

**PHARMACOClinical OBSERVATIONS
ON THE EVOLUTION OF CARDIOVASCULAR
VARIABLES AND ACID-BASE BALANCE
UNDER THE COMBINATION OF
ACEPROMAZINE-MORPHINE IN DOG**

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ABSTRACT - The paper investigated the intensity of the main cardiorespiratory values, which were modified in the case of acepromazine-morphine anaesthesia in dog. The study was carried out on 16 dogs, in which the tension of blood gases was checked. The level of sedations was measured by taking into consideration the awareness degree and how long they were able to keep their lateral position. The sedation degree was present at a rate of 23% after using acepromazine (0.4 mg/kg; level 1), 89% after injecting intravenously the morphine (0.02 mg/kg; level 2) and of 100%, after 0.2 mg/kg morphine, which did not produce significant statistical modifications on the values of hemodynamic function. Our experiments have shown that the dose interval, comprised between 0.2 and 0.5 mg/kg of acepromazine, combined with 0.02-0.2 mg/kg morphine, proved to have satisfying effect.

Key Words: anesthesia, dog, morphine, acepromazine, cardiorespiratory variables

REZUMAT - *Considerații farmacoclinice asupra evoluției variabilelor cardiovasculare și a echilibrului acido-bazic în combinația acepromazină – morfină la câine. În lucrare, s-a urmărit aprecierea intensității modificărilor principalelor variabile cardiorespiratorii sub anestezia cu morfină – acepromazină la câine. S-a lucrat pe 16 câini, cărora li s-a analizat tensiunea gazelor sanguine. Nivelul sedației s-a măsurat după gradul de conștiență și menținere a decubitului lateral. Gradul de sedare a fost prezent în proporție de 23% după administrarea acepromazinei (0,4 mg/kg; nivelul 1), apoi de 89% după injectarea intravenoasă a morfinei (0,02 mg/kg; nivelul 2) și de 100% după 0,2 mg/kg morfină, care nu a indus modificări semnificative d.p.v. statistic asupra variabilelor funcției hemodinamice. Un interval de dozaj cuprins între 0,2-0,5 mg/kg acepromazină, combinată cu 0,02-0,2 mg/kg morfină, s-a dovedit a fi satisfăcător în urma experiențelor noastre.*

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Cuvinte cheie: anestezie, câine, morfină, acepromazină, variabile cardiorespiratorii

INTRODUCTION

Morphine (Morphine[®]) was discovered in 1804 by the German chemist Friedrich Wilhelm Adam Serturner, who named it “morphinum”. It is a complete opioid antagonist, which actions at central level. Most of its effects (supraspinal analgesia, euphoria, deep respiration depression, inhibition of the cough centre, miosis, and inhibition of the digestive motility- responsible of constipation) are mainly caused by bounding to the μ (miu) receivers. Bounding to the κ (kappa) receivers determines analgesia to spinal level (less strong), dysphoria, hallucination and slight respiratory depression. The activation of the δ (delta) receivers amplifies the effects of μ and κ stimulation, which is fast metabolized in the liver, by conjugation with glucuronic acid, resulting 2-, 3-, and 6- glucuronide morphine by N-demetilation, at a smaller rate. The 6-glucuronic morphine derivate is more active than morphine, having a greater affinity for receivers (Both, 1982; Năstasă, 2006; Short, 1987).

Acepromazine (Vetranquil[®]) is a neuroleptic substance, which diminishes the motility and calms down the patients. Neuroleptic substances also have other pharmacodynamic actions, such as antiemetic and antihistaminic action. It protects the myocardium against the arrhythmic activity of the catecholamines (Muir et al., 2005; Szabuniewicz et al., 1995; Wiersing et al., 2001). Neuroleptic substances disturb vasomotility centres and inhibit the α_1 - adrenergic receivers from sympathetic system. In healthy dogs, acepromazine is not producing hypotension if made intravenously at a dose of 0.4 mg/kg (Muir, Hubbel, 1985).

MATERIALS AND METHODS

Investigations were conducted on 16 healthy dogs of a common breed. Before starting the experiment, an intravenous catheter was introduced in the femoral artery and the previous brachial cephalic vein, for sampling blood for analysing the pressures of blood gases (PaCO_2 , PaO_2 , PvCO_2 , PvO_2), pHa, pHv, HCO_3^- , HCO_3^- , by using the Compact 2 AVL analyser. For measuring the arterial blood pressure, a non-invasive electronic apparatus was used (made in Tokyo, Japan). The cardiac frequency was appreciated by using a precordial stethoscope. The respiratory frequency was determined by measuring the “trip of thorax”.

