Compounding of Veterinary Drugs for Equine Practitioners

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KEYWORDS

• Compounding • Extralabel drug use • Drugs • Horses

KEY POINTS

- Food and Drug Administration (FDA)–approved drugs have undergone safety and efficacy studies in accordance with federal mandates for quality assurance.
- The Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA) permits equine practitioners to prescribe extralabel uses of certain approved new animal drugs and approved human drugs for horses under certain conditions.
- Compounded veterinary drugs are not approved for any use by the FDA and are considered unapproved new animal drugs.
- Because compounded veterinary drugs are commonly used in horses, it is vital that equine practitioners remain familiar with regulatory recommendations for the use of all compounded drugs.

BACKGROUND

In 2001, the wife of a United Parcel Service (UPS) driver arrived home from work in Walnut Creek, California, to find her 47-year-old husband clutching his head and screaming in pain. He had received a "cortisone" injection that morning for chronic pain. Less than 24 hours after his "cortisone" injection, he was dead. Doctors assumed he died from a burst blood vessel in his brain. His wife wanted to donate his organs but the doctors called her with shocking news; his organs were riddled with bacteria. An autopsy concluded that the seemingly healthy UPS driver died from Serratia meningitis due to a contaminated batch of compounded drug. As a result of the contaminated batch of sterile betamethasone injection, 11 patients were confirmed to have Serratia infection and 3 died.[1] Although this incident caused the

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State of California to institute new regulations and oversight over sterile compounding, deaths across the nation continue to rise.

Since 2001, numerous human deaths have been linked to contaminated compounded "sterile" medications. A few examples are discussed. In 2011, 9 people died in Alabama after receiving contaminated nutritional supplements traced to a contaminated water supply.[2] In 2012, 64 people died and more than 800 were infected as a result of a contaminated "sterile" compounded steroid made by New England Compounding Center.[3] In May 2015, a $200 million settlement plan was approved setting aside funds for the victims and their families. In Texas, 15 people were hospitalized after heart surgery where a compounded calcium gluconate solution was used that had been contaminated with *Rhodococcus equi*.[4] In addition to deaths, a vast number of patients have experienced significant morbidity from sterile compounded products. In 2012, an investigation by the Centers for Disease Control and Prevention and state health departments found 47 human patients who developed fungal endophthalmitis from compounded "sterile" ophthalmic products, some containing triamcinolone. Approximately 98% developed vision loss.[5] In 2016, a US District Court issued a permanent injunction against the owner/operator of this Florida compounding pharmacy. The permanent injunction included limits, however, with an exception for drugs for animal use.

Although the equine industry, which is a large consumer of compounded sterile products, might seem spared from the morbidity and mortality witnessed in human patients, this may reflect the lack of forensic documentation in equine patients after death. To date, only the acute deaths of multiple horses all receiving the same batch of compounded drugs have been evaluated toxicologically, eventually linking deaths to misformulated drugs. Well-known examples of these include the polo pony and pyrimethamine incidences (discussed later).

In 2009, 21 Venezuelan polo ponies, on their way to participate in the US Open Polo Championships, died within hours of receiving a compounded vitamin/mineral injection from a Florida compounding pharmacy. The supplement, made to replicate a European medication (Biodyl, Merial, Lyon, France), contained selenium, magnesium, vitamin B, and potassium. It had been incorrectly formulated with toxic levels of selenium.[6,7] Unfortunately, the supplement was used to treat fatigue in horses and not medically necessary.

In 2014, 4 horses died and 6 became ill after receiving a compounded oral product containing pyrimethamine and toltrazuril from a veterinary compounding pharmacy in Lexington, Kentucky. Two lots (one a paste and the other a suspension) were made that were believed to contain extremely high concentrations of pyrimethamine. One of the compounds was tested by the FDA and determined to contain 2380% of the pyrimethamine concentration stated on the label.[8] This drug combination is not approved for any use in the United States and was used to treat horses with equine protozoal myeloencephalitis (EPM). FDA-approved drugs (pyrimethamine/sulfadiazine, diclazuril, and ponazuril) are available in the United States and labeled for treatment of EPM, but an unapproved product compounded from bulk chemical was administered instead. Remarkably, the veterinary compounding pharmacy in this case filed a third-party complaint against the veterinarian who called in the prescription.[9]

Again, the limited number of reported deaths in equine patients is most likely due to significant under-reporting. Therefore, those reported incidences of compounded-associated equine deaths may only represent the tip of the iceberg. From human medicine, the use of compounded products, in particular "sterile" products, is understood to have the potential to carry a very high risk of contamination or of being wrongly