MINIMUM ALVEOLAR CONCENTRATION OF DESFLURANE IN DOGS PRETREATED WITH LEVOMEPRAMAZINE

(CONCENTRAÇÃO ALVEOLAR MÍNIMA DO DESFLUORANO EM CÃES PRÉ-TRATADOS COM LEVOMEPRAMAZINA)

(CONCENTRACIÓN ALVEOLAR MÍNIMA DEL DESFLURANO EN PERROS PRETRATADOS CON LEVOMEPRAMACINA)

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SUMMARY

The aim of this study was to evaluate the efficacy of the pretreatment of dogs with levomepromazine on the minimum alveolar concentration (MAC) of desflurane. Twenty dogs were equally divided into two groups (G1 and G2). G1 was pretreated with 1 mg/kg levomepromazine intravenously (iv), while G2 received 0.2 ml/kg 0.9% saline (placebo) by the same route. After 15 min, 5 ± 3 mg/kg propofol was administered iv, followed by 1.6 MAC of desflurane. Thirty minutes after the establishment of the initial concentration, the dogs were submitted to an electric stimulus (30 Hz, 200 V, 4 mA, 5 s) applied to the labial fold. If no movement was observed by the end of the stimulus, the reservoir bag was emptied and the MAC was reduced by 0.2 MAC, with the circuit being saturated with the new concentration of the anesthetic (1.4 MAC) and 15 min later another electric stimulus identical to the first one was applied. Desflurane concentration was reduced by 0.2 MAC every 15 min, with the electric stimulus being discontinued when the animal moved. The MAC was defined as the mean concentration between the desflurane dose at which movement was observed and the immediately preceding dose. Respiratory rate and end tidal CO₂ were measured immediately before administration of the drugs (T1), 15 min after levomepromazine or placebo administration (T2), and 30 min after the establishment of the initial concentration of the anesthetic agent (T3). The other measurements were obtained immediately before the application of the electric stimulus (T4, T5 and T6). The numerical data were submitted to profile analysis (p<0.05). The MAC values were submitted to Student t test (p≤0.01). The results led us to conclude that levomepromazine reduces the MAC of desflurane by 40%.


RESUMO

Objetivou-se avaliar a eficiência do pré-tratamento de cães com levomepromazima sobre a concentração alveolar mínima (CAM) do desfluorano. Vinte cães foram separados equitativamente em dois grupos, G1 e G2. Os animais do G1 foram pré-tratados com 1 mg/kg levomepromazina e os do G2 com 0,2 ml/kg de solução salina a 0,9% (placebo), ambos por via intravenosa. Decorridos 15 minutos administrou-se propofol, na dose de 5±3 mg/kg/IV. Ato continuo, iniciou-se a administração de desfluorano (1,6 CAM). Após 30 minutos do estabelecimento da concentração inicial, os cães foram submetidos a um estímulo elétrico (30Hz, 200V, 4mA, 5s.), aplicado na prega labial. Após o término do estímulo, não havendo movimentação do animal, o balão reservatório foi esvaziado e reduziu-se a concentração em 0,2 CAM, sendo o circuito saturado com nova concentração anestésica (1,4 CAM). Decorridos 15 minutos da administração da nova

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concentração, foi aplicado outro estímulo elétrico, idêntico ao anterior. Reduziu-se a concentração do desflurano em 0,2 CAM a cada 15 minutos, sendo os estímulos elétricos interrompidos assim que o animal se movimentou. A CAM foi considerada como a concentração média entre a dose de desflurano em que foi observado movimento e a dose imediatamente anterior. A frequência respiratória e o CO₂ expirado foram mensurados imediatamente antes da aplicação dos fármacos (T1), 15 minutos após a administração da levomepromacina ou placebo (T2) e 30 minutos após estabelecida a concentração inicial do agente anestésico (T3). As demais colheitas foram realizadas imediatamente antes das aplicações dos estímulos elétricos (T4, T5 e T6). Os dados numéricos foram submetidos à Análise de Perfil (p<0,05). Os valores da CAM foram submetidos ao teste t de Student (p<0,01). Os resultados permitiram concluir que a levomepromacina reduz a CAM do desflurano em 40%.


