



doi:10.1016/j.jemermed.2009.09.026

## Pharmacology in Emergency Medicine

### HUMAN HEALTH HAZARDS OF VETERINARY MEDICATIONS: INFORMATION FOR EMERGENCY DEPARTMENTS

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□ **Abstract—Background:** There are over 5000 approved prescription and over-the-counter medications, as well as vaccines, with labeled indications for veterinary patients. Of these, there are several products that have significant human health hazards upon accidental or intentional exposure or ingestion in humans: carfentanil, clenbuterol (Ventipulmin), ketamine, tilimicosin (Micotil), testosterone/estradiol (Component E-H and Synovex H), dinoprost (Lutalyse/Prostamate), and cloprostenol (Estromate/EstroPlan). The hazards range from mild to life-threatening in terms of severity, and include bronchospasm, central nervous system stimulation, induction of miscarriage, and sudden death. **Objective:** To report medication descriptions, human toxicity information, and medical management for the emergent care of patients who may have had exposure to veterinary medications when they present to an emergency department (ED). **Discussion:** The intended use of this article is to inform and support ED personnel, drug information centers, and poison control centers on veterinary medication hazards. **Conclusion:** There is a need for increased awareness of the potential hazards of veterinary medications within human medicine circles. Timely reporting of veterinary medication hazards and their medical management may help to prepare the human medical community to deal with such exposures or abuses when time is of the essence. © 2009 Elsevier Inc.

□ **Keywords—**Veterinary Medications; Human health hazards; emergency department; One Medicine; carfentanil,

clenbuterol (Ventipulmin); ketamine; tilimicosin (Micotil); testosterone/estradiol (Component E-H and Synovex H); dinoprost (Lutalyse/Prostamate); cloprostenol (Estromate/EstroPlan)

#### INTRODUCTION

There has been a contemporary call, and professional encouragement, to unite veterinary medicine and human medicine. This call for “One Medicine” is intended to facilitate the creation of working relationships between human medicine and veterinary medicine for the benefit of public health (1). This global concept is broad in scope, but includes sharing information on the medical management of human patients who have been exposed to, or voluntarily ingested, veterinary medications. Educating human health care professionals on the hazards of certain veterinary medications is one example of the blending of veterinary and human medicine in today’s practice environment to achieve One Medicine.

Human health care professionals may be less familiar with the brand and generic names, intended use, common abuse, and human health hazards of veterinary medications. Emergency department (ED) personnel may lack information on the medical management of human pa-

tients who present to the ED as a result of hazardous veterinary medication exposure or intentional ingestion.

The following eight veterinary label medications will be described and applicable information will be provided to assist ED personnel in the identification and medical management in humans: carfentanil, clenbuterol (Ventipulmin), ketamine, tilimicosin (Micotil), testosterone/estradiol (Component E-H and Synovex H), dinoprost (Lutalyse/Prostamate), and cloprostenol (Estromate/EstroPlan). A review of contemporary toxicology textbooks revealed the greatest amount of information available on ketamine, but with little to no information on the other veterinary medications and their human exposure risks, thus indicating a need for this type of drug information.

## DRUG PROFILES

Table 1 presents descriptions of veterinary medications: generic and brand names, approved veterinary use, indication, status (prescription, over-the-counter, or controlled substance), and potential sources of the medications.

Table 2 presents information and suggestions for the medical management of humans exposed to hazardous veterinary medications.

### *Carfentanil*

**Drug description.** (Carfentanil, formerly known as Wildnil) is a mu-opioid agonist. Commercial production of Wildnil ceased in 2003, and the drug is available only as a compounded dosage form in a concentration of 3 mg/mL, in 10-mL vials. As the name implies, this drug is a fentanyl derivative, related to other potent synthetic opioids such as fentanyl and sufentanil. Carfentanil is a highly water-soluble, clear liquid with no distinguishable odor (2). The medication is a Schedule-II, ultra-potent narcotic with a clinical potency 10,000 times that of morphine and 100 times that of fentanyl. Acceptable use is for rapid immobilization and chemical capture of wildlife such as large hoofstock and exotic animals (3,4). It is used by veterinarians in zoological parks and wildlife management environments to safely immobilize animals for examination, assessment, and procedures. Veterinarians ordering the drug must be placed on the "Approved Carfentanil Users List," and special Drug Enforcement Agency registration medication class approval is required to allow the trained veterinarian to obtain the medication.

