is a major cause of erroneous and dangerous medication (Wallis et al., 2019; Van der Riet, 2021). Drug poisoning in animals usually occurs due to off-label use, incorrect dosage, negligence, accidental ingestion, contaminated drugs, serious adverse reactions, and dangerous drug interactions (Brown et al.,1988; Uppal, 2000; Siroka and Svobodova, 2013). Butself - medication practices remain the principal cause of iatrogenesis in veterinary practice (Ruiz, 2010; Fainzang, 2014; Sala et al., 2019). Sudden death is a complex multifactorial syndrome defined as the sudden unexpected death of an apparently healthy animal with no obvious clinical signs of disease. Published studies on SD in various species of ruminants is more extensive (Benchohra et al., 2024) than that conducted on equines, with the majority of it focused on racehorses (Navas de Solis et al 2018; Morales-Briceno, 2020). However, the literature does not include iatrogenic factors, which can directly cause certain acute deaths in horses or ruminants, among the wide range of SDS causes (Diab et al., 2017; Bennet and Parkin, 2022; Benchohra et al., 2024). The aim of this review is to highlight the importance of iatrogenic factors as potential causative agents of unexpected death in ruminants and horses and their consequent relevance to forensic investigations.

ADVERSE DRUG REACTIONS

Maddison (1992) defines ADR as any undesirable or unintended response by the animal to a drug administered to aid in the diagnosis, treatment, or prevention of disease, which may be related to the drug itself or the excipients contained in the formulation.

In practice, no drug is free from the risk of adverse or side effects, some of which can be life-threatening or even fatal (Fresnay, 2017; Zhao et al., 2023). Several groups of drugs are involved in producing adverse reactions in animals, and it is estimated that about 20% occurs in bovine (Uppal, 2000) and equine (Fresnay, 2017) (Table 1). Some drugs have a very narrow safety margin; consequently, a small variation in the administered dose or in the sensitivity of a particular animal can easily produce an adverse reaction (Keen and Levingston, 1983).

In bovine and equine practice, when several drugs are administered simultaneously, it is difficult to assess with certainty whether an adverse reaction is caused by one of those drugs or by a drug-drug interaction. According to Fresnay (2017), in horses, adverse reactions linked to antiparasitic and nervous system drugs, and vaccines are mostly mild ; whereas, for antibiotics and nonsteroidal anti-inflamatory drugs (NSAIDs), the majority of cases are severe. However, in other species, nervous system drugs and vaccines are generally responsible for relatively severe reactions (Fresnay, 2017).

Anaphylaxis

Anaphylaxis is the most harmful pathophysiological phenomenon among ADRs, leading to fatal outcomes (Siroka and Svobodova, 2013; Khusro et al., 2021). It is defined as a severe and potentially fatal systemic allergic reaction that occurs suddenly after contact with an allergen (Sampson et al., 2006). The anaphylactic reaction usually manifests within minutes after the administration of a sensitizing substance with which had previously been treated (Madisson, 1992), but sometimes it can be delayed for several hours (Liebhart and Panaszek, 2007). In animals, lethal anaphylaxis is characterized by severe airway constriction and/or intense hypotension leading to shock (Uppal, 2000).

The involvement of procaine penicillin in anaphylactic shock and acute death in horses has long been well known (Brown et al., 1988; Madisson, 1992). In some cases, the reaction to

procaine benzylpenicillin may be attributed to the procaine rather than the penicillin itself (Keen and Levingston, 1983); procaine toxicity may account for 90% of adverse events related to procaine penicillin use (Lopez et al., 2020). To sum up, reactions to procaine penicillin may be due to procaine toxicity, allergic reaction to penicillin itself, or an accidental intravenous administration (Madisson, 1992).

Omidi (2009) reports an anaphylactic reaction that occured immediately following an injection of penicillin-streptomycin into a Holstein-Friesian cow; similarly, penicillin induced fatal shock in calf (Tjalve, 1997). Sulfonamide administration causes hypersensitivity reactions and IgE-type anaphylactic reactions in horses, the clinical manifestations being hypotension and collapse (Khusro et al., 2021).

