24-HOUR ALTHESIN-FENTANYL ANAESTHESIA IN DOGS.
TIME COURSE OF HAEMODYNAMIC CHANGES

G. MICHALOT, P. GIRARDET, F. GRIMBERT, D. PIASENTIN and P. STIEGLITZ

SUMMARY
A 24-h anaesthetic using a constant flow infusion of Althesin, fentanyl and pancuronium was given to 10 artificially ventilated dogs. No statistically significant haemodynamic changes occurred during the study, suggesting that the technique may be of value in long-term physiological studies.

Most anaesthetic agents and techniques used during clinical or experimental studies result in unwanted effects which may influence the phenomena being studied (Rushmer, van Otters and Franklin, 1963; Vatner and Braunwald, 1975). A survey of the literature further reveals a paucity of reports of long-term anaesthesia (Muren, 1967; Poyart et al., 1970; Arfors, Arturson and Malmberg, 1971; Danielson et al., 1975; Sjostrom and Wulf, 1975). Since the introduction of Althesin and fentanyl in the practice of anaesthesia, many reports have assessed the favourable therapeutic ratio and the rapid recovery from these drugs when used separately. Their combination for clinical anaesthesia was studied during anaesthesia of several hours' duration with no increase in side-effects compared with the use of either agent alone (Du Caillar et al., 1975). The present study was to assess haemodynamic effects in dogs undergoing 24-h anaesthesia using this combination. An uncertain element was possible drug-induced histamine release with an anaphylactoid reaction (Child, Currie and Twissell, 1971; Lorenz et al., 1971; Davis and Pearce, 1972) from the use of Althesin in the dog.

MATERIALS AND METHODS
Ten mongrel dogs weighing 10–20 kg were anaesthetized with Althesin 5 ml i.v. without premedication; anaesthesia was maintained by continuous infusion of Althesin 0.2 ml kg⁻¹ h⁻¹, fentanyl 8 μg kg⁻¹ h⁻¹ with pancuronium bromide 64 μg kg⁻¹ h⁻¹ in lactated Ringer and 10% glucose solution. The infusion rate was 4 ml kg⁻¹ h⁻¹. The dogs were placed in the supine position, the trachea intubated and the lungs ventilated with room air 200 ml kg⁻¹ min⁻¹ using a volume pre-set ventilator (frequency 12 b.p.m.). Body temperature, monitored using a thermistor probe in the thoracic oesophagus, was kept stable by a thermoregulated heating blanket. A Thomson telco apparatus allowed monitoring of e.c.g. and systemic arterial pressure (right femoral artery). Pulmonary blood flow was measured by the thermodilution method using a Swan–Ganz flow-directed 7F thermodilution catheter (Edwards). This catheter also allowed measurement of the pulmonary arterial and wedge pressures, right atrial pressure, and sampling of blood from the right atrium and pulmonary artery. The right femoral artery was used for systemic arterial blood sampling. The placement of catheters was identified by x-ray and by analysis of the pressure traces.

Heparin 0.1 mg kg⁻¹ h⁻¹ i.v. was given to preserve catheter patency. Vascular pressures were measured with Statham P23 Db Transducers. An Edwards Lab. 9500 cardiac output computer was used for pulmonary blood flow measurement. The thermodilution curves were recorded on a Sefram apparatus for planimetry using the William's formula (Williams, O'Donavan and Wood, 1966). The pulmonary blood flow was taken as the mean of each set of several measurements performed at 1-min intervals without synchronizing the injection with the cardiac or respiratory cycle.

A Beckman oxygen analyser was used to determine oxygen fraction in the inspired gas. Blood-gas tensions were measured with a Radiometer ABL 1 apparatus; oxygen saturation and haemoglobin concentration with an IL CO-oxymeter and oxygen contents with a Lex-Ο₂-Con analyser. Total systemic vascular resistance (TSR) and pulmonary arteriolar
resistance (PAR) were calculated according to the following expressions:

\[ \text{TSR (dyne s cm}^{-5} \text{ m}^{-2}) = \frac{\text{SAP} - \text{RVEDP}}{\text{CO}} \times 80 \]

\[ \text{PAR (dyne s cm}^{-5} \text{ m}^{-2}) = \frac{\text{PAP} - \text{PCWP}}{\text{CO}} \times 80 \]

where \( \text{CO} \) = cardiac output; \( \text{SAP} \) = mean systemic arterial pressure; \( \text{RVEDP} \) = right ventricular end-diastolic pressure; \( \text{PAP} \) = mean pulmonary arterial pressure; \( \text{PCWP} \) = pulmonary capillary wedge pressure.