Carfentanil is typically delivered to animal patients intramuscularly via darting. The drug has rapid onset in animal patients, and is metabolized by the liver and excreted in the bile or by the kidneys (3). Extreme care,

concentration, and personal protective equipment are required when working with this medication. Wax et al. reported in the *Annals of Emergency Medicine* on the possible use of aerosolized carfentanil and the corresponding deaths in the October 2002 Russian military attempt to overthrow Chechen rebels in a Moscow theater (5).

**Human toxicity.** The human health hazard with regard to carfentanil is related to the potency of the medication. Exposure to the medication typically would be accidental via occupational use. Toxic exposure can occur through accidental injection with a syringe or dart, by absorption through mucus membranes (eyes, nose, mouth) or by direct absorption through broken skin (3). Signs and symptoms of exposure are consistent with opioid toxicity and include pinpoint pupils, respiratory depression, and depressed mental status. Other signs and symptoms include dizziness, lethargy, sedation, nausea, vomiting, shallow or absent breathing, cold clammy skin, weak pulse, loss of consciousness, and cardiovascular collapse secondary to hypoxia and death (2,3). The lethal human dose of carfentanil is unknown and there are no data on the effects of carfentanil in humans. Kreeger et al. reported that 0.1 mg administered orally to chimpanzees resulted in respiratory depression (3). Target organ data indicate depression of the central nervous system and depression or failure of the respiratory system (2).

**Medical management.** Ideally, the veterinarian has established protocols whereby the antagonist agent is readily available when carfentanil is used. Medical centers may wish to proactively collaborate with local wildlife or zoo veterinarians to establish treatment protocols, especially if the exposure occurs in a remote, distant environment. Naloxone (Narcan®; Bristol-Myers Squibb, New York, NY) is the opioid antagonist used for the reversal of carfentanil and is the preferred treatment in human health care settings (3,4). However, veterinary practitioners exposed in the field may self-administer the veterinary-labeled naltrexone 50 mg/mL concentration that is made via the same compounding pharmacy source. It is important to note that this medication is not intended for human use, but given the severity of carfentanil exposure, using what is immediately available may be acceptable in a life-or-death situation. Such use of naltrexone is limited to remote exposures outside of a hospital environment when time constraints preclude waiting for emergency medical care. The compounded veterinary naltrexone is acquired from the same compounding source as carfentanil and is used to reverse the effects of carfentanil in the field in animal patients (4). The recommended dose for animal reversal is a ratio of 100 mg of naltrexone for every 1 mg of carfentanil delivered (4).

**Table 1. Veterinary Medication Descriptions**

Generic Name	Brand Name	Veterinary Use	Species	Drug Status	Source
Carfentanil (3 mg/mL)	Only available as a compounded medication.	Immobilization of large animals. The drug has no uses in domestic animals.	Exotic animals in zoos, wildlife parks, and game reserves.	C-II narcotic Compounded by Zoo Pharm, Fort Collins, CO. Telephone #970-484-6267. Compounded drug is available in 10-mL vials. Reversal agent is also compounded by the same source; Naltrexone 50 mg/mL injectable.	Veterinarian ordering the drug must be placed on the "Approved Carfentanil Users List." Special DEA registration drug class approval is required to allow a trained veterinarian to obtain it from ZooPharm.
Clenbuterol (72.5 µg/mL)	Ventipulmin oral syrup	COPD	Horses	Prescription drug manufactured by Boehringer Ingelheim, in 100-, 330-, and 460-mL bottles. Telephone #800-325-9167.	Veterinary drug distributor, licensed veterinarian or layperson caring for animals upon authorization from a prescribing veterinarian
Ketamine (100 mg/mL) Veterinary strength	Ketaject, Ketaset, Ketaved, Ketathesia, and various street names	Anesthetic and chemical restraint use	Approved for cats and subhuman primates. Off-label use in other species is common	C-III non-narcotic, prescription drug with multiple manufacturers	Veterinary drug distributor or a licensed veterinarian Illicit forms are often supplied from Mexico.
Tilmicosin (300 mg/mL)	Micotil 300	Injectable antibiotic of the macrolide class	Beef and dairy cattle and sheep. Is lethal if given to horses or primates.	Prescription drug manufactured by Elanco Animal Health in 50-, 100-, and 250-mL bottles. Drug sponsor asks to report exposures to Rocky Mountain Poison and Drug Center at 800-722-0987.	Veterinary drug distributor, licensed veterinarian or layperson caring for animals upon authorization from a prescribing veterinarian
Testosterone propionate (25 mg) and estradiol benzoate (2.5 mg) per implant pellet	Synovex-H, Component-EH	Increase feed efficiency, rate of gain and muscle marbling	Feedlot heifers	OTC in pellet form that is placed Sub-Q in upper part of the animal's ear. Various manufacturers.	Can be obtained from catalog outlets, online suppliers, veterinary drug distributors or feed stores
Dinoprost (5 mg/mL)	Lutalyse, Prostagmate, or In-Synch	For estrus synchronization or as an abortifacient in cattle, parturient inducing agent in swine, and reproductive management in mares	Beef and dairy cattle, swine and mares. Off-label use in cats and dogs.	Prescription drug manufactured by Pharmacia and UpJohn, and various generic manufacturers. In 10-mL and 30-mL vials.	Veterinary drug distributor, licensed veterinarian or layperson caring for animals upon authorization from a prescribing veterinarian
Cloprostenol (250 µg/mL)	Estrumate, Estroplan	For inducing luteolysis, inducing abortion, treating pyometra and endometritis	Beef and dairy cattle. Off-label use in horses, swine, sheep and goats, and dogs.	Prescription drug manufactured by Schering-Plough Animal Health. In 20-mL vials.	Veterinary drug distributor, licensed veterinarian or layperson caring for animals upon authorization from a prescribing veterinarian