RESUMEN
El objetivo de este estudio fue evaluar la eficiencia del pretratamiento con levomepromacina sobre la concentración alveolar mínima (CAM) del desflurano en perros. Veinte perros fueron distribuidos equitativamente en dos grupos, G1 y G2. Los animales del G1 fueron pretratados con 1 mg/kg de levomepromacina y los del G2 con 0,2 ml/kg de solución salina al 0,9% (placebo), ambos por vía intravenosa. Después de 15 minutos se administró propofol, a la dosis de 5±3 mg/kg/IV. En seguida fue iniciada a administración de desflurano (1,6 CAM). Transcurridos 30 minutos del establecimiento de la concentración inicial fue aplicado un estímulo eléctrico (30Hz, 200V, 4mA, 5s) en el pliegue labial. En la ausencia de movimientos del animal una vez terminado el estímulo el balón reservorios fue desocupado, la concentración del anestésico fue reducida en 0,2 CAM y el circuito fue saturado con la nueva concentración anestésica (1,4 CAM). Después de 15 minutos de la administración de la nueva concentración fue aplicado otro estímulo eléctrico, igual al anterior. Se redujo la concentración del desflurano en 0,2 CAM cada 15 minutos y los estímulos eléctricos fueron interrumpidos al observar movimientos del animal. La CAM fue considerada como la concentración media entre la dosis de desflurano con la cuál se observaron movimientos y la dosis inmediatamente anterior. La frecuencia respiratoria y el CO₂ expirado fueron medidos inmediatamente antes de la aplicación de los fármacos (T1), 15 minutos después de la administración de la levomepromacina o del placebo (T2) y 30 minutos después de establecida la concentración inicial del agente anestésico (T3). Las demás evaluaciones fueron realizadas inmediatamente antes de la aplicación de los estímulos eléctricos (T4, T5 y T6). Los datos numéricos fueron sometidos al Análisis de Perfil (p<0,05). Los valores de la CAM fueron sometidos al teste t de Student (p<0,01). Los resultados permitieron concluir que la levomepromacina reduce la CAM del desflurano en 40%.

PALABRAS CLAVE: concentración alveolar mínima, desflurano, levomepromacina, perros.

INTRODUCTION
Desflurane, the most recent volatile anesthetic, is being used with increasing frequency mainly due to its pharmacokinetic properties, including its low blood solubility coefficient conferring rapid anesthetic induction and recovery (SMILEY, 1992) and its low toxicity (WEISKOPF et al., 1992), which places it above other volatile agents. However, desflurane presents some disadvantages such as low potency, which requires high concentrations of the drug to obtain the desired anesthetic effect (PATEL & GOA, 1995). Therefore, combinations with other drugs which would permit a reduction in desflurane concentrations are highly attractive, since they would provide an even safer anesthesia.

The minimum alveolar concentration (MAC) of desflurane can be decreased by the combined use of other drugs such as nitrous oxide, which at a concentration of 60% causes a 22% reduction in the MAC of desflurane in children (FISHER & ZWASS, 1992), a 45% reduction in adults (RAMPIL et al., 1991), and a 65% reduction in the elderly (GOLD et al., 1993). Fentanyl has also been shown to significantly reduce the MAC of desflurane in man after the administration of a single dose of 3 µg/kg (SEBEL et al., 1992). The combination of fentanyl and droperidol at doses of 15.7 µg/kg and 0.5 mg/kg, respectively, led to a 40% reduction in the MAC of desflurane in dogs (NUNES et al., 2001).

Recent studies have shown an increasing interest in the use of desflurane in combination with preanesthetic drugs able to reduce the MAC of this volatile anesthetic. Particularly outstanding among the tranquilizers used in
veterinary anesthesiology is levomepromazine, a phenothiazine of the mixed series which, in addition to a sedative effect and antiemetic, antihistaminic and antispasmodic properties, exerts a considerable adrenolytic action (MASSONE, 1999). Its marked antiarrhythmogenic potential (NUNES et al., 1999) and its capacity to potentiate the effect of general anesthetics (MASSONE, 1999) are responsible for the increasing use of levomepromazine in the pretreatment of dogs.

