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Original Research

Methadone Increases and Prolongs Detomidine-Induced Arterial Hypertension in Horses, but These Effects Are Not Mediated by Increased Plasma Concentrations of Arginine Vasopressin or Serum Concentrations of Catecholamines

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ABSTRACT

Catecholamines and arginine vasopressin (AVP) release can affect arterial blood pressure (ABP) and hemodynamic stability in standing, sedated horses. Six mature horses were included in this prospective, randomized, crossover, blinded, experimental study. All the horses were sedated with detomidine (DET) alone (0.01 mg/kg, IV) or combined with methadone (MET) (0.01 mg/kg DET and 0.2 mg/kg MET, IV). Cardiopulmonary data and blood samples were collected 30 minutes before (prebaseline and baseline) and for 120 minutes postinjection. The combination DET/MET produced a significant increase (31%) in mean ABP (MAP) 5 minutes after drug administration which lasted for 120 minutes. Detomidine alone induced only a short-term increase in MAP (15%) at 5 minutes compared with baseline. There were significant differences between groups at 5, 15, and from 60 to 120 minutes. Plasma AVP concentrations were higher in horses receiving the treatment DET from 60 to 120 minutes than those in the combination group, for the same period. There were no significant differences in norepinephrine and epinephrine serum concentrations respect to baseline and between treatments. Detomidine induces a short-term MAP increase, and this effect was prolonged and potentiated by MET association. There is no evidence of AVP, norepinephrine, and epinephrine involvement in this effect.

1. Introduction

Detomidine (DET) is a sedative and analgesic drug commonly used in equine practice to produce chemical restrain and sedation for diagnostic or surgical procedures. The cardiovascular effects of this alpha-2 adrenergic agonist include reductions in heart rate (HR) and cardiac output, atrioventricular conduction disturbances, depression of the index of contractility, and increased systemic vascular resistance (SVR) and pulmonary vascular resistance [1,2]. In standing horses, the combination of alpha-2 agonists and

Ethical Considerations: The authors certify that legal and ethical requirements have been met with regards to the humane treatment of animals described in the study and specifying the Universidade Estadual Paulista Animal Care and Use Committee that has overseen this process (under protocol number CEEA 176/2008).

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opioids results in synergistic analgesic effects, reliable sedation, and stable cardiorespiratory function with reduced side effects [3–6].

The use of systemically administered opioids in horses to provide analgesia remains controversial [7,8]. After IV administration, respiratory depression, sympathetic stimulation, and central nervous system (CNS) excitation, increased locomotor activity, and decrease of gastrointestinal tract motility may occur [7,8]. Methadone (MET), a racemic mixture with d- and l-isomers, is a potent synthetic mu (μ) opioid receptor agonist, with similar analgesic properties to morphine, but also with N-methyl-D-aspartate receptor antagonist activity [9]. In horses, IV doses of 0.5 mg/kg increased locomotor activity with poor motor coordination, whereas lower doses (up to 0.2 mg/kg) may reduce the incidence of these adverse behavioral effects [6,10].

Arginine vasopressin (AVP), an essential hormone for both osmotic and cardiovascular homeostasis released by the neurohypophysis, plays an important role in the maintenance of arterial blood pressure (ABP) in the presence of hypotension in compromised patients [11–14]. It acts mainly due to its antidiuretic effects on the kidney and peripheral vasoconstriction via stimulation of V_{1a} receptors leading to increases in ABP [13]. Alpha-2 agonists cause a significant decrease in the plasma AVP concentration in rats [11]. In conscious horses, DET reduced norepinephrine and catecholamine metabolites [15], whereas AVP remained unaffected [16] or with little changes [17] during total intravenous anesthesia (TIVA) with DET, guaiphenesin, and ketamine. Horses anesthetized with inhalant agents showed increases in AVP [17–19], justified as a response to hypotension produced by those agents [17].