DEA = Drug Enforcement Agency; COPD = chronic obstructive pulmonary disease; OTC = over the counter.

**Table 2. Medical Management of Humans Exposed to Hazardous Veterinary Medications**

Drug Name	Human Hazard	Toxicity Information	Medical Management
Carfentanil	CNS and respiratory depression. Effects seen within 1–30 min, depending on route of exposure.	Ultra-potent opioid agonist, 10,000 × stronger than morphine and 100 × stronger than fentanyl	If injected i.m., keep the wound open and attempt to express blood from the site (3). Naloxone is the opioid antagonists for the reversal of carfentanil (3,4) and is the preferred treatment in human health care settings. However, veterinary practitioners exposed in the field may self-administer the veterinary labeled naloxone 50 mg/mL concentration that is made via the same compounding pharmacy source. For full parenteral exposure via needle stick or dart in, administer 10 mg naloxone, if available, i.v. (3). If a vein cannot be accessed, administer the reversal i.m. every 3–5 min until CNS depression is antagonized (3). Repeat dose if no improvement within 1 min of i.v. administration or 3–5 min of i.m. administration. Continue to repeat dose every 3–5 minutes until CNS depression is antagonized (3). After first antagonist dose, if patient is asymptomatic, wait and observe closely. If still asymptomatic after 15 min, no further antagonist may be necessary (3). There are no data on the correct dose of antagonist to administer. Seek medical care. Provide airway support and CPR (3,4). Exposure to mucus membranes: flush with copious amounts of cool or room temperature water. Do not use hot water.
Clenbuterol (Ventipulmin oral syrup)	Cardiac and CNS. Long duration of action and half-life lead to prolonged adverse effects	Consider clenbuterol-tainted heroin or cocaine exposure in suspect patients.	Short-acting, parenteral beta-antagonist agents such as esmolol (Brevibolc™) is an option, assuming no clinical contraindications (10) For suspected cases of clenbuterol contaminated with cocaine, beta agonists are not recommended due to the potential for unopposed alpha receptor stimulation. Additionally, in cases where there are other contraindications to beta receptor antagonism such as bradycardia, avoid beta blockers.
Ketamine injection	Target organs are the CNS, cardiovascular, nystagmus. Frequent complications are agitation and rhabdomyolysis	The range of toxicity or lethal dose is not well established. Deaths have been reported in adults after 900–1000 mg.	i.v. Benzodiazepines such as midazolam, diazepam, or lorazepam for seizures, anxiety, and delirium. Dystonic reactions can be managed through the use of diphenhydramine (20). Cardiac, neurologic, and respiratory monitoring and high flow O <sub>2</sub> .
Micotil (tilmicosin)	Cardiotoxic	Both the drug (tilmicosin) and the solvent (propylene glycol) are toxic to humans, especially with IV injection > 1 mL volumes. Tilmicosin cardiotoxicity is thought to be due to its calcium channel blockade	Dermal exposures—external decontamination and apply ice to the affected site to decrease absorption. Home observation may be adequate for dermal-only exposures. Any patient experiencing cardiovascular symptoms from a dermal exposure should be seen at a health care facility. i.v. Exposures—administer i.v. calcium (calcium chloride or calcium gluconate) to reverse cardiovascular effects. The negative inotropic effects of tilmicosin may be managed with i.v. dobutamine or dopamine (27). Basic supportive measures include continuous ECG and vital sign monitoring. Manage hypotension with isotonic fluids. (30,33). Do not administer beta-blockers, epinephrine, or norepinephrine. Stop abuse of implants. Supportive.
Testosterone propionate (25 mg) and estradiol benzoate (2.5 mg)	Abused by bodybuilders or athletes	Reproductive organs, liver, cardiovascular system	
Dinoprost (5 mg/mL)	Induce asthma attacks or abortion in pregnant females	Bronchial and uterine smooth muscle	Normal supportive measures include immediately decontaminating the area with soap and water. Eye exposures should be flushed with water for 15 min. Nausea and vomiting can be treated with antiemetics. Bronchoconstrictor effects have been reversed with albuterol.
Cloprostenol (250 µg/mL)	Induce asthma attacks or abortion in pregnant females	Bronchial and uterine smooth muscle	Normal supportive measures include immediately decontaminating the area with soap and water. Eye exposures should be flushed with water for 15 min. Nausea and vomiting can be treated with anti-emetics. Bronchoconstrictor effects have been reversed with albuterol.

