

Presumptive Fluphenazine-induced Hepatitis and Urticaria in a Horse

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A 4-year-old Standardbred gelding (450 kg) was examined because of depression, poor appetite, and suspected liver disease. Eight days before examination, the horse had won a race. The next day, depression, muscle stiffness, and transient pyrexia (39.0°C) were observed. The horse was treated with single doses of flunixin meglumine^a (1 mg/kg IV), phenylbutazone^b (0.2 mg/kg PO), methocarbamol^c (4.4 mg/kg PO), N-acetylcysteine^d (6.6 mg/kg PO), and 5 L lactated Ringer's solution IV. A CBC and serum biochemical profile performed 4 days before presentation revealed neutrophilia and moderate increases in serum concentration of the hepatic enzyme activities (Table 1). Moderate urticaria (hives) was present over the trunk of the horse.

On examination, the horse was quiet but alert and was in good body condition. Initial physical examination revealed mild jaundice and mild clinical dehydration. The heart rate (36 bpm), respiratory rate (12 bpm), and rectal temperature (37.6°C) were within normal reference limits. Multiple raised, edematous, nonpruritic nodules (3–5 mm diameter), consistent with urticaria were observed over the trunk and the neck. Auscultation and percussion of the thorax and the abdomen was unremarkable. Neurologic examination was unremarkable. This was the only horse of 19 on the farm affected.

Thirty-three days before referral, the horse had been empirically administered a single dose of a long-acting parenteral preparation of fluphenazine decanoate^e (0.28 mg/kg IM) as a tranquilizer to control anxious behavior. The gelding had daily access to 2 species of weeds, which were estimated to occupy approximately 20% of the turnout paddock area. No grass was available in the paddock because of overgrazing. Nineteen other horses shared the same turnout paddock and had the same management. All horses had access over a fence to lush grass, which had been sprayed with a surfactant-free glyphosphate product^f the week the subject horse was administered fluphenazine. Serum biochemical profiles conducted on the herd mates, 2 days before examination, revealed serum activity of hepatic enzymes and concentration of total bilirubin within reference limits. No other horses in the barn had been administered fluphenazine decanoate. Vaccines administered to the horse included equine influenza, rhinopneumonitis, tetanus toxoid, and West Nile virus. The last dose of which had been administered approximately 8 weeks before referral.

Clinicopathologic abnormalities were limited to hyperbilirubinemia, increased serum activity of hepatic enzymes (glutamate dehydrogenase [GLDH], aspartate aminotransferase [AST], gamma-glutamyl transferase [GGT], and alkaline phosphatase [AP]), and increased total bile acids concentration (Table 1). These findings were interpreted as indicative of impaired bile circulation and active hepatocellular damage. No changes compatible with an inflammatory process were identified. Plasma fibrinogen and blood ammonia concentrations were not determined at that time. Transabdominal ultrasound examination revealed normal hepatic architecture. A fecal bacterial culture for *Salmonella* spp. was negative. The initial therapy consisted of lactated Ringer's solution (60 mL/kg/d IV), trimethoprim-sulfadioxine^g (24 mg/kg IV q12h), and flunixin meglumine (1 mg/kg IV q24h). The diet was restricted to first-cut grass hay to avoid high dietary protein content.

Taxonomic classification of the weed plant species reported by the owner revealed that the predominant plant was "redroot pigweed," *Amaranthus retroflexus* (80% of weeds in paddock), and the other was "Lamb's quarter," *Chenopodium album* (20% of weeds in paddock). *A. retroflexus* has been associated with severe renal disease in cattle,¹ and *C. album* has been associated with nitrate toxicosis in cattle.² To the authors' knowledge, neither has been reported to induce hepatic disease in large animals, and there was no evidence that the horses had consumed them.

Over the next 3 days of hospitalization, the horse remained clinically stable. Vital signs were within normal limits, the jaundice resolved, and the hydration status improved. The attitude and the appetite also improved, but both were still abnormal. The urticaria also improved. No neurologic signs or altered behavior was observed. Despite apparent clinical improvement, subsequent biochemical profiles revealed that indicators of liver damage persisted (Table 1). An ultrasound-guided percutaneous liver biopsy was obtained on day 3.^{3,4}

Histologic examination of the liver tissue revealed changes consistent with hepatitis, characterized by scattered hepatocyte single-cell necrosis; mitoses; early periportal fibrosis with mild biliary hyperplasia; and scattered infiltrates of lymphocytes, plasma cells, and occasional neutrophils, most evident around portal tracts (Fig 1). No bacterial organisms were identified, and histologic stains for copper (rhodamine) were negative. Histologic stains for iron (Pearl's iron) revealed only scant coarse iron staining in Kupffer cells. Histologic examination of a skin biopsy (urticaria) revealed overall normal architecture, with mild superficial dermal edema, occasional lymphocytes within the dermis, and mild epidermal compact hyperkeratosis, consistent with urticaria. Based on this histologic pattern of liver disease and the clinical history,

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Table 1. Serum biochemical data.

