Preliminary investigation of concurrent administration of phenylbutazone and romifidine in healthy, standing horses.

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Abstract

Objective To characterize the cardiorespiratory and electrocardiographic effects of the combined administration of phenylbutazone and romifidine.

Study design Prospective four-period, four-treatment, blinded, randomized, crossover trial.

Animals Five, healthy, mix breed horses.

Methods An intravenous jugular catheter (for central venous pressure, CVP) and carotid arterial catheter (for arterial blood pressure) was introduced before treatment administration. All treatments were administered intravenous (IV) and consisted of saline placebo (PLC), phenylbutazone (PBZ, 4.4 mg kg^{-1}) romifidine (ROM, 80 µg kg^{-1}) and a combination of phenylbutazone (4.4 mg kg^{-1}) and romifidine (80 µg kg^{-1}) with at least one week washout period between treatments. Heart rate (HR), respiratory rate (RR), systolic (SAP), diastolic (DAP) and mean arterial pressure (MAP) and CVP were recorded for baseline (prior to drug administration) and at 5 minute intervals thereafter for 30 minutes. Electrocardiographic

abnormalities were recorded. **For analysis of data a general linear model for repeated measures was used for analysis of variance**.

Results For the cardiovascular variables there were no statistically significant ($p > 0.05$) differences between horses treated with ROM and PBZ_ROM. Statistically significant ($p < 0.05$) differences only occurred between treatments with romifidine (ROM and PBZ_ROM) and without romifidine (PLC and PBZ). Within treatments, for ROM, changes over time were statistically significant ($p < 0.05$) for HR, SAP, DAP, MAP and CVP. For PBZ_ROM, changes over time were statistically significant ($p < 0.05$) for CVP. Sino-atrial and atrio-ventricular blocks occurred in horses treated with ROM and PBZ_ROM.

Conclusions and clinical relevance The combined IV administration of phenylbutazone and romifidine had no statistically significant effect on cardiorespiratory variables, and appears to be a suitable preoperative medication protocol for horses.

Keywords phenylbutazone, romifidine, interaction, cardiovascular effects, respiratory effects, horse.

INTRODUCTION

Non-steroidal anti-inflammatory agents (NSAID) such as phenylbutazone and α_2-adrenergic agonists such as romifidine or detomidine are commonly administered preoperatively to horses (England et al. 1996). To date there is no report of adverse effects following the combined use of these drugs. However there is a perception amongst some anaesthetists at the Onderstepoort Veterinary Academic Hospital that in some instances adverse cardiovascular effects may occur. This was based on two clinical cases that collapsed following intravenous (IV) administration of phenylbutazone and romifidine in the one instance, and phenylbutazone and detomidine in the other instance. In both cases the drugs were administered within 30 min.

of each other (unpublished cases). The purpose of this investigation was to evaluate the possible occurrence of adverse effects such as hypotension or cardiac arrhythmias associated with the concurrent administration of phenylbutazone and romifidine to healthy conscious horses.

MATERIALS AND METHODS

Five healthy horses aged between 4 and 17 years and a body weight between 380kg and 500kg were used in this study. Horses were housed in large grass paddocks where good quality hay and fresh water was available *ad libitum*. All horses had been familiarized with the testing environment prior to the study. For ease of arterial blood sampling and pressure monitoring, subcutaneous transposition of a carotid artery was performed on each of these horses six weeks prior to the commencement of the trial. Horses were judged to be healthy on the basis of physical examination, complete blood count, clinical chemistry and echocadiographic examination.

This investigation was a four-period, four-treatment, blinded, randomized, crossover trial, with at least one week washout period between treatments. All treatments were administered directly after baseline values were recorded and administered IV over a period of 60 sec. The four treatments were:

1. Phenylbutazone (Phenylarthrite, Bayer, Isando, RSA; PBZ) at 4.4 mg kg^{-1}.
2. Romifidine (Sedivet, Ingelheim Pharmaceuticals, Randburg, RSA; ROM) at 80 µg kg^{-1}.
3. Phenylbutazone (PBZ_ROM) at 4.4 mg kg^{-1} followed by romifidine at 80 µg kg^{-1} after 60 sec. The catheter was flushed with 5 mℓ heparinised saline between treatments.
4. Placebo (saline; PLC).

A 12 gauge catheter (B Braun, Melsungen, Germany) was placed in the left jugular vein under local anaesthesia. Sterilized saline-filled medical- grade polythene tubing (SIMS Portex Ltd, UK) was passed through the catheter into the intra-thoracic cranial vena cava. This tube

was connected to a pressure transducer and the patient monitor (GE Datex-Ohmeda Cardiocap/5 for Anesthesia GE Healthcare Finland, Helsinki, Finland) and its position verified by waveform tracing. Once the tube was in the correct place, the catheter was removed from the vein and the tube sutured in place. Central venous pressure (CVP) measurements were made through this tube. A 20G., 8cm arterial catheter (Arrow, Erding, Germany) was placed in the superficial carotid artery under local anaesthesia. The catheter was connected to the patient monitor. Prior to taking each measurement of arterial blood pressure or CVP, the monitor was zeroed with the transducer placed at the level of the left atrium. Three ECG leads were connected to the same monitor in a Y-lead configuration.