Oxytetracycline is an antibacterial drug widely used in ruminants, but it is not totally safe; a few cases of fatal anaphylactic shock have been reported following its administration in cattle (BVD, 1992). Enrofloxacin can also present serious risks, with one case reported of a cow collapsing following treatment with this antibiotic (Tjalve, 1997). Similarly, a case of SD was reported in a calf one minute after an injection of ceftiofur sodium, and a necropsy exam confirmed an anaphylactic shock (BVD, 1992).

In food animal practice, vitamin therapy is frequently used for fattening, therapeutic, or preventive purposes. However, anaphylactic shock has been linked to the injection of vitamin A, D, and E complexes (Uppal, 2000). There have also been reported a number of SD cases in cattle (BVD, 1992) and horses (Brown et al., 1988) after the administration of vitamin B12 plus minerals. Vaccination is not without risk, and in a small proportion of the vaccinated population, the possibility of a potentially fatal allergic reaction exists (Gershwin, 2018). In horses, 28% of post-vaccination responses have been considered important and manifest within 30 minutes of vaccination (Rougier and Laurentie, 2020). Anaphylactic vaccine reactions can cause acute lung edema, with the lungs being the primary site of lesions and collapse and death being the sequelae (Underwood et al., 2015). Tjalve (1997) reported the death of cows following administration of live vaccine of *Trichophyton verrucosum*.

Antibiotics

Antibacterials appear to be the most implicated therapeutic group for adverse reactions in cattle (Tjalve, 1997; Siroka and Svobodova, 2013). However, in horses, analgesics and antiparasitics are more involved in ADRs than antibiotics (Khusro et al., 2021). Procaine penicillin toxicity is low in equine practice, but ADRs can occur at any given time and in a variety of clinical settings (Lopez et al., 2020; Khusro et al., 2021).

Antibiotics, principally ionophores, are often added to ruminant food because of their anticoccidial effects (Plumlee, 2003) and their ability to improve the efficiency and performance of beef and dairy animals (Marques and Cooke, 2021). Their principal property is electrolyte imbalances and changes in K+, Na+, and especially Ca2+ concentrations in cells, leading to disturbances in muscle contractility (Siroka and Svobodova, 2013) and involving acute cardiac rhabdomyocyte degeneration and necrosis (Miller and Gal, 2017).

Excessive ingestion of monensin, maduramicin, and salinomycin causes intoxication in sheep and cows, with symptoms appearing a few hours later (Plumlee, 2003). Myocardial failure results from monensin's specific toxicity to the mitochondria of the heart (Keen and Levingston, 1983). Omidi et al. (2010) observed that calves died of intoxication due to a high dose of salinomycin added to the diet (70 g/kg of concentrate) within 10 hours of ingestion.

Derived from oxytetracycline, doxycycline is a semi-synthetic antibiotic with bacteriostatic activity, a broad spectrum of action, and a higher therapeutic efficacy than other tetracyclines (Turk et al. 2020). Side effects include renal damage, cardiomyopathy, and necrotic myopathy (Brihoum et al., 2011). Doxycycline overdose toxicity in calves has been documented by a number of authors, including cases of acute death (Chiers et al., 2004; Brihoum et al., 2010; Karapinar et al., 2019).

Tilmicosin phosphate is a macrolide antibiotic, approved for treating specific pneumonia in cattle and sheep. The cardiotoxicity of this drug is thought to be mostly due to calcium channel blockade (Lust et al., 2011). Papich (2016) states that tilmicosin administered intravenously in any species can cause acute death. Likewise, when injected by the intramuscular route into young lambs, tilmicosin can lead to death by heart failure. Lastly, sulfabromethazine administered intravenously to calves has been shown to induce ataxia and collapse (Uppal, 2000).

