A SHEEP PREPARATION FOR STUDYING INTERACTIONS BETWEEN BLOOD FLOW AND DRUG DISPOSITION

III: EFFECTS OF GENERAL AND SPINAL ANAESTHESIA ON REGIONAL BLOOD FLOW AND OXYGEN TENSIONS

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SUMMARY

In awake unrestrained sheep the infusions i.v. of five drugs (cefoxitin, pethidine, chlormethiazole, tocainide and lignocaine) with potentially flow-limited clearance were shown to have no significant haemodynamic effects of their own, nor to have any effects on arterial or venous oxygen tensions. Under general anaesthesia (1.5% end-tidal halothane), haemodynamic changes similar to those previously documented in man occurred. Cardiac output and hepatic blood flow were decreased to 70%, and renal blood flow to 50% of control values; heart rate was unchanged and mean arterial pressure decreased by an average of 10%. Hepatic and renal vein oxygen tensions were decreased significantly. Under spinal anaesthesia, apart from a 10% decrease in hepatic blood flow, there were no significant changes in any haemodynamic variables or in the arterial or in any of the venous oxygen tensions. The i.v. infusion of adequate volumes of saline at the time of blockade probably contributed to the maintenance of these indices at their baseline values.

It is known that both general and spinal anaesthesia may have profound effects on the cardiovascular system (Prys-Roberts, 1980; Greene, 1981). Using a previously described sheep preparation (Runciman et al., 1984) it was decided to study the effects of general and spinal anaesthesia on regional blood flow and oxygen tensions in association with studies on the disposition of five drugs with potentially flow-limited clearance. The drugs were chosen because of their clearance by a variety of organs (in man), and because they may be used in patients during the immediate peri-operative period when disturbances in flow are known to occur.

Cefoxitin was chosen as it was thought to be unlikely to have any significant haemodynamic effects of its own, as it has a high renal clearance, and as it was thought to be eliminated exclusively by the kidneys (Brogden et al., 1979). Pethidine was chosen as it has a high hepatic extraction ratio with some renal elimination, and was not expected to exert profound haemodynamic effects at the doses we intended to use (Mather and Meffin, 1978). Chlormethiazole was chosen as it had been demonstrated in pilot studies that there was significant extraction across the lungs as well as across the liver and kidneys (Mather et al., 1981). Tocainide was chosen as it has been shown to have significant hepatic and renal clearance (Lalka et al., 1976). Lignocaine was chosen as a high hepatic clearance drug that could have significant haemodynamic effects at the doses chosen, with the potential to alter blood flow and its own kinetics (Tucker et al., 1977).

In this paper the effects of general and spinal anaesthesia on haemodynamics and oxygen tensions will be described, using pooled data from 60 studies of these five drugs. This approach was adopted since none of the drugs produced remarkable haemodynamic effects when infused alone to the awake unrestrained animal in control studies. The effects of these disturbances on haemodynamics and oxygen consumption during infusions of each of these drugs individually will be described in future reports, together with the effects of general and spinal anaesthesia on the disposition of each drug.

MATERIALS AND METHODS

The studies were carried out in awake unrestrained sheep which had been prepared with chronic intravascular catheters, as described previously (Runciman et al., 1984). Since studies were carried out frequently, the sheep were allowed to eat and drink normally before each experiment. On each experimental day sampling loops (consisting of a double two-way tap interposed between two 70-cm extension lines) were interposed between the side holes of the double two-way taps in each of the catheter flushing systems from which it was in-
tended to sample blood. In this way sampling could proceed without disturbing the sheep. After preparing the sampling loops, 12 ml of arterial blood was taken: 5 ml for routine biochemical screening, 1 ml for routine haematological screening, 1 ml for measurement of haematocrit, and 5 ml for analytical calibration curves (for 125I-iodohippurate (IOH) and the drug being studied). Analytical calibration samples were spiked for both standard curves, with the drug analyses being carried out after the samples had been assayed for IOH in the gamma-counter. If hepatic blood flow was being measured by bromsulphthalein (BSP), an additional 5 ml was taken for the BSP standard curve (Runciman et al., 1984).

The IOH, BSP, and drug solutions were prepared freshly on each day, and were drawn into glass syringes which had each been calibrated previously for the channel of the infusion pump on which they were to be used. The IOH and BSP were infused to steady-state using a two-stage regimen as previously described (Runciman et al., 1984). After 20 min from the start of the second infusion, blood concentrations of BSP and IOH were at steady-state and allowed commencement of the measurements of the control period.

