Veterinary Anaesthesia and Analgesia, 2002, 29, 219–222

BRIEF COMMUNICATION

Serum concentrations and effects of detomidine delivered orally to horses in three different mediums

Edward C Ramsay* DVM, Diplomate ACZM, Dennis Geiser† DVM, Diplomate ABVP, Wyndee Carter‡ BS & Thomas Tobin‡ MVB, PhD

*Department of Comparative Medicine, The University of Tennessee, Knoxville, TN, USA

†Large Animal Clinical Sciences, The University of Tennessee, Knoxville, TN, USA

‡Maxwell H. Gluck Equine Research Center, Department of Veterinary Science, University of Kentucky, Lexington, KY, USA

Correspondence: Dr Ed Ramsay, Department of Comparative Medicine, PO Box 1071, Knoxville, Tennessee 37901–1071, USA.
E-mail: eramsay@utk.edu

Abstract

Objective To compare the effect of orally delivered detomidine on head posture when administered alone or in combination with two different food items, and to determine the serum concentrations of detomidine after oral delivery.

Study Design Prospective randomized experimental study.

Animals Fifteen adult grade mares weighing 328–537 kg.

Methods The horses were randomly assigned to one of the three treatment groups (five horses each). The groups were given detomidine (0.06 mg kg^{-1}): alone; mixed with 3 mL of an apple sauce and gum mixture; or mixed with 3 mL molasses. Head droop, measured before treatment and at 15, 30, 45, 60, 75, 90, and 105 minutes after treatment, was used to evaluate sedation. Yohimbine (0.1 mg kg^{-1} IV) was administered after the 90-minute evaluation. Blood samples were collected from the detomidine-alone group before treatment and at 15, 30, 45, 60, 75, and 90 minutes after treatment. Sera were analyzed for detomidine equivalent concentrations by an ELISA. Head droop percentages were compared using a repeated measures analysis of variance.

Results Significant mean head droop developed in each treatment group by 30 minutes and persisted until reversal with yohimbine. After yohimbine administration, head positions returned to 87–91% of pre-treatment levels. There were no significant differences among the oral treatment groups at any time. Mean serum detomidine equivalents increased slowly until 45-minute post-administration, but never exceeded 30 ng mL^{-1}.

Conclusions Orally administered detomidine results in measurable serum drug concentrations using any of the delivery mediums investigated, and can be expected to produce profound head droop in horses approximately 45 minutes after administration.

Keywords delivery mediums, detomidine, horse, oral delivery, sedation, yohimbine.

Introduction

In veterinary medicine, sedative agents are most commonly administered parenterally, and relatively little attention has been paid to their use via oral administration. One previous study demonstrated that sublingually delivered detomidine effectively sedated horses (Malone & Clark 1993). The present study compared the effect of orally delivered detomidine on head posture when administered alone or mixed with two delivery vehicles to horses. Drug absorption was evaluated by measuring serum detomidine equivalent concentrations produced by oral detomidine administration without a delivery medium.

Materials and methods

Fifteen mixed breed, healthy, adult mares (body weight range = 328–537 kg; median = 420 kg) were moved to individual stocks, 30–60 minutes prior to drug administration. The horses were held in stocks during the treatment trials.

Prior to drug administration, an intravenous jugular catheter was placed percutaneously. A blood sample (2–3 mL) was collected via the catheter, immediately following catheter placement and at 15, 30, 45, 60, 75, and 90-minute post-detomidine or detomidine/food mixture administration. Blood was allowed to clot, centrifuged, and the serum was separated and frozen at −70 C until drug analysis.

Horses were randomly assigned to three treatment groups (five horses each). Each group received 0.06 mg kg^{-1} detomidine (Dormosedan®, SmithKline-Beecham Animal Health, West Chester, PA, USA). Treatment group 1 received detomidine alone. Treatment group 2 received detomidine mixed immediately before administration with 3 mL of a mixture of apple sauce (Mott's Apple Sauce, Mott's Inc., Stamford, CT, USA), and gum (Spray dried Arabic Type #12 4450, Meer Corp., N. Bergen, NJ, USA: 4.8 mL of powdered gum mixed into 110 mL apple sauce). Treatment group 3 received detomidine mixed immediately prior to administration with 3 mL of molasses (Brer Rabbit®, All Natural Molasses, Nabisco Inc., East Hanover, NJ, USA). All detomidine and detomidine-food mixtures were delivered from a plastic syringe into the buccal or oral cavity of the horse. No attempt was made to place the agents in a specific location within the mouth.