CNS = central nervous system; i.m. = intramuscular; i.v. = intravenous; CPR = cardiopulmonary resuscitation; ECG = electrocardiogram.

To date, there are no published case reports of carfentanil effects in humans.

Basic supportive measures are necessary in the field immediately after exposure. Topical or mucus membrane exposure to carfentanil should be flushed immediately with copious amounts of cool or room-temperature water. An exposed patient will need the reversal agent within 60 s (3). For full parenteral exposure via needle stick or dart in humans, administer 10 mg naloxone, if available, intravenously (3). If a vein cannot be accessed, administer the reversal intramuscularly every 3–5 min until central nervous system depression is antagonized (3). The dose can be decreased if the patient is only minimally symptomatic. There are no published case reports of human exposures of carfentanil subsequently treated with the veterinary form of naltrexone, however, it is a very real option for veterinary practitioners. Advanced supportive measures in the ED after exposure include intubation, mechanical ventilation, and establishment of an intravenous line. Additionally, one must consider the potential for renarcotization in the exposed patient. Medical management instructions are summarized in Table 2.

### *Clenbuterol*

**Drug description.** Clenbuterol (Ventipulmin®; Boehringer Ingelheim, Burlington, ON, Canada) is a long-acting, beta-2 adrenergic agonist, available as oral syrup (72.5 mg/mL) approved for use in horses as a bronchodilator in the management of chronic obstructive pulmonary disease (6–10). The medication is approved for use in humans in Europe for asthma at a dose of 20–40 µg orally, twice daily. The drug is available through veterinary drug distributors, licensed veterinarians, and laypersons caring for livestock upon the authorization of a licensed veterinarian. The medication is banned from use in food animals by the Food and Drug Administration (FDA) in the United States. Bodybuilders ingest this drug for its repartitioning and anabolic effects, and others ingest it for its reported weight-loss effects (7–10). Clenbuterol is known on the street as “Clen,” and is abused by bodybuilders due to its ability to increase the rate of muscle protein deposition, resulting in enlargement of muscle fibers and the promotion of lipolysis.

Wingert et al. and Hoffman et al. both have reported the detection of clenbuterol-tainted heroin among illicit drug users (11,12). Still other clinicians, such as Sherry et al., have reported on clenbuterol-tainted cocaine (13). Wingert et al. state that the presence of clenbuterol-tainted heroin “. . . serves as a caution to emergency physicians and toxicologists to consider and test for clenbuterol when treating a suspected heroin user who

presents atypically . . .” (11). As recently as January 2007, counterfeit veterinary clenbuterol surfaced in the United States and tested at more than 70 times the strength of the FDA-approved product, Ventipulmin® (14).

**Human toxicity.** Exposure to the drug typically has been intentional, for its performance enhancement or weight loss attributes. The use of clenbuterol for its anabolic effects occurs at doses much higher than those recommended for asthma control (10). The medication also can be accidentally consumed through contaminated heroin or cocaine usage. When taken by a human as prescribed medication in Europe, it is ingested orally, and at therapeutic doses the drug is specific for beta-2 receptors. However, this selectivity is lost at higher doses, and beta-1 receptor agonist activity is observed. In humans, duration of action of a single dose is 8–12 h, time to peak concentration is 2–3 h, and the elimination half-life is 25–39 h. The drug’s pharmacokinetic parameters contribute to its severe and extended effects (8,10).

