Introduction
Extradural co-administration of opioids and local anaesthetics is a popular method for control of pain [3, 5, 18]. Spinal and epidural administration of opioids produce a profound and long lasting segmental analgesia, which is not associated with sensory, sympathetic, or motor blockade [2, 4]. The side effects of epidural opioids in men are dose-dependent and may include pruritus, nausea, respiratory depression and urinary retention [3, 15]. Respiratory depression is the most serious complication associated with the administration of epidural opioids [15]. The dose of epidural morphine, most commonly used in small animals is 0.1 mg/kg [8, 10, 20]. Unlike humans, this dose does not result in any serious adverse side effects in dogs [21]. Epidural local anaesthetics may cause hypotension secondary to sympathetic blockade [1, 18]. The appropriate combination of an opioid and a local anesthetic provides a better analgesia and simultaneously minimizes the side effects associated with either drug, administered alone.

The objective of this co-administration is the potentiation of analgesia and the reduction of any side effects. However, there is little information on the influence of the interaction on side effects during co-administration of morphine and lidocaine in dogs.

The purpose of this study was to evaluate the cardiovascular and respiratory effects after epidural administration of morphine and lidocaine mixture in dogs, anaesthetized with halothane.
Materials and methods

1) DOGS

The experiment was performed in 6 healthy, mixed breed dogs, 2-5 years old weighing 17.3 ± 3.3 kg. Food was withheld 12 hours before anaesthesia, but water was given ad libitum. The experiment was approved by the Institutional Animal Care Committee. Anaesthesia was induced with halothane in oxygen and nitrous oxide (1:2 ratio) using a face mask. The trachea was intubated and thereafter anaesthesia was maintained with halothane in an O2 flow of 130 ml/kg of body weight. A Bain circuit was used. The body temperature was monitored and maintained between 37-38 °C using a warm water circulating pad.

2) INSTRUMENTATION AND CARDIORESPIRATORY MEASUREMENTS

End-tidal halothane concentration was maintained between 2.0 and 2.5 vol %. Two 20-gauge over the needle catheters (Angiocath, Vascular Access; Becton, Dickinson & Co, Sandy, USA) were percutaneously placed: one in a cephalic vein for administration of a balanced electrolyte solution (Ringer’s) at a rate of 10 ml/kg/h during the procedure; the other in a femoral artery for measurement of systolic (SAP, mm Hg), diastolic (DAP, mm Hg), and mean (MAP, mm Hg) arterial blood pressure (Bell & Howell Physiological Pressure Transducer, USA) and for obtaining arterial blood gas samples. An introducer was percutaneously placed in an external jugular vein. A balloon-tipped thermodilution catheter (Swan-Ganz thermodilution catheter, model 93A-131-7F,110 cm) was directed through the introducer into a pulmonary artery for measurement of mean pulmonary blood pressure (MPP, mm Hg) core body temperature (°C), thermodilution cardiac output, and for collecting mixed venous blood samples for pH and blood gas measurements. The proper positioning of the catheter was verified by obtaining characteristic pulmonary artery pressure waveforms. Cardiac output (CO) was measured by thermodilution. Three milliliters of iced 5% dextrose in water (approx. 0 °C) were hand-injected through the proximal catheter port for each measurement. Recorded CO values were the average of 3 consecutive measurements. When significant differences were encountered, the highest and the lowest values being discarded, and the average of the remaining being calculated.

All pressure transducers were calibrated before baseline measurements with the sternum being a zero point for all cardiovascular measurement. A lead II ECG was obtained (Hellige, Germany). The heart rate (HR, beats/mini) was determined by counting the pulse waves on the oscillograph for a minute. The respiratory rate (RR, min⁻¹) was determined by counting the thoracic expirations during one minute.

Arterial and mixed blood samples were simultaneously obtained for measurement of arterial and mixed venous oxygen (PaO2, mmHg, PvO2, mmHg) and carbon dioxide (PaCO2, mmHg, PvCO2, mmHg) tensions, arterial and mixed venous pH (pHa, pHv), and arterial and mixed venous hemoglobin (Hg, g/dl) concentrations, using a blood gas analyzer (ABL 3, Radiometer, Denmark). All blood gas measurements were corrected to body temperature.

Arterial and mixed venous blood bicarbonate concentration (HCO3a, mmol/l, HCO3v, mmol/l), arterial and mixed venous blood base excess (ABEa, ABEv, mmol/l), arterial and mixed venous blood oxygen contents (CaO2, ml/dl, CvO2, ml/dl). The oxygen consumption (VO2, ml/min/kg), the oxygen delivery (DO2, ml/min/kg) and the oxygen extraction ratio (O2 extr, %); the cardiac index (CI, ml/min/kg), the stroke volume (SV, ml/beat) and the systemic vascular resistance (SVR, dynes.s.kg.cm⁻5) were calculated [9].

3) STUDY DESIGN

The animals were maintained in left lateral recumbence with the hind limbs extended forward for the epidural anaesthesia. A 16-gauge, 8 cm long Tuohy needle (Continuous Epidural Anaesthetic Set PERIFIX 420 Braun Melsungen AG, Germany) was inserted into the epidural space at the interspace between the last lumbar and the first sacral vertebrae. The epidural space was identified by loss of resistance to the injection of 2 ml of air after piercing the ligamentum flavum. A catheter with 3 lateral eyes, 0.6 x 1.05 mm, was threaded forward through the needle for 5 cm beyond the needle level, leaving the catheter in situ.

