CARDIOVASCULAR EFFECTS OF PROPOFOL AND OF THIOPENTONE ANAESTHESIA IN THE SHEEP

W. B. RUNCIMAN, L. E. MATHER AND D. G. SELBY

SUMMARY
We have examined the effects on the cardiovascular system and on regional blood flow of propofol and thiopentone when administered with IPPV (F\textsubscript{1}O\textsubscript{2} 0.4). A longitudinal study design was used in which 16 studies were performed in eight sheep for 30 min before, during the last 30 min of 70 min anaesthesia, and for 6 h after anaesthesia. During anaesthesia with propofol and thiopentone, mean total body oxygen consumption decreased, respectively, by 47\% (P < 0.001) and 24\% (P < 0.01) of pre-anaesthesia baseline values, mean heart rate increased by approximately 50\% (P < 0.05) with both agents, mean arterial pressures increased by approximately 50\% (P < 0.05) with both agents and the mean cardiac output was unaltered with propofol anaesthesia but was decreased by 20\% (P < 0.05) with thiopentone anaesthesia. The changes in arterial pressure and heart rate were unexpected and may have been a result of a species-specific effect. Mean hepatic blood flow decreased consistently by a mean of 17\% (P < 0.01) during propofol anaesthesia, and inconsistently during thiopentone anaesthesia so that it was not significantly different from baseline values. Mean renal blood flow decreased during propofol anaesthesia by 7\% (P < 0.05) and by 27\% (P < 0.001) during thiopentone anaesthesia. Whereas most variables returned to baseline values within 2 h after propofol anaesthesia, this took 5 h after thiopentone anaesthesia.

KEY WORDS

METHODS
Animal preparation
Sixteen studies were performed in eight sheep prepared previously with chronically implanted catheters so that the cardiovascular effects of total i.v. anaesthesia with thiopentone and of propofol could be measured. At the same time, the regional clearances of several indicators and drugs were

The use of propofol for induction and maintenance of anaesthesia by repeated doses or infusion has become widespread in recent anaesthetic practice [1]. There has also been a resurgence of interest in the continuous use of thiopentone for anaesthesia [2]. In most situations, the cardiovascular effects of these agents have been studied in surgical patients in whom the effects of premedicants, surgical stimulus or inhalation anaesthetic agents may have contributed to the observed effects. Also, to date, studies of the effects of propofol on regional blood flow have not been reported. We have studied, therefore, the cardiovascular effects of these agents, in the absence of surgery and other pharmacological agents, using a sheep preparation in which the effects during and after anaesthesia could be compared with baseline measurements in the same animals before anaesthesia.
measured. The details of these studies are presented in accompanying papers. The surgery, the physiological profile of the sheep preparation, and some applications in anaesthesia research have been reported previously in detail [3–5]; the aspects relevant to this study are described briefly here.

Adult merino ewes (weight 33–63 kg) were prepared by placement, under general anaesthesia, of polyethylene catheters so that their tips were at the aortic arch for the measurement of mean arterial pressure and the sampling of arterial blood, in the right atrium for the infusion of drugs, indicator substances and i.v. crystalloid solutions, and in a right hepatic vein, the left renal vein and the posterior vena cava (distal to the site of entry of the renal veins) for sampling, respectively, of hepatic, renal and hindquarter effluent blood. In addition, a quadruple-lumen thermistor-tipped catheter was placed in a pulmonary artery for the measurement of cardiac output. At least 1 week was allowed between catheter placement and study.

**Experimental design**

The studies were divided into two parts, one using the antibiotic drug cefoxitin as an indicator to examine the efficacy of renal elimination of drug [6] and the other using the analgesic agent, pethidine, as indicators to examine the efficacy of hepatic and other routes of elimination of drug [7]. In both parts, renal blood flow was determined using sodium hippuran and hepatic blood flow was determined using sodium bromsulphthalein (BSP) as indicator substances. The infusions of the indicators and drugs were continued throughout the entire study period; the doses used have been shown not to produce significant cardiovascular effects [6, 7].

The first 60-min period was designated as a rest period to allow the animal to adapt to the study room and for the substances to achieve stable blood concentrations. During the next 30-min period, observations were made and appropriate blood samples were collected 10 min apart (i.e. four sets) for baseline measurements. Anaesthesia was induced with commercial preparations of either propofol 250–300 mg over 1 min or thiopentone 750 mg over 1 min, a cuffed tracheal tube was inserted into the trachea and the lungs ventilated to normocapnia with an \( F_{\text{IO}} \) of 0.4. Maintenance infusions of propofol 20–25 mg min\(^{-1}\) at a constant rate or thiopentone 25 mg min\(^{-1}\) decreasing to 10 mg min\(^{-1}\) over the first 30 min were continued for 70 min; the last 30 min of this period was observed as the "anaesthesia" period and measurements were made as for the baseline period. The doses were determined from experience in our laboratory of producing anaesthesia in sheep with these agents. Recovery was observed by repeating the measurements at 0.5, 1.0, 2, 3, 4, 5, 6, 7, 8 and 9 h after the maintenance infusions were stopped. For statistical analysis, these measurements were grouped into early (0.5–2 h), mid (3–5 h) and late (6–9 h) recovery periods.

