EFFECTS OF CERTAIN I.V. ANAESTHETICS ON LIVER BLOOD FLOW AND HEPATIC OXYGEN CONSUMPTION IN THE GREYHOUND

I. A. THOMSON, W. FITCH, R. L. HUGHES, D. CAMPBELL AND R. WATSON

Little is known of how i.v. anaesthetic agents modify blood flow in the hepatic vascular bed. Of the few investigations which have measured changes in liver blood flow in association with i.v. anaesthesia, most have studied the effects induced by thiopentone (Habif et al., 1951; Shackman, Graber and Melrose, 1953; Levy et al., 1961; Galindo, 1965). Information concerning the more recently introduced agents, Althesin and etomidate, is sparse.

This study in the anaesthetized greyhound was undertaken to provide information on the effects of i.v. infusions of certain ultra-short-acting anaesthetics on liver blood flow and hepatic oxygen consumption.

MATERIALS AND METHODS

Anaesthesia

Twenty greyhounds (weight 20–35 kg) were fasted overnight. Anaesthesia was induced with thiopentone 20 mg kg\(^{-1}\) i.v. and maintained with pentobarbitone 30 mg kg\(^{-1}\) i.v. and neuromuscular blockade was produced with pancuronium 0.15 mg kg\(^{-1}\) i.v. Following intubation of the trachea, the lungs were ventilated with a mixture of 75% nitrogen in oxygen at a rate of 14 b.p.m.

Summary

The effects of increasing concentrations of thiopentone, Althesin and etomidate on liver blood flow and hepatic oxygen consumption were investigated in the anaesthetized greyhound. All three agents studied produced dose-related decreases in general cardiovascular indices such as mean arterial pressure, cardiac output and systemic vascular resistance; all three anaesthetics produced decreases in liver blood flow. During the low rates of infusion with Althesin and etomidate, significant decreases in hepatic arterial blood flow were recorded at a time when the systemic circulation was not significantly affected. Indeed, during the low rates of infusion with each of the three agents, hepatic arterial resistance and mesenteric vascular resistance increased by up to 40% above baseline values. During the high rates of infusion, hepatic arterial and mesenteric vascular resistances either returned to or decreased below control values and the decreases in liver blood flow were a consequence of generalized cardiovascular depression. Despite relatively unchanged hepatic oxygen consumption, all the anaesthetics produced significant decreases in the hepatic oxygen supply.

(Barnett Mk2 ventilator). Physiological tensions of carbon dioxide and oxygen in arterial blood were maintained throughout each investigation.

The normal formulation of Althesin is 0.9% alphaxalone and 0.3% alphadolone dissolved in a mixture of Cremophor EL and water. However, there have been only a few studies of the cardiovascular actions of this agent in dogs because an allergic reaction to the Cremophor EL is evident in this species, and the resulting
circulatory depression obscures the cardiovascular effects of the Althesin per se (Child et al., 1971). In this study, this unwanted reaction was prevented by dissolving the two steroids in a mixture of 40% propylene glycol, 10% ethanol and 50% water. (This formulation of Althesin was kindly provided by Glaxo Pharmaceuticals Limited.)

Surgical preparation

Since the surgical preparation has been described in detail previously (Hughes et al., 1979), only the most salient details are presented below. Following laparotomy, the hepatic artery and portal vein were identified and cleared of adventitia to permit the placement of electromagnetic flow probes (Statham). Care was taken during the dissection to ensure that the peri-arterial nerve plexus remained intact. A 3-mm probe was placed around the artery and a 5-mm probe around the vein. These were connected to a pair of synchronized flowmeters (Statham SP2202) which possessed an electronic zeroing facility. Ligation of the gastroduodenal and right gastric arteries ensured that all the blood flowing through the common hepatic artery supplied the liver.

