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CASE REPORT

Zuclopenthixol decanoate toxicity in an 8-month-old colt causing extrapyramidal neurological signs

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Summary

Zuclopenthixol decanoate is a dopamine antagonist licensed for human use to manage schizophrenia and paranoid psychosis. It is in the same drug class (thioxanthene) as fluphenazine decanoate, a drug whose use in horses is reported anecdotally for providing long-acting sedation. This case study describes severe extrapyramidal signs seen in a Thoroughbred colt after zuclopenthixol decanoate administration. The colt was presented to a referral hospital for an unusual manifestation of colic signs. On admission, the colt began to show clear extrapyramidal neurological signs. The initial suspicion was of fluphenazine decanoate toxicity, which in the limited published literature is treated with intravenous formulations of diphenhydramine hydrochloride and benztropine mesylate. At the time of writing both were unavailable in the United Kingdom without an import license. The closest alternative option, oral diphenhydramine was administered alongside intravenous atropine and pergolide. Improvements in the colt's demeanour and neurological status was noted within 24 h. The colt was hospitalised for a total of 26 days and at time of discharge was clinically normal. Follow-up communication 3 months after discharge confirmed that the colt had remained neurologically normal. Crucially, toxicology testing submitted to Cornell University was negative for common toxins, including fluphenazine decanoate. Specific secondary testing was performed after suspicion the administration of zuclopenthixol decanoate was raised, which was positive for this compound. Routine drug testing would, therefore, not identify the use of this behaviour modifying drug. Clinical data regarding the use of zuclopenthixol in animals is limited to its use in the translocation of wildlife to relieve stress and aid acclimatisation. To our knowledge, there is no available literature describing the administration of zuclopenthixol decanoate in equine patients.

KEYWORDS
horse, extrapyramidal, sedative, toxicity, yearling, zuclopenthixol

INTRODUCTION

Zuclopenthixol is a dopamine antagonist licensed in the United Kingdom for use in human patients for management of schizophrenia and paranoid psychosis (Jayakody et al., 2012). It is one of a selection of first-generation antipsychotic drugs available, prescribed in both oral and depot formulations (Royal College of Psychiatrists, 2022). In humans zuclopenthixol acetate is a shorter acting formulation lasting for approximately 72 h and zuclopenthixol decanoate is a longer acting formulation given every 1–4 weeks. The drug is useful where repeated doses of injectable antipsychotics and/or sedation have been required or when patients cannot be relied upon to take oral medications (Jayakody et al., 2012).

In veterinary medicine, zuclopenthixol is used to alleviate stress during handling of wild animals, particularly during translocation. Beneficial effects include general calming, indifference

to new and unnatural surroundings, loss of fear of people and reduction in aggressive behaviour (Read et al., 2000). While reports of a related compound, fluphenazine decanoate, being used in horses as a long-acting sedative for performance enhancement are available, the use of zuclopenthixol has not been reported in this species (Baird et al., 2006).

This case report describes severe extrapyramidal neurological signs seen in a Thoroughbred colt after the administration of zuclopenthixol decanoate. Essentially, routine serum toxicology testing including a related compound, fluphenazine decanoate was negative, and it was only with specific testing that a diagnosis was achieved.

CASE HISTORY

An 8-month-old Thoroughbred colt was stabled and treated with pyrantel in preparation for the sales. The following day, the colt was exhibiting clinical signs that included jaw-clamping, repetitive lateral head and neck movements and 'bowing'. The colt would also show signs of mania, including box-walking, persistent pawing of the ground and striking with the forelimbs. The referring vet had performed an abdominal ultrasound examination and reported the presence of increased small intestinal wall thickness, with no other abnormalities. Oxytetracycline (Engemycin®; MSD Animal Health Ltd.) 5 mg/kg bwt, IV, flunixin meglumine (Flunixin Injection, Norbrook® Ltd.) 1.5 mg/kg bwt, IV and dexamethasone (Rapidexon®, Dechra Ltd.) 0.08 mg/kg bwt, IV were administered at the yard. The colt was sedated for travel with romifidine, an alpha-2-agonist (Sedivet®, Boehringer Ingelheim Ltd.) 0.08 mg/kg bwt, IV and transported to Three Counties Equine Hospital for further investigation and treatment of a suspected unusual presentation of colic.