**Haemodynamic measurements**

Determinations of cardiac output, liver blood flow, portal blood flow, and renal blood flow were undertaken as described previously (Runciman et al., 1984). Using a method described by Runciman, Rutten and Ilsley (1981) it had been shown that the natural frequency of the arterial catheter used was 14 Hz, with an amplitude ratio of 2.6. Therefore, it was decided to record only mean arterial pressures, as systolic and diastolic pressure measurements would be potentially inaccurate. Mean arterial pressure was measured every 10 min during the experimental programme using an aneroid gauge (Minimus nach Dr. von Recklinghausen, Germany), which had been shown to be accurate (range ± 4%) for mean pressures over the range 20–200 mm Hg (Runciman, Rutten and Ilsley, 1981). This was calibrated before and after each experimental day against a standard mercury sphygmomanometer. The arterial pressure was measured by connecting the aneroid gauge to one of the arterial lines via a three-way tap and extension line (SO.306-Tuta Laboratories, Lane Cove, Australia). Measurements of arterial pressure were accepted only if there was a visible pulsation at the saline–air interface in the extension line. The heart rate was counted visually by examining the pulsations of the meniscus, and counting them with a stop watch.

**Measurement of blood-gas tensions and pH**

Blood-gas tensions and pH were measured on systemic and pulmonary arterial, and on renal, hepatic and portal venous blood samples during as many experiments as possible; logistical constraints prevented these measurements from being carried out on every occasion. Two-millilitre blood samples were taken anaerobically into glass syringes, capped and placed in iced water; measurements of blood-gas tensions and pH were completed for all five samples within 15 min. An Instrumentation Laboratories pH/blood-gas analyser (Model 813, IL, Lexington, Massachusetts, USA) was used for the $P_{O_2}$, $P_{CO_2}$, and pH measurements. These were carried out at 37°C. Two-point calibrations of each electrode were carried out before and after the set of five measurements were made, using gases of known composition (containing 0% and 20% oxygen, and 5% and 10% carbon dioxide), and using solutions of known pH (7.840 and 7.384, Cat. No. 31060 and 31070, respectively, Instrumentation Laboratories). The exact partial pressure of each calibration gas was calculated from the barometric pressure and the certified contents of the calibration cylinders (Special Gas Mixture, Commonwealth Industrial Gases, Sydney, Australia). A one-point calibration was carried out before each individual measurement.

**Control-drug study**

Cardiac output, mean arterial pressure and heart rate were measured, and simultaneous arterial, pulmonary artery, hepatic vein, portal vein and renal vein blood samples (1 ml) were taken every 10 min for 1 h for the determination of control values (seven sets of measurements). All blood samples were measured with 1-ml syringes (Terumo Laboratories, Melbourne, Australia) into 15-ml glass tubes (598CL, Johns Professional Products, Cheltenham, Australia) containing heparin 25 i.u. and the appropriate amount of internal standard, and were placed on ice. After the control period, the drug under study was infused using the two-stage infusion which had been designed to achieve steady-state rapidly (Wagner, 1974). These infusions were designed so that the first stage lasted 15 min and the second stage lasted for 75 min. Arterial sampling was arranged so that one sample was taken every 5 min for the first 30 min of the drug infusions, and
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also for 30 min after cessation of the second infusion, to facilitate pharmacokinetic analysis. Arterial, pulmonary artery, hepatic vein and renal vein samples were taken every 10 min, immediately after cardiac output, mean arterial pressure and heart rate had been measured, during the last 60 min of the maintenance infusion of the drug and for 30 min at the end of the drug infusion. Portal vein samples were taken usually only during the last hour of the maintenance infusion of the drug. This was designated a control-drug study. Blood samples were then counted in a refrigerated gamma counter overnight, and the following morning were frozen and stored at −20 °C if drug analysis was not to be carried out immediately.

