SHORT COMMUNICATION

Clinical effects of two doses of butorphanol with detomidine for intravenous premedication of healthy warmblood horses

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Abstract

Objective To compare the effects of two different doses of butorphanol combined with detomidine administered intravenously (IV) on quality of sedation, degree of ataxia and anaesthetic induction in horses.

Study design Randomized, blinded, clinical study.

Animals A total of 40 client-owned healthy warmblood horses scheduled for elective surgery under general anaesthesia.

Methods Horses were randomly allocated to be administered 8 μg kg^{-1} detomidine IV plus either 20 or 50 μg kg^{-1} butorphanol IV, with the principal investigator blinded to group allocation. Head height was measured before drug injection and 2 minutes thereafter. Data were compared using unpaired *t* test. Horses were filmed and scored using Simple Descriptive Scales for sedation (2 and 15 minutes after IV injection), ataxia (at walk, immediately after the 2 minute time point) and quality of swing-door induction following diazepam and ketamine administration. Data are shown as median (and range where appropriate). Scores were compared using chi-square tests ($p < 0.05$).

Results There were 14 and 17 horses in high-dose (HD) and low-dose (LD) groups respectively. Data from nine horses were excluded. Mean head height reduction did not differ between groups ($p = 0.86$), nor did sedation scores at 2 minutes (median = 3 in both groups; $p = 0.09$) or 15 minutes (median = 2 in both groups; $p = 0.63$). There was no significant difference in the requirement for additional detomidine ($p = 0.73$) or in induction quality between groups ($p = 0.99$), but initial ataxia was significantly greater in the HD group 2 (1–3) *versus* 2.5 (1–3) in the LD group ($p = 0.017$).

Conclusions and clinical relevance: In healthy warmblood horses, simultaneous administration of 50 rather than 20 μg kg^{-1} butorphanol with 8 μg kg^{-1} detomidine does not provide greater sedation or affect induction, but it causes more pronounced ataxia shortly after IV injection.

Keywords ataxia, butorphanol, detomidine, premedication, sedation.

Introduction

α_2-Adrenoceptor agonists are often combined with opioids for premedication of horses before general anaesthesia. Butorphanol is a κ-agonist opioid that is commonly used for this purpose in equine practice.

The combination of butorphanol with detomidine or romifidine administered intravenously (IV) produces improved sedation compared to administration of the α_2-adrenoceptor agonist alone (Taylor et al. 1988; DeRossi et al. 2009), while affording limited surgical analgesia (Rigotti et al. 2014). Importantly, ataxia was worse when butorphanol was added to romifidine-based sedation (Ringer et al. 2012b).

The dose of butorphanol detailed on the datasheet for anaesthetic premedication combined with (me)detomidine or romifidine is 20–25 μg kg^{-1} IV, which is lower than the recommended (datasheet) dose for acute visceral (colic) analgesia (100 μg kg^{-1} IV). Although butorphanol's analgesic effects are dose-dependent (Kalpravidh et al. 1984), it remains unclear whether this is true for its effect on the level of sedation in horses, when combined with α_2-adrenoceptor agonists. To be of clinical benefit for anaesthetic premedication, the enhanced sedation achieved when a higher dose of butorphanol is combined with detomidine must not be accompanied by an unacceptable worsening of ataxia.

The aims of this study were to compare the effects of two different doses of butorphanol in combination with a standard dose of detomidine administered IV, on the level of sedation, degree of ataxia and quality of induction in healthy warmblood horses.

Materials and methods

Study design and settings

The study design was a randomized, masked, clinical study using client-owned horses. The study was designed and performed at the Utrecht University Equine Clinic, Utrecht, The Netherlands.

Sample size estimation

With an estimated 46% of horses assigned the maximum sedation score on a 4-point scale in the low-dose (LD) group (based on Taylor et al. 1988) *versus* 84% in the high-dose (HD) group (DeRossi et al. 2009), an α level of 0.05 and statistical power $(1-\beta)$ of 80%, it was determined that 18 horses per group would be needed. Assuming a 10% attrition rate, a total of 40 horses would need to be enrolled.

