A review of clinical approaches to antagonism of alpha2-adrenoceptor agonists in the horse

G. E. Zeiler

Department of Companion Animal Clinical Studies, Faculty of Veterinary Science, University of Pretoria, Onderstepoort, South Africa.
Corresponding author email: gareth.zeiler@up.ac.za

Keywords: horse; α2-adrenoceptor antagonist; atipamezole; tolazoline; yohimbine

Summary
Alpha2-adrenoceptor agonists xylazine, romifidine, detomidine and, in some cases, medetomidine and dexmedetomidine, are fundamental drugs used in equine practice. There are situations where the undesirable pharmacodynamic effects (ataxia, prolonged sedation, bradycardia and ileus) or accidental overdose of these drugs may need to be antagonised. The α2-adrenoceptor antagonists tolazoline, yohimbine and atipamezole can be used to antagonise undesirable effects. However, despite being effective, α2-adrenoceptor antagonists are also not without undesirable pharmacodynamic effects. Excitement, muscle trembling and triggered inappropriate stress responses are a few of the more serious undesirable effects. Horses demonstrate a variable response to the antagonists thus recommending dose rates become fraught with difficulty. It is therefore recommended that the α2-adrenoceptor antagonist should be titrated to the desired clinical effect. Consequently, other reversal agents, such as anticholinergics (atropine, glycopyrrolate and hyoscine), have been administered for the treatment of α2-adrenoceptor agonist-induced bradycardia. Anticholinergics cannot be recommended for routine use in horses due to the undesirable cardiovascular effects and potentiation of α2-adrenoceptor agonist-induced gastrointestinal hypomotility. Novel peripheral acting α2-adrenoceptor antagonists, such as MK-467, are currently under scrutiny in veterinary anaesthesia in an effort to antagonise the undesirable effects of α2-adrenoceptor agonists without compromising on the level of sedation. This review examines the current literature on the α2-adrenoceptor antagonists used in horses and makes recommendations on how to use these drugs safely in an attempt to prevent undesirable pharmacodynamic effects.

Clinical use and pharmacodynamic effects of α2-adrenoceptor agonists
The most reliable sedative drugs currently licensed for use in horses are α2-agonists. Other beneficial effects of these drugs include analgesia, muscle relaxation, reduction of induction and maintenance anaesthetic drug requirements and attenuation of the stress response to pain and surgery (England and Clarke 1996). Also, α2-agonists are used for sedation of horses during transport, as part of preanaesthetic medication for enabling both surgical and nonsurgical standing procedures and as components of analgesic protocols (Vigani and Garcia-Pereira 2014). The beneficial effects of these drugs are mostly due to the interaction with various subtypes of α1 and α2-adrenoceptors found in the central and peripheral nervous system (Knaus et al. 2007). The α1-adrenoceptors are distributed at pre- and post synaptic sites within the sympathetic neuro-effector junctions of many organs (Fig 1). Despite the numerous useful qualities of these drugs there are many undesirable clinical effects that may warrant reversal. Bradycardia, ileus and prolonged sedation associated with ataxia are arguably the more common undesirable clinical effects of α2-agonists.

Administration of α2-agonists results in activation of peripheral receptors (α1 and α2B) on the blood vessels leading to profound vasoconstriction (Knaus et al. 2007). Considering the physiological equation for blood pressure, where blood pressure is equal to cardiac output multiplied by systemic vascular resistance, α2-agonist triggered rise in systemic vascular resistance (due to vasoconstriction) causes an increase in blood pressure. Cardiac output is equal to ventricular stroke volume multiplied by heart rate. The physiological mechanism of countering the pronounced increase in blood pressure is to decrease the heart rate via a baroreceptor mediated stimulation of the vagal (cranial nerve X; parasympathetic) nerve. This is considered as the initial physiological mechanism for the bradycardia associated with α2-agonists. However, once an α2-agonist crosses the blood brain barrier, it is thought to suppress the cardiovascular centre through presynaptic inhibition of norepinephrine release. Furthermore, sympathetic tone is also reduced peripherally following the presynaptic inhibition of norepinephrine release (Knaus et al. 2007). Thus the bradycardia can persist due to central effects, despite the waning of the profound peripheral vasoconstriction and hypertension. What is important to consider is the bradycardia-induced decrease in cardiac
output of up to 40% (England and Clarke 1996). Systemic blood pressure is not a reliable indicator of cardiac output thus, despite an often normal or hypertensive systemic blood pressure, there is a decrease in the volume of blood being circulated every minute resulting in less tissue perfusion and oxygenation. The bradycardia may be associated with conduction blocks such as second degree atrioventricular (most common) and sinoatrial blocks (England and Clarke 1996).