A cannula was placed in the gastroduodenal vein and advanced until it reached the junction with the portal vein. The hepatic vein was cannulated via the external jugular vein. From these cannulae, portal venous and hepatic venous blood samples were obtained and venous pressures could be monitored. Hepatic oxygen supply and oxygen consumption were calculated from measurements of the oxygen content of blood obtained from the hepatic artery, portal vein and hepatic vein (Lex-O₂-Con electrolytic cell; Lexington Instruments) and inserted to the following equations:

Hepatic oxygen supply

\[
\text{hepatic artery } O_2 \text{ supply} = \frac{\text{hepatic arterial blood flow}}{100} \times \text{hepatic artery } O_2 \text{ content} \\
\text{portal vein } O_2 \text{ supply} = \frac{\text{portal venous blood flow}}{100} \times \text{portal vein } O_2 \text{ content} \\
\text{total hepatic } O_2 \text{ supply (ml min}^{-1}\text{)} = \text{hepatic artery } O_2 \text{ supply} + \text{portal vein } O_2 \text{ supply}
\]

Hepatic oxygen consumption

\[
\text{hepatic } O_2 \text{ consumption (ml min}^{-1}\text{)} = \frac{\text{hepatic arterial blood flow}}{100} \times (\text{hepatic artery } - \text{hepatic venous } O_2 \text{ content}) \\
+ \frac{\text{portal venous blood flow}}{100} \times (\text{portal venous } - \text{hepatic venous } O_2 \text{ content})
\]

where hepatic arterial and portal venous blood flows are in ml min\(^{-1}\) and hepatic arterial and portal venous oxygen contents are in ml O\(_2\)/100 ml blood.

Mean arterial pressure was monitored by means of a catheter inserted, via a femoral artery, to the abdominal aorta. Cardiac output was measured (thermal dilution) with a triple-lumen, thermistor-tipped, catheter which had been passed into the pulmonary artery via a femoral vein. Core temperature was also monitored with this catheter and was maintained at 38 °C by means of radiant heat lamps. The fluid balance of the animal was sustained by the infusion of physiological saline 5–15 ml kg\(^{-1}\) h\(^{-1}\) to a brachial vein. Blood-gas tensions and acid-base balance were measured intermittently (Corning 165 blood-gas/pH analyzer) in samples of arterial blood. Since dogs normally maintain a compensated metabolic acidosis (Zweens et al., 1977), a base deficit of no greater than —4 mmol litre\(^{-1}\) was maintained by the administration, when required, of sodium bicarbonate. Systemic vascular, hepatic arterial and mesenteric vascular resistances were calculated according to the formulae published previously (Hughes et al., 1980), having the general form:

\[
\text{Resistance} = \frac{\Delta P}{\text{blood flow}}
\]

where \(\Delta P\) = pressure gradient across vascular bed.

Where possible, the plasma concentrations of the various anaesthetic agents were determined. Plasma alphaxalone concentrations were measured by gas–liquid chromatography (GLC) based on the method of Sear and Prys-Roberts (1979a).
Thiopentone concentration was measured by GLC. The assay used was similar to that reported by Kulpmann and colleagues (1983). (In the present study a different column was used, 3% SP 2250 DA and, instead of cyclobarbitone, amylobarbitone was used as the internal standard.) The plasma concentrations of etomidate were measured using an HPLC technique developed by Kinsler (1981).

**Design of investigation**

Three groups of greyhounds were used and each group received only one anaesthetic which was infused at three different rates. The programme was identical for each group. After the completion of surgery, the preparation was allowed to stabilize for 1 h. Baseline recordings were taken of systemic arterial pressure, cardiac output, portal venous pressure, hepatic venous pressure, hepatic arterial blood flow and portal venous blood flow. Blood samples were drawn from the abdominal aorta, portal vein and hepatic veins. An infusion of the appropriate drug was commenced, and further measurements obtained 20 min later—once mean arterial pressure had stabilized at a new value. This procedure was repeated on two further occasions with increasing rates of infusion. All the data obtained from individual experiments were analysed using an analysis of variance with randomized blocks followed by a Dunnett's multiple comparison procedure (Dunnett, 1964). Comparisons were made between different groups using Student's t test for unpaired data. \( P < 0.05 \) was taken as the level of significance.

The rates of infusion (\( \mu g \text{ kg}^{-1} \text{ min}^{-1} \)) for each anaesthetic are shown in table I.

### RESULTS

There were no significant differences in the control measurements between the different anaesthetic groups (tables II, III, IV).

