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REVIEW ARTICLE

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Is there a place for dexmedetomidine in equine anaesthesia and analgesia? A systematic review (2005–2017)

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The objective of this review was to perform a literature compilation of all the equine publications that used dexmedetomidine as the first article on this topic was published, in 2005. We also aimed to answer the question whether the use of dexmedetomidine can currently be justified. For that, we compiled information from databases, such as PubMed, Google Scholar and Web of Science and the proceedings of the last veterinary anaesthesiology meetings. Dexmedetomidine is an attractive drug to be used in horses, mainly due to its pharmacokinetic profile and pharmacodynamics that favour its use as intravenous constant rate infusion (CRI). Nowadays, its clinical use is popular for sedation in prolonged standing procedures and during partial intravenous anaesthesia (PIVA) and total intravenous anaesthesia (TIVA). However, legal requirements for its use should be taken into account.

1 | INTRODUCTION

In 1999, the Food and Drug Administration (FDA) of the United States of America (USA) approved dexmedetomidine, the most selective α_2-agonist, for use as a constant rate infusion (CRI) to provide sedation and analgesia in intensive care units (ICU) during periods of up to 1 day. The drug was marketed as Precedex® (Hospira, Inc., Lake Forest, IL, USA). A new indication was approved by the FDA in 2008 for sedation in nonintubated patients before and during surgical and nonsurgical procedures. In the European Union (EU), Dexdor® (Orion Corporation, Espoo, Finland) was licenced in 2011 for use as CRI for sedation of adult ICU patients.

In veterinary medicine, the European Commission granted a marketing authorization for Dexdomitor® (Orion Corporation, Espoo, Finland) in 2002 and renewed in 2007. This α_2-agonist is indicated for use as a sedative and analgesic in dogs and cats to facilitate clinical examinations, clinical procedures and minor surgeries, and as a pre-anaesthetic to general anaesthesia. It is the active enantiomer of medetomidine (Savola & Virtanen, 1991), which is entirely responsible for the sedative, analgesic and anaesthetic sparing effects (Ansah, Raekallio, & Vainio, 1998; Kuusela et al., 2000; Segal, Vickery, Walton, Doze, & Maze, 1988). It is slightly more potent than the racemate (Kuusela et al., 2000; Savola & Virtanen, 1991) and less likely to cause drug interactions (Kharasch, Herrmann, & Labroo, 1992).

In equine practice, sedation with α_2-agonists, alone or combined with other drugs, is the cornerstone for standing procedures and prior to general anaesthesia, mainly due to their potent sedative and good analgesic properties. Up to 2005, the use of dexmedetomidine had not been reported in the equine. Since then, several experimental and clinical studies have been published. The main reason for this increase in publications relies on its beneficial pharmacological profile, including a short half-life and a rapid redistribution (Bettschart-Wolfensberger et al., 2005). These properties make this drug attractive, favouring its investigation as intravenous (i.v.) infusions in the currently popular areas of equine standing procedures and partial (PIVA) and total intravenous anaesthesia (TIVA). However, its use may be restricted due to current legislation, which differs between countries around the world (e.g., USA vs. EU). In most European countries, off-label use of drugs

is only allowed if no licensed alternative is available, and only to avoid unacceptable suffering of the animal. In addition, in food-producing animals, off-label use is only allowed for drugs that are included in Table 1 of the Annex of EU Directive 37/2010.

2 | RESEARCH QUESTION

The aim of the present review was to perform a systematic literature compilation including all the equine studies published from 2005 in which dexmedetomidine was used. The second goal was to answer the review title, which questions whether the use of dexmedetomidine in horses can nowadays be justified, taking into account current legislation restrictions.

3 | ARTICLE SELECTION

A literature search strategy included the search engines PubMed, Google Scholar and Web of Science, and proceedings of the last veterinary anaesthesiology meetings (up to 2017). The keywords and terms entered were "dexmedetomidine horse." "dexmedetomidine horses," "dexmedetomidine donkey," "dexmedetomidine pony," "dexmedetomidine ponies" and "dexmedetomidine equine," each of these either alone or in combination with "partial intravenous anaesthesia," "total intravenous anaesthesia," "standing," "pharmacokinetics" or "pharmacodynamics."

The eligibility criteria included abstracts and studies (published or online articles and abstracts presented in congresses) written in English, experimental or clinical, blinded or nonblinded, reporting the use of dexmedetomidine in equine species for standing sedation or during general anaesthesia (PIVA or TIVA), as well as pharmacokinetic and other studies or case reports. All the identified studies were evaluated by the main researcher (MGM) to determine their suitability for inclusion and screened independently by the other three independent reviewers (FG, SPL, SS). Furthermore, all the publications were classified according to the levels of evidence categorized and documented by the Oxford Centre for Evidence-Based Medicine (Howick et al., 2011; Appendix 1).

TABLE 1 Numbers of articles using dexmedetomidine in horses and donkeys (2)

Type of study	Number of articles
PK/PD	4
Other PD	5
PIVA	12
MAC_{NM}	2
TIVA	3
Other	2
Total	28

PK, pharmacokinetics; PD, pharmacodynamics; PIVA, partial intravenous anaesthesia; MAC_{NM}, minimum alveolar concentration no movement; TIVA, total intravenous anaesthesia.

A total of 28 manuscripts published in English in peer-refereed journals or abstracts presented in the proceedings of specialist meetings were reviewed. Most of these papers described the use of dexmedetomidine in horses; four enrolled experimental ponies and two studies were performed in donkeys. The subjects of the different studies are shown in Table 1 and evaluated in Table 2. Due to their study design, some studies are included in different groups, for example, Duke-Novakovski, Palacios-Jimenez, Wetzel, Rymes, and Sanchez-Teran (2015) in both PIVA and TIVA studies.

4 | REPORTED STUDIES (2005–2017)

4.1 | Studies in standing horses (9)

4.1.1 | Pharmacokinetic (PK) and pharmacodynamic studies (PD) (4)

Bettschart-Wolfensberger et al. (2005) first studied the PK of an i.v. 3.5 μg/kg bolus in 14 ponies, eight mature (4.4 ± 1.1 years) and six old adults (20 ± 3.2 years), by means of capillary gas chromatography with negative ion chemical ionization mass spectrometry. A noncompartmental analysis was used, and PK parameters were the following: peak concentration 4.60 ± 2.86 and 3.77 ± 1.52 ng/ml, half-life 19.80 ± 9.63 and 28.96 ± 7.61 min and area under plasma concentration–time curve 34.55 ± 11.37 and 44.28 ± 22.66 ng min ml^{-1} for mature and adults, respectively. Dexmedetomidine plasma levels declined rapidly in both groups and fell beyond limits of quantification (LOQ) (0.05 ng/ml) within 60–90 min. With regard to cardiopulmonary effects, Heart rate (HR) was not different from presedation values, whereas stroke volume (SV) and cardiac index (CI) decreased significantly for 5 and 10 min, respectively, with mean maximal decreases of 34% for SV and 44% for CI. Increases in systemic vascular resistance index (SVRI) (95%), systolic (SAP) (7%), mean (MAP) (8%), diastolic (DAP) (19%) and mean pulmonary (mPAP) (11%) arterial pressures occurred for 5 min. Subsequent reductions in SAP, MAP and DAP occurred between 20 and 45 min and in the respiratory frequency (f_R) for the complete duration of the experiment (60 min). Cardiac output (CO) was obtained by the thermal dilution technique to calculate CI and SVRI.

Rezende, Grimsrud, Stanley, Steffey, and Mama (2015) also considered a noncompartmental analysis to describe the PK of a 5 μg/kg i.v. bolus, by means of liquid chromatography–mass spectrometry (LC-MS). In this study with eight adults, healthy horses, peak concentration was 5.70 ± 3.52 ng/ml, with a rapid decrease (elimination half-life was 8.03 ± 0.84 min). Volumes of distribution and total body clearance (CL) showed a large variation between individuals. Times of last detection varied from 30 to 60 min (LOQ = 0.1 ng/ml), with one individual exception, up to 360 min. Heart rate decreased significantly for 10 min (maximal mean decrease at 4 min after drug administration of 35%), with an "irregular rhythm" detected in four of the horses in that period. A wide variability in f_R was observed between individuals, mostly reductions, but three of them showed tachypnea and one a

TABLE 2 Significant design features, total numbers of animals and results from the reported studies of equines receiving dexmedetomidine (2005–2017)