Alpha2-agonists decrease intestinal motility by peripheral relaxation of the intestine by inhibiting phasic and tonic motor activity, which could perpetuate ileus. This inhibited activity may be associated with stimulation of presynaptic α2-adrenoceptors which cause a reduction in acetylcholine release from post ganglionic parasympathetic (vagal nerve terminals) neuro-effector junctions (Roger and Ruckebusch 1987). The visceral analgesic effects of these drugs have been shown to be better than opioid and nonsteroidal anti-inflammatory drugs (Jöchle et al. 1989). As such, α2-agonists are excellent analgesics in colic horses, especially those suffering spasmodic intestinal movement disorders. Other mechanisms for decreased motility such as profound vasocostriction of the lateral caecal artery, which decreases blood supply to this part of the gastrointestinal tract causing local decreased motility, have been described (Rutkowski et al. 1991). The 4 α2-agonists commonly used in the horse tend to decrease motility in different segments of the gastrointestinal tract, as follows: detomidine tends to decrease gastric emptying (Sutton et al. 2002) and duodenal motility (Merritt et al. 1998) more than xylazine: xylazine decreases jejunal and pelvic flexure motility (Adams et al. 1984) and romifidine decreases small intestinal, caecum and left ventral colon motility (Freeman and England 2001). Medetomidine has not been investigated in horses; however, in the dog it decreases gastric and duodenal motility (Nakamura et al. 1997). The clinical significance of this phenomenon warrants further investigation in horses.

The sedative effects of α2-agonists are mediated through interaction with α2-adrenoceptors in the locus coeruleus neurons in the pons of the lower brain stem (England and Clarke 1996). The sedative effects are often associated with ataxia. The depth and duration of the sedative effects are both dose and individual horse related. Draught horse breeds are more sensitive to the sedative effects compared to Thoroughbred and Arab horse breeds. Isometric dosing (dosing according to bodyweight) is most likely responsible for the increased perception of sensitivity in draught horse breeds, thus allometric scaling (dosing according to body surface area) should be used to avoid this effect (Sharma and McNeill 2009). Romifidine causes less ataxia compared to the other licensed α2-agonists (England et al. 1992). Medetomidine, administered at an equipotent xylazine dose, should be used with caution as it causes more ataxia and may cause the horse to collapse (Bryant et al. 1991). This is especially true if opioids are administered concurrently.

Less clinically significant undesirable effects of α2-agonists include hyperglycaemia, diuresis, increased uterine tone, sweating, muscle tremors, hypersalivation, penile protrusion (England and Clarke 1996) and tachypnoea in pyrexic horses (Kendall et al. 2010). These effects are important considerations to bear in mind but may not warrant reversal.

Reversal of undesirable effects of α2-adrenoceptor agonists
The decision to reverse the undesirable effects of α2-agonists could be based on an emergency situation, such as a horse collapsing or accidental overdose or on non-emergency clinically relevant situations such as a need to decrease the degree of ataxia. Selection of an appropriate antagonist or reversal drug may prevent undue complications such as excitement or poor cardiovascular performance. Dosages of the α2-antagonists described in the text are highlighted in Table 1.

Alpha2-adrenoceptor antagonists
Tolazoline, yohimbine and atipamezole (both central and peripheral acting α2-antagonists) are available in most countries and have been used to antagonise the α2-agonists in horses (Knych and Stanley 2014). Only tolazoline has been approved by the Food and Drug Administration (FDA) in the United States of America for reversal of xylazine effects in horses (Casbeer and Knych 2013). Yohimbine is classified as a Class 2 foreign substance by the Association of Racing Commissioners International (ARCI) (DiMaio Knych et al. 2011a). These pointers are important examples of legal considerations the veterinarian should keep in mind when considering administration of an α2-antagonist to a horse. Veterinarians are encouraged to review the legal aspects of drug administration and rules set down by various associations regulating equine related competitions within their country of practice. Despite the highly prevalent off-label use of α2-antagonists in horses, there is a growing body of evidence to demystify their clinical effects as observed in horses.