Antiparasitics

Levamizole is used both as an anthelmintic and as an immunomodulator, and it has a number of possible adverse and toxic effects. Levamisol acts on nicotinic acetylcholine receptors, leading to respiratory muscle paralysis and asphyxia, but neurotoxicity is the main clinical manifestation (Siroka and Svobodova, 2013). In young animals, whose blood-brain barrier is still developing, the drug can reach the brain and cause neurotoxicity (Keen and Levingston, 1983). Suffocation due to respiratory failure is the main cause of death in cases of lethal levamisole poisoning (Hsu, 1980). In sheep and heifers, clinical symptoms such as dyspnea, ptyalism, and oculopalpebral edema appear one hour after levamisole administration (Uppal, 2000). According to Müller and Dwyer (2016), levamisole treatment resulted in the death of calves 12 weeks old.

Ivermectin is a macrocyclic lactone antiparasitic drug commonly used in ruminants that is effective on both endoparasites and ectoparasites. This drug can enter the central nervous system and have adverse neurological effects due to the increased permeability of the blood-brain barrier (Siroka and Svobodova, 2013). Vermeulen et al. (2016) reported concerns about a fatal oral ivermectin intoxication in calves aged two to four weeks, probably intentional, with a dose eight times higher than the recommended therapeutic dose.

Closantel is a salicylanilide antihelmintic used against several developmental stages of bloodsucking nematodes and trematodes in ruminants and sheep oestrosis. It acts on parasites by interfering with the synthesis of adenosine triphosphate (ATP) by cellular oxidative phosphorylation which disrupts the liquid and ion transport mechanisms in the parasite's membranes and impairs parasite motility (Venkatesh et al., 2019). Ecco et al. (2006) reported accidental poisoning in kid goats weighing 14kg after administration of closantel 10% at a dose 8 to 10 times higher than the manufacturer's recommendation. However, it seems that young lambs were more sensitive to closantel toxicosis with lethal doses begin at two times the recommended dose (Rivero et al., 2015). Clinical orientation signs include nervous disturbances and blindness one to two days after administration of the drug (Ecco et al., 2006).

Nitroxinil is an anthelmintic belonging to the phenolic substitutes group, used for its fasciolicidal, nematodicidal, and estricidal properties. Nitroxinil toxicity occurs in various species, most often as a result of overdosing (Lovatt et al., 2014). A high incidence of lethality has been reported in kids and adult goats, occurring five hours after subcutaneous overdosing (Brito Junior et al., 2021). Frequently reported clinical signs of acute intoxication include respiratory distress, decubitus, and death (Lovatt et al., 2014; Brito Junior et al., 2021).

Vitamins and minerals

Selenium (Se) is a trace element that plays an important role in animal health and production (Mehdi and Dufrasne, 2016). Given the relatively narrow range between recommended feed concentrations and the toxicity limit, a minor mixing error can be responsible for a toxic or even fatal incident (Raisbeck, 2020). Manifestation of Se toxicity includes myocardial necrosis leading to severe pulmonary edema, severe respiratory distress, and death within hours (Amini et al., 2011; McKenzie and Al-Dissi, 2017). Sudden deaths of newborn kids (Amini et al., 2011) and young lambs (McKenzie and Al-Dissi, 2017) have been reported after parenteral Se therapy due toacute selenosis.

In cattle, one case of death was reported following an IM injection of vitamin E and Se by the owner; the other cows treated at the same time showed transient anxiety and dyspnea (BVD, 1992).

DRUG-DRUG INTERACTIONS

Drugs used in combination may interact rather than act independently, which is a major factor in DDIs (Table 1). Physical and/or chemical incompatibility between drugs is common (Hsu, 2008), which can lead to metabolic interactions when one drug inhibits the metabolism of another. The drug's toxicity is increased as its plasma concentration increases due to inhibit metabolism (Wang et al., 2021). Sudden death is a potential consequence of DDIs if phenylbutazone and other NSAIDs are combined (Uppal, 2000). Similarly, the combination of NSAIDs or corticosteroids with certain antibiotics could be harmful. Acute mortality in calves has been reported following treatment with flunexin meglumine and gentamicin sulfate (BVD, 1992), as well as infusion of prednisolone, which is a corticosteroid hormone, with chloramphenicol (Uppal, 2000). In addition to its own ADRs, levamisole can potentially interact with chloramphenicol, with fatal outcomes (Plumb, 2011). Local treatment of mastitis is the most common form of treatment for dairy cows and is commonly practiced by owners without the need for veterinary support. However, anaphylactic shock has been reported following the infusion of a preparation of colistin, streptomycin, and prednisolone for a cow suffering from mastitis (Uppal, 2000).