#### General haemodynamic measurements

Infusions of thiopentone, Althesin and etomidate resulted in dose-dependent decreases in mean arterial pressure. At the highest infusion rates there were similar significant decreases in arterial pressure to around 40% of control (table III) with each agent.

With all three anaesthetics, cardiac output and systemic vascular resistance decreased as the rates of infusion were increased. At the highest rate of infusion for thiopentone, there was a greater percentage decrease in cardiac output (44%) than in systemic vascular resistance, which was 24% less than the control value. However, with Althesin and etomidate, this trend was reversed and systemic vascular resistance decreased to a greater extent than cardiac output (table III).

#### Hepatic haemodynamic measurements

Linear and significant decreases in hepatic arterial blood flow were observed with each anaesthetic; these ranged from approximately 55% with the highest infusion rates of thiopentone and Althesin to 42% of control value with etomidate (fig. 1). There were small decreases in portal venous blood flow during the administration of Althesin, none of which was significant. In the

<table>
<thead>
<tr>
<th><strong>Table I. Infusion rates (( \mu g \text{ kg}^{-1} \text{ min}^{-1} )) for each anaesthetic</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiopentone</td>
</tr>
<tr>
<td>Low</td>
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<tr>
<td>Mid</td>
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<tr>
<td>High</td>
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<thead>
<tr>
<th><strong>Table II. Control measurements (mean ( \pm \text{ SEM} )) for each anaesthetic group. ( n = \text{Number of observations} )</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic arterial blood flow (ml min(^{-1})/100 g liver)</td>
</tr>
<tr>
<td>Thiopentone (( n = 6 ))</td>
</tr>
<tr>
<td>Althesin (( n = 6 ))</td>
</tr>
<tr>
<td>Etomidate (( n = 6 ))</td>
</tr>
</tbody>
</table>
TABLE III. Effects of thiopentone, Althesin and etomidate on mean arterial pressure, cardiac output and systemic vascular resistance (mean ± SEM). n = Number of observations. c = Control; l = low infusion rate; m = mid infusion rate; h = high infusion rate (see table I for infusion rates of each agent). Analysis of variance was performed on the data, followed by Dunnett's test for the comparison of data at each infusion rate with control data. *P < 0.05; **P < 0.001

<table>
<thead>
<tr>
<th></th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Cardiac output (litre min⁻¹ kg⁻¹)</th>
<th>Systemic vascular resistance (mm Hg litre⁻¹ min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiopentone</td>
<td>c 154.0 ± 4.4</td>
<td>0.151 ± 0.009</td>
<td>40.1 ± 3.4</td>
</tr>
<tr>
<td>(n = 8)</td>
<td>l 151.3 ± 5.0</td>
<td>0.153 ± 0.008</td>
<td>39.1 ± 3.9</td>
</tr>
<tr>
<td></td>
<td>m 127.1 ± 9.8**</td>
<td>0.143 ± 0.007</td>
<td>33.6 ± 2.1</td>
</tr>
<tr>
<td></td>
<td>h 63.6 ± 6.9**</td>
<td>0.086 ± 0.011**</td>
<td>30.4 ± 4.6*</td>
</tr>
<tr>
<td>Althesin</td>
<td>c 166.4 ± 6.8</td>
<td>0.158 ± 0.012</td>
<td>42.3 ± 1.8</td>
</tr>
<tr>
<td>(n = 6)</td>
<td>l 153.3 ± 11.5</td>
<td>0.150 ± 0.013</td>
<td>41.1 ± 2.8</td>
</tr>
<tr>
<td></td>
<td>m 122.7 ± 17.5**</td>
<td>0.142 ± 0.012</td>
<td>34.3 ± 3.9</td>
</tr>
<tr>
<td></td>
<td>h 64.7 ± 9.2**</td>
<td>0.111 ± 0.010**</td>
<td>23.3 ± 2.3**</td>
</tr>
<tr>
<td>Etomidate</td>
<td>c 152.5 ± 4.0</td>
<td>0.132 ± 0.016</td>
<td>52.3 ± 8.0</td>
</tr>
<tr>
<td>(n = 6)</td>
<td>l 149.2 ± 9.8</td>
<td>0.126 ± 0.017</td>
<td>51.9 ± 5.6</td>
</tr>
<tr>
<td></td>
<td>m 93.2 ± 9.7**</td>
<td>0.110 ± 0.013*</td>
<td>35.8 ± 3.2*</td>
</tr>
<tr>
<td></td>
<td>h 58.3 ± 5.8**</td>
<td>0.098 ± 0.014**</td>
<td>26.4 ± 2.8**</td>
</tr>
</tbody>
</table>