Authors	Study type	LoE	Blinded?	Randomized?	Client owned?	Group size	Animals excluded?	Placebo controlled?	CO?	Statistics and tests	Conclusion
Bettschart-Wolfensberger et al. (2005)	PK/PD Bolus	IV	No	No	No	Eight mature and six old ponies	No	No	Yes, TD	N/A	DEX 3.5 μg/kg PK, of very short duration, favours its use as CRIs
Rezende et al. (2015)	PK/PD Bolus	IV	No	No	No	Eight horses	One outlier, prolonged elimination	No	No	N/A	DEX eliminates quickly, rapid decrease in plasma concentrations
Grimsrud et al. (2015)	PK/PD & modelling Bolus	III-3	No	No	No	Eight horses	In DEX one outlier, DEX prolonged elimination	No	No	N/A	DEX ↑ CL and ↓ Vd than MED and DET. Less influence in glucose than MED
Ranheim et al. (2015)	PK CRI	IV	No	No	No	Eight horses	One, due to catheter displacement	No	No	N/A	Individual differences, infusion rates must be adjusted to effect
Müller et al. (2012)	PD CRI	II	No	Yes	No	Five horses	No	No	No	ANOVA	DEX 3.5 μg/kg + 7 μg kg^{-1} hr^{-1} equipotent to XYL 0.5 mg/kg + 1 mg kg^{-1} hr^{-1}
Risberg et al. (2014)	PD CRI	II	No	Yes	No	11 horses	One, too nervous	No	No	Mixel model	Antinociception at 4 and 6 μg $kg^{-1}hr^{-1}$. Individual variations in plasma concentrations
Medeiros et al. (2017)	PD CRI	II	Yes	Yes	No	Six horses	No	No	Yes, TD	ANOVA, Friedman, Dunn	Minimal CP effects, DEX 5 alone or 3.5 DEX + 24 μg kg^{-1} hr^{-1} BUT. No steady sedation reached
Lizarraga and Janovyak (2013)	PD Bolus	II	Yes	Yes	No	Six donkeys	No	Yes	No	ANOVA	Bolus DEX produces sedation and antinociception in donkeys comparable to XYL
Lizarraga et al. (2017)	PD Bolus	II	Yes	Yes	No	Six donkeys	No	Yes	No	ANOVA, Friedman, Dunn	3, 4 and 5 μg/kg produce sedation for up to 60 min, with shorter-lasting mechanical antinociception
Marcilla et al. (2010)	PIVA	II	No	Yes	No	Six ponies	No	Yes	Yes, LiDCO	ANOVA	Minimal CP effects of two DEX rates, 1 and 1.75 μg kg^{-1} hr^{-1}

Continues

TABLE 2 Continued

Authors	Study type	LoE	Blinded?	Randomized?	Client owned?	Group size	Animals excluded?	Placebo controlled?	CO?	Statistics and tests	Conclusion
Marcilla et al. (2012)	PIVA	II	Yes	Yes	Yes	40 horses	No	Yes	Yes, LiDCO	ANOVA, Wilcoxon, *T* test, Mann–Whitney	Limited CP effects of a DEX 1.75 μg kg^{-1} hr^{-1}, improved recoveries than saline CRI treatment
Gozalo-Marcilla, Steblaj et al. (2013)	PIVA	II	Yes	Yes	Yes	20 horses	Stopped by recovery complications with MOR CRI	No	Yes, LiDCO	ANOVA, Wilcoxon	Better maintenance and recoveries with DEX than MOR CRIs
Benmansour and Duke-Novakovski (2013)	PIVA	IV	N/A	N/A	Yes	One horse	No	N/A	No	N/A	A DEX CRI is useful in PIVA for long procedures
Benmansour et al. (2014, 2016)	PIVA	II	No	Yes	No	Six horses	One (outlier in shunt and PaO_2 in REM)	No	Yes, TD	ANOVA	Good CP function with DEX CRI alone or with MOR or REM
Duke-Novakovski et al. (2015)	PIVA	II	No	Yes	No	Six horses	No	No	Yes, TD	ANOVA, paired *t*	DEX + KET CRIs + ISO good CP function in arthroscopies
Risberg et al. (2016)	PIVA	II	Yes	Yes	No	Eight Horses	No	Yes	Yes, LiDCO	Student *t*	A DEX CRI of 1.75 μg kg^{-1} hr^{-1} depresses CV function
Sacks et al. (2017)	PIVA	II	Yes	Yes	Yes	60 horses	Two (euthanasia and air embolism)	No	No	ANOVA, *t*-, Chi-squared, Mann–Whitney	18 of 30 horses needed extra DEX, only two of 30 in MED for sedation. Better recoveries with DEX CRI than with MED
Marly-Voquer et al. (2016)	PIVA	IV	N/A	N/A	Yes	Five horses	No	N/A	No	N/A	A DEX CRI provides excellent conditions for TVEC. Three of five horses required extra sedation
Neudeck et al. (2016)	PIVA	II	No	Yes	No	Six horses	No	No	Yes, LiDCO	ANOVA, paired *t*, Dunnett	Saturation and regional blood flow ↓ after DEX bolus. DEX CRI + DESF maintains better CO than TIVA with PPF
Wittenberg-Voges et al. (2016)	PIVA	II	Yes	Yes	Yes	15 horses	No	No	Yes, TD	Permutation Wilcoxon	MK-467 reversed VC, ↓ MAP despite ↑ CO
Gozalo-Marcilla, Hopster et al. (2013)	MAC_{NM}	II	Yes	Yes	No	Six ponies	No	Yes	No	ANOVA	DEX 3.5 μg/kg + 1.75 μg kg^{-1} hr^{-1} ↓ MAC_{NM} of SEVO by 53% ± 15%

Continues

TABLE 2 Continued

Authors	Study type	LoE	Blinded?	Randomized?	Client owned?	Group size	Animals excluded?	Placebo controlled?	CO?	Statistics and tests	Conclusion
Gozalo-Marcilla, Hopster et al. (2014)	MAC_{NM}	II	Yes	Yes	No	Five ponies	No	No	No	ANOVA	DEX + MOR CRIs ↓ MAC_{NM} of SEVO more than DEX alone. MOR CRI ↑ MAC_{NM}
Hopster et al. (2014)	TIVA	II	No	Yes	No	Eight horses	No	No	Yes, TTE	ANOVA, Wilcoxon	TIVA with DEX provides good CP function and recoveries, similar to XYL-based protocols
Duke-Novakovski et al. (2015)	TIVA	II	No	Yes	No	Six horses	No	No	Yes, TD	ANOVA, paired *t*	DEX + KET + PPF CRIs good CP function. O_2 administration!
Neudeck et al. (2016)	TIVA	II	No	Yes	No	Six horses	No	No	Yes, LiDCO	ANOVA, paired *t*, Dunnett	Saturation and regional blood flow ↓ after DEX bolus. DEX + PPF CRIs better pulmonary perfusion and oxygenation than PIVA
Guedes et al. (2017)	Other	II	Yes	Yes	No	Six horses	No	No	No	Paired *t*, McNemar	No differences in recoveries in horses anaesthetized with SEVO, after small doses of DEX and XYL
Ambrisko et al. (2013)	Other	II	N/A	N/A	N/A	N/A	N/A	Yes	LiDCO	Correlation	DEX may cause interaction with LiDCO sensor. This needs to be confirmed in vivo

LoE, level of evidence (according to Howick et al., 2011); CO, cardiac output; N/A, not applicable; PK, pharmacokinetics; PD, pharmacodynamics; CRI, constant rate infusion; PIVA, partial intravenous anaesthesia; TIVA, total intravenous anaesthesia; MAC_{NM}, minimum alveolar concentration (no movement); DEX, dexmedetomidine; MED, medetomidine; XYL, xylazine; BUT, butorphanol; MOR, morphine; REM, remifentanil; KET, ketamine; PPF, propofol; ISO, isoflurane; SEVO, sevoflurane; DESF, desflurane; CL, clearance; Vd, volume of distribution; CP, cardiopulmonary; CV, cardiovascular; O_2, oxygen; PaO_2, arterial partial pressure of oxygen; LiDCO, lithium dilution method for measurement of CO; TD, thermodilution technique for measurement of CO; TTE, transthoracic echography technique for measurement of CO; TVEC, transvenous electrical cardioversion.

very laboured breathing pattern that normalized by 30 min. Reduced gastrointestinal motility occurred for 60 min after drug administration. Statistically significant reductions in head height above the ground (HHAG) were observed for 60 min, with a mean maximal reduction of 70% for up to 10 min, being lower than 50% from baseline values for approximately 30 min. Mechanical nociceptive thresholds were higher than pretreatment data for the first 30 min.

Grimsrud et al. (2015) compared the PK using a two-compartment model by LC-MS, with further PK/PD modelling of i.v. detomidine (30 μg/kg), medetomidine (10 μg/kg) and dexmedetomidine (5 μg/kg), reporting the drug concentration-effect data. Dexmedetomidine had the highest CL, 0.0441 (19) L min^{-1} kg^{-1} (estimate [residual standard error]), approximately twice that of medetomidine (0.0210 [12]) and detomidine was the lowest (0.0132 [4]). Volumes of distribution (L/kg) for the central (V_1) and peripheral (V_2) compartments were approximately twice smaller for dexmedetomidine than medetomidine (0.236 [38] vs. 0.474 [14] for V_1 and 0.163 [38] vs. 0.314 [11] for V_2). With regard to PD parameters, the HR decreased by 31% after medetomidine and dexmedetomidine, whereas with detomidine, it was reduced by approximately 51%. The HHAG drug concentrations required to obtain inhibition at half-maximal effect (IC_{50}) were 10 times greater with detomidine than after medetomidine and dexmedetomidine. Comparing medetomidine and dexmedetomidine, the latter had a significantly lower hyperglycaemic effects.