Animal inclusion

The Utrecht University Institutional Animal Experimentation and Welfare officers were consulted, and they judged this study to be exempt from formal ethical approval requirement. As client-owned animals were used, informed consent was obtained from the owner upon admission of the animal to the Utrecht University Equine Clinic before surgery. Inclusion criteria were: warmblood horse; age > 2 years old; American Society of Anaesthesiologists (ASA) physical status classification I or II; requirement for general anaesthesia. Exclusion criteria were: concurrent administration of other sedatives or tranquilisers; contraindication to detomidine or butorphanol administration; planned standing or major surgery. Horses were weighed and screened for eligibility upon preanaesthetic physical examination. Horses were housed in individual box stalls and allowed food and water up to 2 hours before surgery.

Study protocol

Horses were randomly allocated to one of two groups by blind draw from an envelope containing folded ballots. The LD group were administered 8 μg kg^{-1} detomidine (Domosedan; Orion, Finland) with 20 μg kg^{-1} butorphanol (Dolorex; Intervet, The Netherlands) IV, whereas the HD group were administered 8 μg kg^{-1} detomidine with 50 μg kg^{-1} butorphanol IV. Both drugs were combined in the same syringe, made up to a total volume of 5 mL with sterile saline (BBraun, Germany) labelled 'premedication' by a veterinarian or technician not involved in further study execution.

Immediately prior to IV injection of premedication drugs by the principal investigator (JdG), baseline head height (cm, lower lip—floor) was recorded by the same investigator using a tape measure, while the horse was allowed to carry its head in a natural position with a halter and no tension on the rope (Love et al. 2011). Premedication was administered by IV injection over 10 seconds via a 21 gauge needle (BD microlance 3; Becton Dickinson, UK) into the left jugular vein, with blood aspirated and re-injected before, midway and at the conclusion of the injection. Horses were left undisturbed for exactly 2 minutes, after which head height was again recorded and a sedation score assigned using a Simple Descriptive Scale (SDS; Appendix S1). The horse was taken out of the stall and walked to the induction room while an ataxia score was assigned (Appendix S1). Video recordings of the sedated horse in the stall and at walk were obtained for review by a second masked observer (TvL) after study conclusion.

Upon arrival in the induction room, the horse's mouth was flushed, the halter was changed and an area over the right or left jugular vein was clipped and prepared for catheter placement. At 15 minutes after IV premedication and just before catheter insertion, horses were again videotaped, and a sedation score was assigned. Sedation was again scored after the horse was placed in the swing-door induction stand. If the score was less than 2, an additional 5μg kg^{-1} dose of detomidine was administered IV and 2 minutes was allowed for this to take effect. The number of additional detomidine doses required to achieve a score ≥ 2 was recorded. Anaesthesia was induced with diazepam (Diazepam; Centrafarm, The Netherlands; 0.06 mg kg^{-1}) and ketamine (Narketan; Vetoquinol, France; 2.2 mg kg^{-1}) IV, with the head restrained with a rope. Quality of induction was scored (Appendix S1) and the time recorded.

Data analysis

Computer software was used (SPSS 25.0.1; IBM Corp., NY, USA). Age, body weight, time, and percentage reduction in head height relative to baseline were compared between groups using unpaired *t* tests. Scores for sedation, ataxia and quality of induction were compared using chi-square analysis. Interobserver reliability of sedation and ataxia scoring was assessed using Cronbach α. Statistical significance was set at $p < 0.05$. Data are presented as mean ± standard deviation (SD) for continuous variables, and median (range; minimum — maximum) for categorical variables.

Results

A total of 40 horses were enrolled, with 20 horses randomly allocated to each group. Data from nine horses were excluded from statistical analysis because of protocol violations. Hence, data from 31 horses ($n = 17$ LD, $n = 14$ HD) were analysed.

Mean age (LD: 6.9 ± 3.3 years, HD: 6.7 ± 3.2 years; $p = 0.82$) and body weight (LD: 533 ± 74, HD: 553 ± 75; $p = 0.47$) did not differ significantly between groups. Interobserver reliability was good for both sedation (Cronbach α 0.84; $p < 0.001$) and ataxia scores (Cronbach $\alpha = 0.80$; $p < 0.001$).

Occasional head or muzzle twitching was noted in both groups after detomidine and butorphanol co-administration but was not recorded quantitatively. Relative reduction in head height did not differ significantly between groups ($p = 0.86$; Table 1). Although 13 out of 14 horses in the HD group compared with 10 out of 17 horses in the LD group were awarded the highest sedation score (3) at 2 minutes, this difference did not reach statistical significance ($p = 0.09$, Table S1). Sedation scores were almost identically distributed in the LD and the HD groups at $t = 15$ minutes ($p = 0.63$; Table S1).