Dose-dependent beta agonist adverse effects include headache, dizziness, vertigo, nervousness, palpitations, nausea, muscle tremors, chest pain, and tachycardia. Hypotension, severe chest pain, tachydysrhythmias including supraventricular tachycardia and atrial fibrillation, pulmonary edema, hyperglycemia, and myocardial ischemia are also reported with clenbuterol use (7,8,10). Associated laboratory abnormalities, specifically electrolyte disturbances, hypokalemia, hypomagnesemia, hyperlactemia, and hypophosphatemia can present with clenbuterol use that may contribute to its cardiac toxicity (10,11,13).

**Medical management.** Topical exposure to clenbuterol should be removed via washing with soap and water. The oral consumption of clenbuterol by a human patient should be discontinued immediately. There is no known antidote to clenbuterol, rather, there is only management of side effects and symptoms. Treatment with activated charcoal can be considered if the patient presents within 1–2 h of ingestion.

Basic supportive measures such as intravenous (i.v.) fluid replacement and airway support should be utilized. The potent hemodynamic beta-agonist effects of tachycardia and hypotension may require more than standard supportive care. The administration of a short-acting, parenteral beta-antagonist agent such as esmolol (Brevibloc; Baxter Healthcare Corporation, Deerfield, IL) is an option, assuming the patient has no clinical contraindications. The treatment of clenbuterol-induced tachydysrhythmia has not been well studied. There is no published dose of esmolol for treating uncomplicated clenbuterol adverse effects, and administration of the least concentrated form of esmolol is recommended.

For suspected cases of clenbuterol contaminated with cocaine, beta agonists are not recommended due to the potential for unopposed alpha receptor stimulation. Additionally, in cases where there are other contraindications to beta receptor antagonism such as bradycardia, beta-blockers should be avoided. Consultation with a medical toxicologist at a poison control center would be beneficial in clenbuterol-exposed patients for whom beta agonists are considered.

The most commonly reported associated laboratory abnormality is hypokalemia, but it should not be a primary focus, as it may be the result of intracellular shifts of potassium rather than a total body deficit (10). However, the authors recommend cautious replacement of potassium. Medical management instructions are summarized in Table 2.

### *Ketamine*

**Drug description.** Ketamine (Ketaject™ [Phoenix Pharmaceutical Inc., St. Joseph, MO], Ketaset® [Wyeth, Madison, NJ], KetaVed™ [Vedco Inc., St. Joseph, MO], Ketathesia™ [Butler Animal Health Supply, Dublin, OH], Vetalar™ [Fort Dodge Animal Health, Fort Dodge, IA]) is a dissociative general anesthetic and N-methyl-D-aspartate receptor antagonist. It is a white powder with a characteristic odor and is soluble in water and alcohol. The medication is commonly available through veterinary drug distributors and veterinary clinics. This rapid-acting, non-narcotic, non-barbiturate anesthetic is approved for use in cats and for restraint in subhuman primates, and is often administered by intramuscular (i.m.) or i.v. route (15). However, the drug is used off-label in many other animal species and is utilized by veterinarians to treat certain types of neurological-mediated pain (16–23). The injectable veterinary strength of the drug is 100 mg/mL, whereas the most commonly available human-labeled strength is 10 mg/mL. Ketamine is abused by teenagers and adults and is known on the street as “Special K,” “K,” “Kit Kat,” “Vitamin K,” or “Cat Valium” among other names. Onset of action is rapid and can be intensified by the addition of other sedatives, anesthetics, or analgesic agents in veterinary medicine. Ketamine also can be used as a pre-euthanasia agent that is administered before euthanasia with pentobarbital in an animal shelter setting. Human health care practitioners are familiar with ketamine as a procedural sedation or induction agent.

**Human toxicity.** Outside of a health care setting, ketamine is a drug of abuse, with exposures being intentional for recreational purposes. Accidental occupational exposures might occur by veterinarians or veterinary technicians during routine clinical use. The powder or

injectable form of the drug is usually snorted, injected, applied on smokeable materials, or consumed in drinks (17,18). When abused for recreational purposes, ketamine distorts perceptions of sight and sound, making the user feel disconnected, and producing psychedelic and dissociative effects (17,18). Typical human dosages range from 1–5 mg/kg i.v. or 5–10 mg/kg i.m. The range of toxicity or lethal dose is not well established. Deaths have been reported in adults after 900–1000 mg.