Finally, Ranheim, Risberg, Spadavecchia, Landsem, and Haga (2015) detected substantial individual differences in the PK and PD parameters after a 150 min 8 μg kg^{-1} hr^{-1} dexmedetomidine CRI in seven healthy horses. Dexmedetomidine was detected by LC-MS, and the parameters were calculated using noncompartmental methods. The harmonic mean (*SD*) plasma elimination half-life (Lambda *z* half-life) for dexmedetomidine was 20.9 (5.1) min, CL 0.3 (0.20) L min^{-1} kg^{-1} and volume of distribution at steady state 13.7 (7.9) L/kg. With regard to sedation levels, HHAG varied together with dexmedetomidine plasma concentrations. After the CRI was discontinued, all horses returned to baseline HHAG values within 65 min.

4.1.2 | Other PD studies in standing horses and donkeys (5)

In an experimental, randomized, cross-over study involving five adult healthy horses, Müller, Hopster, Hopster-Iversen, Rohn, and Kästner (2012) compared the sedative and antinociceptive effects of a dexmedetomidine protocol consisting of a bolus of 3.5 μg/kg followed by an infusion of 5 or 7 μg kg^{-1} hr^{-1}, with a xylazine regime (0.5 mg/kg plus 1 mg kg^{-1} hr^{-1} CRI), for 120 min. The lower dexmedetomidine infusion rate (5 μg kg^{-1} hr^{-1}) produced less reduction in HHAG, around 30%–50%, whereas the higher (7 μg kg^{-1} hr^{-1}) produced similar steady reductions as xylazine, around 70% for the duration of the CRIs. The higher rate of dexmedetomidine was calculated based on the lower one, by adding additional *boli* to reach equivalent levels of sedation than the reached by the xylazine regime. Significant decreases in HR were observed during the majority of the CRI, without differences between treatments. First- and second-degree atrioventricular blocks (AVBs) were observed in several horses after the dexmedetomidine *boli* and during the infusions. Decreases in f_R from baseline were seen over the whole period only in those horses receiving the higher rate of dexmedetomidine. Significant increases in the thermal thresholds compared to baseline occurred from 15 min after bolus administration up to the end of the infusions. The higher dexmedetomidine rate prolonged these threshold increases for more 30 min. No differences between treatments were observed.

In another experimental randomized, cross-over study with 10 adults, healthy horses, Risberg, Spadavecchia, Ranheim, Krontveit, and Haga (2014) studied the sedative and antinociceptive effects of dexmedetomidine CRIs at 2, 4 and 6 μg kg^{-1} hr^{-1} after an i.v. bolus 0.96 μg/kg, related to their measured plasma concentrations. Sedation was assessed with a visual analogue scale (VAS), presented as a line of 100 mm, with 0 mm representing no sedation, and 100 mm heavy sedation. The mean sedation VAS scores increased dose-dependently according to the rate infused and were 0 (range 0–10 mm), 20 mm (range 0–46 mm) and 58 mm (range 11–85 mm), for the rates 2, 4 and 6 μg kg^{-1} hr^{-1}, respectively, with large variability between individuals. This may be explained by the large individual variations in plasma concentrations measured. Sedation levels gradually increased over time during the infusion and up to 30 min postinfusion in the 6 μg kg^{-1} hr^{-1} infusion. Antinociception was assessed by application of electrical single and repeated stimulation. Increased electrical thresholds were only observed at 4 and 6 μg kg^{-1} hr^{-1}, which remained for at least 30 min after discontinuing the CRIs.

In an experimental, blinded, randomized, cross-over study involving six adults, healthy horses, Medeiros et al. (2017) compared the sedative and cardiopulmonary effects of a 90-min dexmedetomidine i.v. infusion alone (3.5 μg/kg, followed by a 5 μg kg^{-1} hr^{-1} CRI), or combined with butorphanol (20 μg/kg plus a 24 μg kg^{-1} hr^{-1} CRI). Maximal HHAG reductions for the treatments dexmedetomidine alone (54%) or combined with butorphanol (58%) occurred at 15 min after bolus administration and beginning of the CRIs, with the presence of ataxia. Afterwards, HHAG reduction values were never higher than 50%, failing to maintain a steady sedation. With regard to the cardiopulmonary variables, no differences were observed between treatments. Significant decreases in HR occurred for 90 and 30 min compared to baseline, in treatment dexmedetomidine alone, and the combination, respectively. Second-degree AV-blocks were observed in both groups for the first 15 min, with one horse for up to 60 min in the combination treatment. Thermal dilution technique was used for measurement of CO. In both treatments, CI and oxygen delivery index (DO_2I) were similarly reduced for the first 30 min (maximal reductions at 5 min of 41% and 48% for CI and DO_2I, respectively), while SVRI increased for 15 min (maximal increases of 65% at 5 min). Values of f_R were lower for the whole infusion period with both treatments and for up to 30 min after the end of the CRI when only dexmedetomidine had been infused.

In donkeys, the sedative and antinociceptive effects of different i.v. *boli* of α_2-agonists were reported by Lizarraga and Janovyak (2013) in an experimental, blinded, randomized, cross-over study enrolling six adults, healthy animals, using mechanical stimuli for the

antinociceptive tests. Dexmedetomidine (3.5 μg/kg) produced similar antinociception as xylazine (1.1 mg/kg), detomidine (20 μg/kg), romifidine (100 μg/kg) and medetomidine (5 μg/kg) for 30 min. However, from 30 to 60 min, mechanical thresholds after dexmedetomidine and xylazine were significantly lower than those achieved by detomidine or romifidine. Sedation was 15–25 min longer than antinociception with all treatments. A recent study by Lizarraga, Castillo-Alcala, and Robinson (2017) studied the sedative and antinociceptive (mechanical) dose-dependent properties of 2, 3, 4 and 5 μg/kg of dexmedetomidine in an experimental, blinded, randomized, cross-over study with six adults, healthy donkeys. All the doses produced sedation (lasting up to 60 min), with shorter-lasting (40–55 min), dose-dependent antinociception.

4.2 | PIVA studies (12)

Based on Bettschart-Wolfensberger et al. (2005), Marcilla, Schauvliege, Duchateau, and Gasthuys (2010) designed an experimental study with six adults, healthy ponies. Each pony was anaesthetized once for 150 min, with periods of 30 min alternating saline with low and high doses of dexmedetomidine. After an i.v. sedation dose of 3.5 μg/kg, rates of 1 and 1.75 μg kg^{-1} hr^{-1} produced minimal and comparable cardiopulmonary effects. These changes included minor, but statistically significant decreases in HR, CI, arterial (CaO_2) and venous (CvO_2) oxygen content, and oxygen delivery (DO_2) and increases in systemic vascular resistance (SVR), SAP and right atrial pressure (RAP). No periods of severe bradycardia or AVBs were observed. The authors justified the safe use of those protocols as the decreases in CI and DO_2 were less than 10% of the baseline values and are usually well tolerated in anaesthetized, healthy horses.

In a clinical, blinded, placebo-controlled, randomized study with 40 adults, healthy, client-owned horses, undergoing surgical procedures under general anaesthesia for more than 60 min, the limited cardiopulmonary effects of the 1.75 μg kg^{-1} hr^{-1} rate described in Marcilla et al. (2010) were confirmed (Marcilla, Schauvliege, Segaert, Duchateau, & Gasthuys, 2012). After the 3.5 μg/kg sedation dose, 11 horses required additional doses to obtain acceptable sedation before induction of general anaesthesia. During anaesthesia, only two of 40 horses showed second-degree AVBs, with "no need for treatment." No reduction in the end-tidal isoflurane concentration ($F_E'ISO$) was found compared to a placebo treatment. The authors attributed this to the study design and the fact that the anaesthetist, unaware of the treatment, evaluated the anaesthetic depth in a subjective way. After a bolus of 0.875 μg/kg, better recoveries were observed in the dexmedetomidine treatment compared to the placebo (Marcilla et al., 2012).