Head droop was used to quantify effects and compare treatment groups. Immediately prior to drug administration, the distance from the most dependent point of each horse's head to the floor (FFD) was measured three times using a measuring stick placed next to the horse's head. Care was taken to ensure that the horse did not alter its head position as it was approached with the stick. The mean of these measurements was the horse's pre-treatment FFD (considered 100%). Following oral administration of detomidine or detomidine/food mixtures, the FFD was measured twice each at 15, 30, 45, 60, 75, 90, and 105 minutes for each horse. The mean of each of the two measurements at each time was then divided by the horse's pre-treatment FFD and expressed as a per cent. Yohimbine (0.1 mg kg^{-1} IV; Sigma Chemical Co., St. Louis, MO, USA) was administered to each horse after making the 90-minute measurements.

All head-droop percentages were compared using repeated measures analyses of variance (anova) and post-anova evaluations were made by calculating and comparing the least square means; $p \leq 0.05$ was used as the criterion for significance.

All serum samples were analyzed using a specific detomidine ELISA test (Neogen Corporation, Lexington, KY, USA) similar to the methods used by Sleeman et al. (1997). The detomidine ELISA cross-reacts with the parent compound, detomidine (75%), and some of its metabolites, so the measured values are expressed as equivalents in recognition of this fact (Stanley et al. 1992). Intra- and inter-assay variations for this ELISA are 3.63 and 2.93%, respectively (Bass 1993).

Results

The head-droop patterns of all three groups were similar (Fig. 1). Each group showed minor head droop at 15 minutes and statistically significant head droop by 30 minutes. Head position remained at approximately 40% of pre-treatment height until reversal with yohimbine. The lowest measured mean (±SD) FFD was 32.6 ± 10.5%, which occurred at 75 minutes in treatment group 2. There were no significant differences among any of the groups at any time. The mean head droop for the treatment groups increased to 87–91% of the pre-treatment FFD at 105 minutes, approximately 15-minute post-yohimbine administration. Sweating occurred in a majority of the horses and snoring was observed sporadically in horses in all treatment groups.

Less than 0.5 ng mL^{-1} detomidine equivalents were found in all pre-treatment samples and mean concentrations increased gradually until reaching a peak mean value of 29.1 ± 12.5 ng mL^{-1} at 75-minute post-administration (Fig. 2). Serum detomidine equivalents in one horse never increased above 5 ng mL^{-1}. These concentrations were judged to be below the sensitivity of the ELISA and this animal's serum equivalents were not included in Fig. 2.

Discussion

Measurement of head droop is a simple technique and several studies have demonstrated its usefulness as an indicator of sedation in the horse (Malone & Clark 1993; Kamerling et al. 1988). Previous work (Malone & Clark 1993) identified that 0.04 and 0.08 mg kg^{-1} detomidine, delivered sublingually, produced sedation in ponies. In preliminary dosage

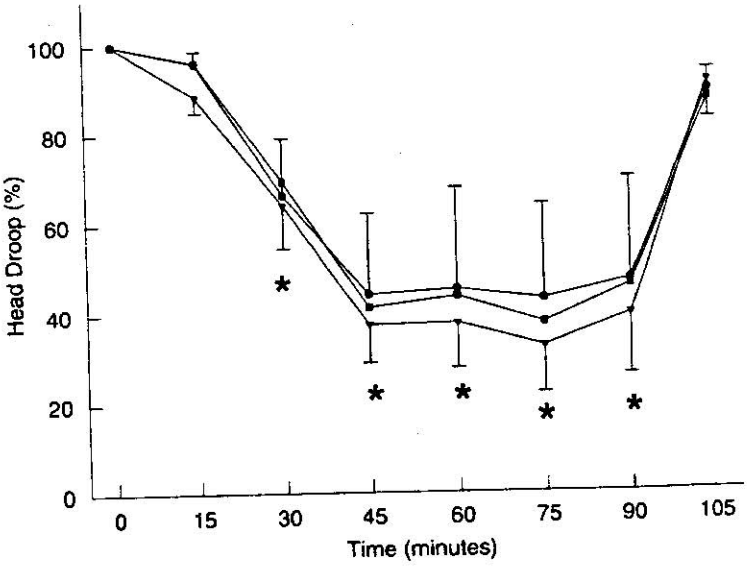

Figure 1 Mean face–floor distances (±SD), expressed as a percentage of pre-treatment face–floor distance produced in horses by the oral delivery of detomidine (0.06 mg kg^{-1}): alone (●); mixed with an apple sauce and gum mixture (▼); and mixed with molasses (■) ($n = 5$, each). Levels at time points marked (*) were significantly different than levels at times 0, 15, and 105 minutes. There were no significant differences between any groups at any time. Yohimbine (0.1 mg kg^{-1}) was administered IV after the 90-minute evaluation.

