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RESEARCH PAPER

Development of a xylazine constant rate infusion with or without butorphanol for standing sedation of horses

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Abstract

Objective To elaborate constant rate infusion (CRI) protocols for xylazine (X) and xylazine/butorphanol (XB) which will result in constant sedation and steady xylazine plasma concentrations.

Study design Blinded randomized experimental study.

Animals Ten adult research horses.

Methods Part I: After normal height of head above ground (HHAG = 100%) was determined, a loading dose of xylazine (1 mg kg^{-1}) with butorphanol (XB: 18 μg kg^{-1}) or saline (X: equal volume) was given slowly intravenously (IV). Immediately afterwards, a CRI of butorphanol (XB: 25 μg kg^{-1} $hour^{-1}$) or saline (X) was administered for 2 hours. The HHAG was used as a marker of depth of sedation. Sedation was maintained for 2 hours by additional boluses of xylazine (0.3 mg kg^{-1}) whenever HHAG >50%. The dose of xylazine (mg kg^{-1} $hour^{-1}$) required to maintain sedation was calculated for both groups. Part II: After the initial loading dose, the calculated xylazine infusion rates were administered in parallel to butorphanol (XB) or saline (X) and sedation evaluated. Xylazine plasma concentrations were measured by HPLC-MS-MS at time points 0, 5, 30, 45, 60, 90, and 120 minutes. Data were analyzed using paired *t*-test, Wilcoxon signed rank test and a 2-way ANOVA for repeated measures ($p < 0.05$).

Results There was no significant difference in xylazine requirements (X: 0.69, XB: 0.65 mg kg^{-1} $hour^{-1}$) between groups. With treatment X, a CRI leading to prolonged sedation was developed. With XB, five horses (part I: two, part II: three) fell down and during part II four horses appeared insufficiently sedated. Xylazine plasma concentrations were constant after 45 minutes in both groups.

Conclusion Xylazine bolus, followed by CRI, provided constant sedation. Additional butorphanol was ineffective in reducing xylazine requirements and increased ataxia and apparent early recovery from sedation in unstimulated horses.

Clinical relevance Data were obtained on unstimulated healthy horses and extrapolation to clinical conditions requires caution.

Keywords ataxia, butorphanol, constant rate infusion, horses, sedation, xylazine.

Introduction

Equine anaesthesia carries a high risk of mortality when compared to general anaesthesia in many species, the overall mortality in horses being 0.24–

1.9% (Johnston et al. 2002, 2004; Bidwell et al. 2007) compared to 0.17–0.24% in cats and dogs (Brodbelt et al. 2008) and <0.002% in humans (Gibbs & Rodoreda 2005). Surgical procedures or diagnostic techniques therefore are performed in the standing, sedated horse whenever possible. However, insufficiently sedated horses undergoing diagnostic procedures or surgical interventions may not tolerate auditory, tactile, or painful stimuli, and may respond with defensive or aggressive behaviour that can be dangerous for people involved. Thus a reliable sedation protocol is essential.

Horses commonly are sedated with a single bolus dose of an alpha$_2$-adrenergic agonist or, more usually, a combination of alpha$_2$-adrenergic agonist with an opioid agent. However, at the doses used, duration of action is usually short, and repeated boluses of alpha$_2$-adrenergic agonists often are required even for minor surgical procedures. Bolus doses of alpha$_2$-adrenergic agonists cause marked changes in vessel tone, together with bradycardia and a consequential fall in cardiac output (England & Clarke 1996; Bettschart-Wolfensberger et al. 1999a). However, with a constant rate infusion (CRI) repeated dosing is unnecessary and, at least with the alpha$_2$-adrenergic agonist medetomidine, (Bettschart-Wolfensberger et al. 1999a), cardiopulmonary function is well maintained. Therefore, a CRI of alpha$_2$-adrenergic agonists is likely to be safer than the administration of repeated boluses as well as allowing a more constant level of sedation and resultant improved flow of work during surgical procedures. To date, only the alpha$_2$-adrenergic agonists detomidine and medetomidine have been studied as CRIs for prolonged standing sedation (Daunt et al. 1993; Wertz et al. 1994; Bettschart-Wolfensberger et al. 1999b; Aguiar et al. 2009; Solano et al. 2009). Xylazine is the shortest acting alpha$_2$-adrenergic agonist (England et al. 1992). Despite the fact that xylazine, contrary to medetomidine, has been registered for use in horses since 1970, its use as CRI for standing sedation has not been studied extensively. A CRI of xylazine has been used during a xylazine antagonism study (Kollias-Baker et al. 1993), the dose rate used being calculated based on experimental data from kinetic studies, but to our knowledge, there are no other published studies.

A problem with horses sedated with alpha$_2$-adrenergic agonists is that they may respond suddenly to stimulation, especially to touch (England et al. 1996). This response, if unexpected, may be dangerous both to the horse and people involved. The combination of opioid drugs with the alpha$_2$-adrenergic agonists appears to reduce such sudden reactions and a synergistic effect regarding sedation and antinociception has been suggested (England et al. 1996; Schatzman et al. 2001; Kohler et al. 2004; Corletto et al. 2005; Kruluc & Nemec 2006; DeRossi et al. 2009). Additionally, all alpha$_2$-adrenergic agonists have a dose-dependent effect on cardiovascular function (Yamashita et al. 2000). By adding an opioid drug, dose requirements of alpha$_2$-adrenergic agonists may be reduced and cardiopulmonary function improved. The addition of opioids does not further impair cardiovascular function (Clarke et al. 1991; Rutkowski et al. 1991). A CRI resulting in constant plasma concentrations in the range associated with analgesia, without important side effects, has been developed for the opioid butorphanol (Sellon et al. 2001). Butorphanol tartrate is a synthetic opioid with agonist-antagonist properties. It is convenient to use, as in most countries it is not subject to such stringent controls as are some other opioids. Furthermore the combination of xylazine and butorphanol at the doses generally used in clinical practice produces minimal and transient haemodynamic effects and no significant respiratory depression (Robertson & Muir 1983). To our knowledge, there is no 'blinded' randomized crossover study regarding the xylazine sparing effects of butorphanol on sedation of horses.

The aim of this study was to elaborate CRI dosing protocols for xylazine and xylazine combined with butorphanol respectively in standing horses, so as to provide deep, constant sedation and steady state plasma concentrations of xylazine. The study was carried out in two parts. In part I, the doses of xylazine necessary to produce a constant level of sedation were found, and a suitable infusion dose calculated from these. In part II, this infusion rate was tested to see if it gave constant sedation, and xylazine plasma concentrations were measured. We hypothesized that a CRI of xylazine can provide constant sedation and constant plasma concentrations and that butorphanol reduces xylazine dose requirements.

Materials and methods

This study was approved by the Ethical Committee of the National Veterinary School of Lyon (N°0807, May 13th 2008). The study was carried out in two parts.

