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CASE REPORT

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Early diagnosis of amanitin exposure (amatoxicosis) in a dog with a point-of-care diagnostic test

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Abstract

Objective: To describe the rapid diagnosis, treatment, and clinical course of a dog that ingested an amanitin-containing mushroom.

Case Summary: A 2-month-old female intact Australian Shepherd presented with diarrhea and vomiting, along with a possible mushroom exposure. Upon presentation, the dog's urine was collected and tested positive by a point-of-care rapid diagnostic test specific for detecting amanitins, the causative agents of amatoxicosis.

New or Unique Information Provided: This is the first reported case of amatoxicosis that was diagnosed using a point-of-care test prior to starting treatment. An early diagnosis helps to guide early treatment decisions in this frequently fatal toxicosis.

KEYWORDS
amatoxins, canine, detection, mushroom poisoning, treatment

1 | INTRODUCTION

The causative agent of mushroom hepatotoxicosis is attributed to the toxins known as the amanitins. Amanitins are RNA polymerase II inhibitors that inhibit protein synthesis. While multiple organ systems can be affected, the liver is the primary target organ. Depending on the dose, liver failure and eventually death may occur. In a retrospective case review of 59 dogs with amatoxicosis, only 26% of treated patients survived.[1]

Amanitins are part of a larger group of toxins known as amatoxins (Figure 1). Amatoxins are naturally produced by some wild mushrooms such as those found in the genera *Amanita*, *Lepiota*, and *Galerina*. Two of the most well-known amatoxin-containing mushrooms are *Amanita phalloides* (the Death Cap) and *Amanita ocreata* (the Western Destroying Angel). In all, there are 10 known structurally similar bicyclic octapeptide molecules that are collectively referred to as amatoxins.[2]

Amatoxins are produced on the ribosome and as such the mushrooms that produce these toxins contain specific DNA that leads to the transcription and then translation of these peptides.[3] Alpha- and β-amanitins are the most well-studied and are often detected at the highest concentrations in mushrooms compared to the other amatoxins. A single mushroom can contain as much as 20 mg of amanitins.[2] The estimated oral median lethal dose (LD_{50}) for α-amanitin is 0.1 mg/kg for people.[4] In dogs, an oral LD_{50} of 0.5 mg/kg was established using synthetic methyl α-amanitin.[5]

Upon ingestion, amanitins are rapidly absorbed through the gastrointestinal tract and enter the bloodstream. In people, α- and β-amanitins are present in plasma for up to 36 hours and in urine for up to 72 hours.[6] While approximately 90% of the toxins are excreted in the urine over the course of a few days,[7] less than 10% of amanitin is excreted in bile.[6,8] Amanitins have been detected in urine, blood, bile, liver, and kidney samples from amanitin-exposed individuals.[7–12]

Currently, a presumptive diagnosis of amatoxicosis in dogs is made when there is a history of possible exposure and consistent clinical signs and biochemical changes. It is rare that an owner has actually witnessed their dog eating a mushroom[1] and often identification of the mushroom is not possible because expertise in species

Abbreviations: ALT, alanine transaminase; CAHFS, Toxicology Section of the California Animal Health and Food Safety Laboratory System, School of Veterinary Medicine, University of California, Davis; LC–MS, liquid chromatography–mass spectrometry; LD_{50}, median lethal dose; LFIA, lateral flow immunoassay; NG, naso-gastric; POC, point-of-care; RI, reference interval.

TABLE 1 Comparison of clinically relevant amanitin detection technologies

	LC-MS[10]	ELISA[15]	LFIA[12]
Detection mechanism	Molecular mass	Antibody binding	Antibody binding
Functional sensitivity	1 ng/ml	1.5 - 5 ng/ml	10 ng/ml
Portability (cage-side testing)	No	Possible	Yes
Time to result (extraction and detection)	1 hour	1 hour	10 minutes
Equipment required	Liquid chromatograph mass spectrometer (LC–MS) instrument	Microtiter plate reader	None
Sample throughput	Samples analyzed sequentially	Samples analyzed simultaneously	Samples analyzed simultaneously
Matrices tested	Urine, serum, liver, kidney, bile, mushroom	Urine, serum, plasma	Urine, mushroom