HISTORY AND CLINICAL EXAMINATION

On arrival the weanling was still under the influence of sedation. Clinical examination revealed congested mucous membranes, normal heart rate (40 beats/min), mild pyrexia (38.6°C) and reduced gastrointestinal borborygmi. The remainder of the clinical examination was unremarkable. Haematology identified mild leucocytosis (white blood cell count 15.6×10^9 cells/L) attributed to a mature neutrophilia (due to stress leukogram). Acute phase proteins (serum amyloid A, fibrinogen) were within normal limits. Abdominocentesis was performed and yielded straw-coloured peritoneal fluid, analysis of which was normal (white blood cell count 1×10^9 cells/L; total protein 12 g/L). Abdominal ultrasonography identified amotile and mildly increased small intestinal wall thickness (between 4 and 5 mm). A nasogastric tube was passed and did not yield any reflux. An indwelling catheter was placed in the left jugular vein and crystalloid intravenous fluid therapy (4 mL/kg/h) was commenced.

Clinical signs resumed once sedation had worn off, including hypersalivation, generalised muscle fasciculations, jaw champing, repetitive lateral head movements and adopting a 'bowing' posture. Stimulation induced unpredictable manic behaviour, rearing and obsessive pawing. When unstimulated, the colt became somnolent. When offered food he did not show any evidence that he was aware of its presence. The signs did not improve with analgesia.

Differential diagnoses included viral encephalitis (Eastern Equine Encephalitis, Western Equine Encephalitis, West Nile Virus, Equine Herpes Virus [EHV], rabies), Equine Protozoal Myeloencephalitis, fumonisin toxicity or an adverse reaction to fluphenazine decanoate. Cerebrospinal fluid centesis was not possible due to the erratic and often dangerous behaviour exhibited by the foal. EHV-1 serum antibody testing and nasopharyngeal swab for EHV-1/4 PCR were performed and were negative. Given the geographical location and no history of foreign travel, fluphenazine decanoate toxicity was considered most likely.

TREATMENT

During the first 12 h of hospitalisation the colt started showing increasing neurological signs and became dangerous to handle. A sedative continuous rate infusion of ketamine (5–10 mcg/kg/min), detomidine (0.2–0.4 mcg/kg/min) was administered and the rate of infusion altered to try to depress manic activity and prevent the colt self-traumatising with additional boluses of detomidine (0.01 mg/kg bwt) and butorphanol (0.01 mg/kg bwt) as required. An intravenous infusion of lipid emulsion (20% soybean oil in water) was administered in case a lipophilic toxin, for example ivermectin, was implicated (Bruenisholz et al., 2012). An intravenous bolus of the anticholinergic atropine sulphate (0.01 mg/kg bwt) was administered. The environment was made as unstimulating as possible by turning the lights out, placing cotton wool in the colt's ears and minimising movement in the barn. The violent and unpredictable nature of the colt made monitoring of vital parameters challenging during this time. The colt was unable to eat due to a combination of inappropriate awareness and response to food, and due to jaw-clamping making it impossible to prehend food.

The weanling initially improved and became more appropriately responsive. However, he then deteriorated and showed persistent extrapyramidal neurological signs, anorexia and no faecal output. Dexamethasone (0.11 mg/kg bwt, IV) and midazolam (0.11 mg/kg bwt, IM) were administered, with no clinical response. Buccal mucosa had become injured as a result of violent head movements.

When the colt failed to improve, discussions with his carers conceded that it was possible that the horse may have received zuclopenthixol decanoate (Clopixol®, Luncbeck Ltd.) which had been intended for another weanling in the same paddock. They had been using the drug to aid handling and yearling preparation. The dose administered was unclear. The use of zuclopenthixol decanoate, and management of toxicity, is not reported in the literature; therefore, management was extrapolated from treatment of fluphenazine decanoate, a closely related compound. It is unclear where they had sourced zuclopenthixol decanoate. The

intravenous formulations of the anticholinergic drugs benztropine mesylate and diphenhydramine hydrochloride were unavailable, therefore given the initial positive response, intravenous atropine (Atropine Sulphate, Hameln Pharma Ltd.) 0.01 mg/kg bwt q24 hours was administered as an anticholinergic and oral diphenhydramine (Nytol™, Omega Pharma Ltd.) 1 mg/kg bwt q12 hours was administered via nasogastric tube. Pergolide (Prascend®, Boehringer Ingelheim Ltd.) at 2 mcg/kg bwt q24 hours was commenced as a dopamine agonist. As the colt could still not prehend food, total parenteral nutrition (TPN) was commenced on day 5 of hospitalisation consisting of 50% glucose (Fresenius Kabi), 10% amino acid (Aminoven-25, Fresenius Kabi) and 20% soyabean oil in water (Intralipid®, Fresenius Kabi).