Table 1 Summary of ADRs and DDIs that may cause acute death in ruminants and horses, with clinical courses and toxicity-determining factors.

Drug	Animals	Route of administration	Clinical course	Toxicity-determining factor	Authors
Antibiotics					
Benzylpenicillin procaine	Cattle	IM	Anaphylactic shock and death.	Procaine toxicity, Accidental IV injection, Pulmonary embolisme.	Dechant (2021) Tjalve (1997) Keen and Levingston (1983)
	Horse	IM, IV	Seizures, collapse, anaphylactic shock, death within few minutes.	Accidental IV injection, A high dose at a single injection site.	Brown et al. (1988) Lopez et al. (2020) Khusro et al. (2021)
Potassium benzylpenicillin	Horse	IV	Allergic anaphylactic reaction.	Allergy to penicillin.	Tjalve (1997)
Penicillin-streptomycin	Cattle	IM	Severe dyspnea, incoordination, anxiety, salivation, lacrimation, rhinitis, and shock.	Allergy to penicillin.	Tjalve (1997) Omidi (2009)

Sulphabromethazine	Calf	IV	Ataxia and collapse.	Unspecified	Uppal (2000)
Trimethoprim-sulfadiazine	Horse	IV, PO	Hypersensitivity, collapse, and death in few minutes. Anaphylaxis, cardio-vascular collapse and cerebral infarction.	Hypersensitivity, collapse, and death in few minutes. Anaphylaxis, cardio-vascular collapse and cerebral infarction.	Tjalve (1997) Desjardins (2010) Khusro et al. (2021)
Trimethoprim	Horse	IV	Acute anaphylactic shock.	5.5 mg/kg dissolved in aqueous lactic acid (50 mg/mL)	Lopez et al. (2020)
Ionophores	All ruminants	In feed	Disturbances in muscle contractility, acute cardiac rhabdomyocyte degeneration and necrosis.	Overdosage	Keen and Levingston (1983) Siroka and Svobodova (2013) Miller and Gal (2017)
	Horse	In feed	Dyspnea, tachycardia, ataxia, myocardial failure and dead.	Off-label use Consumption of ruminant feed.	Hunchak et al. (2014) Keen and Levingston (1983)
Monensin	Horse	In feed	Severe colic, collapse, recumbency. Even death during exercise. Myocardial necrosis.	10 mg/kg Unspisified	Lopez et al. (2020) Desjardins (2010)
Salinomycin	Calf	PO	Death occurs in 10h.	Wrong dosage	Omidi et al. (2010)
Narasin	Horse	In feed	Restlessness, polyuria, dyspnea, sweating, progressive ataxia, recumbency and death.	Off-label use	Lopez et al. (2020)

Oxytetracycline	Cattle	Unknow	Anaphylactic shock.	Unspecified	BVD 1992
	Horse	IM	Fatal colitis.	Off-label use	Keen and Levingston (1983) Lopez et al. (2020)
		IV	Adverse cardiovascular effects and acute renal failure, hypotension and collapse.	Rapid IV administration (Propylene glycol and 2-pyrrolidone excipient).	Lopez et al. (2020) Desjardins (2010)
Doxycycline	Calf	IM	Cardiomyopathy, necrotic myopathy, and renal damages.	Overdose	Brihoum et al. (2011) Karapinar et al. (2019)
	Horse	PO IV	Agitation, anxiety, depression, tachycardia, tachypnea, hypertention, collapse and cardiac arrest.	0.18 to 10 mg/kg IV injection is not recommended	Lopez et al. (2020) Desjardins (2010)
Tilmicosin	All species, Young lamb	IV IM	Cardiotoxicity due to calcium channel blockade. Death by heart failure.	Particularly hypertoxic drug IV route is fatal	Lust et al. (2011) Christodoulopoulos (2009)
Ceftiofur sodium	Calf	SC	Anaphylactic shock, death 1 min after injection.	Unspecified	BVD (1992)
Antiparasitics					
Levamisole	Sheep, heifer	Unknow	Neurologic signs. Vomiting, increased salivation, ataxia, clonic convulsions, respiratory paralysis, and cardiovascular collapse.	Similar to nicotinic effects	Hsu (1980) Uppal (2000) Siroka and Svobodova (2013)
	Young animals	IM	Drugs may enter the brain to exert neurotoxic effects.	Unknow	Keen and Levingston (1983)