In another clinical, blinded, randomized study involving 20 adults, healthy, client-owned horses, the same protocol, 3.5 μg/kg sedation dose followed by a CRI at 1.75 μg kg^{-1} hr^{-1}, seemed to be more adequate than a morphine-based technique (0.15 mg/kg added to the dexmedetomidine sedation dose, followed by a morphine 0.1 mg kg^{-1} hr^{-1} CRI) (Gozalo-Marcilla, Steblaj, Schauvliege, Duchateau, & Gasthuys, 2013), as it guaranteed a more stable anaesthesia with less extra doses of ketamine and reduced the $F_E'ISO$ based on an objective flow chart, adapted from Enderle, Levionnois, Kuhn, and Schatzmann (2008). Better recoveries were seen in horses receiving dexmedetomidine, with no postoperative complications compared with the morphine treatment, where one of the 10 horses developed postoperative colic and pulmonary oedema and two others box-walking (Gozalo-Marcilla, Steblaj et al., 2013). Overall, the cardiopulmonary changes in the dexmedetomidine treatment compared to morphine included significant increases in MAP and DAP values and decreases in CI and stroke volume index (SVI), always within clinically acceptable levels. For the measurement of CO, the authors in Marcilla et al. (2010, 2012) and Gozalo-Marcilla, Steblaj et al. (2013) employed the lithium dilution technique (LiDCO).

A 1.5 μg kg^{-1} hr^{-1} CRI, without loading dose and after sedation with xylazine and anaesthetic maintenance with sevoflurane and remifentanil, was successfully used in a 10-year-old horse for a radical mandibulectomy which lasted for 13 hr (Benmansour & Duke-Novakovski, 2013). In a 60-min experimental, nonblinded, randomized, cross-over, study involving six adults, healthy, isoflurane-anaesthetized horses, no significant differences in cardiopulmonary effects and recovery qualities were detected between a dexmedetomidine CRI alone (loading dose 0.25 μg/kg followed by a CRI of 1 μg kg^{-1} hr^{-1}) and combined with morphine (0.15 mg/kg plus a 0.1 mg kg^{-1} hr^{-1} infusion) or remifentanil, CRI at 6 μg kg^{-1} hr^{-1} (Benmansour et al., 2014). No excitement or colic was seen in the recovery. Blood samples were taken in the remifentanil treatment to measure the concentrations of this drug (Benmansour, Billinsky, Duke-Novakovski, & Alcorn, 2016). In an experimental, nonblinded, randomized, cross-over study with six adults, healthy horses undergoing arthroscopy for periods around 60–90 min, Duke-Novakovski et al. (2015) compared a propofol-based (8 mg kg^{-1} hr^{-1}) TIVA protocol with ketamine (1 mg kg^{-1} hr^{-1} CRI) and dexmedetomidine (1.5 μg kg^{-1} hr^{-1}) infusions with a PIVA technique, replacing the propofol CRI by isoflurane. The horses had been previously sedated with i.v. 0.5 mg/kg of xylazine for instrumentation and extra 0.5 mg/kg before induction, which consisted in i.v. ketamine (2 mg/kg) and propofol (0.4 mg/kg). Mean $F_E'ISO$ in the PIVA protocol was approximately 1% (range, 0.5%–1.3%). The CO, measured by the thermodilution, was significantly reduced for 10 min after induction (15%), only with the PIVA protocol. Between treatments, arterial partial pressure of oxygen (PaO_2) was significantly higher in the PIVA protocol compared to TIVA, for the study period (mean PaO_2 values of 380 and 255 mmHg for PIVA and TIVA at 60 min, respectively), with the use of comparable inspired concentration of oxygen (FiO_2) values (mean values between 77% and 94%).

An experimental, blinded, randomized, cross-over study with eight adults, healthy, isoflurane-anaesthetized horses by Risberg, Ranheim, Krontveit, Lervik, and Haga (2016) compared a PIVA protocol with dexmedetomidine (8 μg/kg for sedation followed by a 1.75 μg kg^{-1} hr^{-1} CRI) versus a saline treatment. At equivalent depths of anaesthesia ($F_E'ISO$ 0.7% ± 0.2% and 0.9% ± 0.2%, for the dexmedetomidine and saline, respectively), statistical significant decreases in HR (16%), CI (22%) and DO_2I (24%) and significant increases in SAP (18%), MAP (19%), DAP (18%) and oxygen extraction (OE) (32%) were present in horses receiving a CRI of dexmedetomidine compared to

those receiving saline. For CO measurement, the LiDCO technique was used. To maintain MAP above 60 mmHg, eight horses in the control and one horse in the dexmedetomidine treatment received dobutamine. Recovery qualities, measured with a VAS scale, were better in group dexmedetomidine, with less attempts to stand. All horses in the dexmedetomidine group stood up at the first attempt, whereas in the control group, horses made a median of three attempts to stand (range 1–8).

Sacks, Ringer, Bischofberger, Berchtold, and Bettschart-Wolfensberger (2017) compared the effects of medetomidine and dexmedetomidine in 60 adults, healthy, isoflurane-anaesthetized, client-owned horses in a blinded, randomized study. For sedation before induction of general anaesthesia, 18 of 30 horses receiving dexmedetomidine required extra top-ups, to fulfil sedation criteria (Taylor, Coumbe, Henson, Scott, & Taylor, 2014), compared to two of the 30 horses receiving medetomidine. Median total sedation doses (range) were dexmedetomidine 4 μg/kg (4–9) or medetomidine 7 μg/kg (7–9). Cardiopulmonary function and influences in F_E'ISO after a subjective control of anaesthetic depth did not differ between treatments. After similar anaesthesia durations (approximate mean of 150 min), recoveries were significantly better in horses receiving dexmedetomidine, with no differences in recovery times.

A similar protocol has been used with success in five adults, client-owned horses with atrial fibrillation (AF) undergoing transvenous electrical cardioversion (TVEC) (Marly-Voquer, Schwarzwald, & Bettschart-Wolfensberger, 2016). The horses were sedated with 3.5 μg/kg dexmedetomidine, in two parts, 1.75 μg/kg together with 30 μg/kg butorphanol i.v. slowly in the box, and the remaining 1.75 μg/kg in the induction room. After induction, general anaesthesia was maintained with isoflurane and dexmedetomidine, at an initial rate of 1.75 μg kg^{-1} hr^{-1}, adjusted later to the horses' requirements. For sedation, the dose of 3.5 μg/kg was only sufficient in two of the five horses [median total sedation dose (range) was 4.5 μg/kg (3.5–10)]. For maintenance, only one horse was maintained with a rate of 1.75 μg kg^{-1} hr^{-1} (median total infusion rate [range] 2.3 μg kg^{-1} hr^{-1} [1.75–5.3]). Good recovery qualities were observed after a 1 μg/kg dexmedetomidine bolus (one horse received 3 μg/kg as it had exhibited difficult behaviour before anaesthesia). In that case series, the authors suggested that dexmedetomidine may have beneficial effects (cardioprotection and energy sparing effects on the myocardium) for these procedures, as electric shocks applied directly to the myocardium may cause a degree of ischaemia. They concluded that the myocardial damage in those patients was "likely minimal" as concentrations of cardiac troponin I were only "mildly elevated" in one horse after 6 and in another for 24 hr.

The influence of these protocols on regional perfusion has also been studied. Neudeck, Hopster, and Kästner (2016) reported a deterioration of the oral, oesophageal and rectal blood flow and oxygenation after a 3.5 μg/kg dexmedetomidine bolus in six experimental horses. When anaesthesia was maintained with desflurane or propofol in combination with dexmedetomidine (7 μg kg^{-1} hr^{-1}), peripheral tissue was well oxygenated, whereas microperfusion remained significantly reduced. The maintenance with propofol provided better pulmonary perfusion with better oxygenation with PaO_2 values significantly higher compared with desflurane, with dead space and the alveolar-arterial gradient significantly lower. Cardiac index was significantly higher with desflurane, whereas SVR was significantly lower. The LiDCO technique was used to measure CO. In 15 isoflurane-anaesthetized horses, the same group of investigators studied the effects of a dexmedetomidine infusion (3.5 μg/kg bolus + 7 μg kg^{-1} hr^{-1}) on the peripheral gastrointestinal α_2-adrenoreceptors when given alone, and in combination with the peripheral antagonist MK-467 (Wittenberg-Voges, Hopster, Raekallio, Kästner, & Vainio, 2016). The antagonist, given as an i.v. bolus (250 μg/kg) after 2 hr of general anaesthesia, reversed the vasoconstriction induced by the dexmedetomidine, resulting in a drop in MAP despite increasing CO. Therefore, gastrointestinal microperfusion decreased, probably as a result of insufficient perfusion pressure. The authors concluded that an ideal agonist/antagonist ratio, and an infusion rate for MK-467, was still to be determined. For this study, CO was obtained by the thermodilution technique.