trials, 0.04 mg kg^{-1} detomidine delivered into the buccal cavity of our horses, did not consistently produce an adequate level of sedation for the performance of minor diagnostic procedures, while 0.06 mg kg^{-1} produced a level of sedation that was more satisfactory (E. Ramsay, unpublished data). The magnitude of the head droop observed in the oral treatment groups of the present study was similar to that observed by Malone & Clarke (1993) for detomidine 0.04 mg kg^{-1}. Physiological parameters and responses to stimuli were not measured in the horses of the present study but these effects in detomidine-treated horses have been described previously (Malone & Clarke 1993; Kamerling et al. 1988). Yohimbine was administered to the horses in the present study to simulate what might occur in out-patient clinical practice.

In four of five horses, orally delivered detomidine, without vehicle, was absorbed slowly following oral delivery. From 45- to 75-minute post-administration,

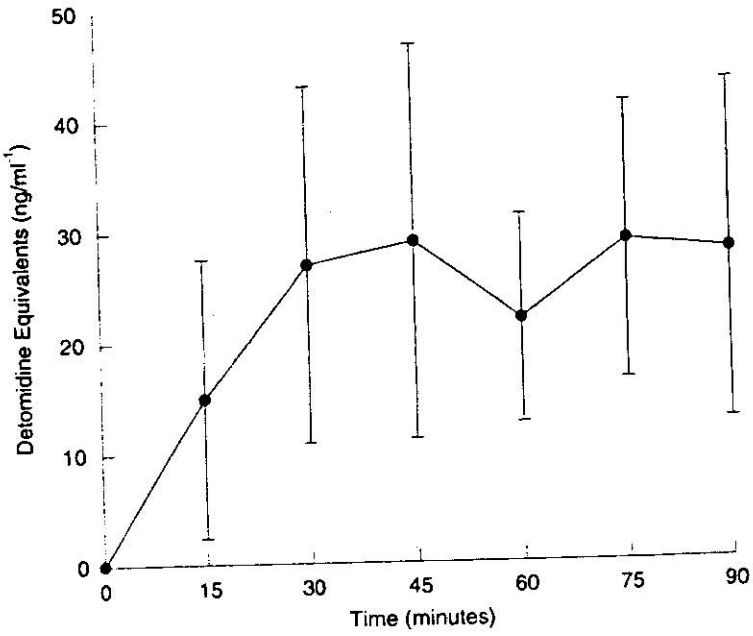

Figure 2 Mean serum concentrations (±SD) of detomidine equivalents after oral administration of detomidine (0.06 mg kg^{-1}) to four horses.

the mean detomidine equivalents were similar to those determined by radio-immunoassay in horses, between 1 and 2 hours after receiving 0.08 mg kg^{-1} IM (Salonen et al. 1989), and during profound sedation produced by constant IV infusion of detomidine (Daunt et al. 1993). It is unclear why serum detomidine equivalents could not be measured in one horse. This horse had similar head-droop levels as the other horses. The failure to measure detomidine in any of these horse samples suggests that either some quality of the horses' serum interfered with the assay or that some problem occurred in the animal's sample handling or processing.

We speculate that the detomidine was absorbed via the horses' oral and pharyngeal mucosa. Work cited by Malone & Clarke (1993) indicated that detomidine, up to 0.1 mg kg^{-1}, was not effective in sedating horses when delivered via stomach tube. This may be due to the drug being diluted in the stomach, absorption being inhibited by gastric acidity, or being metabolized in the liver (first pass effect). The delivery of the detomidine or detomidine mixtures nondiscriminately into the buccal cavity, rather than specifically beneath the tongue, was an attempt to mimic suboptimum conditions that might be encountered in practice. Gum was added to the apple sauce mixture to increase its 'stickiness', with the intention of increasing mixture–oral mucosal contact time and facilitating transmucosal absorption. The head droop produced by the detomidine plus apple sauce and gum mixture was slightly more pronounced but not significantly different from that of the other two treatment groups.