After completion of the instrumentation, each animal was allowed to settle for a ten minutes before baseline variables were recorded. Heart rate (HR), respiratory rate (RR), systolic- (SAP), mean- (MAP), diastolic arterial blood pressure (DAP) and CVP were recorded at 5 minute intervals for 30 minutes. Electrocardiographic abnormalities were noted as they occurred. This study was approved by the Animal Use and Care committee of the University of Pretoria.

Statistical Analysis

The data was analyzed using STATA^{TM} Statistical software: Release 10. ANOVA for repeated measures was used to determine within-treatment- and between-treatment differences, with factors animal sequence, period and carry-over effect. **Shapiro-Wilks test was used to test for normality of data distribution.** Testing was done at the 0.05 level of significance.

RESULTS

The mean ±SD and range values for the variables are reported in Table 1. Overall the differences between treatments were not statistically significant ($p = 0.23$). There were

statistically significant differences ($p < 0.05$) between horses treated with ROM or PBZ_ROM and PLC or PBZ. The differences between PLC and ROM were statistically significant for SAP $p = 0.04$, DAP $p = 0.01$ and CVP $p = 0.02$, but not for HR, MAP and RR ($p > 0.05$). Differences between PLC and PBZ_ROM were statistically significant for HR $p = 0.01$, DAP $p = 0.02$ and CVP $p = 0.01$, but not for SAP, MAP and RR ($p > 0.05$). Differences between PLC and PBZ were not statistically significant for any of the variables ($p > 0.05$). Differences between PBZ and PBZ_ROM were statistically significant for CVP $p = 0.003$, but not statistically significant for the other variables ($p > 0.05$). Differences between PBZ and ROM were statistically significant for SAP $p = 0.04$, DAP $p = 0.01$, MAP $p = 0.04$ and CVP $p = 0.02$, but not statistically significant for HR and RR ($p > 0.\ 05$). Differences between ROM and PBZ_ROM were not statistically significant for any of the measured parameters ($p > 0.05$).

Within treatments, changes for PLC or PBZ over time were not statistically significant for any of the variables: HR $p = 0.33$, $p = 0.29$; SAP $p = 0.30$, $p = 0.17$; DAP $p = 0.15$, $p = 0.21$; MAP $p = 0.35$, $p = 0.12$; CVP $p = 0.32$, $p = 0.02$; RR $p = 0.37$, $p = 0.22$ respectively. For ROM changes over time were statistically significant for HR $p = 0.004$; SAP $p = 0.002$; DAP $p = 0.006$; MAP $p = 0.009$; CVP $p = 0.001$; but not for RR ($p > 0.05$). For PBZ_ROM changes over time were statistically significant for CVP $p = 0.02$, but not for the other variables ($p > 0.05$).

DISCUSSION

No statistically significant changes in cardiorespiratory variables occurred after the combined administration of phenylbutazone and romifidine when compared with romifidine (except for CVP, Table 1) on its own. None of the horses experienced adverse effects subsequent to treatment. Previously in this institution, two horses collapsed after the combined administration of phenylbutazone and α_2-adrenergic agonists. In the first case a healthy horse that had been treated with phenylbutazone (2.2 mg kg^{-1}, IV) and romifidine (10 µg kg^{-1}, IV), developed cardiac arrest during anaesthetic induction with guaifenesin (25 mg kg^{-1}) and ketamine (2.2 mg

kg^{-1}). Resuscitation was not successful. In the second case the horse were prepared for standing castration. Phenylbutazone (2.2 mg kg^{-1}) had been injected slowly IV 15 min. after sedation with detomidine (10 µg kg^{-1}). Approximately one minute after phenylbutazone administration, the horse collapsed with atrial fibrillation. This horse was successfully resuscitated. In both cases drug administration was strict IV with an intravenous catheter.

Two possible adverse effects that could have resulted in cardiovascular collapse in these horses are hypotension and cardiac arrhythmias. The cause of these reactions could have been the combination of the phenylbutazone and the α_2-adrenergic agonists or chemicals added to the commercial drug preparation such as preservatives and solvents. Phenylbutazone is the most commonly used NSAID in horses despite its narrow margin of safety and includes the preoperative administration in combination with sedatives such as the α_2-adrenergic agonists (England et al. 1996, Doucet et al. 2008). Like other NSAIDs, it has anti-inflammatory, analgesic and anti-pyretic properties. Phenylbutazone is highly protein-bound and it is speculated that it may interact with other drugs by protein displacement or several other mechanisms (Plumb. 2005). In an investigation by Young and co-workers it was shown that the effect of thiamylal anaesthesia is not enhanced by the preanaesthetic administration of phenylbutazone. It was speculated that sulphonamide protein binding will enhance the anaesthetic effects from thiamylal (Young et al. 1994). An alterative explanation to the adverse reaction that was associated with a specific commercial sulphonamide preparation was that the solvent resulted in the cardiac arrhythmias after IV administration. The combined administration of a α_2-adrenergic agonist that decreases heart rate may further increase the susceptibility to arrhythmias and terminate in ventricular fibrillation (Prof. Kathy Clarke, personal communication). The package insert for "Phenylarthrite" states that benzyl alcohol is added as a preservative. Benzyl alcohol is commonly used in pharmaceutical preparations. In personal communication with the product representative of the manufacturing company it was stated that other undisclosed compounds are added to the commercial preparation.