thiopentone and etomidate investigations, portal venous blood flow was decreased significantly at the mid and high infusion rates, this effect being greatest with thiopentone, which resulted in a value of portal blood flow of less than 60% of control (fig. 2). Total liver blood flow decreased in a similar fashion to portal blood flow, except that the decrease measured during the administration of Althesin was significant (fig. 3).

During the low infusion rate of etomidate there was a significant increase in hepatic arterial resistance and, although mesenteric vascular resistance increased also, this latter change was not significant. At the high infusion rate (etomidate),
Fig. 2. Effects of increasing infusion rates of thiopentone (+), Althesin (□) and etomidate (△) on portal venous blood flow. Changes in blood flow shown as percentages of control; bars indicate ± SEM. *P < 0.05; **P < 0.001.

Fig. 3. Effects of increasing infusion rates of thiopentone (+), Althesin (□) and etomidate (△) on total liver blood flow. Changes in blood flow shown as percentages of control; bars indicate ± SEM. *P < 0.05; **P < 0.001.
hepatic arterial resistance returned to control values, while mesenteric vascular resistance decreased significantly.

Similar effects on hepatic arterial (fig. 4) and mesenteric vascular (fig. 5) resistances were observed during the administration of thiopentone and Althesin; namely, an initial increase followed, at the high rates of administration, by a decrease...
to or to less than control values. Unlike results with etomidate, none of these effects was significant.

During the infusions of thiopentone, Althesin and etomidate, the oxygen content in hepatic arterial blood decreased significantly by between 10 and 20%, while portal venous oxygen content decreased by 25–35% from control (table IV). Larger decreases were observed in hepatic venous oxygen content which, during the most rapid infusion of etomidate, was decreased on average by almost 50%. The decrease in hepatic venous oxygen content was a result of an increase in hepatic oxygen extraction efficiency which increased from a control value of 17–19% to 33% during the administration of Althesin, and to 40% with thiopentone and etomidate (table IV).

The hepatic oxygen supply was decreased in line with the decreased blood flow and oxygen content. During the high infusion rates, decreases in hepatic arterial and portal venous oxygen supplies ranged from 35 to 65%. Total oxygen supply during Althesin was decreased by 40% from its value during the control period and by approximately 55% with thiopentone and etomidate (table IV). Small, non-significant, decreases in hepatic oxygen consumption were observed with all three anaesthetic agents (table IV). At the highest rates of infusion there were greater decreases in the hepatic oxygen consumption (figs 6, 7, 8).

Total plasma anaesthetic concentrations were measured in some experiments and are presented in table V.

### Table V. Plasma concentrations following administration of thiopentone, Althesin and etomidate (mean ± SEM).

<table>
<thead>
<tr>
<th>Substance</th>
<th>c</th>
<th>l</th>
<th>m</th>
<th>h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiopentone</td>
<td>9.3 ± 2.7</td>
<td>16.1 ± 2.4</td>
<td>22.0 ± 3.6</td>
<td>31.5</td>
</tr>
<tr>
<td>Althesin</td>
<td>0.64 ± 0.11</td>
<td>1.39 ± 0.22</td>
<td>3.03 ± 0.43</td>
<td>6.7 ± 1.3</td>
</tr>
<tr>
<td>Etomidate</td>
<td>2.6</td>
<td>6.7 ± 1.3</td>
<td>13.7 ± 3.3</td>
<td>3</td>
</tr>
</tbody>
</table>

**Plasma concentration (μg ml⁻¹) n**
DISCUSSION

The effects of i.v. anaesthetics on regional haemodynamics, including the brain, heart and kidneys, have been studied widely. However, little is known of their effects on the circulation to the liver. This is certainly true of agents such as Althesin and etomidate, although a few of the earlier studies considered the effects of thiopentone (Habif et al., 1951; Shackman, Graber and Melrose, 1953; Epstein et al., 1961; Levy et al., 1961; Galindo, 1965).