General anaesthesia studies

Cardiac output, mean arterial pressure and heart rate were measured, and simultaneous arterial, pulmonary artery, hepatic vein, portal vein and renal vein blood samples (1 ml) taken every 10 min for 30 min for determination of control values (four sets of measurements), as in the control studies. Anaesthesia was induced with thiopentone 20 mg kg⁻¹ i.v., an endotracheal tube inserted, and anaesthesia maintained by intermittent positive pressure ventilation using 40% oxygen and 1.5% halothane (balance nitrogen). A constant volume ventilator was used (PR2-Bennett, Santa Monica, California). Breath-by-breath analysis was carried out using a mass spectrometer (Centronics, MGA200, Croydon) via a sampling line connected to a special port in the catheter mount of the endotracheal tube, in order to monitor inspired oxygen and expired halothane and carbon dioxide concentrations. The sheep was ventilated to an end-tidal PCO₂ concentration of 35 mm Hg and an end-tidal halothane concentration of 1.5%. To maintain these concentrations the alveolar ventilation and the vaporizer setting were adjusted whenever necessary.

After the induction of anaesthesia, the sheep was placed in a posture that would allow normal venous return. It was placed in a normal lying position with its legs tucked comfortably beneath it, and with its chin propped on the edge of a bucket so that any excess saliva could be collected. It was found, by keeping its head in this position, that less than 200 ml of saliva was usually lost during the procedure. The front legs and sternum were supported on a shaped foam rubber bolster that had been designed specially to balance the animal comfortably in this position without any pressure points, and to leave the abdomen free. The anterior abdominal wall was usually resting on the floor of the metabolic crate, but in such a way as to ensure that there was minimal compression of the abdomen. The same posture was used during studies under spinal anaesthesia. Physiological saline i.v. was used to maintain mean arterial pressure to within 70% of control values.

At least 30 min was allowed to elapse, to allow redistribution of the thiopentone. During this time, sampling and haemodynamic measurements were made to confirm haemodynamic stability under general anaesthesia, then, the drug under study was infused using a two-stage infusion identical to that used in the control experiment. The same programme of cardiovascular measurement and blood sampling was used as for the control-drug study in the awake animal; this was designated a GA study. The sheep was then allowed to recover from the general anaesthetic, care being taken to leave it in the same posture with the tracheal tube in situ until it was clear that the animal had regained its laryngeal reflexes. The trachea was extubated. A member of the research team always remained with the sheep until it appeared fully recovered and able to stand up. This always occurred within 1 h of anaesthesia, by which stage the animal was usually eating.

Spinal anaesthesia studies

Control measurements were made in the same manner as for the general anaesthesia studies. The sheep were then prepared for spinal anaesthesia. Two sheep had chronic subarachnoid catheters placed at the time of their original operation. In the others, a 20-gauge spinal needle was used for the subarachnoid anaesthetic. Five millilitre of 1% isobaric amethocaine hydrochloride was injected to the subarachnoid space over 5 s with barbotage. Two hundred millilitre of 0.9% saline was infused i.v. at this stage, and mean arterial pressure was monitored continuously. If mean arterial pressure decreased to less than 70% of the mean value for the control period, more saline was infused. It was never necessary to infuse more than 500 ml of 0.9% saline. The sheep were monitored until neural blockade was established and circulatory stability restored. At least 30 min was allowed to lapse from the time of no further progression of the blockade and initiation of the next phase of the study, which consisted of drug infusion identical to that conducted in the control-drug and GA studies. This was designated an SA study. Blocks up to between T1 and T6 were obtained. The level of sensory and motor anaesthesia was easy to determine in the sheep as, on prodding
the skin with a finger, the normal reflex flicking reaction was absent under subarachnoid anaesthesia (Kitchen, 1977). The blockade remained stable at least until the steady-state infusion period was completed; on a few occasions the block had regressed one or two segments within 30 min of cessation of the drug infusion. Usually, blockade did not start to regress until 160 min had elapsed, but it had always started to regress by 180 min. Proprioception did not always seem to have returned for some hours; this is in agreement with the findings of others (Adams and Doherty, 1977). If the sheep was not standing up by the end of the day, it was placed in a special sling overnight (Lebaux, 1975), so that it would not injure its legs or develop pressure sores. All sheep were standing by the following morning.

**Drug infusions**

The drug infusions used for the first (15-min) and second (75-min) infusions were, respectively, at rates of: 9.8—10.9 and 3.9-4.4 mg min\(^{-1}\) for cefoxitin; 10.6-11.9 and 4.6-4.9 mg min\(^{-1}\) for pethidine; 14-14.6 and 7.0-7.3 mg min\(^{-1}\) for chlorothiazide; 15.5—37.9 and 0.73—0.93 mg min\(^{-1}\) for tocainide; 11.5-23.3 and 4.6-4.7 mg min\(^{-1}\) for lignocaine.