Tolazoline is a synthetic imidazoline derivative that antagonises α-adrenoceptors nonselectively (Casbeer and
TABLE 1: Summary of α2-adrenoceptor agonist and antagonist doses used in horses, ponies and donkeys

<table>
<thead>
<tr>
<th>α2-adrenoceptor agonist (dose, route)</th>
<th>α2-adrenoceptor antagonist (dose, route)</th>
<th>Reference</th>
<th>Clinical notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>Tolazoline (4 mg/kg bwt i.v.)</td>
<td>Casbeer and Knych (2013)</td>
<td>No change in HHAG; decreased HR, increased AV-B, blood glucose and PCV suggest increased sympathetic stimulation or attenuation of sympathetic inhibition; normal faeces passed</td>
</tr>
<tr>
<td>-</td>
<td>Yohimbine (0.12 mg/kg bwt i.v.)</td>
<td>DiMaio Kynch et al. (2011a)</td>
<td>2 of 8 horses showed signs of sedation; main metabolite hydroxy-yohimbine was detected in urine 96 h post administration suggesting a prolonged withdrawal time is necessary in competing racehorses. Behaviour response consistent in individual horses regardless of dose administered; however, behaviour response (either sedation, excitement or unaffected) was highly variable between horses; muscle fasciculation at doses 0.2 mg/kg bwt and higher; more sensitive to environmental stimulation at all doses; HR increased (tachycardia); PCV and glucose levels unchanged to baseline; dose-dependent increased barbarym</td>
</tr>
<tr>
<td>-</td>
<td>Yohimbine (0.1, 0.2 and 0.4 mg/kg bwt i.v.)</td>
<td>DiMaio Kynch et al. (2011b)</td>
<td></td>
</tr>
<tr>
<td>Detomidine (0.01 and 0.02 mg/kg bwt i.v.)</td>
<td>Atipamezole (6-, 8-, and 10-fold detomidine dose)</td>
<td>Ramseyer et al. (1998)</td>
<td>Ti: 15 min. Atipamezole administered at 0.1 or 0.16 mg/kg bwt is adequate to transiently reverse detomidine-induced moderate and profound sedation, respectively; ataxia was resolved in all horses</td>
</tr>
<tr>
<td>Detomidine (0.02 mg/kg bwt i.v.)</td>
<td>Tolazoline (4 mg/kg bwt i.v.)</td>
<td>Matthews et al. (1995)</td>
<td>Ti: 20 min. Tolazoline transiently increased HR in isoflurane-anaesthetised ponies. A decrease in arterial partial pressure of oxygen reported</td>
</tr>
<tr>
<td>Detomidine (0.03 mg/kg bwt i.v.)</td>
<td>Tolazoline (4 mg/kg bwt i.v.); Atipamezole (0.05 and 0.1 mg/kg bwt i.v.)</td>
<td>Hubbell and Muir (2006)</td>
<td>Ti: 25 min. Single bolus of tolazoline or atipamezole produced partial reversal of detomidine-induced sedation. Tolazoline, but not atipamezole hastened recovery</td>
</tr>
<tr>
<td>Detomidine (0.04 mg/kg bwt i.v.)</td>
<td>Tolazoline (4 mg/kg bwt i.v.)</td>
<td>Carroll et al. (1997)</td>
<td>Ti: 20 min. Tolazoline reversed detomidine-induced sedation and analgesia in ponies; tolazoline precipitated a systemic stress response in all ponies which suggests caution when reversing painful patients; sweating was noted in all treated ponies</td>
</tr>
<tr>
<td>Detomidine (0.04 mg/kg bwt SL)</td>
<td>Tolazoline (4 mg/kg bwt i.v.); Yohimbine (0.075 mg/kg bwt i.v.); Atipamezole (0.12 mg/kg bwt i.v.)</td>
<td>Knych and Stanley (2014)</td>
<td>Ti: 15 min. Detomidine was effective in transiently reversing detomidine-induced sedation, bradycardia, AV-B and hyperglycaemia</td>
</tr>
<tr>
<td>Detomidine (0.01 mg/kg bwt i.v.)</td>
<td>Atipamezole (6-, 8-, and 10-fold detomidine dose)</td>
<td>Roekalla et al. (1990)</td>
<td>Ti: 15 min. Atipamezole transiently reversed detomidine-induced bradycardia without overt undesirable effects</td>
</tr>
<tr>
<td>Xylazine (bolus 1 mg/kg bwt i.v., followed by 0.72 mg/kg bwt/h CR1)</td>
<td>Average doses required to reverse sedation: Yohimbine (0.12 mg/kg bwt i.v.); Tolazoline (7.5 mg/kg bwt)</td>
<td>Kollias-Baker et al. (1993)</td>
<td>Ti: 60 min after start of infusion. Yohimbine and tolazoline successfully antagonised the xylazine-induced bradycardia and sedation in horses. Yohimbine administration demonstrated agitation, muscle tremors and mild excitement, while tolazoline did not produce partial reversal of detomidine-induced sedation, analgesia, ataxia and bradycardia in donkeys</td>
</tr>
<tr>
<td>Xylazine (1.0 mg/kg bwt i.v.)</td>
<td>Atipamezole (0.15 mg/kg bwt i.v.)</td>
<td>Luna et al. (1992)</td>
<td>Ti: 15 min. Atipamezole shortened the recovery time, improved respiratory depression and ataxia post xylazine bolus. No undesirable pharmacodynamics effects were noted</td>
</tr>
<tr>
<td>Medetomidine (bolus 0.005 mg/kg bwt i.v., followed by 0.0035 mg/kg bwt/h CR1)</td>
<td>Atipamezole (0.06 mg/kg bwt i.v.)</td>
<td>Bettschert-Wolfensberger et al. (1999)</td>
<td>Ti: 5 min post infusion. Atipamezole promptly reversed medetomidine-induced sedation without causing stimulation</td>
</tr>
<tr>
<td>Medetomidine (0.01 mg/kg bwt i.v.)</td>
<td>Atipamezole (0.02, 0.04, 0.06 and 0.1 mg/kg bwt i.v.)</td>
<td>Yamashita et al. (1996)</td>
<td>Ti: 15 min. Atipamezole should be bolused at 0.06-0.08 mg/kg bwt i.v. to antagonise medetomidine-induced sedation</td>
</tr>
</tbody>
</table>