4.3 | Minimum alveolar concentration no movement (MAC_{NM}) studies (2)

Two experimental MAC_{NM} studies with six and five ponies, respectively, have been published using dexmedetomidine CRIs using the same methodology. The sevoflurane MAC_{NM} value was reported to be 2.42% ± 0.55% in Gozalo-Marcilla, Hopster et al. (2013). In the same experiment, dexmedetomidine 3.5 μg/kg followed by a 1.75 μg kg^{-1} hr^{-1} CRI significantly reduced the MAC_{NM} of sevoflurane by 53% ± 15%, down to 1.07% ± 0.21%. After an i.v. bolus of 0.15 mg/kg, a morphine CRI (0.1 mg kg^{-1} hr^{-1}) increased the sevoflurane MAC_{NM} up to 2.79% ± 0.73%. However, when the morphine CRI was co-administered with a dexmedetomidine CRI, the MAC_{NM} value was reduced by 67% ± 11%, down to 0.89% ± 0.22% (Gozalo-Marcilla, Hopster et al., 2014).

4.4 | TIVA studies (3)

In an experimental, nonblinded, randomized, cross-over study, Hopster et al. (2014) reported a TIVA protocol for 120 min with dexmedetomidine, comparable with a xylazine-based one, with mild-to-moderate cardiovascular depression in eight adults, healthy horses. This consisted of a 3.5 μg/kg sedation dose, followed by dexmedetomidine (7 μg kg^{-1} hr^{-1}), midazolam (0.1 mg kg^{-1} hr^{-1}) and ketamine (3 mg kg^{-1} hr^{-1}) infusions. To determine an adequate anaesthetic depth, a constant, electrical current was applied at regular intervals. Good to excellent recoveries were observed after reversal of midazolam with flumazenil. Cardiac output was measured by transthoracic echocardiography. Under these circumstances, mean dexmedetomidine half-life (±*SD*) was 46 ± 7 min, shorter than the one of xylazine (64 ± 13 min).

Dexmedetomidine (1.5 μg kg^{-1} hr^{-1}), ketamine (1 mg kg^{-1} hr^{-1}) and propofol (8 mg kg^{-1} hr^{-1}) CRIs after sedation with twice 0.5 mg/kg i.v. xylazine (first dosage to allow thermodilution

catheter insertion for CO measurement) and induction with ketamine (2 mg/kg) and propofol (0.4 mg/kg) were compared with a PIVA regime, replacing the propofol CRI by isoflurane maintenance. This TIVA protocol provided adequate surgical conditions in six adults, healthy horses undergoing arthroscopy for periods around 60–90 min in an experimental, nonblinded, randomized, cross-over study (Duke-Novakovski et al., 2015). However, at comparable mean FiO_2 values ranging from 77% and 94%, the TIVA protocol lowered PaO_2 values for the study period (255 vs. 380 mmHg for TIVA and PIVA at 60 min, respectively). The authors recommended the use of oxygen and the availability of mechanical lung ventilation with propofol-based TIVA techniques. The experimental study of Neudeck et al. (2016) compared regional perfusion between a PIVA with desflurane and TIVA with propofol. After sedation with dexmedetomidine (3.5 μg/kg) and induction with ketamine (1 mg/kg) and propofol (2 mg/kg), maintenance consisted of a 7 μg kg^{-1} hr^{-1} dexmedetomidine CRI with an infusion of propofol, with a minimum infusion rate (MIR) of 0.04 ± 0.01 mg kg^{-1} hr^{-1}. With both protocols, peripheral tissue was well oxygenated, whereas microperfusion was reduced. However, the TIVA protocol provided better pulmonary perfusion and oxygenation. Cardiac index, measured by LiDCO, was better preserved with desflurane, whereas SVR was lower.

4.5 | Other studies (2)

In six healthy horses anaesthetized for 1 hr with sevoflurane, the recovery qualities did not differ after small i.v. *boli* of xylazine (0.2 mg/kg) versus dexmedetomidine (0.875 μg/kg). Although not significant, the VAS scores to grade recovery quality (0 poor recovery, 100 excellent) were 71 ± 21 for xylazine and 84 ± 13 for dexmedetomidine (Guedes, Tearney, Cenani, Aristizabal, & Nieto, 2017).

One in vitro study of Ambrisko, Kabes, and Moens (2013) evaluated the effects of different drugs on the voltage of the sensor used for the LiDCO method to measure CO, which is commonly used in equine studies. Dexmedetomidine was classified as a drug that may interact with the sensor but is unlikely to cause bias in LiDCO measurements in vivo.

5 | DISCUSSION

High-quality research has been performed in the last decade with respect to the use of dexmedetomidine in the equine. Based on the evidence reported by the studies reviewed here, it can be stated that dexmedetomidine is an attractive drug to be used in horses. Its kinetics favour the use of this drug for sedation in prolonged standing procedures and during PIVA and TIVA. However, in some countries depending on national legislation, scientific evidence showing clear advantages compared to licensed drugs should be provided to support its off-label use (e.g., in EU countries). Unfortunately, the literature comparing dexmedetomidine with other α_2-agonists is scarce and a direct comparison between them is difficult.

Bettschart-Wolfensberger et al. (2005) reported the PK and cardiopulmonary effects of a 3.5 μg/kg i.v. dexmedetomidine bolus, with promising results. The authors concluded that this drug might be safe for sedation, with similar cardiopulmonary changes to those produced by other α_2-agonists, but of very short duration. Furthermore, its PK profile characterized by a short half-life and rapid redistribution might be useful in infusions, for long-term sedation and in combination with other general anaesthetics in PIVA and TIVA protocols. It was after its license in the EU in 2007 for dogs and cats that more studies began to be designed in the equine.

When comparing the different PK studies of dexmedetomidine, it is difficult to draw a conclusion, mainly due to the different methodologies used, and also the absence of articles directly comparing its effects with those of other α_2-agonists. Most authors used noncompartmental analysis (Bettschart-Wolfensberger et al., 2005; Ranheim et al., 2015; Rezende et al., 2015). The most interesting finding was the rapid drug elimination. Mean (±*SD*) half-lives of dexmedetomidine following an i.v. bolus in young and adult ponies were 19.8 ± 9.63 and 28.96 ± 7.61 min, respectively, (Bettschart-Wolfensberger et al., 2005) and in horses was shorter, 8.03 ± 0.84 min (Rezende et al., 2015). After CRI termination, Ranheim et al. (2015) reported a harmonic mean (pseudo-SD) value of 20.3 (5.8) min. In horses anaesthetized with a dexmedetomidine-based TIVA protocol, the mean half-life (±SD) was slightly longer (46 ± 7 min) but shorter than that of xylazine (64 ± 13 min) (Hopster et al., 2014), also with higher plasma concentrations, probably due to the reduced CO by the co-administration of other sedatives and anaesthetics.

Only the study of Grimsrud et al. (2015) compared the PK of dexmedetomidine with those of medetomidine and detomidine. Although in the authors' experience, the doses of detomidine were relatively high compared to those of the other drugs, dexmedetomidine was the drug with higher CL and less V_1 and V_2. Extrapolating from other studies, elimination half-times are shorter than those of the racemate medetomidine; mean (±*SD*) half-lives were reported of 51.3 ± 13.1 min in ponies (Bettschart-Wolfensberger, Clarke, Vainio, Aliabadi, & Demuth, 1999) and 29.1 ± 12.5 in horses (Grimsrud, Mama, Steffey, & Stanley, 2012). In a noncompartmental model, the median half-life of detomidine in horses was 24.06 (range 12.68–41.26) min (Grimsrud, Mama, Thomasy, & Stanley, 2009). With a two-compartment model, median elimination half-life of romifidine in horses was 138.2 (range 104.6–171.0) min (Wojtasiak-Wypart et al., 2012). In a three-compartment model, beta and gamma half-lives for xylazine were 167.4 ± 6.3 and 1560 ± 114 min, respectively (Knych, Stanley, McKemie, Arthur, & Kass, 2017).

The higher α_2:α_1 adrenoreceptor sensitivity (ratio of 1620:1), compared to xylazine (160:1), detomidine (260:1) and romifidine (340:1), may lead to less adverse effects. In their PK/PD modelling study comparing the PK effects of detomidine, medetomidine and dexmedetomidine, and their PD responses, Grimsrud et al. (2015) explained the higher reductions in HR and HHAG with detomidine through its lower α_2:α_1 ratio. Moreover, dexmedetomidine would be preferable in those cases in which an increase in plasma glucose concentrations is not desired, such as in horses with insulin resistance.

Therefore, based on its PK profile, dexmedetomidine may be useful for both short- and long-term standing procedures. Rates of 7 μg kg^{-1} hr^{-1} after a bolus of 3.5 μg/kg were proven to be equisedative to a sedation dose of xylazine at 0.5 mg/kg followed by a 1 mg kg^{-1} hr^{-1} CRI (Müller et al., 2012). Antinociception was present at rates of 4 and 6 μg kg^{-1} hr^{-1} (Risberg et al., 2014). However, under clinical circumstances, the veterinarian should be ready to adapt the theoretical rates to each patient, due to individual variations in plasma concentrations (Ranheim et al., 2015; Risberg et al., 2014). Indeed, steady sedation was not reached when using 5 μg kg^{-1} hr^{-1} alone, or 3.5 μg kg^{-1} hr^{-1} combined with butorphanol (Medeiros et al., 2017).