**RESULTS**

The effects of general and spinal anaesthesia on haemodynamics, IOH kinetics and oxygen tensions are presented in figure 1 and tables I, II and III. For the pooled data (all drugs) under general anaesthesia, significant decreases occurred in cardiac output, renal and hepatic blood flows, renal fraction of cardiac output, mean arterial pressure, IOH extraction ratio and clearance, as well as in hepatic and renal vein oxygen tensions ($P<0.05$; two-tailed $t$ test for paired data). A significant decrease in hepatic fraction of cardiac output occurred under spinal anaesthesia ($P<0.05$; one-tailed $t$ test for paired data). For individual drugs, under general anaesthesia, the decreases in cardiac output (for pethidine and chlorothiazide), renal blood flow (for all drugs except tocainide), hepatic blood flow (for pethidine and chlorothiazide), renal fraction of cardiac output (for lignocaine), IOH extraction ratio (for cefoxitin) were statistically significant ($P<0.05$).

**Table I. Summary of haemodynamic and IOH kinetics data.**

<table>
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<tr>
<th>Drug</th>
<th>CO</th>
<th>RBF</th>
<th>HBF</th>
<th>R. FR</th>
<th>H. FR</th>
<th>I. ER</th>
<th>I. CL</th>
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<td>Mean</td>
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<td>7</td>
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<th>R. FR</th>
<th>H. FR</th>
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For results of statistical analysis see text.
FIG. 1. Summary of blood flow and IOH data. The mean value of each variable during control-drug, general anaesthesia or subarachnoid anaesthesia studies has been expressed as a percentage of the mean value of the corresponding variable during the control pre-infusion period on the same day. The mean and SD of these percentages for all five drugs studied are displayed. See text for results of statistical analysis.

DRUG = control-drug study; GA & DRUG = general anaesthesia study; SA & DRUG = subarachnoid anaesthesia study; CO = cardiac output; RBF = renal blood flow; HBF = hepatic blood flow; RENAL FR = renal fraction of cardiac output; HEPATIC FR = hepatic fraction of cardiac output; MAP = mean arterial pressure; HR = heart rate; ER = extraction ratio; CL = clearance; PA = pulmonary artery.

Individual absolute measurements of portal blood flow could not be made reliably, as a result of streaming of the IOH indicator (Runciman et al., 1984). However, averaged values calculated from the mean IOH counts indicated that portal blood flow accounted for 80% of total hepatic blood flow (140 measurements over 20 studies) in the awake unrestrained animal, whereas it accounted for 91% under general anaesthesia (55 measurements in eight studies).

DISCUSSION

The day-to-day variations in haemodynamic indices, and the consequent importance of obtaining repeated control measurements in awake unre-
strained animals on each experimental day have been emphasized previously (Runciman et al., 1984). No progressive changes occurred in any of the haemodynamic, IOH, biochemical or haematological parameters in the sheep used in this study.

Control-drug studies

The mean values for the haemodynamic and IOH kinetic parameters for the pooled data during all control-drug studies remained within 5% of the corresponding control values, except for the mean hepatic blood flow and fraction which increased (non-significantly) by 12 and 9%, respectively. The only notable changes that occurred in any of these variables during studies of individual drugs was a 19% increase in cardiac output during the pethidine infusions (associated with a decrease in peripheral vascular resistance), and a 28% increase in hepatic blood flow during the chlormethiazole infusions. The lack of any significant haemodynamic effects of lignocaine infusions, which contrasts to previously reported findings in man (Tucker et al., 1977) may have been caused by the relatively low blood concentrations reached at steady-state (average 2.7 mg litre$^{-1}$). There were no significant changes in the arterial or in any venous oxygen tensions during the control-drug studies (table III).

General anaesthesia studies

**Mean arterial pressure.** Under general anaesthesia in the sheep, mean arterial pressure was decreased to 88% of the mean control value. The decreases during each drug study were within 10% of this value, except in the case of pethidine, with which the reduction was to 70% of the corresponding mean control value. Pethidine concentrations were five times greater than those required for postoperative analgesia in man (Austin, Stapleton and Mather, 1980).