Acute clinical signs and symptoms in humans include tachycardia, palpitations, nystagmus, slurred speech, increased intracranial and intraocular pressure, dizziness, anxiety, confusion, vivid dreams, agitation, and delirium. Nosebleeds can result from snorting the drug. Bronchodilation, increased salivary secretions, and problems verbalizing also have been reported. Additional pharmacological effects are hypertension, agitation, paranoid psychoses, hyperthermia, and seizures (18,20–24). Ketamine is not detected on routine toxicologic screens.

**Medical management.** Ketamine overdose is usually treated by supportive care that includes cardiac, respiratory, vital sign, and neurologic status monitoring, and high-flow oxygen as needed (20,21,23). Potential pharmacological interventions are i.v. benzodiazepines such as midazolam, diazepam, or lorazepam for seizures, anxiety, and delirium. Dystonic reactions have been reported from ketamine and can be managed through the use of diphenhydramine (20). Medical management instructions are summarized in Table 2.

### *Tilmicosin*

**Drug description.** Tilmicosin phosphate (Micotil 300®; Elanco Animal Health, Greenfield, IN) is a semi-synthetic, bacteriostatic, macrolide antibiotic available as a concentrated injectable drug at a dose of 300 mg/mL in a solvent of 25% propylene glycol (16,25–27). The injection is a clear yellow to amber-colored solution and is approved for treating specific infectious diseases (e.g., pneumonia) caused by *Pasturella* and *Actinobacillus* species in cattle and sheep. The drug is administered via subcutaneous routes but can be fatal to cattle and sheep if injected intravenously. Tilmicosin is known to be fatal to horses, primates, and pigs, presumably due to the cardiotoxicity of the drug. Tilmicosin is available from veterinary drug distributors, licensed veterinarians, and laypersons caring for livestock upon the authorization of a licensed veterinarian. Livestock producers who use tilmicosin should not use automatic syringes to administer the drug due to the high potential for needle-sticks and accidental injection. In cattle, peak tilmicosin levels are reached within 1 h of administration, and detectable levels of the drug are found in the serum beyond 3 days (25).

*Human toxicity.* Human exposure results from accidental or occupational exposures or suicide attempts, and both are associated with fatalities. There are several documented case reports of accidental or intentional injection of tilimicosin that resulted in human deaths (27–32). Historical data are reported to document at least 13 confirmed fatalities associated with the drug worldwide from 1995–2000, most associated with intentional suicides (33). More recently, in Oakes and Seifert's report of poison control center data, 1291 tilimicosin exposures occurred from the year 2001 to 2005, with four deaths (32). Of the four deaths, two were suicides. On average, there are over 250 cases of human tilimicosin exposures per year reported to poison control centers (32).

The cardiotoxicity of this drug dominates as the human health hazard and is thought to be mostly due to calcium channel blockade. Parenteral exposures involve greater toxicity than non-parenteral routes of exposure (30,32,34). Oakes and Seifert report that 75% of all patients exposed to tilimicosin and more than 80% of parenterally exposed persons become symptomatic (32). Minor clinical signs and symptoms are possible with injections of < 0.5 mL, whereas doses in excess of 5 mL result in fatalities (32). Investigative reports of accidental human injections report an approximate interval of 15 min from the time of injection until signs and symptoms of cardiotoxicity appear (28,29,33).

Upon accidental or intentional parenteral exposures in humans, acute signs and symptoms include chest pain, shortness of breath, pulmonary edema, electrocardiogram (ECG) abnormalities, myocardial depression, respiratory distress requiring intubation, negative inotropic effects, hypotension, and tachycardia progressing to dysrhythmias (23,27). Additional clinical signs and symptoms can include headache, nausea, dizziness, tachycardia, chest pain, anxiety, and severe pain at the injection site.

The drug's solvent, propylene glycol, may contribute to the toxicity of the drug, especially when injected rapidly i.v. But, the true cardiotoxic contribution of the solvent has been questioned by some (31).

*Medical management for parenteral exposure.* Local reactions such as injection site pain, bleeding, swelling, or inflammation have been reported with low-volume tilimicosin needle-stick exposure in occupational settings (e.g., feedyards, cattle-handling facilities). There is no specific antidote for tilimicosin toxicity. The cardiovascular system is the target of toxicity and should be closely monitored. There is in vitro and in vivo evidence that the drug acts as a potent calcium channel antagonist with clinical signs similar to dihydropyridine overdose such as nifedipine. The drug is known to persist in tissues for several days after injection (27). In 2005, the manufacturer of the drug, Elanco, updated treatment guide-

lines on the potential benefits of i.v. calcium in patients with cardiovascular effects. Treatment of parenteral exposure is supportive with calcium chloride or possibly calcium gluconate infusions, thought to be effective for reversing the cardiovascular effects of i.v. tilimicosin (27). However, there is no published dose of calcium salts for treating tilimicosin overdoses, and practitioners should be aware that the recommendation is based on animal studies.