Arterial blood concentrations of propofol [8] and thiopentone (see Appendix 1) each were measured by high pressure liquid chromatography (HPLC) to relate the results to published anaesthetic blood drug concentrations. The sensitivity of both assays was 0.02 mg litre\(^{-1}\). The coefficients of variation of the assays for propofol and thiopentone, determined at concentrations of 2.0 mg litre\(^{-1}\) were, respectively, 3.6% and 2.4%.

**Cardiovascular measurements**

A saline-filled extension line was connected to an aortic catheter and to a calibrated anaeroid gauge to measure mean arterial pressure. Heart rate was determined by counting the rate of oscillation of a small air bubble placed in this line. Cardiac output was determined by thermodilution with a commercially available cardiac output computer after right atrial injection of ice-cold saline and corrected in each animal by calibration against dye dilution. Standard Fick methods were used for measurement of hepatic and renal blood flows. Hepatic blood flows were determined from the ratios of infusion rates to arterio–hepatic venous blood concentration differences of BSP (3.8 mg min\(^{-1}\) infused into the right atrium and measured by HPLC [3]). The sensitivity of the assay was 0.2 mg litre\(^{-1}\) and the coefficients of variation of the assay at concentrations of 3.0 and 1.0 mg litre\(^{-1}\) (typical arterial and hepatic venous concentrations) were 2.8 and 2.0%, respectively. Renal blood flows were determined from the ratios of infusion rates to aortic–renal venous blood concentration differences of hippuran sodium (15 mg min\(^{-1}\) infused into the right atrium and analysed by HPLC, see Appendix 2). The sensitivity of the assay was 0.2 mg litre\(^{-1}\) and the coefficients of variation of the assay at 25 and 2 mg litre\(^{-1}\) (typical arterial and renal venous concentrations) were 1.0 and 1.3%, respectively.
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Total body oxygen consumption

The total body oxygen consumption was measured in 13 of these studies, to relate the results of this study to others in this laboratory. It was determined from the product of cardiac output and the arterial-pulmonary arterial oxygen content difference. Blood oxygen content was measured using a commercially available Lex-O_2-Con apparatus (Lexington Instrument Corp., Waltham, Massachusetts, U.S.A.).

Statistical analysis

A longitudinal study design was used that permitted detection of significance with small sample sizes. On inspection, the absence of obvious cardiovascular effects and differences between the studies using cefoxitin and pethidine was confirmed [5]. Hence, the results from these studies were pooled. The baseline values of each variable in each individual study have been tabulated in absolute units (table I). The respective mean value in the “baseline” period of each individual study was assigned a value of 100% and one-sample t tests against this value were performed for each parameter expressed as percentage means and SD of the corresponding baseline values. Two-tailed probabilities of P < 0.05 were considered statistically significant.

RESULTS

The values of mean arterial pressure, heart rate, cardiac output and renal and hepatic blood flows before anaesthesia (baseline values) are given in table I; those during and after anaesthesia have been shown in figures 1 and 2 as the percentage means and SD of the individual mean baseline values in the same study. The overall mean arterial blood concentration of propofol during anaesthesia was 6.8 (SD 2.6) mg litre\(^{-1}\); that of thiopentone was 47 (21) mg litre\(^{-1}\). Individual mean values of arterial blood propofol concentrations during anaesthesia for the animals receiving pethidine were 4.9 (1.7), 7.9 (1.1), 9.2 (2.2) and 7.9 (0.7) mg litre\(^{-1}\); those for the animals receiving cefoxitin were 3.0 (1.3), 8.7 (3.5), 7.6 (1.4) and 8.0