Analyte	Days After Admission							Reference interval
	−4 ^a	1	3	4	8	32	60	
GGT, U/L	136	138	170	176	187	81	74	7–54
GLDH, U/L	—	58	102	97	23	—	—	1–7
Bile acids, $\mu\text{mol/L}$	—	20	46	44	12	—	—	0–6
Total bilirubin, $\mu\text{mol/L}$	57	71	69	63	38	31	33	21–57
Conjugated bilirubin, $\mu\text{mol/L}$	—	3	4	5	2	—	—	2–3
Unconjugated bilirubin, $\mu\text{mol/L}$	60	68	65	58	36	—	—	18–55
AP, U/L	262	485	571	594	525	199	170	119–329
AST, U/L	746	759	807	747	587	475	354	259–595
Ammonia, $\mu\text{mol/L}$	—	—	—	—	4	—	—	7.6–63

GGT, gamma glutamyl transferase; GLDH, glutamate dehydrogenase; AP, alkaline phosphatase; AST, aspartate aminotransferase.

^a Four days before admission; external laboratory reference intervals: total bilirubin, 10–45 $\mu\text{mol/L}$; free bilirubin, 0–50 $\mu\text{mol/L}$; AP, 60–220 U/L; GGT, 8–60 U/L, and AST, 200–500 U/L.

immune-mediated hepatitis, idiopathic chronic active hepatitis, individual chronic exposure to hepatic toxicants, and idiosyncratic drug reaction were suspected. Antibiotic and anti-inflammatory therapy was continued for 3 additional days.

Because the presence of antinuclear antibodies (ANA) has been reported in most cases of drug-induced chronic hepatitis in humans,⁵ serum ANA titers were determined. This horse had a high ANA titer of 1:80, which was indicative of autoimmune disease. However, this finding was not considered specific for liver disease, because ANAs can also be present in other diseases and can be identified in clinically normal animals.⁶

Individual exposure to other hepatotoxic plants and chemicals⁷ could not be documented, with the exception of concurrent exposure to fluphenazine and glyphosate. Because fluphenazine decanoate injections have resulted in prolonged serum concentrations and neurologic adverse effects in horses,^{8–10} fluphenazine concentration was determined in sera from days 1 and 2 by using a high-performance liquid chromatography method.¹¹ The flu-

phenazine concentrations for days 1 and 2 were 0.34 and 0.45 ng/mL, respectively. The presence of fluphenazine 33 days after injection was indicative of prolonged exposure and a likely risk factor for drug-induced cholestatic hepatitis, as reported in humans.^{12,13}

To objectively assess the likelihood of correctly diagnosing this horse with presumptive drug-induced hepatitis, 2 clinical diagnostic scales designed for humans were used as a guideline, the International Consensus Criteria (ICC) and the Maria and Victorino's Clinical Diagnostic Scale (CDS).¹⁴ These diagnostic scales are based on the temporal relation between the administration of the drug and the development of clinical signs, the exclusion of other causes of liver disease, and the resolution of clinical signs after withdrawal of the drug, provided irreparable damage has not occurred. Reproduction of clinical signs after a second controlled exposure is another criterion described for short half-life medications but not recommended for medications with long half-lives and severe adverse effects, eg, fluphenazine. The use of the ICC system classified this case as drug-related hepatitis (3 of 4 criteria were met for classification), whereas the CDS produced a score of 11–13 of 20, which classified this case as a “possible” drug hepatotoxicity. The sensitivity and the specificity of the CDS for correctly classifying cases of drug-related hepatotoxicity in humans are 88% and 98%, respectively, if a cutoff score of 9 of 20 is used.¹⁴ Although, these scoring systems have not been validated for horses, the results were supportive of a presumptive drug-related hepatitis.

Throughout the remaining hospitalization period, the vital signs were normal, and the horse's attitude and appetite returned to normal. By day 8, serial serum biochemical analyses also revealed normalization of bilirubin concentration and AST, and a gradual reduction of bile acids concentration and GLDH; AP and GGT concentrations remained high (Table 1). Fluid and antibiotic therapy was discontinued; whereas flunixin meglumine (1 mg/kg q24h, PO for 3 days) was maintained until day 9. The horse was discharged from the hospital on day 9 at the owner's request. Management recommendations included stall rest and good-quality