Phenothiazines have been associated with a decrease in respiratory rate generally compensated for by an increase in tidal volume (GLEED, 1987). However, NATALINI (1993), studying the combination of levomepromazine and tiletamine/zolazepam in dogs, did not observe significant alterations in respiratory rate. Levomepromazine produces discrete analgesia and is widely used in humans for the treatment of psychiatric disorders and as an analgesic (HALS & DAHL, 1995). NATALINI et al. (1991) showed a potentiation of the analgesic effects of the tiletamine/zolazepam combination in dogs receiving levomepromazine as preanesthetic medication. NATALINI (1993), still studying the use of the association of levomepromazine and tiletamine/zolazepam in the clinical practice, also observed that the mean dose of tiletamine/zolazepam required for surgical procedures in dogs pretreated with levomepromazine was the same as that described by McGrath and cited by NATALINI (1993), who used acepromazine and morphine as preanesthetic medication. With respect to the action of levomepromazine on the MAC of volatile anesthetics, there aren’t reports confirming or not its efficacy.

Propofol is an exclusively intravenous, hypnotic agent with a short anesthetic action and rapid and smooth recovery. As a non-barbituric general anesthetic, it is indicated for induction and maintenance of general anesthesia. In contrast to thiopental, propofol does not exert a cumulative effect and is rapidly redistributed from the brain to other tissues (MORGAN & LEGGE, 1989) and metabolized in plasma (ZORAN et al., 1993), providing a rapid recovery from anesthesia even after repeated administration (GLEED, 1980). MORGAN & LEGGE (1989), in a study on dogs and cats submitted to short-term surgical procedures and receiving propofol as an induction agent or as the single anesthetic, concluded that the drug does not possess a cumulative effect and does not exhibit a residual analgesic potential.

Based on the above considerations, the objective of the present study was to determine the efficacy of levomepromazine pretreatment in dogs, induced with propofol, on desflurane MAC.

**MATERIAL AND METHODS**

This experiment was performed in accordance with the Animal Care and Use Committee of the University. Twenty healthy, adult mongrel dogs of both sexes, with estimated age ranging from 1 to 5 years, weighting 6 to 28 kg, were provided by the kennel of Hospital Veterinário “Governador Laudo Natel”, Faculdade de Ciências Agrárias e Veterinárias - FCAV/UNESP, Câmpus de Jaboticabal, SP, Brazil. The animals were selected and randomly divided into two groups of 10 dogs each (G1 and G2). The health of the dogs was confirmed by clinical examination, complete blood count, blood chemistry profile and serologic tests for toxoplasmosis and leptospirosis. Additionally, vaccination and deworming were performed and the dogs were observed for 30 days before the beginning of the experiment.

G1 animals received 1 mg/kg of levomepromazine (Neozine - Rhodia S.A. Divisão Farmacêutica), intravenously. After 15 min, general anesthesia was induced by intravenous administration of propofol (Diprivan - Zeneca Farmacêutica do Brasil Ltda.), with doses ranging from 5 to 8 mg/kg, using the minimum dose necessary to permit orotracheal intubation.

The dogs were intubated using a Magill endotracheal tube and immediately submitted to inhalation anesthesia with desflurane (Suprane - Baxter Caribbean Inc) diluted in O₂ at a flow rate of 30 ml/kg/min, using a semi-closed type anesthetic circuit (Ohmeda - model Excel 210 SE), equipped with a thermocompensated and microprocessor-controlled vaporizer (Ohmeda - model TEC 6) calibrated for the anesthetic agent.