Oxygen consumption was calculated according to Fick’s equation. Measurements were made after placement of the catheters and every 4 h for 24 h. Blood was sampled at the beginning and at the end of the experiment for measurement of serum electrolytes and enzymes. The depth of anaesthesia was assessed by detection of recovering reflexes (eyelid reflexes), tolerance of endotracheal tube and ventilation, and lack of reaction to surgical stimulation.

**RESULTS**

The data are summarized in table I. Two-way analysis of variance with a significance level of \( P<0.05 \) shows that only pulmonary capillary wedge pressure and pulmonary arterial pressure varied significantly over 24 h (\( P<0.01 \) and \( P<0.025 \) respectively). However, the slope of the regression lines corresponding to the overall points for each of these two pressures is not great (\( \beta = 0.072 \) and \( \beta = 0.17 \) respectively). Comparison of the slopes of individual regression lines (for each dog) showed no significant difference for pulmonary capillary wedge pressure, although there was a difference in pulmonary arterial pressure (\( P<0.05 \)). Comparison between the individual correlation coefficients according to Fisher’s method (Fisher, 1967) demonstrated

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>0</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>20</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI (litre min(^{-1}) m(^{-3}))</td>
<td>3.14</td>
<td>3.25</td>
<td>3.29</td>
<td>3.35</td>
<td>3.21</td>
<td>3.22</td>
<td>3.40</td>
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<tr>
<td>HR (beat min(^{-1}))</td>
<td>175</td>
<td>166</td>
<td>171</td>
<td>165</td>
<td>190</td>
<td>176</td>
<td>185</td>
</tr>
<tr>
<td>RVEDP (mm Hg)</td>
<td>12</td>
<td>11</td>
<td>6</td>
<td>14</td>
<td>7</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>PAP (mm Hg)</td>
<td>15.5</td>
<td>20.43</td>
<td>18.93</td>
<td>20</td>
<td>19</td>
<td>20.43</td>
<td>22.14</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>3.50</td>
<td>5.14</td>
<td>5.36</td>
<td>5.14</td>
<td>5.00</td>
<td>5.64</td>
<td>6.00</td>
</tr>
<tr>
<td>SAP (mm Hg)</td>
<td>103.7</td>
<td>91.8</td>
<td>96.4</td>
<td>96.7</td>
<td>102.5</td>
<td>95.7</td>
<td>103.1</td>
</tr>
<tr>
<td>TSR (dyne s cm(^{-5}) m(^{-2}))</td>
<td>2747</td>
<td>2229</td>
<td>2355</td>
<td>2280</td>
<td>2519</td>
<td>2438</td>
<td>2474</td>
</tr>
<tr>
<td>PAR (dyne s cm(^{-5}) m(^{-2}))</td>
<td>322</td>
<td>385</td>
<td>338</td>
<td>361</td>
<td>359</td>
<td>382</td>
<td>402</td>
</tr>
<tr>
<td>( P_{O_2} ) (kPa)</td>
<td>9.79</td>
<td>9.80</td>
<td>10.29</td>
<td>10.49</td>
<td>10.29</td>
<td>10.24</td>
<td>9.32</td>
</tr>
<tr>
<td>( P_{CO_2} ) (kPa)</td>
<td>6.05</td>
<td>6.23</td>
<td>6.31</td>
<td>6.24</td>
<td>5.91</td>
<td>6.19</td>
<td>5.89</td>
</tr>
<tr>
<td>( Vo_2 ) (ml min(^{-1}) m(^{-3}))</td>
<td>171.7</td>
<td>165.2</td>
<td>187.2</td>
<td>201</td>
<td>217.2</td>
<td>194.7</td>
<td>218.7</td>
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<td>( P_{O_2} ) (kPa)</td>
<td>23.5</td>
<td>8.04</td>
<td>16.6</td>
<td>10.8</td>
<td>17.7</td>
<td>15.8</td>
<td>9.2</td>
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<tr>
<td>( P_{CO_2} ) (kPa)</td>
<td>5.08</td>
<td>4.88</td>
<td>4.69</td>
<td>4.71</td>
<td>4.45</td>
<td>5.11</td>
<td>5.12</td>
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<td>pHa</td>
<td>7.32</td>
<td>7.34</td>
<td>7.36</td>
<td>7.36</td>
<td>7.39</td>
<td>7.34</td>
<td>7.34</td>
</tr>
<tr>
<td>Significance</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>P&lt;0.025</td>
<td>P&lt;0.01</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

*Two-way analysis of variance*
homogeneity, which means that the individual correlation coefficients $r$ were from the same $p$. However $p$ was not significantly different from zero at the 5% level. Therefore, we conclude that these two measurements were essentially stable.