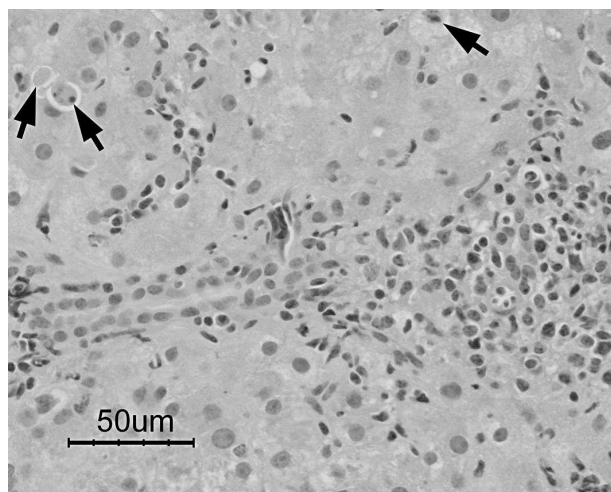


Fig 1. Photomicrograph of liver tissue, demonstrating the predominantly lymphoplasmacytic portal inflammatory infiltrate, which extends into the adjacent hepatic parenchyma, and scattered hepatocyte single-cell necrosis (arrows). Hematoxylin and eosin.

grass hay and a diet based on beet pulp, pelleted concentrates, and molasses.⁷ Because cross-sensitivity among phenothiazine derivatives can occur,¹² avoiding the use of tranquilizers, eg, acepromazine, was recommended. Follow-up serum biochemistry profiles revealed that serum AP activity returned to reference intervals within 3 weeks of discharge, but GGT concentrations remained high 8 weeks after discharge.

Fluphenazine decanoate is a decanoate ester of a trifluoromethyl phenothiazine derivative, which is a potent, lipophilic, antipsychotic drug that has been widely used for the treatment of schizophrenia and other psychotic disorders in humans.¹⁵ Adverse effects in humans vary with the therapeutic protocol and include the induction of serious extrapyramidal signs, including parkinsonism, bradykinesia, dystonia, and akathisia,¹⁵ and a serious uncommon (incidence of up to 3%) complex termed "neuroleptic malignant syndrome,"¹⁶ which may be accompanied by acute renal failure, hyperthermia, and muscle rigidity.¹⁷

Therapeutic plasma concentrations of fluphenazine in people with schizophrenia have been reported to be between 0.25 and 0.80 ng/mL¹⁸; however, plasma concentrations can vary greatly and reach higher concentrations even 7 days after injection.¹¹ In horses affected with fluphenazine-induced extrapyramidal signs, the plasma fluphenazine concentrations appear to vary greatly after administration of doses recommended for humans.⁸ Although in this horse the concentration of fluphenazine was determined in serum rather than in plasma, the detection of fluphenazine 33 days after administration indicates the presence of the agent but does not reflect tissue concentrations. Previous reports revealed that plasma and tissue concentrations, and dosage versus plasma concentration do not correlate well,¹⁹ and accumulation in soft tissues with concentrations greatly exceeding serum values has been demonstrated.²⁰

Administration of fluphenazine or other related drugs to humans has been associated with increased serum activity of liver enzymes²¹ and with cholestatic hepatocellular injury, characterized by cholestasis, scattered focal areas of necrosis, and apoptosis, and a predominantly lymphocytic portal inflammatory response.¹² Comparable histologic changes have also been reported for other psychotropic drugs, including phenothiazines.^{12,22} Urticaria is a clinical feature also reported in phenothiazine cholestatic jaundice in humans.^{12,22} The histologic changes in the liver biopsies from this horse were similar to those reported in humans, with the exception of significant intracanalicular cholestasis.

The hepatotoxic mechanism of phenothiazine drugs is not completely understood but may involve a combination of physiochemical, immune, and direct toxic effects.^{5,12} The fact that this horse was also exposed to glyphosate, a carboxylic ester organophosphorus compound herbicide, might also be considered to be another risk factor for hepatitis, because direct hepatic injury and impaired liver metabolism have been recently documented.^{23,24} This exposure was, however, limited, and other exposed horses revealed no clinical or serum

biochemical abnormalities. According to the product insert, fluphenazine should be used cautiously in human patients exposed to phosphorus insecticides. However, the authors could not verify supporting literature for such association when the pharmaceutical company was contacted. Although fluphenazine preparations are known to be used in equine private practice, no scientific literature supporting their therapeutic value for horses is available.

Footnotes

^a Banamine, Schering Canada, Pointe Claire, QC, Canada

^b Phenylbutzone, Vetoquinol, Lavaltrie, QC, Canada

^c Robaxin, Schwarz Pharma Inc, Milwaukee, WI

^d Parvovex, Bioniche Life Sciences Inc, Belleville, ON, Canada

^e Modecate, Bristol-Myers Squibb Canada Co, St-Laurent, QC, Canada

^f Glyphos, Cheminova Canada Inc, Mississauga, ON, Canada

^g PotenSulf, Bimeda-MTC, Animal Health Inc, Cambridge, ON, Canada

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