Levamisole + Oxyclosanide	Cattle	PO	Anaphylactic shock. Death within one houre from onset of clinical signs.	Unspecified	Jadhav et al. (2017)
Ivermectin	Goat kids, young lambs	PO	Nervous signs, blindness, and death.	8 to 10 times recommended dose. Two times the recommended dose in lambs.	Ecco et al. (2006) Siroka and Svobodova (2013) Rivero et al. (2015)
	Horse	SC, IM	Depression, mydriasis, ataxia, muscle fasciculation, and death may occur.	Overdose	Brown et al. (1988) Siroka and Svobodova (2013)
		IV	Anaphylactic shock and sudden death.	Off-label use	Lopez et al. (2020)
Moxidectin	Horse	Injection	Signs similar to ivermectintoxicity.	Overdose	Hunchak et al (2014)
Nitroxynil	Sheep, cattle, goat	PO, SC	Respiratory distress, recumbency and death.	Overdose	Lovatt et al. (2014) Brito Junior et al. (2021)
Diaminazen (babesicidal)	Cattle	IM	Sudden death.	Unknow	Tjalve (1997)
Imidocarb dipropionate (babesicidal)	Horse	IM	Salivation, diarrhea, abdominal pain, and death in some cases.	Anticholinesterase activity at therapeutic dose (2.4mg/kg)	Abutarbush et al. (2013)
Vitamins and minerals					
Selenium	Kids	PO	Cardiac faillur leading to severe respiratory distress.	Overdose	Amini et al. (2011)
	Young lamb	IM	Death within few hours.	1.2 mg/kg of BW	McKenzie and Al-Dissi (2017)
	Sheep	IM	Death may occur.	Overdose 0.2-0.5 mg/kg of BW	Daunoras (2012)
	Cattle	Unknow	Death may occur.	Overdose 1.2 mg/kg of BW	Reis et al. (2010)

Selenium + Vitamin E	Cattle	IM	Acute anaphylaxis.	Unspecified	BVD (1992)
Analgesics and anesthetics					
Droperidol-fentanyl (neuroleptanalgesia)	Ruminants Horse	Unknow	Bradycardia and respiratory depression within 10 min of injection.	Unspicified	Uppal (2000)
Xylazine	Heifer	IM	Vomiting and death.	Unspecified	Tjalve (1997)
Xylazine + Butorphanol + Tolazoline	Horse	IV IV slowly	Agitated, then agonal and death.	100 mg 5 mg 1.000 mg	Scofield et al. (2010)
Xylazine + Detomidine + Yohimbine	Horse	IV	Recumbency and death within 4 min.	600 mg 5 mg 25mg (Yohimbine is off-label use in horses)	Scofield et al. (2010)
Xylazine + Butorphanol +Yohimbine	Horse	IV	Death.	100 mg 5 mg Off-label use	Scofield et al. (2010)
Detomidine + Yohimbine Lidocaine (used as antiarrhythmic)	Horse Horse	IV Slow IV	Anxiety, tremors, seizure and collapse.	Overdose	Mitchel (2017)
Other drugs					
Dinoprost (cloprostenol)	Cow	IV, IM	Local reaction to injection, systemic illness and death.	Unspecified	Tjalve (1997) BVD (1992)
Furosemide (strong diuretic)	Horse	IM	Fatal arrhythmogenesis.	Unspecified Horses racing on furosemide are 62% more at risk of sudden death.	Bennet and Parkin (2022)