Desflurane was administered at an initial concentration of 1.6 MAC (11.5%), with 1 MAC considered to be equivalent to 7.2 V% (DOORLEY et al., 1988; EGER, 1992; CLARKE et al., 1996), which was measured by an infrared gas analyzer (Gaz analyser model 5220, Ohmeda) whose sensor was adapted at the far end of the endotracheal tube, connected to the anesthetic circuit. The gas analyzer was calibrated before each use. Thirty minutes after the establishment of the initial concentration, the dogs were submitted to an electric stimulus provided by an electrostimulator (Eletroestimulador Tonus PDS – Dolsch Ltda.), which consisted of an alternating current with a frequency of 30 Hz, an amplitude of 200 V, 4-mA current intensity and duration of 5 s. The electric stimulus was applied through electrodes positioned at the left superior labial fold, in the region of the canine and first premolar teeth, as described by NUNES et al. (2001).

At the end of the stimulus application, the reservoir...
bag of the equipment was emptied and the MAC was reduced by 0.2 MAC, with the anesthetic circuit being saturated with the new anesthetic mixture (1.4 MAC). After 15 min, another electric discharge of the same frequency, amplitude, intensity and duration as the previous one was applied. Desflurane concentration was reduced by 0.2 MAC at every 15 min as described above, until the animal moved (head/neck movement or movement of the limbs intending to remove the electrodes) in response to the electrical stimulus. The MAC was defined as the mean concentration between the inhalant anesthetic dose at which movement was observed and the immediately preceding dose, according to the methodology established by VALVERDE et al. (1989).

The same methodology was used for G2 animals, with levomepromazine being replaced with 0.9% physiologic solution (placebo) administered through the same route and at the same amount in ml as G1 (0.2 ml/kg).

In order to minimize the effects of body temperature on MAC, the temperature was maintained between 38.3° and 39.0°C using a heat pad (Gaymar model TP-500 Gaymar industries Inc). This parameter was first monitored by measuring the rectal temperature with a clinical thermometer and, after the tracheal intubation, by a multiparametric digital device (Digimax 5000 - model ESFMN 2T, Digicare Tecnologia Biomédica), whose thermal sensor was introduced into the esophagus until the region close to the heart basis.

The following variables were studied in both groups. End tidal CO2 (ETCO2) was directly measured with an oxycapnograph (Dixtal model DX 7100, Dixtal Biomedica), with the aspiration sensor positioned in the nostrils at T1 and T2 and the main flow sensor connected between the gas analyser probe and the anesthesia circuit at the other time points. The numerical values were obtained immediately before application of the drugs (T1), 15 min after the administration of levomepromazine or placebo (T2), and 30 min after the establishment of the initial concentration of the anesthetic agent (T3). The other values were obtained immediately before the application of the electrical stimulus (T4, T5, and T6).

The respiratory rate (RR) was measured by an oxycapnograph using the same sensors, sensor positions and time intervals as described above for ETCO2.

The mean arterial pressure (MAP) was measured by an oscilometric pressure monitor (Digimax 5000 - model ESFMN 2T, Digicare Tecnologia Biomédica), using the same time intervals as described above.

Statistical analysis of the variables, except for MAC, was performed using profile analysis (p<0.05) (MORRISON, 1967; CURI, 1980) for the interpretation of possible effects leading to alterations in the mean of each variable studied at the different time points. The number of time points for each group and each animal presented individual variations along the experiment and therefore, to permit statistical analysis, the hypotheses were tested up to T6. Mean MAC were compared between groups using the Student t-test, with the level of significance set at 1% (p £ 0.01).

RESULTS AND DISCUSSION

No significant differences in RR were observed between groups, probably due to the wide variability in the parameter as shown by the high coefficients of variation. Although GLEED (1987) suggested an association between phenothiazines and a reduction in RR, the group pretreated with levomepromazine did not show significant variation in mean RR values along time, indicating that it did not interfere with RR. This finding corroborates the results obtained by NATALINI (1993), who did not observe any interference of levomepromazine in the respiratory rate of dogs anesthetized with the association of tiletamine/zolazepam. Levomepromazine may also have contributed to RR stability, even under the action of desflurane, since no alterations in mean values were observed in this group after the administration of the volatile agent.