Detomidine is a lipophilic, weak base with wide tissue distribution after IM or IV administration (Salonen 1986). The commercially available detomidine is combined with HCl and has a pH of 4.68. Nonionic drugs pass more readily through the mucosa than those with strong ionic charges (Hussain et al. 1985). The mixing of detomidine with acidic compounds, such as the apple sauce and gum mixture (pH = 3.85) or molasses (pH = 5.34), did not significantly affect the detomidine absorption in these horses. Using more basic food mixtures with detomidine may decrease the amount of ionized detomidine delivered and favor transmucosal absorption.

This study indicates that detomidine, 0.06 mg kg^{-1}, alone or mixed with either of two commonly available food items and placed in the buccal cavity, produces profound head droop in horses in approximately 45 minutes. This dosage and route should allow veterinarians or owners to pre-medicate nontractable horses orally with detomidine and possibly prevent injuries to individuals trying to sedate 'needle shy' horses.

Acknowledgements

This study was supported by Centers of Excellence Funds, The University of Tennessee, Knoxville, TN, USA. The authors would like to thank Ms. M. Daughtridge-Coppock for technical assistance, Dr Arnold Saxton for statistical assistance, and Mr Shawn Magsig, of The Neogen Corp., for supplying ELISA plates.

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Received 24 January 2002; accepted 18 May 2002.

Veterinary Anaesthesia and Analgesia, 2002, 29, 157–158

Editorial

It is an honour to introduce the first special equine edition of Veterinary Anaesthesia and Analgesia. Equine anaesthesia remains a challenge, both to those undertaking clinical anaesthesia and to those carrying out research to elucidate some of the peculiarities of anaesthetic pathophysiology in this species. The number of equine papers submitted for this edition reflects the interest and activity in clinical and basic anaesthetic research in this species. As a consequence, a second special equine edition is planned for July 2003. Two major areas have received most attention. This edition addresses some of the methods used to manage or prevent the range of anaesthetic-induced abnormalities that are unique to the horse. The second edition will be largely concerned with analgesia. Equine analgesia has only recently begun to receive the attention this subject has been given in small animal medicine and surgery, and it is highly appropriate that this journal should have a special place for it.

It is well recognised that smooth and safe anaesthesia is more difficult to accomplish in horses than in small animals and man. In this issue (page 159), the first large, multicentre prospective epidemiological study of equine perianaesthetic mortality reports a death rate in non-colic horses of approximately 1% from some 35 000 cases, in general agreement with the figures previously reported from single centre studies (Johnston et al. 2002). The majority of the deaths were related to cardiovascular accident. Cardiac arrest accounted for 33% of the deaths, and post-operative myopathy and fractures (at least some of which are likely to be associated with myopathy) for a further 7 and 26%, respectively. Most of the anaesthetics in this series were maintained with a volatile agent, but where total intravenous anaesthesia (TIVA) was used, the death rate was significantly lower. It is well recognised that volatile agents depress cardiovascular function; perhaps, this is a feature contributing to the high equine anaesthetic-related mortality. Edner et al. (2002), page 182, investigated the effects of TIVA on cardiovascular function and blood flow and showed that maintaining anaesthesia with propofol and ketamine, dispensing with volatile agents completely, resulted in much improved cardiovascular function and blood flow.

A number of methods are used in clinical equine anaesthetic practice to prevent or manage the cardiovascular depression. It is widely accepted that myopathy develops as a result of poor muscle perfusion during anaesthesia, due at least in part to myocardial depression, low cardiac output and hypotension (Grandy et al. 1987). Inotropes are commonly used to treat hypotension during anaesthesia, in particular to prevent post-operative myopathy. The ultimate effect, and indeed the relative importance, of maintaining flow (cardiac output) and pressure (arterial blood pressure (AP)) on muscle blood flow during anaesthesia is not yet clear, although using AP as an easily measured guide to perfusion is practically possible and apparently useful (Young & Taylor 1993). Ephedrine, which stimulates both α- and β-adrenergic receptors, is one of the agents used to treat hypotension in equine anaesthesia. In this issue, Lee et al. (2002) describe the effect of ephedrine on both cardiovascular function and muscle blood flow. They demonstrate a relatively prolonged improvement on AP, cardiac output and muscle blood flow, particularly at the higher dose of 0.2 mg kg^{-1}, suggesting that this is a valuable agent for use in equine anaesthesia.