Due to legal implications, a blood sample was submitted to Cornell University Toxicology Laboratory for their equine drug screen, which included testing for fluphenazine decanoate. This was positive for the presence of ketamine and detomidine, which were administered in the hospital, but negative for the presence of other compounds. After discussion regarding the case with the laboratory, specific testing for zuclopenthixol decanoate was pursued and confirmed presence of this compound. Therefore, the colt was diagnosed with extrapyramidal symptoms secondary to zuclopenthixol decanoate administration.

A gradual Improvement in demeanour was observed approximately 7 days after hospitalisation. The colt appeared progressively more lucid and responsive to the environment. The frequency and severity of manic episodes gradually reduced and the colt was keen and able to eat and drink 24 h after the first dose of diphenhydramine hydrochloride. Once the colt was believed to be capable of swallowing, the diphenhydramine hydrochloride tablets were administered orally by syringe or added to a small bowl of feed. The sedative continuous rate infusions were tapered and stopped. Improvement in clinical signs and desire to eat and drink enabled TPN and intravenous fluid therapy to cease. The colt was administered diphenhydramine hydrochloride and pergolide for a total of 17 days until complete resolution of all neurological signs.

DISCUSSION

Zuclopenthixol is a neuroleptic in the thioxanthene class that has an affinity for both dopamine D1 and D2 receptors (Coutinho et al., 2000). In human medicine, the drug is available in three combinations: an oral short acting formulation (zuclopenthixol dihydrochloride), an intramuscular injection lasting several weeks (zuclopenthixol decanoate) and an intramuscular injection that lasts for 2–3 days (zuclopenthixol acetate). These all come under a broader category of 1st generation antipsychotics that are esterified long chain fatty acids contained in a base oil. Once injected, the ester bonds are broken down releasing the active drug into the bloodstream.

Zuclopenthixol acetate and decanoate, along with other long-acting antipsychotic drugs, are reported in the literature to cause extrapyramidal side effects in humans caused by a dopamine blockade in the basal ganglia (Blair & Dauner, 1992). The lack of dopamine can mimic idiopathic pathologies of the extrapyramidal system, particularly in overdose situations (Korchia et al., 2018). Administration in humans is generally commenced with a 'test dose' to monitor sensitivity to the drug (NHS Prescribing Management Group, 2023).

Published data regarding the use of zuclopenthixol formulations in veterinary medicine is mostly limited to use in wildlife translocation. The long-acting formulation is described in many wild species as being useful in reducing stress, injuries and mortalities during transportation and episodes of captivity (Laubscher et al., 2016; Read et al., 2000). Extrapyramidal signs following administration of zuclopenthixol are described. A double blinded study of nine Namibian cheetahs found that when zuclopenthixol acetate was used alone and in combination with other neuroleptic drugs, it caused side effects including ataxia, inappetence, extrapyramidal signs, somnolence and hypothermia (Huber et al., 1999). A nonblinded clinical trial based at Ngongoni Farm, South Africa involving 29 captive blue wildebeest were found to show a suitable level of sedation after administration of zuclopenthixol acetate (Laubscher et al., 2016). Similarly, a group of 23 wild wapiti in Manitoba, Canada, were assessed for acclimatisation to being handled during a period of translocation (Read et al., 2000). Those treated with zuclopenthixol acetate were overall less active and reactive. No animals showed extrapyramidal side effects after administration of zuclopenthixol acetate. A longer case study followed the activity of 18 red deer over a 10-week period and monitored reaction to management practices that were likely to cause stress for example, herding and handling (Diverio et al., 1993). The group was split into three groups, the first was 'undisturbed', the second treated with two types of neuroleptics (zuclopenthixol acetate and perphenazine enanthate) and 'stressed' and the third treated with two types of neuroleptics (zuclopenthixol acetate and perphenazine enanthate) and 'undisturbed'. The study found animals treated with a combination of long and short acting neuroleptics to be more approachable and easier to handle. Overall, it was concluded that the treatment provided a more normal activity pattern when disturbed. The 1998 Namibian Ministry of Environment and Tourism' capture protocol reports zuclopenthixol as providing excellent sedative effects to black rhinoceros during capture (Reuter & Winterbach, 1998). A single dose is described to last 3 days, ideal to reduce aggressive behaviour in rhinos confined to enclosures.