When used during general anaesthesia as a CRI, as part of PIVA protocols, dexmedetomidine fulfils the principles of equine "balanced anaesthesia," which include mainly three requirements: (i) an adequate intraoperative cardiopulmonary function, (ii) reduction in the inhalant agent requirements and (iii) smooth and coordinated recoveries (Bettschart-Wolfensberger & Larenza, 2007; Gozalo-Marcilla, Gasthuys, & Schauvliege, 2014, 2015).

First, in their experimental study, Marcilla et al. (2010) reported clinically acceptable cardiopulmonary effects observed in healthy ponies at both rates studied, 1 and 1.75 μg kg^{-1} hr^{-1}. However, the design of that study comprised one important limitation. Potential carry-over effects of the CRI infused during the first period may have influenced the cardiopulmonary effects of the second period. A blinded, randomized, cross-over study with three treatments, a saline and the two dexmedetomidine CRIs, would have been more appropriate. Under general anaesthesia, the limited cardiopulmonary effects of dexmedetomidine CRIs ranging from 1 to 1.75 μg kg^{-1} hr^{-1} were confirmed in both experimental (Benmansour et al., 2014) and clinical studies (Marcilla et al., 2012). Whereas the low dose was used in combination with different opioid infusions (Benmansour et al., 2014), the use of the higher rate was justified by its theoretically higher sedative, analgesic and inhalant sparing effects (Marcilla et al., 2012). Neudeck et al. (2016) demonstrated that dexmedetomidine causes a decrease in regional blood flow, but further studies are needed to assess the clinical importance of these changes. It is also very important to note that all the studies involved healthy horses. While it may be discussed whether or not the reductions in cardiopulmonary function in the study of Risberg et al. (2016) are of clinical importance in healthy horses, these changes may be of huge importance in colic horses.

Second, a dexmedetomidine CRI halved the sevoflurane MAC_{NM} values under experimental conditions (Gozalo-Marcilla, Hopster et al., 2013). The same study design reported an increase in MAC_{NM} value when morphine was infused alone, and its further reduction when both CRIs are co-administered (Gozalo-Marcilla, Hopster et al., 2014). There is only one study with similar methodology in α_2-agonists reporting a reduction of 28% in the desflurane requirements when infusing a medetomidine CRI (Bettschart-Wolfensberger, Jäggin-Schmucker, Lendl, Bettschart, & Clarke, 2001). Experimental studies describing these effects of infusions of xylazine, detomidine and romifidine in the equine are missing. Blinded clinical studies appear not to be good options to detect reductions in inhalants, especially when depth of anaesthesia is evaluated subjectively, according to clinical signs. This is of extreme importance in horses with infusions of α_2-agonists, in which a "lighter" appearance, compared with traditional inhalant protocols, is common (Kalchofner et al., 2006). No isoflurane concentration reductions were demonstrated after romifidine (Devisscher, Schauvliege, Dewulf, & Gasthuys, 2010), detomidine (Schauvliege et al., 2011) and dexmedetomidine (Marcilla et al., 2012). The same happened in the comparison between medetomidine and dexmedetomidine (Sacks et al., 2017). This may be solved using objective methods, such as the flow chart described by Enderle et al. (2008). With this tool, Gozalo-Marcilla, Steblaj et al. (2013) showed that with initial F_E'ISO values of 0.9%, a dexmedetomidine CRI maintained a more stable surgical anaesthetic depth, with fewer ketamine "top-ups" and lower isoflurane requirements compared with a morphine infusion. The isoflurane-sparing effects of a xylazine CRI in a clinical study were demonstrated, using a "more or less objective" scoring system, based on clinical signs and MAP. However, these results have to be interpreted carefully as the main anaesthetist was aware of the drugs administered (Pöppel, Hopster, Geburek, & Kästner, 2015).

Finally, as the third requirement for PIVA protocols, recovery qualities after dexmedetomidine infusions are from good to excellent, with no apparent signs of excitement (Benmansour et al., 2014; Marly-Voquer et al., 2016; Risberg et al., 2016). After a CRI of dexmedetomidine during isoflurane anaesthesia, followed by a small bolus for recovery, the recoveries were better than after infusions of saline (Marcilla et al., 2012), medetomidine (Sacks et al., 2017) and morphine (Gozalo-Marcilla, Steblaj et al., 2013). After a dexmedetomidine infusion, small doses of romifidine have been administered by other authors (Benmansour & Duke-Novakovski, 2013; Duke-Novakovski et al., 2015), probably due to personal preferences. Small doses of xylazine, detomidine and romifidine are well known to improve the quality of recovery in horses after inhalant anaesthesia (Santos et al., 2003), with no differences between xylazine and dexmedetomidine (Guedes et al., 2017). However, as the study of Guedes et al. (2017) included only six horses, further studies with more individuals are required to confirm that there are not real differences between those α_2-agonists.

The clinical applicability of these protocols was confirmed under different circumstances, for medium term (Gozalo-Marcilla, Steblaj et al., 2013; Marcilla et al., 2012; Sacks et al., 2017) and prolonged anaesthesias (Benmansour & Duke-Novakovski, 2013). Its use in the last case is justified by the favourable kinetics. Moreover, Marly-Voquer et al. (2016) suggested that, in horses with AF for TVEC, the use of an intraoperative infusion of dexmedetomidine may be of benefit due to the cardioprotective properties of this drug, based on the minimal changes in the concentrations of cardiac troponin I. However, cardiac troponin I values were also normal after 3 hr after TVEC in six horses sedated with detomidine prior general anaesthesia (De Clercq et al., 2008). Further research is required to confirm whether this drug may have any benefit from other α_2-agonists.

Dexmedetomidine can also be used in TIVA protocols which normally include an α_2-agonist, a centrally acting muscle relaxant and an i.v. anaesthetic agent, mostly ketamine (Hopster et al., 2014). These regimes produce general anaesthesia, avoid the cardiopulmonary

effects of inhalant anaesthetics and reduce mortality but must be limited to surgical procedures of less than 60–90 min (Johnston, Eastment, Wood, & Taylor, 2002). The use of dexmedetomidine is attractive in these cases, as recovery times, though not statistically different, were shorter compared to xylazine-based protocols, mainly due to the longer elimination half-time of xylazine (Hopster et al., 2014). Both oxygen supplementation and mechanical ventilation are recommended when propofol-based TIVA protocols are used (Duke-Novakovski et al., 2015).

However, the use of dexmedetomidine is mainly limited due to current legal requirements. Worldwide, dexmedetomidine is not licensed for use in food-producing animals, but only for dogs and cats. For example, in the EU, the cascade system does not allow the off-label use of dexmedetomidine in food-producing horses, and a reason for its preferential use over other sedatives is mandatory in nonfood-producing horses. Moreover, in countries where this drug is licensed for veterinary use, its elevated costs make its use for private practitioners and/or practices limited.

A common complaint from anaesthetists and practitioners is that dexmedetomidine does not provide a reliable level of sedation. Assuming preliminary results from their laboratory, 3.5 μg/kg was shown to be the equisedative to 1 mg/kg of xylazine or 7 μg/kg of medetomidine (Bettschart-Wolfensberger et al., 2005). However, clinically the proposed dose of 3.5 μg/kg does not seem to provide a reliable level of sedation, and incremental dosing is frequently needed to obtain adequate sedation levels (Marcilla et al., 2012; Marly-Voquer et al., 2016; Sacks et al., 2017).

A possible criticism to some of the studies presented in this review is that the LiDCO was used for CO measurement (Gozalo-Marcilla, Steblaj et al., 2013; Marcilla et al., 2012; Neudeck et al., 2016; Risberg et al., 2016). This method to evaluate the cardiopulmonary function is nowadays of huge value in research, mainly under clinical circumstances, due to minimal invasiveness. The in vitro study of Ambrisko et al. (2013) confirms that dexmedetomidine is a drug that may interact with the sensor but unlikely to cause bias in LiDCO in vivo. The use of other drugs, such as ketamine, may have caused a more influencing bias due to interaction with the sensor in studies with anaesthetized horses.

6 | CONCLUSION

The evidence provided by the studies reviewed here supports the use of dexmedetomidine in the horse. Dexmedetomidine's PK profile favours its clinical application, mainly for standing sedation, PIVA and TIVA procedures. However, due to strict legislation requirements, further research is needed (mainly directly comparing dexmedetomidine to other α_2-agonists) to allow its off-label use in countries under EU regulations.

CONFLICT OF INTEREST

None of the authors declare conflict of interest.

AUTHOR CONTRIBUTIONS

MGM involved in main literature search and evaluation of the studies, writing of the manuscript and critical review of the manuscript. FG, SPL and SS involved in independent screening of the literature and critical review of the manuscript. SS wrote the manuscript.