**General haemodynamics**

In the present investigation, infusions of thiopentone, Althesin and etomidate produced dose-related effects on mean arterial pressure, cardiac output and systemic vascular resistance. These changes were probably the result of peripheral vasodilatation or myocardial depression, or both. At the highest rate of infusion for each anaesthetic, there was a large decrease in mean arterial pressure of approximately 60%. In man, infusions of thiopentone and Althesin do not generally result in such marked cardiovascular depression (Becker and Tonnesen, 1978; Carlon et al., 1978; Sear and Prys-Roberts, 1979b). Thus, the anaesthetized greyhound is apparently more sensitive to the cardiovascular effects of thiopentone and Althesin than is man. This difference in responsiveness may result from species variation or may be a result of an interaction of these short-acting i.v. anaesthetic agents with the background pentobarbitone anaesthesia, as suggested by Child and colleagues (1972).

Infusions of etomidate in man have been reported to have minimal effects on the cardiovascular system (Booij, Rutten and Crul, 1978; Lees, 1981). In this series of investigations, the lowest rate of infusion for etomidate resulted in a mean plasma concentration of 2.6 \( \mu g \) ml\(^{-1}\), a value similar to therapeutic concentrations measured in man (van Hamme, Ambre and Ghoneim, 1977; Schuttler et al., 1980) and, as in man, had no effect on mean arterial pressure, cardiac output or systemic vascular resistance. However, even in the absence of systemic effects, the hepatic circulation was significantly affected, with decreases both in blood flow and in oxygen delivery.

The plasma concentrations measured following the most rapid infusion rates of thiopentone (31.6 \( \mu g \) kg\(^{-1}\)) and Althesin (3.1 \( \mu g \) kg\(^{-1}\) (alphaxalone was measured)), are in the same range as those encountered clinically in man (Brodie et al., 1950; Becker, 1978; Sear and Prys-Roberts, 1979a; Blunnie et al., 1981). However, in the present experiments the highest etomidate infusion rate of 318 \( \mu g \) kg\(^{-1}\) min\(^{-1}\) and, thus, the resulting mean plasma concentration of 13.7 \( \mu g \) ml\(^{-1}\), was considerably higher than previously reported during
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Fig. 7. Effects of increasing infusion rates of Althesin on hepatic oxygen supply (\( \Delta \)) and consumption (+). Changes in supply and consumption shown as percentages of control; bars indicate \( \pm \) SEM. *\( P < 0.05 \); **\( P < 0.001 \).

Fig. 8. Effects of increasing infusion rates of etomidate on hepatic oxygen supply (\( \Delta \)) and consumption (+). Changes in supply and consumption shown as percentages of control; bars indicate \( \pm \) SEM. **\( P < 0.001 \).
surgical anaesthesia in man (Booij, Rutten and Crul, 1978; Renou et al., 1978; Schuttler et al., 1980). Thus, although the three agents were approximately equipotent with respect to their effects on mean arterial pressure, it is possible that the amount of etomidate administered (especially at the high infusion rate) was relatively greater than the amounts of thiopentone or Althesin. However, Kissin, McGee and Smith (1981) have pointed out that the relative potency of etomidate vis-à-vis thiopentone can vary between 5 and 15, depending on which index of potency is utilized.

**Hepatic haemodynamics**

All three anaesthetics studied had qualitatively similar effects on the hepatic vascular bed and responses varied only quantitatively. Hepatic arterial blood flow was decreased significantly during the low infusions of Althesin and etomidate. These changes occurred at a time when systemic variables such as mean arterial pressure, cardiac output and systemic vascular resistance were unchanged. The decreases in flow may have resulted from vasoconstriction in the hepatic arterial bed, since marked increases in hepatic arterial resistance were recorded. Etomidate caused the largest increase in hepatic arterial resistance (40%) and also the largest decrease in hepatic arterial blood flow at this infusion rate. As the rate of delivery of each anaesthetic was increased, the initial increase in hepatic arterial resistance was reversed until, by the end of the study, the resistance in the hepatic arterial bed had either returned to control values (etomidate) or had decreased even further to more than 30% below control (Althesin). At this point, mean arterial pressure and cardiac output were markedly decreased and hepatic arterial blood flow continued to decrease, despite the decreasing arterial resistance.

