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Equine Veterinary Education

CLINICAL COMMENTARY

Zuclopenthixol decanoate toxicity

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A psychopharmaceutical describes a drug that has an impact on the mental state of the user. These medications are often used preventively to modify the behavioural response to stress in ungulate prey species, for example, to facilitate transportation and/or introduction into a new area, group or herd. Zuclopenthixol is a long-acting neuroleptic (LAN) or antipsychotic agent that has been used to facilitate wildlife translocation in conservation projects. In human medicine, this drug is used to treat psychiatric disorders including schizophrenia and psychosis. It is a long-acting dopamine D1 and D2 receptor antagonist, with a duration of action of 3–4 days (acetate ester) up to 2–3 weeks (decanoate) in wild ungulates, depending on the pharmaceutical formulation (Swan, 1993; Read, 2002).

Our understanding of equine behaviour and in particular learning theory, has deepened over the past few years. We now recognise that most problematic behaviours can quickly be resolved with appropriate training (McLean & Christensen, 2017; Pearson, 2019) and this knowledge should markedly reduce the need for psychopharmaceutical use during the routine management of horses. Yet, as this knowledge is still not embedded into mainstream equestrianism, and considering we know most people overestimate their understanding of horse behaviour (Warren-Smith & McGreevy, 2008; Wentworth-Stanley, 2013; Pearson et al., 2020), psychopharmaceuticals remain an attractive option to many. Moreover, some problematic behaviours coincide with marked levels of emotions such as fear, which impairs a horse's ability to learn. By directly reducing fear, judicious psychopharmaceutical use may optimise retraining, improve welfare and maximise safety.

When it comes to pharmacological behavioural modification in horses, there is an intricate ethical balance between safely promoting equine welfare during stressful events versus the inherent risks of abuse. Antipsychotics like zuclopenthixol are also classified as neuroleptics or major tranquilisers, as they superficially appear to reduce agitation and have a resultant calming effect. This is why this class of drug has a high potential for abuse in equine sports. They have been denoted 'banned substances' by the Fédération Equestrian Internationale (FEI) as they are considered to have no legitimate use in equine medicine (FEI equine prohibited substance list, https://inside.fei.org/fei/cleansport/ad-h/prohibited-list), and they are likewise prohibited in horseracing (International Federation of Horseracing Authorities, International Agreement on Breeding, Racing and Wagering, 2018). A true anxiolytic reduces fear while allowing the animal to otherwise function normally, however, antipsychotics reduce motor activity and blunt all emotional responsiveness (Cromwell-Davies & Landsberg, 2018). As a consequence, they are contra-indicated as a stand-alone treatment in companion animal behavioural medicine where fear or anxiety is suspected (Cromwell-Davies & Landsberg, 2018; Pereira et al., 2024).

Zuclopenthixol first gained attention as a potential drug of abuse in equestrian sports when the gold medal showjumping horse Waterford Crystal tested positive for the drug after the 2004 Olympics in Rome, with samples sent to the official doping laboratory testing positive for both fluphenazine (a closely related antipsychotic drug) and zuclopenthixol. With antipsychotic use on the rise in humans globally, comprehensive assays based on LC/tandem MS have been developed for forensic and toxicology screening as well as for doping detection in equine samples (Wong et al., 2020).

It is known that through exposure and availability, racetrack workers and equestrian trainers are at increased risk of diversion and toxicity from self-ingestion of drugs (mis)used in equestrian sports (Newton & Rose, 1991; Sawalha et al., 2021). It is a less common occurrence perhaps for horses to be dosed with drugs acquired for human medical conditions, but the case reported here highlights that we must be vigilant of this possibility whenever a horse presents with unexplained behavioural signs, be it excitatory or aggressive behaviour, or excessive somnolence.

Zuclopenthixol toxicity in the horse has, to the authors' knowledge, not previously been described, although recent studies were

undertaken in Sweden to elucidate dynamics of zuclopenthixol acetate (a shorter acting zuclopenthixol, 1–3 days) in $n = 4$ healthy warmblood trotters. Two of the four horses in this study showed side effects at doses of 0.25, 0.5 and 1 mg/kg bwt and comprised extrapyramidal symptoms, muscle fasciculations, inappetence, aggressive behaviour, tachycardia, colic and submandibular oedema (Ödmark, 2016). These signs are very similar to those described by the authors of the case report in this edition of EVE. The dopaminergic system in horses and other ungulates is prominent and dopamine's involvement as a neuromediator in the basal ganglia is responsible for its complex effects on locomotor function, flight response, impulse control and mood.