The use of zuclopenthixol formulations in horses is not accounted for in the literature. Veterinarians are aware of 'off-licence' use for its sedative and anxiolytic effects, but information about dosing and risks of usage are not accessible. Fluphenazine administration is more widely described by owners and veterinarians, particularly when preparing youngsters for the sales. Fluphenazine decanoate is another form of 1st generation antipsychotic medication available in the United Kingdom to human patients (Royal College of Psychiatrists, 2022). Its mechanism of action and side effects are very similar to those observed in this case. Clinical signs included restlessness, profuse sweating, hypermetria, aimless circling, intense pawing and rhythmic swinging of the head and neck

(Baird et al., 2006). Baird et al. (2006) documents the series of events in four horses who suffered from adverse extrapyramidal effects following fluphenazine decanoate administration. All four horses were treated with diphenhydramine hydrochloride (0.67–1.5 mg/kg bwt, IV). Two horses responded and showed clinical improvement between 1 min and 6 h after administration. The aggressive neurological signs and extreme depression ceased and both horses became alert and responsive.

Diphenhydramine hydrochloride is a centrally acting anticholinergic drug reported to restore an appropriate dopamine-acetylcholine balance to treat extrapyramidal signs (Baird & Maylin, 2011). The drug is reported to treat extrapyramidal side effects from fluphenazine decanoate (Baird et al., 2006; Baird & Maylin, 2011) at a dose of 0.67–1.0 mg/kg bwt, IV bolus over 20 min. Results are mixed, with repeated doses and/or the addition of further anticholinergic drugs such as benztropine mesylate required. An intravenous formulation of diphenhydramine hydrochloride was not available in the United Kingdom without an import licence at the time of admission. An oral formulation, an antihistamine and sedative for human use was the closest way the active ingredient diphenhydramine hydrochloride could be incorporated to the treatment plan. A dose of 1 mg/kg bwt, orally every 12 h was administered and improvement seen within 10 h. The oral bioavailability of diphenhydramine hydrochloride in horses is unknown; however, the commencement of treatment with a combination of diphenhydramine hydrochloride and intravenous atropine coincided with clinical improvement. To the authors' knowledge, this is the first time that an oral formulation of diphenhydramine hydrochloride has been used to successfully treat extrapyramidal signs in equine species.

Pergolide is a potent dopamine agonist used to treat Parkinson's disease in humans (Fuller & Clemens, 1991), and pituitary pars intermedia dysfunction in horses (Rendle et al., 2019). It interacts directly with D1 and D2 receptors and its affinity for the same D1 and D2 dopamine receptors as zuclopenthixol offered an interesting opportunity for treatment. The drug is licensed in horses with minimal side effects; therefore, treatment was commenced on this basis. It is unlikely that this resulted in improvement in this situation as pergolide takes 3 days to reach steady-state concentrations in plasma. To our knowledge, there has been no reported use of pergolide for treatment of overdose of zuclopenthixol in horses.

Toxicology testing was performed in the USA due to the limited availability of laboratories that perform fluphenazine decanoate toxin testing. Interestingly, the blood sample tested negative for fluphenazine decanoate and its derivatives, and specific testing had to be applied to positively identify zuclopenthixol in the sample. This has legal, competition and sale implications for the identification of animals administered this drug as it would not be identified by routine drug screens during competition or pre-purchase examination. As diagnostic testing is limited, results were not available for several weeks; therefore, clinical signs were used to guide treatment in the absence of a confirmed diagnosis. The diagnosis of drug-induced extrapyramidal signs may have been hindered had further discussion not revealed the possibility of accidental administration of a sedative drug. The similarly formulated 1st generation antipsychotic fluphenazine decanoate has been banned by the Association of Racing Commissioners International, and liquid chromatography testing means that the drug is traceable for extended periods of time (Costello et al., 2013).

CONCLUSIONS

Information regarding recently administered medications when presented with a horse showing extrapyramidal neurological signs cannot be underestimated in enabling a precise treatment plan to be made. Prognosis for this colt, and for those reported in the literature that have been administered fluphenazine decanoate, was good (Baird et al., 2006). However, there are very limited reports; therefore, caution should be exercised when giving prognosis, especially if the horse has severe signs that make management difficult or dangerous. Administration of human antipsychotics to horses is not advised given the unpredictable nature of adverse extrapyramidal signs that may follow. Further information regarding the use of zuclopenthixol decanoate and other long-acting antipsychotic drugs is required in order to accurately assess its potential danger to equine patients. Zuclopenthixol testing should be considered when presented with a horse displaying extrapyramidal symptoms when other differential diagnoses have been excluded.

AUTHOR CONTRIBUTIONS

Alice Addis: Conceptualization; investigation; methodology; writing – original draft; writing – review and editing. **Victoria Savage:** Conceptualization; investigation; methodology; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

No conflicts of interest have been declared.

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ETHICS STATEMENT

Only treatment deemed appropriate at the time was used. Information regarding treatment was recorded for publishing retrospectively, no decisions were made regarding treatment on the basis of a paper being published.

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