A review of clinical approaches to antagonism of alpha2-adrenoreceptor 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

Summary
Alpha$_2$-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 α_2-adrenoceptor antagonists tolazoline, yohimbine and atipamezole can be used to antagonise undesirable effects. However, despite being effective, α_2-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 α_2-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 α_2-adrenoceptor agonist-induced bradycardia. Anticholinergics cannot be recommended for routine use in horses due to the undesirable cardiovascular effects and potentiation of α_2-adrenoceptor agonist-induced gastrointestinal hypomotility. Novel peripheral acting α_2-adrenoceptor antagonists, such as MK-467, are currently under scrutiny in veterinary anaesthesia in an effort to antagonise the undesirable effects of α_2-adrenoceptor agonists without compromising on the level of sedation. This review examines the current literature on the α_2-adrenoceptor antagonists used in horses and makes recommendations on how to use these drugs safely in an attempt to prevent undesirable pharmacodynamic effects.

Introduction

Alpha$_2$-adrenoceptor agonists (xylazine, romifidine, detomidine, medetomidine and dexmedetomidine) are clinically important drugs used in equine veterinary medicine. Xylazine, romifidine and detomidine are licensed for equine use in most countries. However, medetomidine (England and Clarke 1996) and dexmedetomidine (Bettschart-Wolfensberger *et al*. 2005; Marcilla *et al*. 2012) have also been administered to horses and ponies despite not being licensed for use. In most cases the package inserts do not provide information on how to antagonise or reverse the pharmacodynamic effects of these drugs in horses and ponies. This review will focus on the α_2-antagonists (tolazoline, yohimbine and atipamezole) and other drugs that can be considered to reverse undesirable α_2-agonist effects. An outline of a clinical approach for safe use of these antagonists is also provided.

Clinical use and pharmacodynamic effects of α_2-adrenoceptor agonists

The most reliable sedative drugs currently licensed for use in horses are α_2-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, α_2-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 α_1 and α_2-adrenoceptors found in the central and peripheral nervous system (Knaus *et al*. 2007). The α-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 α_2-agonists.

Administration of α_2-agonists results in activation of peripheral receptors (α_1 and α_{2B}) 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, α_2-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 α_2-agonists. However, once an α_2-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
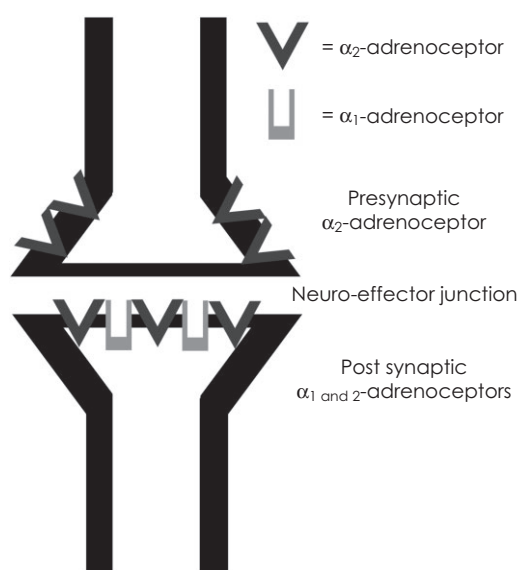
= α_2-adrenoceptor

= α_1-adrenoceptor

Presynaptic
α_2-adrenoceptor

Neuro-effector junction

Post synaptic
$\alpha_{1 \text{ and } 2}$-adrenoceptors

Fig 1: The distribution of pre- and post synaptic α-adrenoceptors within the neuroeffector junction of sympathetically innervated organs. Presynaptic α_2-adrenoceptor activation causes inhibition of norepinephrine and epinephrine release, vasodilation and gastrointestinal hypomotility. Post synaptic α_1-adrenoceptor activation causes profound vasoconstriction. Post synaptic α_2-adrenoceptor activation causes sedation, analgesia, anxiolysis, vasoconstriction and inhibition of insulin release.