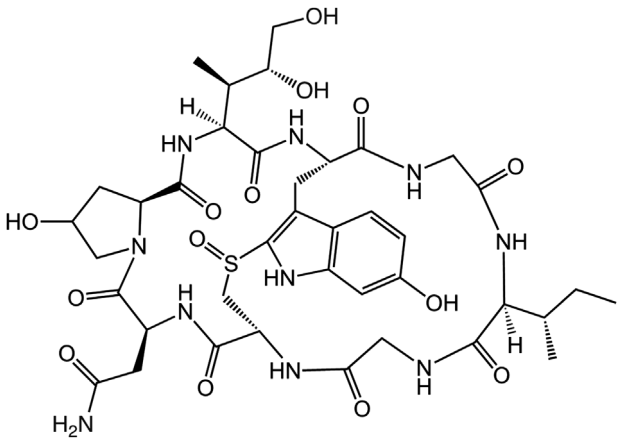

FIGURE 1 Molecular structure of α-amanitin

identification is not readily available or because the material is fragmented or only available in vomitus. Clinical signs of amatoxicosis include vomiting, lethargy, fever, hepatopathy, and hypoglycemia. If mushroom ingestion is not suspected or witnessed, the initial symptoms are not pathognomonic and can be confused with more common clinical conditions, such as acute anaphylaxis, sepsis, or other causes of acute liver failure, including exposure to blue-green algae, Sago palm, xylitol, or acetaminophen.

A definitive diagnosis of amatoxicosis can be made by detecting amanitin in either the patient or in something they were known to have ingested. Based on toxicokinetics, in a clinically sick patient, the preferred specimen to detect amanitin is urine, but in select cases toxin can also be documented in serum/plasma, bile, vomitus, or postmortem kidney or liver tissue.[6,7,9] Some select toxicology laboratories have validated analytical methods to detect amanitins, but currently the Toxicology Section of the California Animal Health and Food Safety Laboratory System, School of Veterinary Medicine, University of California, Davis (CAHFS), to the best of our knowledge, is the only veterinary laboratory performing this analysis. The lack of readily available antemortem diagnostic testing is often an impediment for early confirmation of amanitin exposure.

The most clinically relevant detection methods for amanitins include liquid chromatography–mass spectrometry (LC–MS), ELISA, and lateral flow immunoassay (LFIA) (Table 1). The key differences in these 3 methods are the detecting mechanism, sensitivity, portability, speed of analysis (time to result), and equipment requirements. LC–MS first physically separates molecules in a sample using liquid chromatography, based on the relative polarity of the mobile phase and the individual molecules. Then, the chemicals are detected using mass spectrometry to identify the mass of the chemical or chemicals of interest. LC–MS analysis is limited to specialized laboratories and requires the use of experienced technicians and expensive instrumentation. At CAHFS, the test is performed using LC–MS technology and costs approximately US $125 (USD).

Antibody-based methods, such as ELISAs and LFIAs, utilize antibodies to detect individual molecules based on the molecular recognition binding of the antibody protein for the 3-dimensional molecular shape and charge of the intended molecule it aims to detect. This binding is then translated into a signal by a secondary material such as an enzymatic turnover of a visible chromogenic substrate (ie, ELISA) or the accumulation of a visible label (visually pink/red in color if using colloidal gold) at a specific location (ie, LFIA). ELISAs require less specialized instruments, but the equipment needed is often beyond the capabilities of most veterinary clinics. LFIA requires no specialized equipment, can be performed cage-side, requires no sample processing, and produces results in as little as 10 minutes. For LC–MS and ELISA, the time to result is 1 hour, but due to the need for sample transportation and preparation, results are usually provided to the patient within 24 hours. LFIAs offer the advantages of being inexpensive, rapid, portable, and easy to use.

A LFIA point-of-care (POC) test for amanitin detection[13] has been developed and is now commercially available and inexpensive (US $10 [USD] per test) (Figure 2).[a] This POC test was initially developed for the analysis of amanitin from potential food sources, and as such, the test can also be used to determine if a mushroom contains amanitins.[14] If a small fragment of mushroom is suspended in saline, the amanitin dissolves into the suspension and the suspension can be placed on the test strip. In many cases of mushroom exposure, an expert mycologist is not available or the specimen is too macerated to be identifiable. Thus, the POC test provides the clinician with valuable information of whether or not a mushroom sample contains amanitins.