In dogs, plasma AVP increased up to 40 times after MET administration [12,20]. It has been suggested that the release of this hormone may lead to a vasoconstrictive response, that is, increased SVR index [21]. Both in conscious and isoflurane anesthetized dogs receiving MET, SVR, ABP, circulating catecholamines, and AVP rose [22]. In horses, cardiovascular stimulation, such as increases in HR, cardiac index, and ABP [23] may follow CNS stimulation after opioid administration, especially at high doses and when not experiencing pain [7,8]. To the authors' knowledge, there is no information about the influence of MET alone or combinations in AVP and catecholamine plasma concentrations and the possible effect of these hormonal changes in cardiovascular stimulation in horses. According to that, the authors hypothesize that increases of plasma AVP and catecholamines produced by MET administration may potentiate DET-induced hypertension by means of peripheral vasoconstriction.

The aim of this study was to evaluate the cardiopulmonary effects and AVP and catecholamine changes of DET alone or in combination with MET in healthy standing, sedated horses.

2. Material and Methods

2.1. Animals

This study was approved by the Institutional Ethics Committee on Animal Use (protocol number 176/2008) and is the Phase 2 of a previously reported article [6]. A washout period of 4 weeks between phases was allowed. Six healthy mature Arabian horses (two males and four females) weighing 415 ± 20 kg were enrolled in the present trial. Health status was assessed on the basis of physical and laboratory investigation (complete blood cell count, serum biochemistry, venous blood gas analysis, and electrocardiogram [ECG] tracing). Before starting the study, the animals were acclimated to the experimentation room, remaining undisturbed and calm while restrained in the stocks.

2.2. Instrumentation and Variables Recorded

Hay and water were provided ad libitum until just before the beginning of each experiment. Concentrate food was not provided during the day of the experiment. Instrumentation was performed with horses restrained in the stocks. Lidocaine [(Xylestesin 2%; Cristália, São Paulo, Brazil), 0.5 mL subcutaneous per site] was topically administered to place both arterial and venous catheters. A 14-gauge Teflon catheter (BD Angiocath; Becton & Dickinson, São Paulo, Brazil) was aseptically inserted into both jugular veins: the left vein for drug administration and the right for blood collection.

A 20-gauge Teflon catheter (BD Insight; Becton & Dickinson, São Paulo, Brazil) was placed into a transverse facial artery and used to collect blood samples in heparinized syringes for blood gas analysis (348 pH Blood Gas Analyzer; Corning Medical and Scientific, MA) and to record ABP values. Proper position of the arterial catheter was confirmed by observation of the characteristic pressure waveform. Arterial blood gas parameters were corrected to body temperature. The arterial catheter was connected to a pressure transducer (TruWave; Edwards Lifesciences Critical Care Division, CA), zeroed at atmospheric pressure and leveled at the level of the right atrium (olecranon in the standing horse). The accuracy of these transducers was confirmed with a mercury column before each experiment. Heart rate and rhythm were assessed by means of a base apex lead ECG (Spacelabs 90,309 Pc Scout; Spacelabs Medical, Ontario, Canada) with adhesive electrodes (Monitoring Electrode 2223; 3M, São Paulo, Brazil). From the ECG printout recorded during 30-second periods, the percentage (%) of second degree atrioventricular block (AVB) was calculated according to the formula: (number of P waves not followed by QRS-T complexes)/(total number of P waves recorded) × 100.

2.3. Study Protocol

With the catheters in place, each horse was allowed to stand undisturbed in the stocks for at least 30 minutes prior the beginning of the experiment. Once prebaseline (T −30 and T −15) and baseline (T 0) values for the different parameters were recorded, the assigned treatment was administered. Prebaseline values were taken to allow acclimatization of the horses. Comparisons with baseline values refer to T 0. Heart rate (from ECG); respiratory rate (direct observation of thorax wall movements); rectal temperature; systolic, mean ABP (MAP), and diastolic ABPs;