The negative inotropic effects of tilimicosin may be managed with i.v. dobutamine or dopamine (27). Basic supportive measures include continuous ECG and vital sign monitoring. Hypotension should be managed with isotonic fluids. Beta-adrenergic antagonists, such as propranolol, should be avoided, as they exacerbate the negative inotropy of tilimicosin in dogs. Routine use of epinephrine or norepinephrine is also discouraged due to worsened outcomes in animal studies (27). Recent data analysis resulted in a recommendation that includes health care facility referral for all parenteral exposures with a minimum of 8 h of observation (32).

*Medical management for non-parenteral exposure.* Dermal exposures have not resulted in fatalities (32). Topically, tilimicosin is classified as a severe allergen because repeated unprotected exposures are likely to cause allergic reactions (26). The propylene glycol solvent is also known to have adverse effects in humans with topical exposures, resulting in dermal reactions such as contact dermatitis and pruritis. Dermal reactions occur more frequently and severely with increasing concentrations of the solvent (23). Topical exposures should be decontaminated with soap and water. Home observation may be adequate for dermal exposures only. Any patient experiencing cardiovascular symptoms from a dermal exposure should be seen at a health care facility.

Elanco Animal Health, the drug's sponsor, suggests reporting all human exposures of tilimicosin to 1-800-722-0987. The authors also suggest calling your regional poison control center at 800-222-1222. Medical management instructions are summarized in Table 2.

#### *Testosterone and Estradiol*

*Drug description.* Testosterone propionate and estradiol benzoate (Component E-H™ [Vetlife, Overland Park, KA] and Synovex H™ [Wyeth Animal Health, Guelph, ON, Canada]) are FDA-approved, over-the-counter implants used to increase the rate of weight gain and improve feed efficiency in steers, and to increased the rate of weight gain in heifers fed in confinement for slaughter (35,36). The drugs are administered subcutaneously. The ingredients contribute to more marbling in

edible muscle tissues, which can result in more valuable cuts of beef, contributing to overall palatability. A single pellet contains 25 mg of testosterone and 2.5 mg estradiol benzoate. The drugs are included on the Drug Enforcement Administration's exempt anabolic steroid list (37). The implants also come in a form containing an antibiotic, tylosin (Tylan®; Elanco Animal Health) to prevent implant site infection and abscesses. The medication can be purchased via catalog outlets and online animal health distributors. The implants are intended for slow release over an extended time period, so human exposures to these drugs rarely result in acute clinical signs and symptoms. There are Internet blogs that give instructions and photos demonstrating how to remove the testosterone component.

*Human toxicity.* Human exposures are typically intentional for performance-enhancing purposes. The implants may be abused by athletes and bodybuilders who try to remove the anabolic component from the implants and inject it as a means of increasing muscular strength or as a performance enhancer (38–43). The misuse or abuse of cattle implants can lead to a fine or imprisonment (44).

There are a number of human health hazards related to abuse of anabolic steroids. Seldom acute in nature, the adverse effects are seen over extended periods of use. The vascular and cardiac abnormalities that present with the abuse of anabolic steroids are of a serious nature and include myocardial infarction, cerebrovascular accident, hypertension, and edema (45,46). Subjective adverse effects include steroid-induced acne, sexual dysfunction, mood alterations, gynecomastia, insomnia, local site reactions, loss of hair, and testicular atrophy (38,40,43,47–49). Serious adverse effects include possible hepatotoxicity and sudden death due to abuse of anabolic steroids (38,41–43). Onset and duration of action of single i.m. injections of testosterone in humans is 2–4 weeks. In chronic abusers of anabolic steroids, abnormalities of liver function tests, serum lipid profiles, and electrolyte disturbances may be seen.

*Medical management.* Treatment is supportive and removal of the abusive agent(s). There is no antidote for testosterone toxicity. Medical management suggestions are summarized in Table 2.

### *Dinoprost*

*Drug description.* Dinoprost (Lutalyse® [Pfizer Animal Health, New York, NY], Prostate® [Vet Tek Inc., Blue Springs, MO], In-Synch™ [ProLabs Ltd., St. Joseph, MO]) are 5-mg/mL injectable forms of naturally

occurring prostaglandin  $F_{2\alpha}$ . The medication is FDA approved and administered i.m. for estrus synchronization, treatment of pyometra, and abortion in cattle. In swine and mares, the medication is used for reproductive management (16,50). In February 2009, a press release was issued by the American Veterinary Medical Association cautioning veterinarians about possible misuse of these drugs by teenagers in efforts to terminate unwanted pregnancies (51).