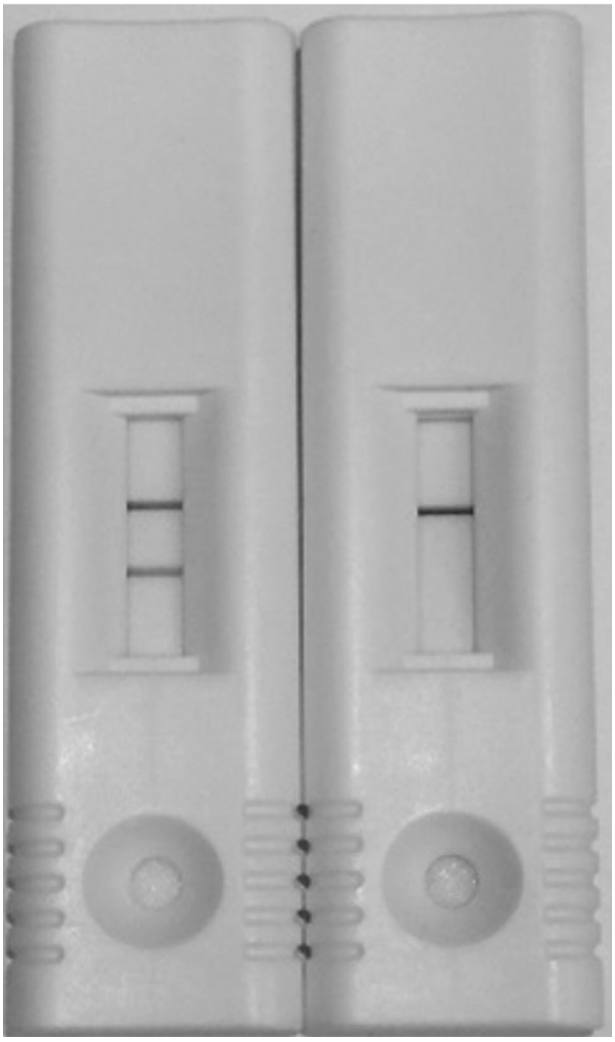

FIGURE 2 A picture of the Amatoxtest[a] showing a negative result (left) and a positive result (right)

The POC amanitin test is an antibody-based assay that indicates the presence or absence of the toxins. The test operates as a competitive assay, such that when the toxin is present in the sample, the toxin competitively interferes with the gold-labeled antibody binding to the test line (which appears as a dark pink line). The observed effect is a reduced signal intensity at the test line. Up to a threshold concentration of 10 ng/ml of amanitins, the reduction in signal is proportional to the amount of toxin detected; however, for simplicity, a sample is deemed positive when the test line is absent or nearly so. The test detects α-, γ-, and β-amanitins, collectively referred to as amanitins. This POC amanitin test has been validated for research use with urine samples.[13] Here, we present the first case in which the POC test indicated a positive reaction for amanitin in a dog's urine.

2 | CASE DESCRIPTION

A 2-month-old, 4 kg, female intact Australian Shepherd was presented with a 1 day history of intermittent vomiting, progressing to diarrhea and lethargy. The owners reported that they pulled part of a mushroom from the dog's mouth several hours prior to the onset of vomiting. (The mushroom was not available for identification or testing.)

On presentation, the dog was afebrile at 37.8°C (100.0°F) and had ptyalism and both brown diarrhea and hematochezia staining the perineum. Initial diagnostics included a negative Snap test for parvovirus[b] and a full CBC and biochemistry panel. On CBC, there was a mild neutrophilia (31.25×10^9/L [$31.25 \times 10^3/\mu$l]) (reference interval [RI]: 5.05–16.76 $\times 10^9$/L [5.05–16.76 $\times 10^3/\mu$l]) and a mild thrombocytosis (571×10^9/L [$571 \times 10^3/\mu$l]) (RI: 148–484 $\times 10^9$/L [148–484 $\times 10^3/\mu$l]). On serum biochemistry, there was a mild increase in alanine transaminase (ALT) activity (444 U/L [444 units/L]) (RI: 8–75 U/L [8–75 units/L]), a mild hypoglobulinemia (21.0 g/L [2.1 g/dl]) (RI: 23.0–38.0 g/L [2.3–3.8 g/dl]), and a mild hyperphosphatemia (3.42 mmol/L [10.6 mg/dl]) (RI: 1.65–3.40 mmol/L [5.1–10.4 mg/dl]). Given the history of mushroom exposure, the prevalence of amanitin-containing mushrooms in local region, and the increase in ALT activity, amatoxicosis was suspected.