In G2, a dose-dependent action of desflurane was observed, with the mean RR value at T3, which corresponds to the higher desflurane concentration, being lower than at the other time points. Thereafter, mean RR values increased, while the concentration of the volatile agent decreased (EGER, 1992; CLARKE et al., 1996; STEFFEY, 1996; SANTOS et al., 2000). In contrast, PATEL & GOA (1995) observed that in man, desflurane concentrations above 1.66 MAC provokes a reduction in end-tidal volume with increasing RR.

ETCO2, which serves as an indicator of ventilation quality (O’FLAHERTY et al., 1994; JONES, 1996), showed variations inversely proportional to RR, as was expected based on the strict correlation between these variables. The highest mean ETCO2 values observed for both groups occurred at T3 and T4, which corresponded to the higher desflurane concentration, thus confirming respiratory depression due to high concentrations of the drug (EGER, 1992; CLARKE et al., 1996; STEFFEY, 1996; SANTOS et al., 2000). The subsequent reduction in mean ETCO2 up to T6 following the decrease in the concentration of the volatile anesthetic demonstrates the dose-dependent character of respiratory depression (CLARKE et al., 1996; SANTOS et al., 2000). In a study on the cardiopulmonary effects of desflurane...
in cats, McMURPHY & HODGSON (1996) obtained similar results, with arterial CO₂ partial pressure being higher at elevated concentrations of the volatile anesthetic.

The mean ETCO₂ values obtained were within the normal range (O’FLAHERTY et al., 1994; JONES, 1996), except in G2 at T3, when a difference between groups was also observed. Although G2 presented a lower RR at T3, consequently increasing the end tidal CO₂ concentration, analysis of other variables such as pulmonary shunt, pulmonary arterial pressure and lung blood flow may clarify these findings. (TABLE 1)

The MAC is defined as the lowest concentration of a volatile anesthetic present in the alveoli that at a pressure of 1 atmosphere impairs the response to a noxious stimulus in 50% of the animals (JONES, 1996). Each volatile anesthetic possesses a specific MAC which can be used to determine its efficacy (MASSONE, 1999). The MAC varies between different species and between individuals of the same species (EGER, 1992). Several factors can be responsible for a reduction in MAC, including increased age, hypothermia and depressor drugs such as midazolam, fentanyl and nitrous oxide (EGER, 1992; CLARKE et al., 1996).

Desflurane was synthetized from isoflurane by replacing a chloride with a fluor atom. This small substitution resulted in various pharmacological alterations, producing an anesthetic with a very low blood/gas solubility coefficient (EGER, 1992; SMILEY, 1992). On the other hand, it led to a reduction in the potency of desflurane by one fifth the potency of isoflurane, with high concentrations of the agent being required to reach adequate anesthetic levels.

Analysis of the present results demonstrated that levomepromazine interferes with the MAC of desflurane, as the group pretreated with the phenothiazine showed a 40% reduction in this variable compared to the untreated group. (TABLE 2) These findings may be explained by a possible analgesic effect of levomepromazine, as described by NATALINI et al. (1991) and NATALINI (1993) for dogs, by LUNA et al. (1992) for horses and by HALS & DAHL (1995) for man. Another possibility which can be proposed based on the results obtained is an intense depressor effect on the central nervous system (HAMMOND et al., 1994; MASSONE, 1999), which increases the tolerance of