**DISCUSSION**

The technique described in the present study was associated with remarkable haemodynamic stability. Several authors have already reported lack of cumulative side-effects of Althesin (Du Caillar et al., 1975), corroborating experimental studies of the kinetics and metabolism of the drug (Child, Currie and Twissell, 1972; Card, McCulloch and Pratt, 1972). Liu and colleagues (1976) clearly showed in the dog that large doses of fentanyl (0.05 to 0.15 mg kg$^{-1}$) given as a constant infusion were necessary to produce significant cardiovascular changes. However, in a clinical study, Du Caillar and colleagues (1978) demonstrated progressively increasing plasma concentrations of fentanyl 45 min after the continuous infusion of an Althesin-fentanyl mixture, throwing some light on current concepts of fentanyl metabolism (Van Wijngaarden and Soudijn, 1968; Michiels, Hendricks and Heykants, 1977; Schleimer et al., 1978). These findings were corroborated by Hug (1978), who reported increasing plasma concentration of fentanyl following repeated administration of a standard dose. Thus, it is of interest to know if side-effects occur in the course of a long anaesthetic using fentanyl. The choice of the dog as an animal model might appear inappropriate since cremophor EL, the solvent for Althesin, has been thought to be responsible for anaphylactoid reaction in dogs. Indeed anaphylactoid reactions were demonstrated in the dog following injection of polymeric compounds (Krantz et al., 1948), but the frequency of adverse reactions to Althesin in this species has not been established. In our study none of the dogs showed signs of hypersensitivity. The doses of Althesin and fentanyl were determined during preliminary investigations without pancuronium and we found that dogs could endure marked surgical stimulation without responding; pancuronium bromide was used to counter residual spontaneous ventilatory movements and thoracic rigidity. Changes in blood oxygen and carbon dioxide tensions may be important factors influencing the time course of haemodynamic variations (Carson et al., 1965). In the present study, the ventilatory pattern was set so that arterial $P_{CO_2}$ and pH were approximately in the normal range for the dog (Mitruka and Rawnsley, 1977). The perfusion rate was calculated to equal the normal urinary output in dog (Arfors, Arturson and Malmberg, 1971; Mitruka and Rawnsley, 1977). Our results compared with normal values in the dog (Mitruka and Rawnsley, 1977) show a greater cardiac index and heart rate—known effects when using Althesin separately (Patschke et al., 1976). The systolic index did not vary, the cardiac output in the dog being regulated through variations in heart rate (Rushmer, van Citters, and Franklin, 1963). The systemic arterial pressures were within the normal range, whereas the pressures in the pulmonary circulation were greater than normal, as previously reported with Althesin alone (Patschke et al., 1974; Patschke et al., 1976). Therefore, the haemodynamic values under Althesin–fentanyl anaesthesia were similar to those observed with administration of a single injection of Althesin. In particular, we did not observe bradycardia or systemic arterial hypotension which has been reported following administration of fentanyl (Kriffa, Moret and Gemperle, 1971; Liu et al., 1976), probably in part because of dose dependence (Liu et al., 1976). Similar observations were made during later experiments performed under the same technique in our laboratory (Grimbert et al., 1978). The stability of the preparation over 24 h would be satisfactory for physiological studies of such duration.

**REFERENCES**


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**ANESTHESIA OF CHIENS A L'ALTHESINE-FENTANYL PORTANT SUR 24 H: PORTEE DES CHANGEMENTS HEMODYNAMIQUES**

**RESUME**

Dix chiens, ventilés artificiellement, ont reçu pendant 24 h une anesthésie à base d'althésine, de fentanyl et de pancuronium par infusion à débit constant. Il n'y a eu aucun changement hémodynamique statistiquement significatif pendant l'étude, ce qui semble indiquer que cette technique peut présenter un intérêt pour les études physiologiques à long terme.

**VIERUNDZWANZIGSTUNDIGE ALTHESIN-FENTANYLNARKOSE BEI HUNDEN: ZEITABLAUF HÄMODYNAMISCHER VERÄNDERUNGEN**

**ZUSAMMENFASSUNG**

Eine 24-stündige Narkose mit konstanter Infusion von Althesin, Fentanyl und Pancuronium wurde 10 künstlich belüfteten Hunden verabreicht. Im Verlauf dieser Studie kam es zu keinen statistisch wesentlichen Veränderungen hämodynamischer Art, was zeigt, dass diese Methode für langfristige physiologische Studien von Nutzen sein könnte.

**ANESTESIA DE 24 H POR ALTESINA-FENTANIL EN PERROS: EVOLUCION TEMPORAL DE CAMBIOS HEMODINAMICOS**

**SUMARIO**

Se administró un anestésico de 24 h a 10 perros artificialmente ventilados al usar una infusión de flujo constante de Altesina, fentanilo y pancuronio. No ocurrieron cambios hemodinámicos algunos que tuvieran significado desde el punto de vista estadístico durante el estudio, lo que hace pensar que dicha técnica puede tener valor en estudios fisiológicos a largo plazo.