LACK OF BETA-ADRENERGIC ACTIVITY OF ISOFLURANE IN THE DOG: A COMPARISON OF CIRCULATORY EFFECTS OF HALOTHANE AND ISOFLURANE AFTER PROPRANOLOL ADMINISTRATION

D. M. PHILBIN AND E. LOWENSTEIN

SUMMARY
The studies were undertaken to determine whether isoflurane inhalation is associated with a degree of beta-adrenergic action that is potentially important in clinical situations, and to compare the circulatory tolerance to isoflurane and halothane in dogs following beta blockade. We measured arterial and pulmonary artery pressure, left and right ventricular filling pressure, heart rate and cardiac output, and derived stroke volume and systemic and pulmonary vascular resistances in 13 mongrel dogs. The haemodynamic response to 1 MAC and 2 MAC isoflurane was studied in seven dogs and was similar before and after propranolol 0.1 mg/kg i.v. In six dogs, propranolol 0.5 mg/kg caused no significant changes in the circulatory response to 1 MAC and 2 MAC isoflurane or 1 MAC halothane. However, in three dogs, administration of 2 MAC halothane after propranolol 0.5 mg/kg resulted in such profound circulatory depression as to preclude further study. These data suggest that (a) isoflurane possesses no clinically important beta-adrenergic stimulating activity; (b) there is no adverse drug interaction upon the circulation with the combination of isoflurane and propranolol; (c) in the presence of moderate to profound beta-adrenergic blockade, 2 MAC isoflurane may be tolerated better than 2 MAC halothane.

The anaesthetic management of patients receiving beta-adrenergic blocking drugs for relief of angina pectoris is controversial (Merin, 1972). If therapy is discontinued before induction of anaesthesia, myocardial oxygen demand and supply may become unbalanced, leading to myocardial ischaemia. According to Miller and colleagues (1975), six of 20 patients sustained either a life-threatening or a fatal cardiac incident (including ventricular tachycardia, fatal myocardial infarction and sudden death) within 2 weeks after abrupt withdrawal of beta-adrenergic blockade produced by 160–320 mg of propranolol daily. Viljoen, Estafanous and Kellner (1972) advised that a 2-week interval be mandatory between the last dose of propranolol and administration of anaesthesia on the basis of a series of five fatalities occurring in the presence of “profound” beta-adrenergic blockade. In contrast, Prys-Roberts and others (1973) have recommended administration of beta-adrenergic blockers immediately before anaesthesia, since they demonstrated a dramatic decrease in the incidence of ischaemic e.g. changes during induction of anaesthesia and tracheal intubation in hypertensive patients pretreated with practolol, a cardioselective beta-adrenergic blocking agent.

Since increasing numbers of patients are receiving beta-adrenergic blocking agents (Pitt and Ross, 1969; Johnstone, 1970; Miller, Amsterdam and Mason, 1975), it has become important to know if an anaesthetic agent possesses a beta-adrenergic stimulating action of any clinical significance and whether the anaesthetic agent is tolerated in the presence of beta-adrenergic blockade. Stevens and co-workers (1971) have suggested that some of the haemodynamic effects of isoflurane are consistent with beta-adrenergic stimulation. In our previous study (Philbin and Lowenstein, 1975) we were unable to demonstrate any central beta-adrenergic effect of 1 MAC isoflurane inhalation in the presence of profound beta blockade produced by propranolol 0.5 mg/kg in the dog, and the evidence for a peripheral beta-adrenergic action was not compelling. The primary purpose of these studies was to determine if a beta-adrenergic action of isoflurane could be demonstrated at greater concentrations of isoflurane or during less profound blockade, or both, and to compare the effect of halothane and isoflurane in the presence of beta-adrenergic blockade. In addition, we wished to
exclude the possibility that chloralose-urethane basal anaesthesia had been responsible for our previous findings.

METHODS

Thirteen healthy mongrel dogs weighing between 18 kg and 22 kg were divided arbitrarily into two groups. In group I (n = 7) basal anaesthesia was provided by sodium thiopentone 10 mg/kg i.v. The trachea was intubated with a wide-bore-cuffed tube and the dog was ventilated with 1.5% isoflurane in oxygen using a non-rebreathing system via a Harvard animal respirator. In group II (n = 6) basal anaesthesia was provided by the inhalation of 0.85% halothane (~1 MAC) (Eger et al., 1965), using oxygen as the carrier gas.