Adverse interactions between the α_2-adrenergic agonist detomidine and IV sulphonamide injection have been reported in horses. This interaction is reported to cause cardiac arrythmias, hypotension, apnoea and death (Dick et al. 1987, Taylor et al. 1988). Interactions between romifidine and IV sulphonamides have not been reported, but manufacturers include a warning in the package insert that α_2 adrenergic agonists may cause fatal cardiac arrhythmias when used concurrently with intravenous potentiated sulphonamides. The exact incidence of adverse or fatal effects in cases where these drugs have been used together is uncertain, because no responsible practitioner will risk using these drugs together and studies are lacking. If this interaction has anything to do with protein binding, there may be a risk in injecting α_2 adrenergic agonists concurrently with IV injection of any other highly protein bound drug (such as phenylbutazone).

The pharmacological effects of romifidine can explain all of the significant changes within and between treatments in the present investigation. Between treatments the statistically significant changes that were observed, were between treatments that included romifidine and those without romifidine. Cardiovascular and respiratory effects of romifidine in healthy, standing horses includes bradycardia, hypertension, increased systemic vascular resistance, hypotension, increased central venous pressure, heart blocks, decreased stroke volume and decreased respiratory rate. The effects from romifidine in this investigation are similar to the findings reported previously by other authors (England et al. 1996, Freeman et al. 2002). The absence of adverse cardiovascular and respiratory effects from phenylbutazone in the present study is consistent with the findings of previous authors (Hinchcliff et al. 1994, Manohar et al. 1996). In this investigation it appeared that the administration of phenylbutazone minimized the cardiovascular changes associated with romifidine on its own (within treatment effects) as only statistically significant changes occurred after romifidine but not after the PBZ_ROM combination (except for CVP, Table 1).

Recent advances in pharmacogenomics show that there are genetic variations of adrenergic receptors within human populations which influence receptor expression, activation and

desensitization (Kirstein et al. 2004). The same may be true for horses, in which case idiosyncratic reactions may result. Idiosyncratic adverse reactions or interactions to either one or both of the drugs used in this trial may not have been ruled out due to inadequate sample size. Such reactions could have been responsible for the adverse events that occurred in two hospitalized patients, but an unattainably large sample size would be necessary to definitively rule this out.

In summary, phenylbutazone does not appear to exacerbate romifidine's cardiovascular or respiratory effects. We did not find an acute interaction between these drugs, but idiosyncratic drug reactions cannot be ruled out.

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Table 1: Cardiorespiratory values from five standing horses treated with intravenous saline placebo, phenylbutazone, romifidine and a combination of phenylbutazone and romifidine.

Parameter	PLC		PBZ		ROM		PBZ_ROM	
	Mean ±SD	**Range**	**Mean ±SD**	**Range**	**Mean ±SD**	**Range**	**Mean ±SD**	**Range**
HR (beats min^{-1})	37±7.1[d]	35.2, 39.2	40±10.5	37.8, 44.6	29±8.9	26.4, 40*	32±8.2[d]	28.2, 43.2
RR (breaths min^{-1})	23±14.4	18.6, 26	16±3.2	14.4, 18.4	17±7.2	12.6, 20.8	16±6.3	12.6, 21.8
SAP (mmHg)	140±12.5[a]	136.4, 144.4	147±16.0[h]	139.4, 159.4	146±17.1[a,h]	130.6, 161.4*	148±17.1	140, 154.4
DAP (mmHg)	99±11.8[b, e]	96.8, 104.4	98±8.1[i]	94.2, 105.8	101±11.6[b, i]	89.2, 114.2*	102±15.6[e]	97.8, 106.8
MAP (mmHg)	116±12.8	114, 121.4	119±10.5[j]	113.2, 130	117±11.8[j]	105.6, 128.8*	122±13.5	116.2, 125.2
CVP (mmHg)	5±3.2[c,f]	3.8, 6.2	5±3.4[g, k]	4, 6.6	11±5.2[c,k]	6.2, 13.8*	12±4.3[f,g]	7.6, 14*

Data are expressed as mean ±SD. [n-n] Statistically significant ($p < 0.05$) differences between treatments are indicated by similar superscript letters (Mean column); * Indicates statistically significant ($p < 0.05$) changes over time within treatments (Range column); HR, heart rate; RR, respiration rate; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure; CVP, central venous pressure; PLC, Placebo; PBZ, Phenybutazone; ROM, Romifidine; PBZ_ROM, Phenylbutazone-Romifidine combination