Ataxia at walk was significantly more pronounced in the HD group ($p = 0.017$; Table 1), with 50% of HD horses assigned the maximum ataxia score of 3, *versus* 6% in the LD group (Table S1). There was no significant difference in additional detomidine requirement, time from premedication to induction, or quality of induction (Table 1) between groups. Induction was rated 'good' or 'excellent' in 94% of animals (Table S1).

Discussion

This study reports the level of sedation, degree of ataxia and quality of anaesthetic induction after premedication of healthy mature warmblood horses with 8 μg kg^{-1} detomidine administered IV with either 20 or 50 μg kg^{-1} butorphanol.

Table 1 Effects of premedication on relative reduction in head height, additional doses of detomidine, sedation score, ataxia score and induction score of healthy mature warmblood horses administered 8 μg kg^{-1} detomidine and 20 μg kg^{-1} (low dose, LD) or 50 μg kg^{-1} (high dose, HD) butorphanol intravenously. Data are shown as mean ± standard deviation or median (minimum − maximum range), where *n* is the number of horses; $p < 0.05$ is considered significant

Variable	LD ($n = 17$)	HD ($n = 14$)	*p* value
Relative reduction in head height (% from baseline)	48.7 ± 22.7	47.4± 17.1	0.86
Horses needing additional detomidine (proportion)	10/17 (59)	7/14 (50)	0.73
Horses needing two additional detomidine doses (proportion)	2/17 (12)	1/14 (7)	0.99
Sedation score	3 (1−3)	3 (2−3)	0.09
T = 2 minutes	2 (0−3)	2 (1−3)	0.63
T = 15 minutes			
Ataxia score	2 (1−3)	2.5 (1−3)	0.017
Induction score	1 (0−2)	1 (0−2)	0.72
Time premedication − induction (minutes)	25.8 ± 6.9	26.2 ± 8.2	0.89

Improved sedation and enhanced analgesia after the combination of butorphanol with an α_2-adrenoceptor agonist has been noted in multiple studies (Clarke et al. 1991; DeRossi et al. 2009) and is the basis of its use for equine premedication. However, not all studies have found unequivocal improvement of sedation when butorphanol was added, compared to the α_2-adrenoceptor agonist alone (Love et al. 2011; Ringer et al. 2012a,b). As far as the authors are aware, no formal dose−response study for butorphanol enhancement of detomidine-based sedation or ataxia has been published. In the current study, observer blinded evaluation of two different dosages of butorphanol administered with the same dose of the α_2-adrenoceptor agonist was performed. Using this study design, we determined whether a higher dose of butorphanol resulted in enhanced sedation or ataxia or both and how it affected the quality of subsequent anaesthetic induction.

With respect to the level of sedation, there appeared to be no benefit in combining detomidine with 50 μg kg^{-1} dose of butorphanol compared to the lower 20 μg kg^{-1} (datasheet) dose. We found a nonsignificant trend for an increased level of sedation 2 minutes after IV injection with the higher dose of butorphanol. The exclusion of six HD horses resulted in a 7.4% power loss, which may have caused failure to reach statistical significance. However, this study still had >80% power to detect a 42% (rather than the *a priori* 38%) difference in the proportion of horses achieving the maximum sedation score. Therefore the impact of the loss of statistical power is considered limited. Any dose effect on sedation was short-lived, as it had waned completely by the time the horse reached the induction room (a distance of approximately 200−300 m taking on average 3 minutes). It is important to note that we did not evaluate quality of sedation, but only the level of sedation, i.e. the degree of sedation without external stimuli imposed (Ringer et al. 2012a). Also, any potential enhancement of analgesia was not evaluated. It is possible that for brief noxious procedures, a higher dose of butorphanol could transiently provide a better quality of sedation.