Polyethylene catheters for monitoring and sampling were introduced into the abdominal aorta via the femoral artery, and into the right atrium via the jugular vein, and a balloon-tipped flow-directed catheter was introduced into the pulmonary artery (Swan et al., 1970). Systemic arterial (AP) and pulmonary artery (PA) pressure, right atrial pressure (RAP) and pulmonary capillary wedge pressure (PCW) were measured using a transducer and recorded on a Hewlett-Packard recorder. The heart rate was calculated from the e.c.g.

End-tidal isoflurane and halothane concentrations were measured using a Beckman LB-2 infra-red gas analyser. Cardiac output was determined by indicator-dilution using cardiogreen dye and a Gilford densitometer with pulmonary artery injection and sampling from the catheter in the abdominal aorta. $P_{\text{aO}_2}$, $P_{\text{aCO}_2}$ and pHa were measured by standard polarographic techniques.

Systemic and pulmonary vascular resistances and stroke volume were calculated according to the following formulae (Yang, Bentivoglio and Maranhao, 1972):

\[
\text{SVR} = \frac{\overline{AP} - \overline{RAP}}{\text{CO}} \quad (1)
\]

\[
\text{PVR} = \frac{\overline{PA} - \overline{PCW}}{\text{CO}} \quad (2)
\]

\[
\text{SV} = \frac{\text{CO}}{\text{HR}} \quad (3)
\]

where

SVR = systemic vascular resistance (units)

\( \overline{AP} \) = mean arterial pressure (mm Hg)

\( \overline{RAP} \) = mean right atrial pressure (mm Hg)

\( \overline{PA} \) = mean pulmonary artery pressure (mm Hg)

\( \overline{PCW} \) = mean pulmonary capillary wedge pressure (mm Hg)

SV = stroke volume (ml/beat)

HR = heart rate (beat/min)

CO = cardiac output (litre/min)

Data were analysed by Student's t test. A P value of less than 0.05 was considered significant.

The procedure for these studies is shown in table I.

<table>
<thead>
<tr>
<th>TABLE I. Procedure</th>
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<tbody>
<tr>
<td><strong>Group I</strong></td>
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<tr>
<td><strong>Period II</strong></td>
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<td><strong>Period III</strong></td>
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<td><strong>Period IV</strong></td>
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<td><strong>Period V</strong></td>
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<td><strong>Period IV</strong></td>
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<td><strong>Period V</strong></td>
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<td><strong>Period VI</strong></td>
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**Group I.** Initial measurements (period I) were obtained at a concentration of 1.5% isoflurane at a minimum of 1 h after administration of thiopentone. (Joas and Stevens (1971) have obtained a MAC value of 1.46 ± 0.25% in the dog.) The concentration of isoflurane was then increased to 2 MAC (3%) and the measurements were repeated (period II). The concentration was reduced to 1 MAC and a third set of measurements was obtained (period III). Propranolol 0.1 mg/kg i.v. was then administered and measurements were made at 1 MAC, 2 MAC and 1 MAC isoflurane (periods IV–VI).

**Group II.** Measurements were obtained at 1 MAC halothane (period I) and then at 1 MAC isoflurane (period II). Propranolol 0.5 mg/kg i.v. was administered and the measurements were repeated at 1 MAC halothane (period III), then 1 MAC, 2 MAC and 1 MAC isoflurane (periods IV–VI). After the administration of propranolol, beta blockade was confirmed by the absence of a haemodynamic response to isoproterenol 2 µg injected as a bolus. A minimum of 20 min of a given concentration of anaesthetic was administered in both groups before measurements were performed.
Table II. Haemodynamic effects of 1 and 2 MAC isoflurane anaesthesia before and after propranolol 0.1 mg/kg i.v. in the dog (n = 7)*. For explanation of abbreviations see text