Acepromazine (Vetranquil[®], solution 1%) was administered after recording the basic values at the intravenous dosage of 0.4 mg/kg, over 30 seconds. The measurement of cardiorespiratory variables was repeated every 15 minutes after the administration of acepromazine. Immediately after the second set of measurements, the first dose of morphine was administered intravenously, respectively 0.02 mg/kg, during the same interval of 30 seconds. The measurements of cardiorespiratory variables were done 15 minutes later. The second dose of morphine, respectively 0.18 mg/kg, was administered

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after measurements, the total cumulated doses being of 0.2 mg/kg. Measurements were done at 15 minutes after the injection.

The scale used to appreciate the level of sedation was established according to the degree of consciousness and maintenance of the lateral recumbency. We noted with 0-conscious dog, 1- semiconscious dog, and inconstant lateral recumbency, and 2-unconscious dog, permanent lateral recumbency.

The statistical assessment was done by using the ANOVA test (variance analysis), for repeated measurements. For a value of $P < 0.05$, the results were significant. Data are presented like $M \pm SD$.

RESULTS AND DISCUSSION

The level of sedation was significantly higher after the administration of the combination acepromazine-morphine, comparatively with the base values. This is present at a ratio of 23 % , after the administration of acepromazine (0.5 mg/kg, the first level), then of 89 % , after the intravenous administration of the first dose of morphine (0.01 mg/kg, the second level) and of 100 % , after the administration of the next dose of morphine (0.2 mg/kg, the second level). Instead, an important diminution in the respiratory frequency was recorded at a rate of 59 % , after the intravenous administration of acepromazine (*Table 1*).

Table 1
The evolution of modifications in cardiorespiratory variables and blood gases in 16 dogs, after administering the acepromazine-morphine combination

Variables	Reference values	Acepromazine (0.4 mg/kg)	Morphine (0.02 mg/kg)	Morphine (0.2 mg/kg)	ANOVA P value
SHP (mm/Hg)	154±15	118±12	117±8	113±6	< 0.001
DHP (mm/Hg)	92±14	75±11 *	72±10	65±10	< 0.001
AHP (mm/Hg)	120±13	97±12*	90±9	88±9	< 0.001
HF (beatings/min.)	98±14	96±21	80±25	69±18	< 0.01
RF(respirations/min.)	48±35	25±11*	23±22	17±13	< 0.01
pHa (U)	7.42±0.02	7.42±0.02	7.41±0.04	7.40±0.02	< 0.001
PaCO ₂ (mm/Hg)	31.8±3.0	28.8±4.7	33.0±3.2*	33.9±3.7	< 0.01
PaO ₂ (mm/Hg)	87.8±5.9	90.0±90.2	87.9±5.4	90.9±9.8	I
H ₂ CO _{3a} (mEq/l)	21.1±2.0	19.0±2.6	19.6±1.9	21.0±1.7	I
pHv (U)	7.40±0.01	7.40±0.01	7.38±0.02*	7.38±0.02*	< 0.001
PvCO ₂ (mm/Hg)	34.9±3.6	34.6±2.8	38.3±2.5*	39.6±2.9*	< 0.001
PvO ₂ (mm/Hg)	41.0±3.8	41.0±5.0	40.9±4.0	40.7±2.3	I
H ₂ CO _{3v} (mEq/l)	21.8±1.5	21.0±1.6	21.5±1.5	22.4±1.5*	< 0.05

* The significant difference ($P < 0.05$) versus the previous value. Data are presented as $M \pm SD$; SHP- systolic heart pressure; DHP- diastolic heart pressure; AHP- average heart pressure; HF - heart frequency; RF - respiratory frequency; pHa - arterial pH; PaCO₂ - arterial tension of CO₂; H₂CO_{3a} - concentration in arterial bicarbonate; pHv - venous pH; PvCO₂ - venous tension of CO₂; PvO₂ - tension of oxygen; H₂CO_{3v} - concentration in venous bicarbonate; I-insignificant.

Most of the significant modifications in the variables of hemodynamic function were recorded after the administration of acepromazine. The average heart rates were reduced by 11 % after the administration of acepromazine. This value did not differ significantly from the base values. The arterial pressure was also reduced after the administration of acepromazine. Morphine did not induced statistically significant modifications in the variables of hemodynamic function, excepting the heart rate that recorded a diminution by 7 %, after the administration of a high level of morphine (*Table 1*).

CONCLUSIONS

The results of this experiment proved that the association between acepromazine and morphine, at a clinically relevant dose, is well tolerated from the point of view of the hemodynamic function. The decrease of data recorded in blood pressure had an average intensity and could be attributed to draining the sympathetic activity. This activity was much increased during the period of measuring the base values and after the administration of acepromazine. By adding morphine to a dosage until 10 times higher than the usual clinical dosage, an important sedative effect resulted, without an essential damage of heart-respiratory variables, in non-anaesthetized healthy dogs.

A range of dosage which varied between 0.2-0.5 mg/kg acepromazine, associated with 0.02-0.2 mg/kg morphine, and administered intravenously, could be considered satisfactory, according to the results obtained by our experiments.

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