![Fig. 1. Effects of propofol (open panels) or thiopentone (hatched panels) anaesthesia on heart rate and mean arterial pressure in the sheep. To facilitate comparisons in this and accompanying figures, the mean values during a 30-min baseline period have been assigned a value of 100% and values during subsequent test periods have been expressed as mean (SD) of the mean baseline values in the respective studies. Test periods were observed during the last 30-min of a 70-min period of anaesthesia (GA), during early recovery after anaesthesia (0.5–2 h), during mid recovery after anaesthesia (3–5 h) and during late recovery after anaesthesia (6–9 h). Significant differences compared with baseline (two-tailed): * P < 0.05; ** P < 0.01.](https://academic.oup.com/bja/article-abstract/65/3/353/374728)
FIG. 2. Effects of propofol (open panels) or thiopentone (hatched panels) anaesthesia on cardiac output, renal blood flow and hepatic blood flow in the sheep. To facilitate comparisons in this and accompanying figures, the mean values during a 30-min baseline period have been assigned a value of 100% and values during subsequent test periods have been expressed as mean (SD) of the mean baseline values in the respective studies. Test periods were observed during the last 30 min of a 70-min period of anaesthesia (GA), during early recovery after anaesthesia (0.5-2 h), during mid recovery after anaesthesia (3-5 h) and during late recovery after anaesthesia (6-9 h). Significant differences compared with baseline (two-tailed): *P < 0.05; ***P < 0.001.

(0.8) mg litre⁻¹. Individual mean values of arterial blood concentrations of thiopentone during anaesthesia in the animals receiving pethidine were respectively, not obtained for the first two animals, 32.7 (1.6) and 46.5 (0.6) mg litre⁻¹; those for the animals receiving cefoxitin were, respectively, 25.0 (2.0), 41.0 (4.4), 75.3 (12.1) and 45.7 (6.0) mg litre⁻¹.

The mean heart rate (fig. 1) during anaesthesia with propofol was 158 (41)% of baseline (P < 0.01) and that during anaesthesia with thiopentone was 137 (35)% of baseline (P < 0.05). Recovery to baseline values occurred during the late recovery period after both propofol and thiopentone anaesthesia. The mean of the mean arterial pressures (fig. 1) increased during propofol anaesthesia to 144 (36)% of baseline (P < 0.05) and to 146 (21)% of baseline (P < 0.001) during thiopentone anaesthesia. Recovery to baseline values occurred during the late recovery period after both propofol and thiopentone anaesthesia.

Mean cardiac output was 94 (17)% of baseline (ns) during propofol anaesthesia and 81 (17)% of baseline (P < 0.05, n = 6) during thiopentone anaesthesia (fig. 2). Mean renal blood flow decreased during propofol anaesthesia to 93 (7)% of baseline (P < 0.05, n = 6) and to 74 (9)% of baseline (P < 0.001, n = 7) during thiopentone anaesthesia; the duration of the effect was greater after thiopentone (fig. 2). Mean hepatic blood flow (fig. 2) decreased during propofol anaesthesia to 83 (10)% of baseline (P < 0.001, n = 7). During thiopentone anaesthesia, five of seven animals had a decreased mean hepatic blood flow; in one animal mean hepatic blood flow was virtually unchanged and in the other animal mean hepatic blood flow increased (to 228% of baseline), so that the overall mean hepatic blood flow was 102 (58)% of baseline (fig. 2).

During propofol anaesthesia, the total body oxygen consumption decreased to 57 (23)% (P < 0.01, n = 7); during thiopentone anaesthesia, it was decreased to 76 (12)% of baseline (P < 0.01, n = 6).

DISCUSSION

Despite many reports on thiopentone and propofol, there is little information on their cardiovascular effects when used alone for the maintenance of anaesthesia. In these sheep, anaesthesia with propofol for 70 min produced an increased heart rate and mean arterial pressure, and decreased hepatic and renal blood flows. Anaesthesia with thiopentone produced similar changes in heart rate and mean arterial pressure, and decreases in cardiac output and renal blood flow and in hepatic blood flow in five of seven
animals. Although cefoxitin and pethidine also were infused throughout the studies, we have shown previously that these drugs, at the dose rates used in this study, produced no significant cardiovascular changes [5–7].

Thiopentone has become the standard with which all other i.v. anaesthetics are compared [9], but it has been studied principally in relation to induction of anaesthesia, most frequently in premedicated patients. The direct myocardial depressant effects of thiopentone are well-known: a decreased cardiac output usually occurs, associated with a decreased stroke volume and an increased heart rate [9, 10]. Hypotension usually occurs depending, among other factors, on the rate of thiopentone injection and the degree of compensatory increase in total systemic vascular resistance. Recent reports suggest that relatively greater hypotension usually occurs with propofol induction of anaesthesia [11–13].