<table>
<thead>
<tr>
<th>Period</th>
<th>AP (mm Hg)</th>
<th>Heart rate (beat/min)</th>
<th>CO (litre/min)</th>
<th>PA (mm Hg)</th>
<th>PCW (mm Hg)</th>
<th>RAP (mm Hg)</th>
<th>PVR (units)</th>
<th>SVR (units)</th>
<th>SV (ml/min)</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>94.2</td>
<td>131.7</td>
<td>2.23</td>
<td>10.7</td>
<td>4.8</td>
<td>4.7</td>
<td>2.74</td>
<td>42.1</td>
<td>17.2</td>
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<tr>
<td>Iso-1 MAC</td>
<td>13.6</td>
<td>12.2</td>
<td>0.58</td>
<td>0.8</td>
<td>1.2</td>
<td>1.6</td>
<td>0.95</td>
<td>11.2</td>
<td>5.2</td>
</tr>
<tr>
<td>II</td>
<td>51.7†</td>
<td>121.7</td>
<td>1.45‡</td>
<td>10.3</td>
<td>5.0</td>
<td>5.7</td>
<td>3.67</td>
<td>31.6‡</td>
<td>12.0‡</td>
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<tr>
<td>Iso-2 MAC</td>
<td>10.8</td>
<td>8.3</td>
<td>0.18</td>
<td>1.6</td>
<td>1.3</td>
<td>0.8</td>
<td>1.10</td>
<td>6.9</td>
<td>1.5</td>
</tr>
<tr>
<td>III</td>
<td>94.7</td>
<td>130.7</td>
<td>2.24</td>
<td>10.5</td>
<td>5.0</td>
<td>4.7</td>
<td>2.59</td>
<td>41.9</td>
<td>17.3</td>
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<tr>
<td>Iso-1 MAC</td>
<td>14.2</td>
<td>11.0</td>
<td>0.54</td>
<td>0.5</td>
<td>0.6</td>
<td>1.2</td>
<td>0.79</td>
<td>11.0</td>
<td>4.6</td>
</tr>
<tr>
<td>IV</td>
<td>100.8</td>
<td>118.0</td>
<td>2.47</td>
<td>12.5</td>
<td>5.7</td>
<td>5.0</td>
<td>2.82</td>
<td>40.1</td>
<td>21.0</td>
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<tr>
<td>Iso-1 MAC + prop</td>
<td>19.1</td>
<td>9.8</td>
<td>0.46</td>
<td>2.6</td>
<td>1.4</td>
<td>1.1</td>
<td>0.95</td>
<td>11.0</td>
<td>4.1</td>
</tr>
<tr>
<td>V</td>
<td>53.3†</td>
<td>115.0</td>
<td>1.47‡</td>
<td>11.7</td>
<td>7.3</td>
<td>6.8</td>
<td>2.94</td>
<td>32.9‡</td>
<td>12.9‡</td>
</tr>
<tr>
<td>Iso-2 MAC + prop</td>
<td>14.7</td>
<td>9.6</td>
<td>0.36</td>
<td>2.4</td>
<td>2.7</td>
<td>3.1</td>
<td>0.76</td>
<td>14.5</td>
<td>3.4</td>
</tr>
<tr>
<td>VI</td>
<td>95.0</td>
<td>120.0</td>
<td>2.40</td>
<td>13.0</td>
<td>6.7</td>
<td>6.0</td>
<td>2.80</td>
<td>40.0</td>
<td>20.1</td>
</tr>
<tr>
<td>Iso-1 MAC + prop</td>
<td>18.7</td>
<td>12.6</td>
<td>0.64</td>
<td>1.8</td>
<td>2.5</td>
<td>2.8</td>
<td>0.81</td>
<td>15.2</td>
<td>5.3</td>
</tr>
</tbody>
</table>

* Mean ± SD.
† P < 0.01 period II compared with periods I and III.
‡ P < 0.05 period V compared with periods IV and VI.
Iso = isoflurane; prop = propranolol.

Results

Table II presents the haemodynamic data from group I. Before the administration of propranolol, 2 MAC isoflurane (period II) was associated with a significant decrease in mean arterial pressure (P < 0.01), CO (P < 0.05), stroke volume (P < 0.05) and systemic vascular resistance (P < 0.05) when compared with 1 MAC isoflurane. The values obtained after administration of propranolol 0.1 mg/kg at 1 MAC and 2 MAC isoflurane were similar (P > 0.2) to those obtained before blockade, that is periods I and III were similar to periods IV and VI, and period II was similar to period V.

Table III contains the data for group II. Isoflurane 1 MAC, compared with halothane 1 MAC, was associated with a slightly faster heart rate, a larger CO and a smaller SVR. These differences did not achieve statistical significance (P > 0.10). The administration of propranolol 0.5 mg/kg produced no significant change in any of the haemodynamic parameters measured at either 1 MAC halothane (period III) or 1 MAC isoflurane (periods IV and VI). The data obtained in period V (isoflurane 2 MAC + propranolol 0.5 mg/kg) did not differ significantly from those obtained in group I at 2 MAC isoflurane before or after propranolol administration (table II, periods II and V, and fig. 1).