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REFERENCES

Ambrisko, T. D., Kabes, R., & Moens, Y. (2013). Influence of drugs on the response characteristics of the LiDCO sensor: An in vitro study. *British Journal of Anaesthesia*, *110*, 305–310. https://doi.org/10.1093/bja/aes380

Ansah, O. B., Raekallio, M., & Vainio, O. (1998). Comparison of three doses of dexmedetomidine with medetomidine in cats following intramuscular administration. *Journal of Veterinary Pharmacology and Therapeutics*, *21*, 380–387. https://doi.org/10.1046/j.1365-2885.1998.00155.x

Benmansour, P., Billinsky, J., Duke-Novakovski, T., & Alcorn, J. (2016). Blood concentrations of remifentanil during and after infusion in horses anesthetized with isoflurane and dexmedetomidine. *Research in Veterinary Science*, *107*, 202–206. https://doi.org/10.1016/j.rvsc.2016.06.008

Benmansour, P., & Duke-Novakovski, T. (2013). Prolonged anesthesia using sevoflurane, remifentanil and dexmedetomidine in a horse. *Veterinary Anaesthesia and Analgesia*, *40*, 521–526. https://doi.org/10.1111/vaa.12048

Benmansour, P., Husulak, M. L., Bracamonte, J. L., Beazley, S. G., Withnall, E., & Duke-Novakovski, T. (2014). Cardiopulmonary effects of an infusion of remifentanil or morphine in horses anesthetized with isoflurane and dexmedetomidine. *Veterinary Anaesthesia and Analgesia*, *41*, 346–356. https://doi.org/10.1111/vaa.12149

Bettschart-Wolfensberger, R., Clarke, K. W., Vainio, O., Aliabadi, F., & Demuth, D. (1999). Pharmacokinetics of medetomidine in ponies and elaboration of a medetomidine infusion regime which provides a constant level of sedation. *Research in Veterinary Science*, *67*, 41–46. https://doi.org/10.1053/rvsc.1998.0274

Bettschart-Wolfensberger, R., Freeman, S. L., Bowen, I. M., Aliabadi, F. S., Weller, R., Huhtinen, M., & Clarke, K. W. (2005). Cardiopulmonary effects and pharmacokinetics of i.v. dexmedetomidine in ponies. *Equine Veterinary Journal*, *37*, 60–64.

Bettschart-Wolfensberger, R., Jäggin-Schmucker, N., Lendl, C., Bettschart, R. W., & Clarke, K. W. (2001). Minimal alveolar concentration of desflurane in combination with an infusion of medetomidine for the anaesthesia of ponies. *Veterinary Record*, *148*, 264–267. https://doi.org/10.1136/vr.148.9.264

Bettschart-Wolfensberger, R., & Larenza, M. P. (2007). Balanced anesthesia in the equine. *Clinical Techniques in Equine Practice*, *6*, 104–110. https://doi.org/10.1053/j.ctep.2007.05.002

De Clercq, D., van Loon, G., Schauvliege, S., Tavernier, R., Baert, K., Croubels, S., … Deprez, P. (2008). Transvenous electrical cardioversion of atrial fibrillation in six horses using custom made cardioversion catheters. *The Veterinary Journal*, *177*, 198–204. https://doi.org/10.1016/j.tvjl.2007.08.019

Devisscher, L., Schauvliege, S., Dewulf, J., & Gasthuys, F. (2010). Romifidine as a constant rate infusion in isoflurane anaesthetized horses: A clinical study. *Veterinary Anaesthesia and Analgesia*, *37*, 425–433. https://doi.org/10.1111/j.1467-2995.2010.00556.x

Duke-Novakovski, T., Palacios-Jimenez, C., Wetzel, T., Rymes, L., & Sanchez-Teran, A. F. (2015). Cardiopulmonary effects of dexmedetomidine and ketamine infusions with either propofol infusion or isoflurane for anesthesia in horses. *Veterinary Anaesthesia and Analgesia*, *42*, 39–49. https://doi.org/10.1111/vaa.12194

Enderle, A. K., Levionnois, O. L., Kuhn, M., & Schatzmann, U. (2008). Clinical evaluation of ketamine and lidocaine intravenous infusions to reduce isoflurane requirements in horses under general anaesthesia. *Veterinary Anaesthesia and Analgesia*, *35*, 297–305. https://doi.org/10.1111/j.1467-2995.2007.00391.x

Gozalo-Marcilla, M., Gasthuys, F., & Schauvliege, S. (2014). Partial intravenous anaesthesia in the horse: A review of intravenous agents used to supplement equine inhalation anaesthesia. Part 1: Lidocaine and ketamine. *Veterinary Anaesthesia and Analgesia*, *41*, 335–345. https://doi.org/10.1111/vaa.12179

Gozalo-Marcilla, M., Gasthuys, F., & Schauvliege, S. (2015). Partial intravenous anaesthesia in the horse: A review of intravenous agents used to supplement equine inhalation anaesthesia. Part 2: Opioids and alpha-2 adrenoceptor agonists. *Veterinary Anaesthesia and Analgesia*, *42*, 1–16. https://doi.org/10.1111/vaa.12196

Gozalo-Marcilla, M., Hopster, K., Gasthuys, F., Hatz, L., Krajewski, A. E., & Schauvliege, S. (2013). Effects of a constant-rate infusion of dexmedetomidine on the minimal alveolar concentration of sevoflurane in ponies. *Equine Veterinary Journal*, *45*, 204–208. https://doi.org/10.1111/j.2042-3306.2012.00613.x

Gozalo-Marcilla, M., Hopster, K., Gasthuys, F., Krajewski, A. E., Schwarz, A., & Schauvliege, S. (2014). Minimum end-tidal sevoflurane concentration necessary to prevent movement during a constant rate infusion of morphine, or morphine plus dexmedetomidine in ponies. *Veterinary Anaesthesia and Analgesia*, *41*, 212–219. https://doi.org/10.1111/vaa.12090

Gozalo-Marcilla, M., Steblaj, B., Schauvliege, S., Duchateau, L., & Gasthuys, F. (2013). Comparison of the influence of two different constant-rate infusions (dexmedetomidine versus morphine) on anaesthetic requirements, cardiopulmonary function and recovery quality in isoflurane anaesthetized horses. *Research in Veterinary Science*, *95*, 1186–1194. https://doi.org/10.1016/j.rvsc.2013.09.014

Grimsrud, K. N., Ait-Oudhia, S., Durbin-Johnson, B. P., Rocke, D. M., Mama, K. R., Rezende, M. L., … Jusko, W. J. (2015). Pharmacokinetic and pharmacodynamic analysis comparing diverse effects of detomidine, medetomidine, and dexmedetomidine in the horse: A population analysis. *Journal of Veterinary Pharmacology and Therapeutics*, *38*, 24–34. https://doi.org/10.1111/jvp.12139

Grimsrud, K. N., Mama, K. R., Steffey, E. P., & Stanley, S. D. (2012). Pharmacokinetics and pharmacodynamics of intravenous medetomidine in the horse. *Veterinary Anaesthesia and Analgesia*, *39*, 38–48. https://doi.org/10.1111/j.1467-2995.2011.00669.x

Grimsrud, K. N., Mama, K. R., Thomasy, S. M., & Stanley, S. D. (2009). Pharmacokinetics of detomidine and its metabolites following intravenous and intramuscular administration in horses. *Equine Veterinary Journal*, *41*, 361–365. https://doi.org/10.2746/042516409X370900

Guedes, A. G. P., Tearney, C. C., Cenani, A., Aristizabal, F., & Nieto, J. (2017). Comparison between the effects of postanesthetic xylazine and dexmedetomidine on characteristics of recovery from sevoflurane anesthesia in horses. *Veterinary Anaesthesia and Analgesia*, *44*, 273–280. https://doi.org/10.1016/j.vaa.2016.04.002

Hopster, K., Müller, C., Hopster-Iversen, C., Stahl, J., Rohn, K., & Kästner, S. (2014). Effects of dexmedetomidine and xylazine on cardiovascular function during total intravenous anaesthesia with midazolam and ketamine and recovery quality and duration in horses. *Veterinary Anaesthesia and Analgesia*, *41*, 25–35. https://doi.org/10.1111/vaa.12095

Howick, J., Chalmers, I., Glasziou, P., Greenhalgh, T., Heneghan, C., Liberati, A., … Thornton, H. (2011) *The 2011 Oxford Levels of Evidence (Introductory Document)*. OCEBM Levels of Evidence Working Group, Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/ocebm-levels-of-evidence/.