After instrumentation, dogs were kept at 1.5 vol % end-tidal halothane concentration.

Baseline (time 0) data were determined. Then, 2 mg morphine and 2 % 0.26 ml/kg body weight lidocaine (M+L) were injected into the epidural space.

Cardiovascular variables were measured at minutes 5, 15, 30, 45, 60, 75, 105 and 120. Arterial and mixed venous blood samples were obtained at minutes 15, 45, 90, 115, 120 after the M+L bolus was given.

4) STATISTICAL ANALYSIS

Data were analyzed by means of ANOVA for repeated measures. When significant differences were encountered, comparison of means was made using the Tukey’s test. A value of P < 0.05 was considered significant. All values were reported as mean ± SEM.

Résultats

The respiratory effects after the epidural administration of the mixture lidocaine - morphine (table I) were not statistically significant. It must be emphasized that the increase in RR did not result in a respective PaCO2 increase. An insignificant decrease was observed in CaO2, DO2, VO2. The respiratory movements became deeper and rarer.

Changes in cardiovascular variables are presented in table II and figures 1-4. At minutes 30, 45, 60, 75 and 90 the HR decreased significantly (P < 0.05) (fig. 1). SAP and MAP decreased between minutes 5 and 90 min; DAP - between

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minutes 30 and 90 (P < 0.05). CO decreased significantly at min 90 (fig. 3) and CI - between minutes 75 to 90 (P < 0.05) (fig. 4).

Discussion

The epidural administration of morphine in dogs caused moderate changes in HR, the blood pressure (SAP, MAP, DAP), CO and CI.

The appropriate combination of an opioid and a local anaesthetic improved analgesia and simultaneously minimized the side effects associated with either drug. The side effects were dose related.

In veterinary practice, morphine was usually applied epidurally in doses of 0.1 mg/kg [20]. It is established that in human patients there is no correlation between pain relief and weight or pain relief and height of the patients [12]. The same author states that 2 mg morphine is optimal dose for post-operative pain relief with minimal incidence of untoward reactions. Increasing doses lead to side effects such as urinary retention, pruritus and respiratory depression. For this reason in this research we used dose of 2 mg/kg and 0.26 ml 2 % lidocaine.

Respiratory depression is the most serious complication associated with the administration of epidural opiates. They, by an action on brain stem neurons, depress the carbon dioxide drive and accordingly, the tidal volume [13]. In human beings, extradural analgesia with 2 mg morphine reduced significantly the ventilatory response to carbon dioxide while ventilatory depression was not suggested by the other ventilatory values of f, VT, Ve and PaCO2 [16]. The extradural co-administration of morphine and lidocaine did not however produce any significant changes in the venti-
FIGURE 1. — Changes in the average heart rate values (min⁻¹) after the epidural administration of the mixture lidocaine - morphine in dogs (n = 6). Level of significance * $p < 0.05$; ** $p < 0.01$.

FIGURE 2. — Changes in the average SAP, MAP and DAP values (mmHg) after the epidural administration of the mixture lidocaine - morphine in dogs (n = 6). Level of significance * $p < 0.05$; ** $p < 0.01$. 
FIGURE 3. — Changes in the average CO values (l/min) after the epidural administration of the mixture lidocaine - morphine in dogs (n = 6). Level of significance * p < 0.05; ** p < 0.01.

FIGURE 4. — Changes in the average CI values (ml/kg/min) after the epidural administration of the mixture lidocaine - morphine in dogs (n = 6). Level of significance * p < 0.05; ** p < 0.01.
tulatory response. The mechanism of action may differ from that of synergistic analgesic effects, that is modulation of binding to opioid receptors [17].

The epidural administration of lidocaine alone and lidocaine and fentanyl in dogs does not produce any significant changes in ventilatory response to carbon dioxide and PaCO₂ [1]. In this research an insignificant decrease of the respiratory rate without significant changes in PaCO₂ has been established. DAHL et al. [5] demonstrated a significant increase in ventilatory response to carbon dioxide after extradural lidocaine, when the plasma lidocaine concentration was 1.79 ± 0.42 (g/ml. The effect of lidocaine on ventilatory response may moderate the depressant effect of morphine.

Epidurally administered morphine has no effect on sympathetic fibers [3] unlike local anesthetics that can induce hypotension secondary to sympathetic blockade.

Epidurally administered morphine (0.1 mg/kg) does not adversely affect the hemodynamic function in halothane-anesthetized dogs [20]. Other authors state that intrathecally administered morphine has no effect on resting HR or MBP in non-anesthetized cats [23]. In previous researches it has been established that the epidural administration of lidocaine and lidocaine and fentanyl causes a decrease in the MBP with 28-34 % and 8-9 % [1]. TORDA and al. [18] reported that bupivacaine alone caused a greater decrease in arterial pressure and a higher incidence of hypotension (reduction in arterial pressure greater than 25 % of pre-treatment mean arterial pressure) than fentanyl (10 %) or the fentanyl-bupivacaine mixture (15 %). Change in pharmacokinetics of each drug may occur when they are co-administered.

In conclusion, the epidural application of a mixture of morphine and lidocaine is a safe and effective method for achieving reliable analgesia with minimal respiratory and moderate respiratory side effects.

References