In both groups mean $P_{a_{CO_2}}$ in all periods ranged from 26 mm Hg to 31 mm Hg, the mean pH in units from 7.40 units to 7.42 units and the mean $P_{a_{O_2}}$ from 483 mm Hg to 506 mm Hg. No significant changes occurred in any of these measurements at any time during the study.

Discussion

The most important finding in this study is that the circulatory response of the dog to 1 MAC or 2 MAC isoflurane is not influenced by the i.v. administration of propranolol 0.1 mg/kg or 0.5 mg/kg. The results
suggest also that there is no clinically important beta-adrenergic action of isoflurane. The administration of propranolol did not affect the heart rate; this was not unexpected, since Shell and Sobell (1973) reported that as much as 2 mg/kg may be necessary to produce a change in rate in the dog. That our data signify a response to isoflurane, and are not dependent upon a specific pretreatment, is suggested by the similarity of the responses to isoflurane in group I (thiopentone induction), group II (halothane induction) and our previous study (chloralose-urethane basal anaesthesia) (Philbin and Lowenstein, 1975).

In group II, the administration of propranolol 0.5 mg/kg did not change the circulatory response to 1 MAC halothane or 1 MAC isoflurane. Neither drug caused changes suggestive of beta-adrenergic stimulation. When the isoflurane concentration was increased to 2 MAC, the decrease in arterial pressure and CO was of the same magnitude as in group I, although the dose of propranolol was increased five-fold (fig. 1). In three animals of group II a halothane concentration of 2 MAC was administered following period VI. The ensuing circulatory depression was so profound as to preclude further study. This preliminary evidence suggests that, in the presence of profound beta-adrenergic blockade, deep isoflurane anaesthesia may be tolerated better than deep halothane anaesthesia. Saner and colleagues (1975) have recently demonstrated profound circulatory depression when beta-adrenergic blockade was established by practolol administration in dogs receiving 0.4% methoxyflurane. Thus there may be a range of circulatory tolerances to different anaesthetic agents in the presence of beta-adrenergic blockade.

While our use of intact, anaesthetized dogs does not allow us to exclude beta-adrenergic action following isoflurane, such an action would appear unlikely. If it is present, it is hard to conceive of circumstances in which it would be of any clinical significance.

ACKNOWLEDGEMENT

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REFERENCES


LACK OF $\beta$-ADRENERGIC ACTIVITY OF ISOFLURANE


MANCE D'ACTIVITE $\beta$-ADRENERGIE BETA DE L'ISOFLURANE CHEZ LE CHIEN: COMPARAISON DES EFFETS CIRCULATOIRES DE L'HALOTHANE ET DE L'ISOFLURANE APRES ADMINISTRATION DE PROPRANOLOL

RESUME

Ces études ont été entreprises pour déterminer si l'inhala
tion d'isoflurane est associée à un certain degré d'action $\beta$-adrénergique, et pour comparer la tolérance circulatoire à l'isoflurane et à l'halothane des chiens après un blocage $\beta$-adrénergique. Nous avons mesuré la tension artérielle et la pression artérielle pulmonaire, la pression de remplissage ventriculaire gauche et droite, les battements de cœur et le débit cardiaque, le volume systolique dérivé ainsi que les résistances vasculaires pulmonaire et systémique sur 13 chiens bâtards. La réaction hémodynamique à 1 MAC (concentration alvéolaire minimale) et à 2 MAC d'isoflurane a été observée sur sept chiens, réaction qui a été similaire avant et après l'administration de propranolol (0,1 mg/kg).

Sur six chiens, le propranolol (0,5 mg/kg) n'a provoqué aucun changement significatif dans la réaction circulatoire à 1 MAC et à 2 MAC d'isoflurane ou à 1 MAC d'halothane. Cependant, sur trois chiens, l'administration de 2 MAC d'halothane après le propranolol (0,5 mg/kg) a provoqué une dépression circulatoire tellement profonde qu'il a fallu cesser tout autre étude. Ces données permettent de penser que (a) l'isoflurane ne possède aucune activité adrénergique $\beta$ stimulante importante du point de vue clinique; (b) qu'il n'y a aucune interaction de médicament adverse sur la circulation avec la combinaison de l'isoflurane et du propranolol; (c) qu'en présence d'un blocage adrénergique $\beta$ modéré à profond, 2 MAC d'isoflurane peuvent être mieux tolérées que 2 MAC d'halothane.