NSAIDs	Horse	Unknow	GI toxicity such as GI hemorrhage and ulceration, and fatal outcome.	Unspecified	Modi et al. (2012)
Clenbuterol (bronchodilator)	Horse	PO	Fatal outcome due to acute renal failure, rhabdomyolysis, and cardiomyopathy.	Overdose	Thompson et al. (2011)
Quinidine (antiarrhythmic)	Horse	IV	Exacerbation of heart failure, cardiovascular collapse and sudden death.	Unspecified	Navas de Solis (2020)
Magnesium Sulfate (antiarrhythmic)	Horse	IV diluted in 0.9% NaCl	Neuromuscular blockade with respiratory depression and cardiac arrest.	Overdose	Mitchel (2017)
Flecainide (antiarrhythmic)	Horse	IV	Sudden death after cardiac arrest.	Two consecutive infusions	Carstensen et al. (2018) Navas de Solis (2020)

SELF-MEDICATION AND IATROGENESIS

The use of medicines by individuals to treat self-recognized or self-diagnosed conditions or symptoms is known as self-medication (Ruiz, 2010). It represents a major public health problem due to the threat of ADRs, DDIs, disease masking, and increased morbidity (Baracaldo-Santamaría et al., 2022). This practice is growing among breeders and people unaware of the toxic risks of certain veterinary drugs, which are generally not subjected to any official control in developing countries (Kisaka and Tumwebaze, 2023). Also, in developed countries, self-medication is increasingly identified as the main iatrogenic threat in bovine medicine (Sala et al., 2019). The high incidence of drug poisoning in animals is attributed to off-label use, incorrect dosing, and inadvertent administration (Siroka and Svobodova, 2013). It is expected that drug intoxications constitute 10 to 30% of poisonings in animals, and some routine therapies carried out by farmers result in severe or fatal events (Siroka and Svobodova, 2013; Sala et al., 2019). In this regard, it is crucial to make a difference between iatrogenesis, which refers to damage induced to a patient through medical ignorance or negligence, and ADRs, which can be induced by almost any medication (Lopez et al., 2020).

Sala et al. (2019) found in their retrospective study that the most frequent problem was incorrect administration of medication in 43% of cases. This includes cases where drugs administration

does not comply with the instructions in the leaflet, particularly regarding dosage and route of administration, as well as cases where injections are carried out by untrained staff (Sala et al., 2019). Using a drug against the manufacturer's instructions can significantly increase its adverse effects. In fact, Morales-Briceno et al. (2018) report that hypersensitivity reactions caused by illicit drug use are the cause of 5% of horses' unexpected deaths.

Ramsay et al. (2005) reported unexpected sudden death two hours after intravenous injection of the vaccine. Similarly, tetracycline administered intravenously to cattle can cause a profound drop in blood pressure and serious cardiac disorders (Keen and Levingston, 1983). Also reported was the sudden death of a calf following an IV injection of sulbactam and ampicillin (BVD, 1992). Cases of convulsions and pulmonary embolism have been reported when procaine benzylpenicillin has been given intravenously (Keen and Levingston, 1983). Because of the risk of embolism, insoluble suspensions must not be given intravenously. Intravenous injection of cloprostenol has also been reported to be fatal in cows (BVD, 1992). Clenbuterol is a β(2)-adrenergic receptor agonist authorized for veterinary use as a bronchodilator and sometimes used in racehorses to improve breathing capacity. Fatal adverse events have been reported following a deliberate overdose of clenbuterol in two racehorses (Thompson et al., 2011).

Drug self-making is a fairly rare practice, which has very harmful consequences. Thus, Genetzky et al. (1994) reported the loss of calves after 30 minutes of intravenous treatment with spectinomycin prepared from a water-soluble powder. Furthermore, the risks associated with inappropriate use will be further complicated by the deliberate administration of drugs with an expired date (Lopez et al., 2020; Kisaka and Tumwebaze, 2023).

Drug toxicity or drug reactions can lead to the death of one or more animals. The situation becomes even more complicated if self-medication is denied, making the elucidation of the context of death even more problematic. The owner's attitude can be explained by feelings of remorse or guilt, or by a desire to conceal the treatment history for insurance purposes or for forensic concerns.