Similar changes in mesenteric vascular resistance and portal venous blood flow were observed: a small initial increase in mesenteric vascular resistance accompanied by a small decrease in portal blood flow. Again, during the high infusion rates, there were large decreases in mesenteric vascular resistance. A decrease in resistance in this vascular bed might be expected to maintain portal venous blood flow but, in the face of decreasing mean arterial pressure and cardiac output, flow in the portal vein tended to decrease also.

Thus, in the anaesthetized greyhound, thiopentone, Althesin and etomidate, in relatively low concentrations, seemed to result in a moderate splanchnic vasoconstriction which may have been responsible for the decreases in liver blood flow. Apparently, this vasoconstrictor response was a local effect, since the systemic circulation was unaffected by low concentrations of these agents. A similar effect has been observed by other groups with halothane (Thulin, Andreen and Trestedt, 1975; Benumof et al., 1976; Hughes, Campbell and Fitch, 1980) and methoxyflurane (Libonati et al., 1973). As the rate of infusion and, consequently, the plasma concentrations increased, this local vasoconstriction was overridden by the more powerful systemic effects of high anaesthetic concentrations, such as peripheral vasodilatation and myocardial depression.

Hepatic oxygen consumption was well maintained throughout despite large decreases in the oxygen delivery to the liver via both the hepatic artery and the portal vein. This decrease in oxygen supply resulted not only from the decrease in liver blood flow, but also from a decrease in the oxygen content of the blood reaching the liver. The oxygen content of the hepatic arterial blood was decreased slightly. However, the oxygen content of blood in the portal vein was decreased to a greater extent. Presumably, this was because of the unaltered oxygen requirements of the preportal tissues such as the stomach and the intestines, which had to extract the same amount of oxygen from a decreased supply. Similarly, the liver maintained its oxygen consumption by extracting increased amounts from the available supply. The hepatic oxygen extraction efficiency increased greatly and this was reflected by the decreases in hepatic venous oxygen content.

Physiologically, the liver receives an over-supply of oxygen—of which it extracts a small proportion. However, if there are substantial variations in this supply, it is conceivable that this reserve could be exhausted. Indeed, Shingu, Eger and Johnson (1982) and van Dyke (1982) have suggested that this could be one factor responsible for the liver damage seen in animal models of anaesthetic-related hepatotoxicity.

The phenomenon of reciprocal blood flow in the liver has been reported (Cohn and Kountz, 1963; Hanson and Johnson, 1966; Kock et al., 1972). An intrinsic mechanism by which hepatic arterial blood flow increases in response to a decrease in portal venous blood flow, and the resulting decrease in portal oxygen supply, would offer an excellent buffer system with which to maintain
adequate oxygenation of the liver during periods of stress. However, this relationship was not apparent under the conditions imposed during the present investigations. During periods when portal venous blood flow was decreasing, one might have expected a parallel decrease in hepatic arterial resistance, thus allowing an increase in blood flow via the arterial supply. In fact, initially, hepatic arterial resistance tended to increase, resulting in a decrease in hepatic arterial blood flow. Only when the rate of administration of the anaesthetics was increased did the hepatic artery dilate. However, this was not a localized response, but appeared to be a result of systemic cardiovascular depression. Thus thiopentone, Althesin and etomidate all appear to override this potentially beneficial intrinsic response of the hepatic vasculature.

Obviously, the withdrawal of Althesin and the current ban on infusions of etomidate have decreased substantially the direct clinical relevance of this investigation. However, there is no doubt that there remains a place for the administration of suitable drugs by infiltration and we would submit that the observed effects on the physiological responsiveness, and oxygen supply, of the liver are relevant considerations whatever the actual drug(s) used.

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