Another approach to the problem of volatile agent-induced hypotension is to use supplementary intravenous (IV) agents to reduce the dose of the volatile agent. Steffey et al. (2002) on page 223 report that detomidine reduces isoflurane MAC as expected from previous work with xylazine. However, although isoflurane requirements were much reduced, blood pressure was actually decreased after detomidine at both 30 and 60 μg kg^{-1}. This suggests that α_2-agents, at least at this dose of detomidine, are not the best choice of IV agent to allow reduction of volatile agent dose in order to improve hypotension. Edner et al. (2002) further showed that detomidine, even at 10 μg kg^{-1} decreased muscle blood flow.

Although there is wide use of α_2-agents in equine anaesthesia, these data from Steffey et al. (2002) and Edner et al. (2002) suggest that they should be used with care, as they do not improve cardiovascular function even though volatile agent requirements are reduced. There is no doubt that α_2-agents will continue to be widely used in equine clinical practice, as their sedative properties are so good. Ramsay et al. (2002) (page 219) describe further evidence of the value of oral administration of detomidine, first reported by Malone & Clarke (1993), which is of

considerable value in difficult horses. Hence, it is particularly pertinent, as we continue to use these valuable drugs, that their potency and potential for serious side effects is always taken into account.

Ketamine is another IV agent commonly used in horses for induction of anaesthesia and to supplement volatile agents. This agent has also recently taken on a new lease of life as its analgesic properties are recognised and exploited, particularly for their pre-emptive analgesic effect. Presumably ketamine used at induction contributes to post-operative analgesia in horses, although this effect has not been studied in this species. In addition, alternative routes of administration of ketamine appear worthy of investigation. Redua et al. (2002) on page 200 performed an elegant study demonstrating that epidural ketamine reduced central sensitisation and secondary hyperalgesia in horses. This is one of very few analgesic studies in horses, and has considerable potential for clinical use. If the same analgesic effect is produced during anaesthesia, pre-operative epidural ketamine might have huge potential in reducing anaesthetic dose requirement and enhancing post-operative analgesia.

Johnston et al. (2002) reported that fractures occurring in the recovery period accounted for 26% of the deaths in their epidemiological study. Many factors contribute to violence, ataxia and excitement during recovery, which may cause irreparable fractures. The characteristics of the anaesthetic agents used are likely to be significant. Wagner et al. (2002) on page 207 investigated the effects of a number of different IV anaesthetic combinations on behaviour during induction and recovery. Induction quality was not dramatically affected by the agent, but recovery was improved when propofol was used in combination with either thiopental or ketamine. This is in agreement with several other studies, finding recovery from propofol or propofol combinations to be good. These data support the concept of supplementing traditional anaesthetic methods with new (for the horse) IV agents in order to improve the quality of equine anaesthesia.

Hypoxaemia has long been recognised as a common and potentially hazardous side effect of anaesthesia in horses. Although a link between death and hypoxaemia has not been demonstrated, common sense suggests that hypoxaemia is likely to be harmful, and any treatment that does not cause other problems is likely to be valuable. Roberston et al. (2002) (page 212) describe an elegant yet simple method of supplying the β_2-agonist albuterol (salbutamol) to the respiratory tract to achieve its bronchodilatory effect on the airway without significant systemic effects. Given in this way, 2 $\mu g\ kg^{-1}$ produced a two-fold increase in arterial oxygen tension without any obvious effects on the cardiovascular system. Further research is needed to detail the effects on the cardiovascular system, particularly to evaluate cardiac output and oxygen delivery. However, from the data already supplied, it appears that at last we have a simple and effective method to treat the hypoxaemia that so often occurs in anaesthetised horses.

This issue of Veterinary Anaesthesia and Analgesia highlights the need for investigation of the apparent beneficial effect of acepromazine in equine anaesthesia (Johnston et al. 2002). Acepromazine is an old drug that has been used in thousands of animals: why should it confer protection in anaesthetised horses? Is it because acepromazine decreases the afterload and enables the depressed myocardium to pump more effectively and produce better perfusion? Is it because acepromazine decreases the likelihood of fatal ventricular dysrhythmias occurring?

Inevitably, all the questions cannot be answered. However, this special issue on equine anaesthesia has shed new light on some of the problems and peculiarities of anaesthesia in horses. New methods, particularly the use of alternative IV anaesthetic agents, appear worthy of evaluation in the clinical setting. Studies such as those of Bettschart-Wolfensberger et al. (2001) evaluating TIVA in horses under experimental and clinical conditions are to be much encouraged.

PM Taylor
Taylor Monroe, Gravel Head Farm,
Downham Common, Little Downham,
Ely, Cambs CB6 2TY, UK

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