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 α_2-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, α_2-agonists are excellent analgesics in colic horses, especially those suffering spasmodic intestinal movement disorders. Other mechanisms for decreased motility such as profound vasoconstriction 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 α_2-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 duodenum motility (Merritt *et al.* 1998) more than xylazine; xylazine decreases jejunum 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 α_2-agonists are mediated through interaction with α_2-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 α_2-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 α_2-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 α_2-adrenoceptor agonists

The decision to reverse the undesirable effects of α_2-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 α_2-antagonists described in the text are highlighted in **Table 1**.

Alpha2-adrenoceptor antagonists
Tolazoline, yohimbine and atipamezole (both central and peripheral acting α_2-antagonists) are available in most countries and have been used to antagonise the α_2-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 α_2-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 α_2-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

α₂-adrenoceptor agonist (dose, route)	α₂-adrenoceptor antagonist (dose, route)	Reference	Clinical notes
-	Tolazoline (4 mg/kg bwt i.v.)	Casbeer and Knych (2013)	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
-	Yohimbine (0.12 mg/kg bwt i.v.)	DiMaio Kynch et al. (2011a)	2 of 8 horses showed signs of sedation; main metabolite hydroxyl-yohimbine was detected in urine 96 h post administration suggesting a prolonged withdrawal time is necessary in competing racehorses
-	Yohimbine (0.1, 0.2 and 0.4 mg/kg bwt i.v.)	DiMaio Kynch et al. (2011b)	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 borborygmi
Detomidine (0.01 and 0.02 mg/kg bwt i.v.)	Atipamezole (6-, 8-, and 10-fold detomidine dose)	Ramseyer et al. (1998)	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
Detomidine (0.02 mg/kg bwt i.v.)	Tolazoline (4 mg/kg bwt i.v.)	Matthews et al. (1995)	TI: 20 min. Tolazoline transiently increased HR in isoflurane-anaesthetised ponies. A decrease in arterial partial pressure of oxygen reported
	Tolazoline (4 mg/kg bwt i.v.); Atipamezole (0.05 and 0.1 mg/kg bwt i.v.)	Hubbell and Muir (2006)	TI: 25 min. Single bolus of tolazoline or atipamezole produced partial reversal of detomidine-induced sedation. Tolazoline, but not atipamezole hastened recovery
	Atipamezole (0.1 mg/kg bwt i.v.)	Raekallio et al. (1990)	TI: 15 min. Atipamezole transiently reversed detomidine-induced bradycardia without overt undesirable effects
Detomidine (0.03 mg/kg bwt i.v.)	Yohimbine (0.2 mg/kg bwt i.v.)	Knych et al. (2012)	TI: 15 min. Detomidine increased yohimbine plasma concentration, decreased the volume of distribution and clearance thus affecting withdrawal time
	Yohimbine (0.2 mg/kg bwt i.v.)	DiMaio Knych et al. (2012)	TI: 15 min. Yohimbine was effective in transiently reversing detomidine-induced sedation, bradycardia, AV-B and hyperglycaemia
Detomidine (0.04 mg/kg bwt i.v.)	Tolazoline (4 mg/kg bwt i.v.)	Carroll et al. (1997)	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
	Tolazoline (4 mg/kg bwt i.v.); Atipamezole (0.4 mg/kg, i.v.)	El-Kammar and Gad (2014)	TI: 15 min. Tolazoline was more effective than atipamezole in reversing detomidine-induced sedation, analgesia, ataxia and bradycardia in donkeys
Detomidine (0.04 mg/kg bwt SL)	Tolazoline (4 mg/kg bwt i.v.); Yohimbine (0.075 mg/kg bwt i.v.); Atipamezole (0.12 mg/kg bwt i.v.)	Knych and Stanley (2014)	TI: 60 min. Yohimbine, tolazoline and atipamezole transiently reversed the detomidine-induced sedation and bradycardia
Detomidine (0.01 mg/kg bwt i.v.)	MK-467 (0.25 mg/kg bwt i.v.)	Vainionpää et al. (2013)	TI: administered at same time. MK-467 prevented detomidine-induced bradycardia and gastrointestinal hypomotility without compromising on the level of sedation
Xylazine (bolus 1 mg/kg bwt i.v., followed by 0.72 mg/kg bwt/h CRI)	Average doses required to reverse sedation: Yohimbine (0.12 mg/kg bwt i.v.); Tolazoline (7.5 mg/kg bwt)	Kollias-Baker et al. (1993)	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
Xylazine (1.0 mg/kg bwt i.v.)	Atipamezole (0.15 mg/kg bwt i.v.)	Luna et al. (1992)	TI: 15 min. Atipamezole shortened the recovery time, improved respiratory depression and ataxia post xylazine bolus. No undesirable pharmacodynamics effects were noted
Medetomidine (bolus 0.005 mg/kg bwt i.v., followed by 0.0035 mg/kg bwt/h CRI)	Atipamezole (0.06 mg/kg bwt i.v.)	Bettschart-Wolfensberger et al. (1999)	TI: 5 min post infusion. Atipamezole promptly reversed medetomidine-induced sedation without causing stimulation
Medetomidine (0.01 mg/kg bwt i.v.)	Atipamezole (0.02, 0.04, 0.06, 0.08 and 0.1 mg/kg bwt i.v.)	Yamashita et al. (1996)	TI: 15 min. Atipamezole should be bolused at 0.06–0.08 mg/kg bwt i.v. to antagonise medetomidine-induced sedation