Within 4 hours of presentation to the hospital, urine was tested using the POC amanitin test and was found to be positive for the toxin (Figure 2). Coagulation times (PT/PTT) were assessed as normal, and within 5 hours of presentation, percutaneous cholecystocentesis was performed using ultrasound guidance to remove a total of 5 ml of bile, effectively emptying the gallbladder.

Initial treatments were focused on addressing dehydration and nausea, as the dog continued to vomit once admitted to the hospital. The dog received an initial bolus of balanced isotonic crystalloid[c] (20 ml/kg) and then was continued on crystalloids at a rate of 5 ml/kg/h. Additional therapies initiated during the first 8 hours in the hospital included maropitant citrate[d] (1 mg/kg, IV, q 24 h), ampicillin sulbactam[e] (30 mg/kg, IV, q 8 h), pantoprazole[f] (1 mg/kg, IV, q 12 h), ondansetron[g] (0.5 mg/kg, IV, q 12 h), phytonadione[h] (1 mg/kg, SQ, q 12 h), and *N*-acetylcysteine[i] (140 mg/kg, IV once, then 70 mg/kg, IV, q 6 h for an additional 7 doses). Once vomiting had stopped, an attempt was made to administer activated charcoal[j] orally, but dog was not tolerant to the oral administration, so a naso-gastric (NG) tube was placed with radiographic confirmation of placement. The dog was started on metoclopramide[k] (0.2 mg/kg IV once, followed by constant rate infusion of 2 mg/kg/day) for prokinetic effect, and then activated charcoal via NG tube (2 ml/kg, via NG tube, q 6 h for 4 doses). Administration of the charcoal via this route was well tolerated.

Vital parameters including temperature were monitored every 4 hours, and a pyrexia was documented 8 hours following admission to hospital. When the pyrexia persisted, the decision was made to extend antimicrobial coverage with enrofloxacin[l] (5 mg/kg, IV, q 24 h).

Blood glucose concentrations were monitored every 4 hours, and when concentrations decreased to the low normal range (4.33 mmol/L [78 mg/dl], RI: 4.27–8.33 mmol/L [77–150 mg/dl]) 16 hours after hospital admission, dextrose 2.5%[m] was added to the IV crystalloid fluid therapy.

Liver enzyme activities, including ALT, and coagulation times (PT/PTT, prothrombin time and activated partial thromboplastin time) were rechecked during hospitalization. Eight hours after admission

to the hospital, ALT activity progressively increased (1344 U/L [1344 units/L]) but coagulation times remained within RI.

Twenty-four hours after admission, the dog began showing interest in eating food, and IV dextrose support was discontinued and the dog remained normoglycemic. The dog was gradually transitioned to oral therapies over the subsequent 3 days. Additional treatments included s-adenosylmethionine and silybin-phosphatidylcholine complex A + B (22.5 mg/kg, PO, q 24 h),[n] silybin phytosome[o] (90 mg/kg, PO, q 8–12 h), metronidazole[p] (12.5 mg/kg, PO, q 12 h), and sucralfate[q] (25 mg/kg, PO, q 8 h). The dog was discharged from the hospital after 4 days of hospitalization. At the time of discharge, ALT activity was improving (511 U/L [511 units/L]). The dog ultimately made a full recovery and remains asymptomatic. One year after intoxication, a complete CBC and biochemistry panel was unremarkable.

Urine and bile that were collected 5 and 5 hours, respectively, after presentation to the hospital (approximately 24 h after the owner had removed the mushroom fragments from the dog's mouth) were refrigerated and later submitted to CAHFS for α-amanitin quantification using LC–MS.[10] Matrix-specific calibration curves using α-amanitin standards were generated against which the bile and urine concentrations were determined. The concentration of α-amanitin was determined to be 3 ppb (3 ng/ml) in the bile and 5.3 ppb (5.3 ng/ml) in the urine. This confirmed the positive results from the POC testing performed at the time of presentation on an aliquot of the same urine specimen.