It has been well documented that halothane causes a dose-related decrease in arterial pressure
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(Deutsch et al., 1962; Prys-Roberts et al., 1974). In unstimulated normocarbic human volunteers at 2 MAC, mean arterial pressure was decreased to about 65% of control values (Smith, Eger and Calverly, 1978). Within the first 30 min of the sheep experiments, mean arterial pressure was decreased by a similar amount. However, by the time the "steady-state" periods had started (usually about 80 min after induction), some adaptation had occurred (see below), and arterial pressure had recovered towards control values.

**Heart rate.** During each drug infusion the mean heart rate under general anaesthesia in the sheep remained within 5% of the control value. It has been well documented in man (Prys-Roberts et al., 1974; Hickey and Eger, 1980) and in dogs (Seagard et al., 1982) that halothane, in spite of causing dose-related hypotension, does not change the heart rate. This is at least partially accounted for by the finding that halothane depresses the baroreceptor reflex (Prys-Roberts et al., 1974; Hickey and Eger, 1980).

**Cardiac output.** At 2 MAC halothane in the sheep the cardiac output was decreased for the pooled data to a mean of 71% of the mean awake control value. The values during each drug study were within 14% of this, except in the cases of pethidine and chlormethiazole, in each of which instances cardiac output was reduced to 54% of awake control values. The mean mixed venous (pulmonary artery) oxygen tension remained within 1% of the mean awake control value (35 mm Hg).

Halothane has been shown to cause a dose-dependent decrease in cardiac output; at 2MAC in normocarbic human volunteers cardiac output was decreased to about 65% of control values (Hickey and Eger, 1980). In reviewing more than 60 studies on halothane in a total of nine species, Smith, Eger and Calverley (1978) pointed out that each came to the conclusion that halothane depressed the heart. The findings in the sheep are in agreement with this and other recent reviews on the effects of halothane on the heart (Prys-Roberts et al., 1974; Hickey and Eger, 1980; Smith, 1980). The general conclusion is that halothane causes a dose-dependent depression of myocardial contractility both in isolated papillary muscles and in the intact animal, and that the reduction in stroke-volume is caused by a decrease in left ventricular power.

Myocardial oxygen consumption was not measured in these experiments, as coronary sinus catheters were not placed routinely at that stage. However, reports from studies in man (Sonntag et al., 1979; Reiz et al., 1982), in dogs (Smith, Rogers and Thorburn, 1980) and in pigs (Lowenstein et al., 1982) indicate that myocardial oxygen consumption and blood flow are both depressed to a similar extent under halothane anaesthesia; furthermore, coronary sinus lactate did not change in these studies, indicating that myocardial oxygenation was adequate under halothane anaesthesia. The decrease in arterial pressure and lack of change in heart rate are important in reducing myocardial oxygen consumption under halothane anaesthesia (Lowenstein et al., 1982; Smith, Rogers and Thorburn, 1980).

One phenomenon merits further comment with respect to cardiac output. It was frequently observed that the cardiac output tended to increase progressively with time under general anaesthesia. This phenomenon of "adaptation" to halothane has been well documented; both catecholamine release and activation of the Frank-Starling mechanism (with progressive left ventricular end-diastolic dilatation) have been suggested as possible mechanisms (Smith, 1980).

**Renal blood flow.** In these sheep studies under general anaesthesia, renal blood flow was decreased to 52% of its mean awake control value. Decreases produced by each drug were within 9% of this. The effects of anaesthesia on the renal circulation have been reviewed by Bastron (1980), who emphasized that many studies were complicated by large numbers of uncontrolled variables. However, in a well-controlled series carried out in healthy young volunteers, halothane at 1.5% inspired concentration caused a 38% decrease in estimated renal plasma flow, a finding similar to that in the sheep. Similar decreases have been reported in patients (Cousins and Mazze, 1973).

Bastron (1980) also noted that the assumption that anaesthetics do not alter the extraction of paraaminohippurate has been validated only for "light" halothane anaesthesia in a few patients. That the para-aminohippurate extraction ratio may decrease under anaesthesia and in hypovolaemic states has been emphasized in a review by Eklund (1978). In these sheep studies, the IOH extraction ratio was decreased under general anaesthesia to 88% of the mean awake control value; the decreases for chlormethiazole and tocainide were within 5% of this value, whereas the IOH extraction ratio decreased to 64% of its control value with cefoxitin. In the cases
of lignocaine and pethidine, the IOH extraction ratio remained within 4% of the control values on that day. It would seem, therefore, that assumptions regarding the extraction ratios of even tracer quantities of drugs are questionable, especially in the presence of drugs that are cleared by renal tubular secretion as well as filtration. It is also of note that the IOH extraction ratio, in the presence of cefoxitin, decreased markedly under anaesthesia, but was reduced by only 5% in the awake animal. As a result of the combined influences of decreased flow and extraction, IOH clearance was reduced under general anaesthesia for the pooled data to 45% of the mean control value; the decreases for each drug were within 8% of this value.