In these studies, the increased heart rate and mean arterial pressure during the maintenance of anaesthesia with propofol and with thiopentone were unexpected. The mechanism of these changes is not known. In patients, induction and maintenance of anaesthesia with propofol are associated with decreased mean arterial pressure [14]. Thus it is uncertain if the observed effects were species-specific effects of these anaesthetic agents in sheep or were a result of the animals being only lightly anaesthetized and being stimulated by the tracheal tube. While no specific measures of reflex suppression were made, there is evidence against the latter possibility. First, the total body oxygen consumption was reduced significantly to extents similar to those observed for 1–1.5% halothane and 2% isoflurane anaesthesia [Selby and colleagues, unpublished observations]. Second, the measured blood anaesthetic concentrations (propofol overall mean 6.8 (2.6) mg litre\(^{-1}\) and thiopentone overall mean 47 (21) mg litre\(^{-1}\)) were similar to those thought necessary for surgical anaesthesia in humans: propofol 2–4 mg litre\(^{-1}\) [15] and thiopentone 10–42 mg litre\(^{-1}\) [16, 17]. Moreover, the magnitude of the cardiovascular changes in individual animals did not correlate significantly with the individual mean arterial blood anaesthetic concentrations. If the changes were caused by light anaesthesia, negative correlations might have been expected. Third, the animals did not cough during intubation and tolerated controlled ventilation without the use of neuromuscular blocking drugs. These results, taken together, suggest either that the cardiovascular effects observed were an unusual response to these agents in sheep or that they represent a normal response to the prolonged infusion of either propofol or thiopentone alone without the balancing effects of surgical stimulation.

Whereas both agents usually reduced hepatic blood flow, propofol was more sparing of cardiac output and renal blood flow than was thiopentone. Overall, the i.v. anaesthesia regimens used in these studies disturbed regional blood flow less than did 1 or 1.5% halothane, 2% enflurane or 2% isoflurane (each approximately 1.6 MAC in the sheep) in other studies in this laboratory [5; Selby and colleagues, unpublished observations]. In broad agreement with these results, others have reported that cardiac output in the anaesthetized greyhound remains unaffected by doses of thiopentone equivalent to those used in these studies, but that hepatic blood flow was decreased [18]. It had been suggested that thiopentone induction of anaesthesia caused decreased glomerular filtration rate and renal blood flow secondary, at least in part, to decreased arterial pressure [19, 20]. More recent data from studies in ASA class I and II patients have failed to confirm a decreased renal blood flow from thiopentone induction of anaesthesia [21]. Indeed, other data obtained from induction doses of thiopentone in dogs have shown a transient increase in renal blood flow in parallel with a transient increase in arterial pressure [22]. The present study has shown clearly different effects during the maintenance of anaesthesia with either thiopentone or propofol, as decreases in renal blood flow were observed in the presence of increased mean arterial pressure. It has been reported that “light” general anaesthesia (with ether, oxygen and suxamethonium) did not alter glomerular filtration rate or renal blood flow [23]. It would seem, therefore, that the decreased renal blood flow is more likely to be a direct effect of the anaesthetic agents rather than a non-specific consequence of the state of anaesthesia. While the reductions in renal and hepatic blood flows with continuous propofol and thiopentone anaesthesia in the sheep were not related to concomitant changes in arterial pressure, they were of smaller magnitude and shorter duration than those observed for halothane, enflurane and isoflurane under similar circumstances [Selby and colleagues, unpublished observations].
APPENDIX 1

DETERMINATION OF THIOPENTONE BY HPLC

Internal standard solution (thiamylal sodium 25 μg, 25 μl) and acetonitrile 500 μl were added to plasma 0.2 ml in a stopped polypropylene tube (1.5 ml, Eppendorf). The solution was vortex mixed for 30 s and centrifuged at 3000 g for 5 min. Clear supernatant 50 μl was injected into a high pressure liquid chromatograph equipped with a 15-cm, 5-μm C18 reverse phase column and perfused with mobile phase (50:50 methanol:0.1% sodium dihydrogen phosphate solution containing 5% methanol and tetrabutyl ammonium phosphate 0.005 mol litre⁻¹) at a flow rate of 2.0 ml min⁻¹. Detection was by u.v. spectroscopy at 280 nm. Under these conditions, the retention times of thiopentone and thiamylal were, respectively, 5.5 and 6.6 min.

APPENDIX 2

DETERMINATION OF HIPPURAN BY HPLC

Internal standard solution (metacetamol 5.0 μg, 25 μl) and acetonitrile 160 μl were added to plasma 0.1 ml in a stopped polypropylene tube (1.5 ml, Eppendorf). The solution was vortex mixed for 30 s and centrifuged at 3000 g for 5 min. Clear supernatant 15 μl was injected into a high pressure liquid chromatograph equipped with a 15-cm, 5-μm C18 reverse phase column, and perfused with mobile phase (5:95 acetonitrile:water containing tetrabutyl ammonium phosphate 0.005 mol litre⁻¹). Detection was by u.v. spectroscopy at 254 nm. Under these conditions, the retention times of para-aminohippurate and metacetamol were, respectively 4.1 and 7.9 min. Iothalamate, with a retention time of 5.8 min, could be quantitated simultaneously, if present.

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