mg/kg = milligrams per kilogram; bwt = bwt; i.v. = intravenous; i.m. = intramuscular; SL = sublingual; HHAG = head-height-above-ground measurement; HR = heart rate; AV-B = atrioventricular block; PCV = packed cell volume; CRI = constant rate infusion; Ti = time interval between agonists and antagonist administration.
Knych 2013) and possesses histaminergic and cholinergic effects (El-Kammar and Gad 2014). Tolazoline administered i.v. at 4 mg/kg bwt alone has the following pharmacokinetic profile: systemic clearance, steady state volume of distribution and terminal elimination half-life of 0.82 ± 0.18 l/h/kg, 1.68 ± 0.38 l/kg and 2.69 ± 0.21 h, respectively (Casbeer and Knych 2013). The pharmacodynamic profile when tolazoline is administered alone demonstrates minimal behavioural responses; a decreased heart rate (most likely due to the increased sympathetic tone raising blood pressure and stimulating a baroreceptor mediated increase in vagal tone) with second degree atrioventricular blocks; an increase in blood glucose level and packed cell volume (increased sympathetic tone causing splenic contraction) and unchanged head-height-above-ground (measurement used to determine the level of sedation in horses) compared to baseline readings (Casbeer and Knych 2013). Tolazoline, in isoflurane-anaesthetised (Matthews et al. 1995) or awake sedated ponies (Carroll et al. 1997), is effective in transiently antagonising detomidine-induced bradycardia without inducing arrhythmias or significant alterations to blood pressure. However, Matthews et al. (1995) reported a significant decrease in the arterial partial pressure of oxygen; thus this must be considered when reversing detomidine-induced bradycardia with tolazoline in isoflurane-anaesthetised patients. Detomidine-induced sedation (assessed by measuring head-height-above-ground that returns to baseline readings) is effectively antagonised with tolazoline (Carroll et al. 1997). Transient sweating, hypersalivation and gingival hyperaemia may be noticed without overt signs of excitement. Blood glucose, cortisol and free fatty acid levels increase after administering tolazoline which suggests activation of a stress response. This is a clinically significant finding and antagonism of an α2-agonist with tolazoline may perpetuate an inappropriate stress response in horses that have undergone a surgical procedure or are in pain for some other reason (Carroll et al. 1997). Stress, in the presence of pain, could culminate in a distressed patient which causes significant metabolic derangements not conducive to convalescence (Gaynor and Muir 2009).