The medication is available from veterinary drug distributors, licensed veterinarians, or laypersons caring for livestock upon the authorization of a licensed veterinarian. Administration via the i.v. route can potentiate adverse reactions in animals.

*Human toxicity.* Human exposures are typically accidental via occupational exposure. Dinoprost has pharmacologic actions of uterine contraction and bronchial smooth muscle contraction (16,50–58). Dinoprost is a concern to humans, particularly asthmatics and pregnant women. The medication is readily absorbed through the skin and can cause abortion in pregnant women or in those who may be pregnant (50,56,59). Exposure to dinoprost may present as bronchial constriction similar to an asthma attack, or spontaneous uterine contraction. The drug reportedly demonstrates rapid absorption and distribution with a serum half-life of only minutes after i.m. injection in rodent models (16). It is best for pregnant females and asthmatics to avoid exposure to this medication.

The most common acute, adverse reactions to dinoprost in humans are fever, nausea, vomiting, and diarrhea. Additionally, hypertension, hypotension, respiratory distress, termination of pregnancy, and cardiorespiratory failure culminating in prolonged coma and death have been reported (59).

*Medical management.* There are no antidotes for dinoprost exposure. Normal supportive measures include immediately decontaminating the area with soap and water. Eye exposures should be flushed with water for 15 min. Nausea and vomiting can be treated with antiemetics, and bronchoconstrictor effects can be reversed with albuterol. Medical management suggestions are summarized in Table 2.

### *Cloprostenol*

*Drug description.* Cloprostenol (Estrumate® [Schering-Plough Animal Health, Kirkland, QC, Canada], Estroplan™ [Agri Laboratories, St. Joseph, MO]) is a 250- $\mu$ g/mL injectable, aqueous-based solution. It is FDA approved for i.m. administration to induce luteolysis, induce abortion, and treatment of pyometra and endome-

tritis in cattle. The medication is available from veterinary drug distributors, licensed veterinarians, or laypersons caring for livestock upon the authorization of a licensed veterinarian.

*Human toxicity.* Human exposures are typically accidental via occupational exposure. Cloprostenol is a synthetic prostaglandin analogue, structurally related to prostaglandin F<sub>2</sub> $\alpha$ , that stimulates the contraction of uterine and bronchial smooth muscle and produces vasoconstriction of some blood vessels. Women who are pregnant or of childbearing age, asthmatics, or people with bronchial disease are at greatest risk for the human health hazards of this drug. Cloprostenol is readily absorbed through the skin (16). Bronchial muscle contraction resulting in acute bronchoconstriction, and uterine muscle contractions resulting in abortions are the sites most affected by cloprostenol (16).

*Medical management.* There are no antidotes for cloprostenol exposure. Normal supportive measures include immediately decontaminating the area with soap and water. Eye exposures should be flushed with water for 15 min. Cloprostenol may damage fertility of the unborn child and cause damage to the respiratory system from repeated exposure at high doses (60). Supportive care is required for systemic exposure (61). Medical management instructions are summarized in Table 2.

## DISCUSSION

There is a need for increased awareness of the potential hazards of veterinary medications within human medicine circles. Timely reporting of veterinary drug hazards and their medical management can prepare the human medical community to deal with such exposures or abuses when time is of the essence.

Information on the abuses, misuses, or accidental exposures for many of these veterinary medications can be easily found on Internet blogs, websites, or discussion postings.

An evidence-based literature and consensus guideline analysis identified 16 specific antidotes to be stocked in hospitals that accept emergency admissions (62). Of these, naloxone and calcium salts are specifically described for management of toxicity from the eight veterinary drugs highlighted. The management of poisonings secondary to several of the veterinary medications discussed in this manuscript are not found in some of the contemporary classic toxicology books, thus underscoring the scarcity of information available on human exposures to hazardous veterinary medications (62–64).

## CONCLUSIONS

The potential human hazards of veterinary drugs are seldom presented or discussed in human health care curriculums. There is a tendency to outsource veterinary drugs to licensed veterinarians, which is appropriate for veterinary medical treatment. However, when humans are accidentally or voluntarily exposed to hazardous veterinary medications, there is an immediate need to utilize the principles supported by “One Medicine.” The information contained in this article is meant to serve as a quick resource for hazardous veterinary medications and always should be used in consultation with a poison control center professional (telephone 1-800-222-1222).

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