Dopamine plays a key role in motivational salience, with increases signalling pleasure and satisfaction and reductions signalling fear or aversive stimuli (Wenzel et al., 2015). It is therefore fundamental in learning; dopamine release is upregulated through either positive reinforcement (increasing a behaviour through reward) or negative reinforcement (increasing behaviour through release of pressure)—in contrast, tonic dopamine release dips in response to punishment (suppressing a behavioural response) (McBride et al., 2017). When initially training a new response using negative reinforcement, an aversive stimulus (e.g. pulling on the reins) results in a dip in tonic dopamine release, this motivates the horse to try new behaviours to resolve the aversive stimulus. When the horse trials slowing down, the rider should release the pressure to reinforce the desired behaviour and this results in a dopamine surge. Over time, as learning occurs, the horse slows from light (non-aversive) pressure on the reins and this results in a dopamine spike without an initial reduction. This example demonstrates the importance to the animal of maintaining tonic baseline levels of dopamine activity, since when these dip, the animal is highly motivated to alter its behaviour to restore them. At the same time, they are also motivated to repeat behaviours that result in a dopamine surge, as this makes them feel good. Moreover, chronic dopamine depletion such as occurs with Parkinson's or PPID is associated with low mood states and behavioural depression. The intricate relationship between dopamine and how an animal might feel should be carefully considered when using dopamine antagonists.

Antipsychotics act as dopaminergic antagonists and, as discussed by Addis and Savage (2024), clearly have beneficial effects when used in wild animals to facilitate stressful events and where the risk of physical harm is high. Nonetheless, the reductions in stress as measured by cortisol may actually be secondary to a reduced flight response through inhibited motor activity rather than by actually promoting calmness. In companion animal behavioural medicine, it is accepted that dopamine antagonists have no anxiolytic properties, and instead block or attenuate motor responses without altering the sensory experience for the individual animal. As such, the animal may still experience fear but be less able to move away from it; as a consequence, they may become more fearful overtime. These drugs are therefore contraindicated for phobic states (Pereira et al., 2024). At the same time, they are recommended where the flight response is so intense it is likely to result in harm, and/or when combined with an anxiolytic (Cromwell-Davies & Landsberg, 2018). Horses are a domesticated species but have maintained a strong flight response. As a species, they can be considered to sit between wild ungulates and domesticated companion animals—so is there any justification for using antipsychotics in horses?

While the authors have no experience of zuclopenthixol decanoate or fluphenazine decanoate, all equine veterinarians will be familiar with the antipsychotic acepromazine, which has for a long time been used to manage horses in need of tranquilisation. Its use in equine anaesthesia, as part of premedication for general anaesthesia or to augment standing sedation (both combined with alpha-2 agonists and opioids) is commonplace, and in such protocols, it can help reduce excitability and smoothen recovery. For behavioural management, as a dopamine antagonist, acepromazine alone has no appreciable anxiolytic properties and it likely has a negative (depressive) impact on mood. Be that as it may, the reduction in spontaneous motor activity may provide safety benefits when used in horses that may otherwise injure themselves. Ideally, when horses are excessively fearful or anxious, an anxiolytic should be used in the first instance (e.g. trazodone, alprazolam or fluoxetine for longer-term use), and both authors have seen increased efficacy when acepromazine is combined with an anxiolytic. However, under some circumstances, such as horses competing under FEI rules, these agents are banned so cannot be used, and acepromazine may be the only option to keep a horse (and its handlers) safe.

The use of behaviour modifying drugs/psychopharmaceuticals can be well justified in individual cases of equine problematic behaviour, and/or horses subjected to highly stressful (medical) interventions, and it would be detrimental to consider any behavioural modifying drug to have no place in equine practice—in fact, many sedatives and anaesthetic agents can impact how an animal feels and are behaviour modifying. While such drugs have no place in competition or performance enhancement, it is the authors' personal experience and opinion that for individual horses showing problematic behaviours, a psychopharmaceutical, ideally alongside a behaviour modification programme, is beneficial and underutilised. As a result, fractious, fearful or frustrated horses needing to undergo veterinary procedures are more likely to be darted or tele immobilised and/or receive high dosages of alpha-2 agonists, (strong) opioids or ketamine, with higher risk of complications following sedation and anaesthesia. Prudent pretreatment with anxiolytics such as alprazolam or trazodone can be justified on an individual case-by-case basis and can greatly enhance welfare and safety of chemical restraint in extremely difficult horses. Be that as it may, it is difficult to justify their use for routine handling, especially as most procedures can be trained with minimal stress to the horse if using learning theory and modifying the training according to current emotional state.

Racing, and equestrianism generally, is already under pressure to maintain its social licence to operate, and a key component is transparency (Pearson et al., 2023). It is difficult to maintain that weaning, handling during sales preparation and the sales themselves are not stressful for horses, when the use of antipsychotic drugs, such as acepromazine, is commonplace. How would the general

public feel about this? Equine vets are well positioned to advise on the judicious use of psychopharmaceuticals where indicated for an individual case, and potentially also to support trainers in making changes to their management, increasing their knowledge of equine behaviour or seeking help from a clinical animal behaviourist as required (Doherty et al., 2017; Pearson, 2019; Wolframm et al., 2023). Ultimately, welfare represents how an animal feels, and so we have a responsibility to maximise positive emotional states and minimise negative ones.

AUTHOR CONTRIBUTIONS

Janny C. de Grauw: Conceptualization; data curation; writing – original draft. **Gemma Pearson:** Conceptualization; data curation; writing – original draft.

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CONFLICT OF INTEREST STATEMENT

No conflicts of interest have been declared.

ETHICS STATEMENT

Not applicable to this clinical commentary.

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