VETERINARY FORENSIC AND IATROGENIC THREATS

Veterinary forensics is a relatively new and important discipline, which is experiencing a significant increase in the application of forensic medicine to investigations centered on crimes against animals (Parry andStoll, 2019). Additionally, veterinary malpractice and insurance claims are among its growing areas of interest (Parry and Stoll, 2019). However, veterinary forensics could be necessary, especially in cases of unexpected animal deaths (Cooper and Cooper, 2008).

The fundamental principles of any veterinary forensic investigation must involve objectivity, meticulous recordkeeping, and maintaining the chain of evidence (Newbery and Munro, 2011); thus, toxic materials and drugs constitute evidence at a hypothetical crime scene (Parry and Stoll, 2019). However, drug-related deaths are difficult to prove at postmortem examination, particularly if the forensic pathologist has not been informed of the nature of the drugs administered prior to death (Elliot, 1975). Unfortunately, the reference range of toxic products established by veterinary toxicology laboratories is fairly limited and generally does not include any potentially toxic drugs. This list consists of heavy metals and minerals, certain rodenticides, plant toxins, and mycotoxins, which leads to perplexity with regard to drug intoxications, for which no reference value exists (Gwaltney-Brant, 2016).

CONCLUSION

The differences between domestic animal species, as well as variations in body weight, age, sex, and physiological and pathological conditions within the same species, are all factors responsible for

different reactions to certain drugs. However, self-medication is by far the greatest cause of drug off-label use, amplifying the risks of adverse reactions and making them potentially fatal. Furthermore, in veterinary practice and forensic medicine, the sudden loss of one or more animals as a result of medical treatment can interfere with the SDS. The situation is further complicated if the practitioner has not been informed of this medical act, whether intentionally or inadvertently. This review, therefore, demonstrates, on the one hand, that knowledge of the adverse effects of certain drugs intended for ruminants and horses, combined with analysis of clinical data, can provide answers to many cases of death whose cause is iatrogenic, and on the other hand, it provides a guiding tool for medico-legal investigations, where it may be an act of negligence, malpractice, or even deliberate intent to kill an animal using drugs. In light of this, it seems appropriate to consider iatrogenic factors as a hypothetical cause in the differential diagnosis of SDS.

ACKNOWLEDGEMENTS

We wish to thank Mr. Benaoumer Bessekek for proofreading.

CONFLICT OF INTEREST

The author declares that he has no conflict of interest.

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IZNENADNA SMRT POVEZANA S AKUTNIM JATROGENIM STANJIMA KOD DOMAĆIH PREŽIVARA I KONJA: PREGLED

SAŽETAK

Trovanje lijekovima kod životinja generalno nastaje usljed neželjenih djelovanja (ADR), interakcija među lijekovima (DDI) ili jatrogenezom. Svaki lijek može imati rizik od neželjenh djelovanja ili nuspojava. Akutno trovanje lijekovima ili ADR može uzrokovati neočekivanu smrt životinje, s tim da anafilaksa predstavlja najštetniji patofiziološki fenomen. Uzročnici anafilakse su prvenstveno antibiotici, bilo pojedinačno ili interakcijom sa drugim lijekovima.

Nadalje, samoinicijativno davanje lijekova koje je široko rasprostranjena praksa u veterinarskoj medicini pojačava rizik jatrogeneze. ADR, DDI i jatrogeneza predstavljaju potencijalno ozbiljne rizike koji mogu izazvati iznenadnu smrt (SD) kod preživara i konja. U ovakvim situacijama je potrebna forenzična medicina kako bi se odredio uzrok smrti, a veterinarske forenzične analize mogu postati neophodne uprkos nepostojanju referentnih toksikoloških vrijednosti u veterinarskim toksikološkim laboratorijama. Na taj način se čini odgovarajućim razmotriti jatrogene faktore kao potencijalni uzrok u diferencijalnoj dijagnozi sindroma iznenadne smrti (SDS).

Ključne riječi: Interakcije među lijekovima, jatrogeneza, iznenadna smrt, konj, neželjeno djelovanje lijekova, preživari