Johnston, G. M., Eastment, J. K., Wood, J. L. N., & Taylor, P. M. (2002). The confidential enquiry into perioperative equine fatalities (CEPEF): Mortality results of Phases 1 and 2. *Veterinary Anaesthesia and Analgesia*, *29*, 159–170. https://doi.org/10.1046/j.1467-2995.2002.00106.x

Kalchofner, K. S., Ringer, S. K., Boller, J., Kästner, S. B., Lischer, C., & Bettschart-Wolfensberger, R. (2006). Clinical assessment of anesthesia with isoflurane and medetomidine in 300 equidae. *Pferdeheilkunde*, *22*, 301–308. https://doi.org/10.21836/PEM20060309

Kharasch, E. D., Herrmann, S., & Labroo, R. (1992). Ketamine as a probe for medetomidine stereoisomer inhibition of human liver microsomal drug metabolism. *Anesthesiology*, *77*, 1208–1214. https://doi.org/10.1097/00000542-199212000-00023

Knych, H. K., Stanley, S. D., McKemie, D. S., Arthur, R. M., & Kass, P. H. (2017). Pharmacokinetic and pharmacodynamics of xylazine administered to exercised thoroughbred horses. *Drug Testing and Analysis*, *9*, 713–720. https://doi.org/10.1002/dta.2047

Kuusela, E., Raekallio, M., Anttila, M., Falck, I., Mölsä, S., & Vainio, O. (2000). Clinical effects and pharmacokinetics of medetomidine and its enantiomers in dogs. *Journal of Veterinary Pharmacology and Therapeutics*, *23*, 15–20. https://doi.org/10.1046/j.1365-2885.2000.00245.x

Lizarraga, I., Castillo-Alcala, F., & Robinson, L. S. (2017). Comparison of sedation and mechanical antinociception induced by intravenous administration of acepromazine and four dose rates of dexmedetomidine in donkeys. *Veterinary Anaesthesia and Analgesia*, *44*, 509–517. https://doi.org/10.1016/j.vaa.2016.08.003

Lizarraga, I., & Janovyak, E. (2013). Comparison of the mechanical hypoalgesic effects of five α2-adrenoceptor agonists in donkeys. *Veterinary Record*, *173*, 294. https://doi.org/10.1136/vr.101684

Marcilla, M. G., Schauvliege, S., Duchateau, L., & Gasthuys, F. (2010). Cardiopulmonary effects of two constant rate infusions of dexmedetomidine in isoflurane anaesthetized ponies. *Veterinary Anaesthesia and Analgesia*, *37*, 311–321. https://doi.org/10.1111/j.1467-2995.2010.00537.x

Marcilla, M. G., Schauvliege, S., Segaert, S., Duchateau, L., & Gasthuys, F. (2012). Influence of a constant rate infusion of dexmedetomidine on cardiopulmonary function and recovery quality in isoflurane anaesthetized horses. *Veterinary Anaesthesia and Analgesia*, *39*, 49–58. https://doi.org/10.1111/j.1467-2995.2011.00672.x

Marly-Voquer, C., Schwarzwald, C. C., & Bettschart-Wolfensberger, R. (2016). The use of dexmedetomidine continuous rate infusion for horses undergoing transvenous electrical cardioversion - A case series. *Canadian Veterinary Journal*, *57*, 70–75.

Medeiros, L. Q., Gozalo-Marcilla, M., Taylor, P. M., Campagnol, D., Oliveira, F. A., Watanabe, M. J., & Aguiar, A. J. A. (2017) *Sedative and cardiopulmonary effects of dexmedetomidine infusions randomly receiving, or not, butorphanol in standing horses*. *Veterinary Record*, 181, 402. https://doi.org/10.1136/vr.104359

Müller, C., Hopster, K., Hopster-Iversen, C., Rohn, K., & Kästner, S. B. R. (2012). Elaboration of a xylazine and dexmedetomidine infusion regime which provides a constant level of sedation in horses. *Pferdeheilkunde*, *28*, 668–674.

Neudeck, S., Hopster, K., & Kästner, S. B. R. (2016) Comparison of desflurane and propofol at equipotent dosages in combination with a constant-rate infusion of dexmedetomidine on global and regional perfusion and oxygenation in horses. *Proceedings of AVA Spring Meeting Lyon, France*, 20-22 April 2016, p.142.

Pöppel, N., Hopster, K., Geburek, F., & Kästner, S. (2015). Influence of ketamine or xylazine supplementation on isoflurane anaesthetized horses–a controlled clinical trial. *Veterinary Anaesthesia and Analgesia*, *42*, 30–38. https://doi.org/10.1111/vaa.12176

Ranheim, B., Risberg, Å. I., Spadavecchia, C., Landsem, R., & Haga, H. A. (2015). The pharmacokinetics of dexmedetomidine administered as a

constant rate infusion in horses. *Journal of Veterinary Pharmacology and Therapeutics*, *38*, 93–96. https://doi.org/10.1111/jvp.12157

Rezende, M. L., Grimsrud, K. N., Stanley, S. D., Steffey, E. P., & Mama, K. R. (2015). Pharmacokinetics and pharmacodynamics of intravenous dexmedetomidine in the horse. *Journal of Veterinary Pharmacology and Therapeutics*, *38*, 15–23. https://doi.org/10.1111/jvp.12138

Risberg, Å. I., Ranheim, B., Krontveit, R. I., Lervik, A., & Haga, H. A. (2016). The cardiovascular status of isoflurane-anaesthetized horses with and without dexmedetomidine constant rate infusion evaluated at equivalent depths of anaesthesia. *Veterinary Anaesthesia and Analgesia*, *43*, 412–423. https://doi.org/10.1111/vaa.12315

Risberg, A., Spadavecchia, C., Ranheim, B., Krontveit, R., & Haga, H. A. (2014). Antinociceptive effects of three escalating dexmedetomidine and lignocaine constant rate infusions in conscious horses. *The Veterinary Journal*, *202*, 489–497. https://doi.org/10.1016/j.tvjl.2014.09.007

Sacks, M., Ringer, S. K., Bischofberger, A. S., Berchtold, S. M., & Bettschart-Wolfensberger, R. (2017). Clinical comparison of dexmedetomidine and medetomidine for isoflurane balanced anaesthesia in horses. *Veterinary Anaesthesia and Analgesia*, *44*, 1128–1138. https://doi.org/10.1016/j.vaa.2016.12.061

Santos, M., Fuente, M., Garcia-Iturralde, R., Herran, R., Lopez-Sanroman, J., & Tendillo, F. J. (2003). Effects of alpha-2 adrenoceptor agonists during recovery from isoflurane anaesthesia in horses. *Equine Veterinary Journal*, *35*, 170–175.

Savola, J. M., & Virtanen, R. (1991). Central alpha 2-adrenoceptors are highly stereoselective for dexmedetomidine, the dextro enantiomer of medetomidine. *European Journal of Pharmacology*, *195*, 193–199. https://doi.org/10.1016/0014-2999(91)90535-X

Schauvliege, S., Marcilla, M. G., Verryken, K., Duchateau, L., Devisscher, L., & Gasthuys, F. (2011). Effects of a constant rate infusion of detomidine on cardiovascular function, isoflurane requirements and recovery quality in horses. *Veterinary Anaesthesia and Analgesia*, *38*, 544–554. https://doi.org/10.1111/j.1467-2995.2011.00659.x

Segal, I. S., Vickery, R. G., Walton, J. K., Doze, V. A., & Maze, M. (1988). Dexmedetomidine diminishes halothane anesthetic requirements in rats through a postsynaptic alpha 2 adrenergic receptor. *Anesthesiology*, *69*, 818–823. https://doi.org/10.1097/00000542-198812000-00004

Taylor, P., Coumbe, K., Henson, F., Scott, D., & Taylor, A. (2014). Evaluation of sedation for standing clinical procedures in horses using detomidine combined with buprenorphine. *Veterinary Anaesthesia and Analgesia*, *41*, 14–24. https://doi.org/10.1111/vaa.12055

Wittenberg-Voges, L., Hopster, K., Raekallio, M., Kästner, S. B. R., & Vainio, O. M. (2016) Effect of dexmedetomidine and xylazine followed by MK-467 on gastrointestinal microperfusion in anaesthetized horses. *Proceedings of AVA Spring Meeting Lyon*, France, 20-22 April 2016, p.44.

Wojtasiak-Wypart, M., Soma, L. R., Rudy, J. A., Uboh, C. E., Boston, R. C., & Driessen, B. (2012). Pharmacokinetic profile and pharmacodynamic effects of romifidine hydrochloride in the horse. *Journal of Veterinary Pharmacology and Therapeutics*, *35*, 478–488. https://doi.org/10.1111/j.1365-2885.2011.01347.x

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APPENDIX 1 Levels of evidence are categorized and reported adapted from Howick et al. (2011)

Level of evidence	Description
I	Evidence obtained from a systematic review of all relevant controlled trials
II	Evidence obtained from at least one properly designed, randomized controlled trial
III-1	Evidence obtained from well-designed, pseudorandomized controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomized (cohort studies), case–control studies or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical controls, two or more single-arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pretest and post-test
V	Expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”