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 treatment.

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 α_2-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 α_1-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 excitation 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 Knych 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 α_2-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 (Bettschart-Wolfensberger *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 α_2-adrenoceptor antagonists have been compared in a single study to antagonise α_2-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

sedation and bradycardia. However, tolazoline antagonises detomidine-induced sedation more completely and hastens recovery compared to atipamezole. The clinical effects of tolazoline last longer compared to atipamezole in detomidine treated horses (Hubbell and Muir 2006; El-Kammar and Gad 2014). Apprehension may be anticipated in tolazoline-treated horses while atipamezole does not seem to demonstrate this clinical effect (Hubbell and Muir 2006). Knych and Stanley (2014) have recently reported on the antagonistic effects of tolazoline, yohimbine and atipamezole on sublingually administered detomidine. Yohimbine, but neither tolazoline nor atipamezole, is able to completely return the head-height-above-ground measurements, despite the effect being short-lived (5 min). Yohimbine transiently antagonises detomidine-induced bradycardia to baseline values (predetomidine administration), while tolazoline demonstrates a slight transient increase in heart rate above baseline values. Atipamezole mildly increases the heart rate without returning it to baseline. Tolazoline increased the packed cell volume, unlike yohimbine and atipamezole which had no effect on it. The detomidine-induced hyperglycaemia is antagonised by yohimbine (return to baseline values), worsened by tolazoline (increase in hyperglycaemia) and atipamezole demonstrates no effect on blood glucose level (Knych and Stanley 2014). The antagonistic properties of tolazoline and yohimbine have been compared in xylazine sedated horses (Kollias-Baker et al. 1993). Yohimbine and tolazoline successfully antagonise xylazine-induced bradycardia and sedation. However, yohimbine has a quicker onset and shorter duration of action compared with tolazoline. Yohimbine is also associated with tremors, agitation and excitement, while tolazoline does not demonstrate these behavioural signs in xylazine treated horses. Tolazoline results in a normalisation of the heart rate to baseline readings but is associated with systemic hypertension in the presence of xylazine-induced bradycardia (Kollias-Baker et al. 1993).

A novel peripheral α_2-adrenoceptor antagonist known as MK-467 (previously L-659'066) has been studied on detomidine sedated horses (Vainionpää et al. 2013). MK-467 prevents detomidine-induced bradycardia and gastrointestinal hypomotility without affecting the quality of sedation. In dogs, MK-467 has been investigated more comprehensively and demonstrates cardiovascular sparing effects without compromising on the level of sedation or general anaesthesia (Honkavaara et al. 2011; Rolfe et al. 2012; Salla et al. 2014). Dexmedetomidine induced alterations in glucose, insulin, free fatty acids and lactate levels are attenuated by MK-467 (Restitutti et al. 2012).