3 | DISCUSSION

Detection of any amount of amanitin in an animal is considered clinically significant. At CAHFS, LC–MS testing is typically reported as positive if it is at or above the 1 ng/ml reporting limit or trace if it is detectable but is <1 ng/ml, but the technique does allow for quantification of α-amanitin in any given sample.[11] The ELISA method detects α- and γ-amanitin with a functional sensitivity of 1.5 ng/ml.[15] The POC LFIA method is the least sensitive with a detection limit of 10 ng/ml.[13]

The clinical course of amatoxicosis is multiphasic.[6] Gastrointestinal signs of vomiting and diarrhea develop 6–24 hours after ingestion of the mushroom, followed by a convalescent phase, and then progression toward hepatic failure and multiorgan dysfunction syndrome. While these distinct phases of illness are not always identified in dogs that present to the emergency clinic,[1] it is important to recognize that there is a delay in clinical signs following ingestion of the toxin. Although the plasma half-life of amanitins in dogs is only 25–50 minutes, amanitins should be detectable in the urine for up to 72 hours.[16] This POC test provides an opportunity for clinicians to make a diagnosis earlier to better inform case management and prognosis.

It is clear that critically ill patients from amatoxicosis benefit from intensive supportive care, as they often present in hypovolemic shock, with severe gastroenteritis, hypoglycemia, and coagulopathy. Initial treatments typically include aggressive IV fluids to restore intravascular volume and preserve renal perfusion and urine output, antiemetics, and gastroprotectants. This dog was started on broad spectrum antimicrobials, due to risk of sepsis, as is standard practice in people with acute liver failure or hepatic encephalopathy.[17] Dextrose support is also an important component of supportive therapy in amatoxicosis. In a case review of 59 dogs suffering from amatoxicosis, 95% developed hypoglycemia.[1] Fresh frozen plasma, which is frequently used as part of the treatment protocol in cases of amatoxicosis,[1,18] was not indicated in this dog, as a coagulopathy was not documented.

Silybin, which is a component of milk thistle, inhibits the uptake of amanitin into hepatocytes,[19] and when administered early (within 5–24 h after exposure), IV silybin is known to be protective against the effects of the toxin.[19–21] IV silybin[r] is approved for use in Europe, but it is not FDA approved for use in people in the United States,[22] and it is not available for veterinary use, so this dog was treated with an oral form of the supplement. Oral silybin has poor bioavailability and there are no studies that prove it is efficacious for this purpose in the dog, but it is considered safe and it is recommended in people when the IV form is not available.[4] Silybin bioavailability is significantly improved when given in a form that is complexed with phosphatidylcholine.[23,24]

Since most dogs that are sick from amatoxicosis present relatively late in the course of illness and have already vomited at home, gastric decontamination is not likely to be of significant benefit but there may be some benefit in addressing enterohepatic recirculation of toxin. While it has been shown that approximately 90%–99% of amanitin is excreted through urine,[7] measurable amounts are detectable in bile.[6,8] Techniques that have been considered include activated charcoal to bind toxin, octreotide to reduce gallbladder motility, cholestyramine to adsorb bile acids, and also direct biliary drainage.[10,12,25]

A recent case series of 5 dogs that suffered from amatoxicosis[18] describes a protocol of treatment focused on therapeutic cholecystocentesis, coupled with therapies to suspend enterohepatic circulation, that is, not giving anything by mouth and administering octreotide. While the 5 dogs in this series did survive, no controlled or retrospective studies have shown improved survival in human or veterinary patients that undergo this type of decontamination.

The decision was made to perform a therapeutic cholecystocentesis in the dogs described in this case report, following the rationale that removing bile would decrease the amount of amanitin undergoing enterohepatic recirculation. Because a diagnosis of amatoxicosis was confirmed using the POC test, cholecystocentesis was performed within several hours of presentation to the hospital. The dog was not coagulopathic and the risks were assessed as relatively low. The gallbladder was emptied in its entirety (approximately 24 h after the toxin was ingested), removing a total of 5 ml of bile. Later, in order to determine how much toxin was actually removed via cholecystocentesis, the bile was submitted for quantification of α-amanitin. We found that there was 3 ng/ml of α-amanitin in the bile.

To our knowledge, biliary concentrations of amanitins have not been reported in dogs, except in experimental cases wherein a continuous biliary drainage tube was inserted prior to amatoxin ingestion.[25] In this experimental case series, the researchers demonstrated that establishing this biliary drainage prior to toxin ingestion greatly reduced amanitin absorption from the intestine, presumably because the presence of bile in the intestine enhances absorption of the toxin. However, this

study did not show how biliary drainage might impact enterohepatic recirculation.