The renal fraction of cardiac output was decreased significantly under general anaesthesia in the sheep studies to a mean of 79% of the mean awake control value (P<0.05). The decreases for each drug were within 15% of this value. The conflicting evidence in relation to renal auto-regulation under anaesthesia has been reviewed by Bastron (1980). The salient fact that emerged from his review is that, although isolated perfused kidneys exposed to 1 MAC of halothane showed autoregulation, this was impaired in vivo, particularly with perfusion pressures of less than 100 mm Hg. There is also evidence that sympathetic nervous stimulation in the presence of halogenated hydrocarbons may lead to further decreases in kidney blood flow (Cousins and Mazze, 1973).

Renal vein PO$_2$ decreased from a mean of 48 mm Hg in the awake animals to a mean of 38 mm Hg under anaesthesia. Therefore, the functional reserve for oxygen availability to the kidneys must have been reduced under anaesthesia. It is interesting that this occurred in the only organ in which oxygen requirement is not generally considered to be a determinant of blood flow under normal conditions (Zelis, 1975). This decrease occurred whilst mixed venous (pulmonary artery) oxygen tension remained virtually unaltered, implying a decrease in oxygen consumption by some other areas of the body.

**Hepatic blood flow.** Hepatic blood flow was decreased under general anaesthesia in the sheep to 71% of the mean awake control value; decreases produced by each drug were within 10% of this, except in the cases of pethidine and chlorothiazole, in which there were reductions to mean values of 54% and 63%, respectively. Similar decreases in hepatic blood flow during 2 MAC halothane anaesthesia have been reported in man (to 70–75% of awake control values) and in other species (Epstein, 1966; Price et al., 1966; Cowan, Jackson and Thompson, 1975; Alfery and Beenumof, 1981). As the hepatic blood flow was reduced to about the same extent as cardiac output under halothane anaesthesia, the hepatic fraction of cardiac output remained within 13% of the awake control values for each drug.

Portal blood flow accounted for 91% of total hepatic blood flow during 2 MAC halothane anaesthesia, compared with 80% in the awake state. This is in agreement with reports that there may be increased hepatic arterial resistance under halothane anaesthesia (Strunin, 1980). The implications of this observation may be important, as it has been suggested that, in the awake animal, hepatic arterial flow is not related to the metabolic demands of the liver, but rather to those of the whole organism (Lautt, 1977). Thus, while portal blood flow may fluctuate widely according to gastrointestinal demands, hepatic arterial blood flow is maintained per se to prevent fluctuations in hepatic clearance of both endogenous and exogenous substances. It is this component of hepatic blood flow, which is well maintained in the awake animal, that may be most compromised under halothane anaesthesia.

A recent study in swine reported that hepatic arterial blood flow (measured using microspheres) increased under halothane anaesthesia (Tranquilli et al., 1982). This finding was accompanied by marked decreases in gut and spleen blood flow. The same pattern has been observed in sheep, using microspheres. However, we suggest that the increase in hepatic arterial flow is only an apparent increase as a result of microspheres passing through arterio-venous anastomoses in gut which open under halothane anaesthesia; this phenomenon also occurs during heat stress and pharmacologically-induced fever in sheep (Hales, personal communication). A collaborative study is planned to investigate this problem.