MANGEL AN BETA-ADRENERGISCHER AKTIVITAT VON ISOFLURAN BEIM HUND: VERGLEICH DER KREISLAUFWIRKUNGEN VON HALOTHAN UND ISOFLURAN NACH PROPRANOLOL-VERABREICHUNG

ZUSAMMENFASSUNG

Diese Studien wurden durchgeführt, um festzustellen, ob Isoflurans-Inhalation mit einem gewissen Mass von $\beta$-adrenergischer Aktivität verbunden ist, die in klinischen Situationen von potentieller Bedeutung ist, und auch um die Kreislauf toleranzen auf Isoflurans und Halothan bei Hunden nach Beta-Blockierung zu vergleichen. Wir messen den arteriellen und lungenarteriellen Druck, den Fülldruck im linken und rechten Ventrikel, die Pulszahl und das Herzminutenvolumen, und wir stellten das Schlagvolumen und die systemischen und Pulmonarfrequenz-widerstände bei 13 gemischtrassigen Hunden fest. Die hämodynamische Reaktion auf 1 MAC (minimal Alveolar-Konzentration) und 2 MAC Isoflurane wurde bei sieben Hunden studiert und war vor und nach der intravenösen Verabreichung von 0,1 mg/kg Propranolol ähnlich. Bei sechs Hunden bewirkten 0,5 mg/kg Propranolol keine signifikanten Änderungen der Kreislaufreaktion auf 1 MAC und 2 MAC Isoflurane oder auf 1 MAC Halothan. Bei drei Hunden hingegen führte die Verabreichung von 2 MAC Halothan nach 0,5 mg/kg Propranolol zu einer so schweren Kreislaufunterdrückung, dass weitere Studien nicht möglich waren. Diese Daten zeigen, dass (a) Isoflurane keine klinisch bedeutsame $\beta$-adrenergisch stimulierende Aktivität besitzt; (b) dass es bei der Kombination von Isofluran und Propranolol zu keiner für den Kreislauf schädlichen Wechselwirkung auf den Kreislauf kommt; und dass in Anwesenheit einer mässigen bis starken $\beta$-adrenergerischen Blockierung 2 MAC Isoflurane besser toleriert werden dürften als 2 MAC Halothan.

CARENCIA DE ACTIVIDAD BETA-ADRENERGICA DEL ISOFLURANO EN EL PERRO: UNA COMPARACION DE LOS EFECTOS CIRCULATORIOS DEL HALOTANO E ISOFLURANO TRAS ADMINISTRACION DE PROPRANOLOL

SUMARIO

Se efectuaron estos estudios a fin de determinar si la inhalación de isoflurano está asociada con un grado de acción beta-adrenérgica que sea potencialmente importante
en situaciones clínicas, y para comparar la tolerancia circulatoria al isoflurano y halotano en los perros, tras un bloqueo-beta. Medimos las tensiones arterial y arteropulmonar, la presión ventricular de repleción izquierda y derecha, frecuencia y gasto cardíacos, y descarga sistólica derivada y resistencias vascular pulmonar y generalizada en 13 perros cruzados. La respuesta hemodinámica a 1 CAM (concentración alveolar mínima) o 2 CAM de isoflurano fue estudiada en siete perros y fue similar antes y después de 0,1 mg/kg de propranolol endovenosamente. En seis perros, 0,5 mg/kg propranolol no causó cambios significativos en la respuesta circulatoria a isoflurano 1 CAM y 2 CAM o halotano 1 CAM. Sin embargo, en tres perros, la administración de halotano 2 CAM tras 0,5 mg/kg propranolol resultó en una depresión circulatoria tan profunda que impidió cualquier nuevo estudio. Estos datos sugieren que (a) el isoflurano carece de cualquier actividad estimulante beta-adrenérgica de importancia clínica; (b) no hay ninguna interacción medicamentosa adversa sobre la circulación de isoflurano y propranolol; (c) en presencia de bloqueo beta-adrenérgico moderando a profundo, isoflurano 2 CAM pudiera ser mejor tolerado que halotano 2 CAM.