Yohimbine is an indole alkaloid derived from several biological sources (bark of the Pausinystalia yohimbe tree and root of the Rauwolfia serpentina plant) that nonselectively antagonises α-adrenoceptors in the horse (DiMaio Knych et al. 2011a,b). Yohimbine has been shown at high doses to activate other receptor types including α1-adrenoceptors, dopamine and serotonin receptors and to inhibit monoamine oxidase (DiMaio Knych et al. 2011b). Yohimbine administered at 0.12 mg/kg bwt i.v. alone has the following pharmacokinetic profile: systemic clearance, steady state volume of distribution and terminal elimination half-life of 13.6 ± 2.0 ml/min/kg, 3.2 ± 1.1 l/kg and 4.4 ± 0.9 h, respectively, for a 2 compartment model (DiMaio Knych et al. 2011a). Higher i.v. doses of yohimbine (0.2 and 0.4 mg/kg bwt) are associated with an increase in the plasma concentration that decreases in a dose-dependent manner, an increased volume of distribution and slower clearance. The elimination half-life remains consistent (DiMaio Knych et al. 2011b). Detomidine increases the plasma concentration and decreases the clearance and volume of distribution of yohimbine (Knych et al. 2012). This is clinically significant especially in racehorses where yohimbine is listed as an ARCI Class 2 foreign substance (DiMaio Knych et al. 2011a); veterinarians would need to allow longer withdrawal periods. Pharmacodynamic effects of yohimbine alone are highly variable among horses, regardless of the dose administered (DiMaio Knych et al. 2011b). Sedation or excitation (some horses may demonstrate rearing, striking, running in circles, generalised muscle tremors, agitation and exaggerated but mild excitement in horses exposed to sudden environmental stimulation) are typical pharmacodynamic effects that can be expected and usually resolve within 1–2 h after yohimbine administration (DiMaio Knych et al. 2011b). Transient cardiovascular and gastrointestinal effects such as an increase in heart rate with disappearance of atrioventricular blocks and an increase in borborygmi, respectively, may be present post yohimbine administration (DiMaio Knych et al. 2011b), Yohimbine antagonism of detomidine has been studied in horses (DiMaio Knych et al. 2012). Yohimbine is effective in antagonising detomidine-induced sedation, bradycardia and atrioventricular blocks. However, the pharmacodynamic response is variable among horses which include transient (approximately 10 min) vocalisation, increased arousal and return to normoglycaemia after detomidine-induced hyperglycaemia (DiMaio Knych et al. 2012).

There is no therapeutic indication or justification to use tolazoline (Casbeer and Kynch 2013) or yohimbine (DiMaio Knych et al. 2011b) as a sole agent to treat unsedated horses, due to their unpredictable pharmacodynamic effects.

Atipamezole is a potent, highly selective α2-adrenoceptor antagonist (Ramseyer et al. 1998). There is a lack of pharmacokinetic and pharmacodynamics studies based on atipamezole administered alone in horses. Atipamezole antagonism of detomidine-induced sedation (Ramseyer et al. 1998) and bradycardia (Raekallio et al. 1990) have been studied in horses. Atipamezole results in satisfactory but incomplete reversal of detomidine-induced sedation (Raekallio et al. 1990; Ramseyer et al. 1998). However, the level of ataxia is reduced significantly which allows the horse to ambulate properly (Ramseyer et al. 1998). Atipamezole demonstrates a dose dependant increase in undesirable effects such as sweating, hyperexcitability in horses subjected to external stimuli and head shaking that tended to resolve within 10–15 min of injection in detomidine treated horses. Visual signs of arousal are apparent within 2 min of i.v. administration (Ramseyer et al. 1998). Atipamezole transiently antagonises detomidine-induced bradycardia, decreases the frequency of atrioventricular blocks and normalises the arterial blood pressure (Raekallio et al. 1990). Atipamezole effectively antagonises medetomidine constant rate infusion-induced sedation without causing untoward excitement. However, within 2 min of injection, the horse or pony should raise their head, become alert and may even demonstrate signs of shivering and intolerance to surgical drapes or physiological parameter (electrocardiogram leads, noninvasive blood pressure cuffs, etc) monitoring instrumentation (Bettchart-Wolffensberger et al. 1999). Atipamezole also antagonises medetomidine (Yamashita et al. 1996) or xylazine (Luna et al. 1992) induced sedation after a single i.v. bolus with no apparent undesirable effects.