When combining a higher dose of butorphanol with detomidine, the risk of more profound ataxia should be weighed against the potential for a greater level of sedation. In the current study, ataxia was significantly aggravated by the combination of detomidine with 50 rather than 20 μg kg^{-1} butorphanol. More ataxia was reported after the addition of butorphanol (18 μg kg^{-1}) to romifidine- and xylazine-based sedation (Ringer et al. 2012a,b); the bolus dose of butorphanol used in the latter study was lower than the 'low dose' used in our study, and no higher dose was investigated. In the current study, ataxia was only evaluated at one time point for

practical reasons; therefore the more profound ataxia associated with the higher dose of butorphanol may be short-lived. However, if the combination is injected IV and the horse still has to walk some distance to the induction area, marked swaying (seen in seven HD horses) or even stumbling (seen in two HD horses) should be anticipated when 50 rather than 20 μg kg^{-1} butorphanol is co-administered.

The higher dose of butorphanol did not reduce the requirement for additional detomidine prior to anaesthetic induction, nor was there a group difference in subsequent quality of induction. Importantly, as 50% or more of horses in both groups required additional detomidine prior to induction, this is a major confounding factor and induction quality may not reflect the initial butorphanol dose. The time between premedication and induction was on average 26 minutes, which may also have reduced the likelihood of detecting a difference between groups. The horses that required additional detomidine were not necessarily those in which more time had elapsed between premedication and induction. This indicates that despite the imposed age and breed limitations, interindividual variability (horse effects) probably affected the level of sedation (Clarke et al. 1991; Ringer et al. 2013). A separate 'temperament' score might have been useful to address individual horse effects. External stimuli were controlled where possible within the clinical setting by using the same room and following the same sequence of events for each horse.

We conclude that combining a higher (50 μg kg^{-1}) rather than a lower (20 μg $kg^{-1)}$ dose of butorphanol with 8 μg kg^{-1} detomidine administered IV did not provide a significantly greater level of sedation. The higher dose did not reduce the requirement for additional detomidine prior to anaesthetic induction nor did it affect the quality of anaesthetic induction. However, it caused greater ataxia shortly after IV injection in healthy warmblood horses premedicated for general anaesthesia.

Authors' contributions

JdG: study design, data interpretation, statistical analysis, and preparation of manuscript. TvL: study design, data management, preparation of manuscript.

Conflict of interest statement

The authors declare no conflict of interest.

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Supporting Information

Additional Supporting Information related to this article can be found at https://doi.org/10.1016/j.vaa.2019.11.010.

Appendix S1 Simple Descriptive Scales (SDS) used to assess level of sedation, degree of ataxia, and quality of anaesthetic induction in healthy mature warmblood horses premedicated with 8 μg kg^{-1} detomidine and 20 μg kg^{-1} (LD; $n = 17$) or 50 μg kg^{-1} (HD; $n = 14$) butorphanol administered IV.

Variable	Score	Description	Criteria
Sedation	0	None	Head carried normally, attentive ears and eyes, normally responsive to external stimuli (auditory, visual)
	1	Mild sedation	Head slightly lowered, reduced focus of eyes and ears, but easily aroused by external stimuli
	2	Moderate sedation	Head below withers, reduced focus of ears and eyes, reduced response to external stimuli
	3	Profound sedation	Head near ground height, eyes partly closed and/or ears sideways, markedly reduced response to external stimuli
Ataxia	0	None	Does not drag toes, no hesitance to leave stall, no deviation from straight line, no overshooting in bends
	1	Mild ataxia	Drags toes slightly, hesitant when leaving stall, slight lateral deviations on straight line, slightly overshooting in bends
	2	Moderate ataxia	Drags toes, hesitant to leave stall, obvious lateral deviations from straight line that do not need correction on the tail
	3	Severe ataxia	Drags toes, may need support/correction at the head to navigate stall door, marked lateral deviations from straight line needing constant tail support
Induction quality	0	Excellent	Smooth relaxation without momentary tension or excitation, hindquarters relax before forequarters
	1	Good	Smooth relaxation without excitation, but a moment of tension may be seen, or the hindquarters relax after the front
	2	Acceptable	Horse becomes recumbent after <10 seconds of excitation; hindquarters may relax after front; horse does not need immediate top-up medication
	3	Poor	Horse becomes recumbent after >10 seconds of excitation, hindquarters may relax after front; horse needs immediate top-up medication once recumbent
	4	Catastrophic	Horse does not become recumbent and/or breaks loose from induction box, (risk of) serious injury to horse and/or personnel

Sedation and ataxia scores modified from Ringer et al. (2013) and Taylor et al. (2014), and induction score modified from Wakuno et al. (2017).