In human accidental intoxication cases, there are little data on how much amanitin can be recovered in bile. In 1 case, an endoscopic nasobiliary drainage catheter was placed on day 5 after ingestion and left in place for 2 days. Over this time period, 280 ml of bile was recovered, removing a total of 656 ng of α- and β-amanitins. The average concentration of amanitin in the bile was 2.34 ng/ml (or 1.7 ng/ml of the α-amanitin fraction).[12] In a second case, the biliary drainage catheter was placed on day 2 and left in place for 3 days, recovering 240 ml of bile. In this patient, 4.03 mg of α- and β-amanitins were quantified in the bile, an average of 16.791 μg/ml (or 7.5 μg/ml of α-amanitin).[10]

As alluded to earlier, a specific LD_{50} for dogs is not known for α-amanitin. Estimated values have been described for a synthetic methyl α-amanitin and from human evaluations. Therefore, if we use an estimated oral LD_{50} for dogs that ranges from 0.1 to 0.5 mg/kg, for this 4-kg dog, this would amount to an LD_{50} of 0.4–2 mg (or 4×10^5 to 2×10^6 ng) of toxin. At the time of cholecystocentesis, the gallbladder contained 5 ml of bile or 15 ng of α-amanitin toxin. It seems unlikely that removing this small amount of toxin, effectively 3.75×10^{-3} to 7.5×10^{-4} percent of the α-amanitin LD_{50}, would have made a clinical difference in the dog's recovery, though controlled studies are needed and we still do not know whether this amount of amanitin in bile is typical for most dogs.

It is impossible to conclude that the early diagnosis and treatment resulted in a successful outcome in this case or that any of the treatments provided a clearly defined benefit to recovery. More studies using this POC test must be performed to know if survival rates improve with earlier detection.

It is worth noting that this POC test could result in false negatives, as its detection limit is higher than LC–MS.[13] Although the detection limit of the POC test is functionally stated as 10 ng/ml (total amanitins), a sample containing 5 ng/ml (α-amanitin), as was the case in this report, could be interpreted as positive because the POC test detects other amatoxins not measured by LC–MS, thus resulting in a cumulative amatoxin concentration at or above 10 ng/ml. If the POC test is found to be negative but clinical signs are strongly suggestive of amatoxicosis, then it is recommended that LC–MS confirmatory testing be performed. Studies using the POC test conducted to date indicate false positives are unlikely.[13]

In conclusion, our report describes the early detection and full recovery of a dog affected by amatoxicosis. Without chemical detection, this case would likely have been documented as more broadly hepatotoxicosis. We feel it is likely that early detection of amanitin will allow clinicians to document more cases of amatoxicosis, including those of less severely affected patients that might not have been otherwise definitively diagnosed because they never developed fulminant liver failure. Early intervention in cases that present within hours of ingestion, prior to the development of clinical illness, might be where aggressive and early decontamination can have the most significant impact.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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ENDNOTES

[a] Amatoxtest, LLC, Ann Arbor, MI.
[b] CPV Antigen Test Kit, IDEXX Laboratories, Westbrook, ME.
[c] Lactated Ringer's Injection USP, B. Braun Medical Inc, Bethlehem, PA.
[d] Cerenia, Zoetis Inc, Kalamazoo, MI.
[e] Ampicillin and Sulbactam, Piramal, Bethlehem, PA.
[f] Pantoprazole, AuroMedics Pharma LLC, E. Windsor, NJ.
[g] Ondansetron, West-Ward, Eatontown, NJ.
[h] Vitamin K1, Sparhawk Laboratories Inc, Lenexa, KS.
[i] Acetylcysteine 20%, Hospira, Lake Forest, IL.
[j] ToxiBan, Lloyd Inc, Shenandoah, IA.
[k] Metoclopramide, Hospira, Lake Forest, IL.
[l] Enrocite, Norbrook Laboratories Limited, Northern Ireland.
[m] Dextrose 50%, Nova-Tech, Inc., Grand Island, NE.
[n] Denamarin, Nutramax Laboratories, Lancaster, SC.
[o] UltraThistle (silybin phytosome), Natural Wellness, Montgomery, NY.
[p] Metronidazole, Viona Pharmaceuticals Inc, Cranford, NJ.
[q] Sucralfate oral suspension, Par Pharmaceutical, Chestnut Ridge, NY.
[r] Legalon SIL, Madeus, Colongne, Germany.

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