Other pharmacological drug interventions

The α_2-agonist-induced bradycardia and intestinal hypomotility can be partially or completely reversed using drugs other than the α_2-antagonists. In the past, bradycardia was reversed with traditional anticholinergic drugs (atropine and glycopyrrolate). However, these drugs decrease gastrointestinal motility even further which may contribute to ileus and are thus not recommended for routine use (Pimenta et al. 2011; Perotta et al. 2014). Their use may still be valuable in emergency reversal of profound bradycardia (<24 beats/min) in association with hypotension (mean arterial pressure <60–65 mmHg). Hyoscine-N-butylbromide (hyoscine), a nontraditional anticholinergic alkaloid agent derived from *Hyoscyamus niger* (Henbane), has been used as a successful

alternative to atropine to reverse detomidine-induced (Pimenta et al. 2011) and medetomidine-induced (Perotta et al. 2014) bradycardia in sedated horses. The detomidine-induced gastrointestinal hypomotility is not perpetuated by hyoscine, unlike atropine. Hyoscine has a shorter duration of action when compared to atropine in horses. However, pronounced tachycardia, systemic hypertension, increased myocardial workload and oxygen demand negate the routine use of hyoscine in combination with detomidine or medetomidine (Pimenta et al. 2011; Perotta et al. 2014). The intramuscular route of administration is preferred for the anticholinergics to minimise the unwanted cardiovascular effects (Perotta et al. 2014).

Gastrointestinal hypomotility and post operative ileus are clinical concerns in equine practice (Zullian et al. 2011). The odds of developing post operative ileus following xylazine treatment are not significantly different from those not receiving xylazine (Cohen et al. 2004). Despite tolazoline and yohimbine being used as prokinetics in patients suffering from ileus (Cohen et al. 2004; Zullian et al. 2011), the veterinarian must consider that pain can contribute to ileus (Cohen et al. 2004) and that α_2-agonists are excellent visceral analgesics (Jöchle et al. 1989). Thus lidocaine may suffice as an alternative drug to consider, despite its mechanism of action not being fully understood. Treating horses with lidocaine for post operative ileus or enteritis results in shorter hospital stays (Malone et al. 2006). Lidocaine may be infused in combination with α_2-agonists. Other prokinetic agents such as erythromycin, metoclopramide, tegaserod and bethanechol could also be considered in the treatment of ileus.

Clinical approach to reversal of undesirable α_2-adrenoceptor agonist effects

The review has covered the current literature and understanding of α_2-antagonists that can be used in horses to reverse undesirable pharmacodynamic effects of α_2-agonists. However, a few considerations need to be highlighted:

1) The dose time interval from administering the α_2-agonist to cause sedation until the horse receives the antagonist is somewhat consistent (approximately 20 min) in academic studies. This may not reflect true clinical practice. The α_2-antagonist should be dosed according to the expected plasma concentration of the α_2-agonists. The depth and duration of the sedative effects is dose dependent. The higher the dose, the deeper and longer the sedation. However, after a single bolus, the plasma concentration will gradually decrease over time due to redistribution, metabolism and elimination of the drug. Thus, if the veterinarian still considers it necessary to antagonise the clinical effects of the α_2-agonist, then the longer the interval between administering the agonist and antagonist the lower the initial antagonist dose should be to prevent unwanted effects (such as excitement). An acceptable approach is to administer a quarter to a third of the recommended i.v. dose initially (**Table 1**), followed by the same aliquot dose 5–10 min later until an acceptable clinical response is achieved.

2) The dose titration, as described in (1), may be of added benefit due to the variable and unpredictable response between horses to the α_2-antagonists. Horses tend to demonstrate more obvious variability in response to

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 α_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 α_2-agonist-induced bradycardia.

6) The end point of α_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 α_2-antagonists.

7) The analgesic properties of the α_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 α_2-antagonists 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 α_2-agonist-induced bradycardia in the presence of hypotension. Hyoscine, compared to atropine or glycopyrrolate, may be more appropriate as it does not potentiate α_2-agonist-induced gastrointestinal hypomotility.

A case report by Di Concetto *et al.* (2007) highlights the importance of titration of an α_2-antagonist to clinical effect. They described atipamezole reversal of a detomidine (300 µg/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 (Raekallio *et al.* 1990; Ramseyer *et al.* 1998), which in this case would have been unnecessary.

Conclusion

This review examined the current literature regarding α_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 α_2-adrenoceptor antagonist, MK-467, has demonstrated promising results in antagonising undesirable α_2-adrenoceptor agonist-induced bradycardia and ileus while unaffecting the quality of sedation. It is evident from the review that further clinically-orientated research is warranted to improve our understanding of α_2-adrenoceptor antagonism in horses.

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