<table>
<thead>
<tr>
<th>Variables</th>
<th>Groups</th>
<th>Before treatment</th>
<th>15 minutes after treatment</th>
<th>30 minutes (11.5V%)</th>
<th>45 minutes (10%)</th>
<th>60 minutes (8.5%)</th>
<th>75 minutes (7.2 V%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>G1</td>
<td>16±5.6a</td>
<td>17±9.68a</td>
<td>10±4.15b</td>
<td>16±8.00b</td>
<td>24±15.56b</td>
<td>33±33.18b</td>
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<tr>
<td></td>
<td>G2</td>
<td>16±3.12a</td>
<td>19±7.60a</td>
<td>9±6.21b</td>
<td>18±18.10c</td>
<td>41±38.43d</td>
<td>59±48.22c</td>
</tr>
<tr>
<td>ETCO₂</td>
<td>G1</td>
<td>30.80±4.36a</td>
<td>25.10±5.58a</td>
<td>43.70±6.71b</td>
<td>38.60±5.94b</td>
<td>34.40±6.18c</td>
<td>31.30±5.25c</td>
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<tr>
<td></td>
<td>G2</td>
<td>33.20±4.56a</td>
<td>30.60±6.22a</td>
<td>52.10±8.25b</td>
<td>46.10±10.2b</td>
<td>38.80±7.67c</td>
<td>31.80±7.36d</td>
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<tr>
<td>MAP</td>
<td>G1</td>
<td>103±13a</td>
<td>94±9.5ab</td>
<td>88±15ab</td>
<td>86±13b</td>
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<td>G2</td>
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<td>88±9</td>
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<td>97±7.3</td>
<td>95±8.6</td>
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</table>

Values are expressed as means ± standard deviation;
Differences between groups at the same time (profile analysis p<0.05);
a,b,c,d Different letters denote differences occurring with time within the same group (profile analysis p<0.05)

(Table should be inserted on page 8, as indicated in the text)
the animals to the noxious stimulus. However, further studies are necessary to elucidate the mechanisms by which levomepromazine interferes with the MAC of desflurane.

Since a reduction in body temperature can cause a reduction in MAC (HAMMOND et al., 1994; STEFFEY, 1996), this parameter was maintained stable within the normal limits of the species to minimize its influence on the results.

The use of propofol for the induction of anesthesia in the animals studied was necessary since desflurane has been found to be inappropriate for mask induction due to intense irritation of the airways (YOUNG & APFELBAUM, 1995). Apparently, propofol did not interfere significantly with the present results since, although causing sympathetic inhibition in dogs (DEEGAN et al., 1991), this reduction in sympathetic activity was insufficient to block it (WEISKOPF et al., 1994). DANIEL et al. (1996) showed that, despite being able to block the increase in epinephrine concentrations, propofol failed to attenuate the transitory cardiovascular response resulting from sympathetic activation induced by rapid increases in desflurane concentration.

Furthermore, after the administration of propofol the animals continued to receive 1.6 MAC of desflurane for 30 min before T3 measurements were obtained, a period which seems to be sufficient for redistribution and elimination of the drug, with dissipation of most, if not all, effects of propofol (WEISKOPF et al., 1994). ILKIW et al. (1992), studying the pharmacokinetics of propofol in animals with induced hypotension, observed that 30 min after anesthesia induction with the drug, all measured values had returned to values similar to those obtained before administration of the anesthetic. Similar findings were obtained by CULLEN et al. (1991), who showed that the reduction in arterial pressure and the increase in heart rate observed before propofol administration returned to pre-induction values 20 min after its application.

The present results led us to conclude that levomepromazine reduces the MAC of desflurane by 40%, and also contributes to the respiratory rate stability.

Table 2 - Desflurane mean MAC (V%) obtained in two groups of 10 dogs pretreated with levomepromazine (G1) or placebo (G2), and the individual desflurane MAC for each animal.

<table>
<thead>
<tr>
<th>G1</th>
<th>Desflurane MAC (V%)</th>
<th>G2</th>
<th>Desflurane MAC (V%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>3.25</td>
<td>01</td>
<td>7.75</td>
</tr>
<tr>
<td>02</td>
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<tr>
<td>10</td>
<td>4.75</td>
<td>10</td>
<td>6.25</td>
</tr>
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</table>

**Desflurane Mean MAC for G1** 4.45±1.18a (0.66 MAC) **Desflurane Mean MAC for G2** 7.45±0.63b (1.06 MAC)

Values are expressed as means ± standard deviation; Different letters denote difference between groups (Student t-test p<0.01)

(Table should be inserted on page 8, as indicated in the text)
ACKNOWLEDGMENTS

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