Two or more α2-adrenoceptor antagonists have been compared in a single study to antagonise α2-agonists. The antagonistic properties of tolazoline and atipamezole have been compared in detomidine-sedated horses (Hubbell and Muir 2006) and donkeys (El-Kammar and Gad 2014). Both agents produce partial antagonism of detomidine-induced
sédation et bradycardie. Cependant, tolazoline antagonise les effets bradycardiques du detomidine de manière complète et rapide, tandis que l’administration simultanée de tolazoline et de yohimbine renforce l’effet bradycardique. L’administration de yohimbine à des doses égales ou plus faibles que celles utilisées pour antagoniser le detomidine, dans la mesure du possible, est une alternative à l’atropine. L’administration de yohimbine est associée à une diminution de la pression sanguine artérielle moyenne (mean arterial pressure, MAP) de 5 à 8 mmHg, par rapport à l’administra…
yohimbine, in comparison to atipamezole and tolazoline, in that order.

3) Tolazoline appears to activate a systemic stress response which should be taken into consideration if antagonising a painful \( \alpha_2 \)-agonist sedated horse.

4) Yohimbine appears to cause more pronounced transient excitement in comparison to atipamezole and tolazoline, in that order.

5) Atipamezole is the shortest acting and tends to completely or partially antagonise medetomidine- or detomidine-induced sedation, respectively. It is considered a good choice to antagonise \( \alpha_2 \)-agonist-induced bradycardia.

6) The end point of \( \alpha_2 \)-agonist-induced sedation antagonism should be when the horse can move freely without ataxia. This is because the complete antagonism (return of head-height-above-ground measurement) tends to be transient for all \( \alpha_2 \)-agonists.

7) The analgesic properties of the \( \alpha_2 \)-agonists may be antagonised and should be a consideration in patients that are painful or who have undergone a surgical procedure. Nonsteroidal anti-inflammatory and/or opioid drugs should be included in the analgesic management protocol of these patients. However, the \( \alpha_2 \)-agonists may also antagonise opioid based analgesia that is dependent upon spinal adrenergic pathways (Morales et al. 2001).

8) Anticholinergic drugs should only be reserved for emergency reversal of \( \alpha_2 \)-agonist-induced bradycardia in the presence of hypotension. Hyoscine, compared to atropine or glycopyrrolate, may be more appropriate as it does not potentiate \( \alpha_2 \)-agonist-induced gastrointestinal hypomotility.

A case report by Di Concetto et al. (2007) highlights the importance of titration of an \( \alpha_2 \)-antagonist to clinical effect. They described atipamezole reversal of a detomidine (300 \( \mu \)g/kg bwt in total) overdose in a pony. The atipamezole dose was titrated until the desired clinical effect (pony standing) and they did not notice any undesirable clinical effects of atipamezole. The total dose administered was 3.9 times greater than the detomidine total dose (Di Concetto et al. 2007). The recommended dose in horses is 5–10 times the detomidine dose (Roekallo et al. 1990; Ramseyer et al. 1998), which in this case would have been unnecessary.

**Conclusion**

This review examined the current literature regarding \( \alpha_2 \)-adrenoceptor antagonists tolazoline, yohimbine and atipamezole in horses. Horses appear to be sensitive to the undesirable pharmacodynamic effects of the antagonists and demonstrate excitement, sweating, muscle trembling and inappropriate stress response, to name but a few. Current antagonist dose recommendations tend to be larger than clinically necessary. Horses tend to demonstrate variable responses to the different antagonists. Thus, these agents should ideally be titrated to clinical effect to avoid the undesirable effects. A peripheral acting \( \alpha_2 \)-adrenoceptor antagonist, MK-467, has demonstrated promising results in antagonising undesirable \( \alpha_2 \)-adrenoceptor agonist-induced bradycardia and ileus while unafflicting the quality of sedation. It is evident from the review that further clinically-orientated research is warranted to improve our understanding of \( \alpha_2 \)-adrenoceptor antagonism in horses.

**Author's declaration of interests**

No conflicts of interest have been declared.

**Acknowledgements**

The author would like to express thanks and appreciation to the reviewers for their guidance and assistance in improving this review article.

**References**