In the sheep studies, mean portal vein oxygen tension was decreased under anaesthesia from 46 mm Hg in the awake animal to 39 mm Hg with 1.5% halothane. Mean hepatic vein oxygen tension was reduced by 25% from 36 mm Hg in the awake animal to 27 mm Hg under anaesthesia. Hepatic oxygen consumption decreased under anaesthesia by only 10% from control values on the day, whereas hepatic blood flow decreased by nearly 30%. In
reviewing the relationship of splanchnic oxygen consumption to liver blood flow, Strunin (1980) commented that, with the volatile anaesthetic agents, all the ratios (blood flow as a percentage of control:oxygen consumption as a percentage of control) were less than unity, suggesting the possibility of hypoxic conditions occurring within the liver under anaesthesia (Cooperman, 1972; Strunin, 1980). Strunin reported a ratio of 0.82 for halothane with controlled ventilation; the ratio in the sheep studies was 0.79. However, as found in studies in man (Cooperman, 1972; Strunin, 1980) there was no evidence of anaerobic metabolism in the sheep studies (there was no significant change in the “base excess” on blood-gas analysis of hepatic venous blood samples) or, on sequential liver function tests, of abnormal liver function (Runciman, 1982). However, as the hepatic venous blood was significantly desaturated, the functional reserve of oxygen availability was decreased. Again, it is worth noting that this occurred whilst mixed venous oxygen tensions were unaltered from control values.

**Spinal anaesthesia studies**

The mean values of all IOH and haemodynamic indices under spinal anaesthesia were within 10% of the corresponding mean control values, except for the hepatic fraction of cardiac output, which was decreased significantly to 86% of the mean control value.

The haemodynamic effects of spinal anaesthesia are the consequence of preganglionic sympathetic blockade in the subarachnoid space and are related to the level of blockade. The level of sympathetic blockade was not tested in the sheep, but the upper levels of motor and sensory block were always between T1 and T6 during the steady-state period of drug infusion, and were usually about T4. Sympathetic blockade usually extends two to three segments higher than sensory blockade.

**Mean arterial pressure.** With the regimen of fluid preloading, mean arterial pressure had returned to within a few percent of the control value by the start of the infusions, and remained within a mean of 1% of the control value during the cefoxitin, lignocaine and tocainide infusions. With the infusion of pethidine the animals appeared mildly stimulated, and mean arterial pressure increased by 18%, and with the infusion of chloromethiazole the animals became slightly sedated and mean arterial pressure decreased by 14%. Similar, but less marked effects had occurred during the control infusions of these two drugs (when the arterial pressure increased to 106% and decreased to 94% of the respective control values). It has been shown that arterial pressure may be well maintained under spinal anaesthesia by the infusion of fluid to compensate for increased venous capacitance, by increased sympathetic tone above the level of blockade, and by residual autonomous vessel tone in the region of the block (Greene, 1981).

**Heart rate.** There was a slight increase in heart rate (of between 5 and 9%) with all drugs except lignocaine, suggesting some increased sympathetic drive above the block and confirming that the block was not higher than T1 (there is no sympathetic outflow from the spinal cord above T1). Bradycardia is a common feature under spinal anaesthesia in man. However, in an exhaustive review of the literature, Greene (1981) concluded that the degree of bradycardia correlated with the degree of arterial hypotension and decreased venous return. Since both were maintained in the sheep studies, this may account for the lack of bradycardia.

**Cardiac output.** Under spinal anaesthesia in the sheep, cardiac output remained within 6% of control values for chloromethiazole, lignocaine and tocainide. It increased by 13% during the cefoxitin infusion and by 26% during the infusion of pethidine. The increase with pethidine was of an order similar to that seen in the control study. As arterial pressure was not increased to the same extent as cardiac output, there was a decrease in peripheral vascular resistance (as in the control studies). Thus, there was no evidence of myocardial depression at the pethidine blood concentrations achieved in the control or spinal anaesthesia studies.

The mean mixed venous oxygen tension increased under spinal anaesthesia from a mean control value of 35 mm Hg to 37 mm Hg. This finding contrasts with several studies in man in which prehydration was not carried out and hypotension occurred, but is in agreement with a study cited by Greene (1981) in which arterial pressure was maintained by vasopressors. As mean cardiac output for the pooled data was 109% of the mean control value, mean oxygen consumption by the whole animal was not decreased under spinal anaesthesia.

**Renal blood flow.** Renal blood flow under spinal anaesthesia remained within 5% of the mean control value for each drug, except in the case of lignocaine,
with which it was increased by 13%. It has been well documented that, normally, renal vascular resistance is not dependent on neurogenic control, and that sympathetic denervation, whether produced by pharmacological or surgical means, or by spinal anaesthesia, produces no change in renal blood flow (Greene, 1981). It has also been documented that renal blood flow does not change, even in the surgically denervated kidney, or under spinal anaesthesia, in the range from 80 to 160 mm Hg mean arterial pressure (Greene, 1981). Decreases in renal blood flow may still occur, however, in the presence of sympathetic nervous stimulation when the sympathetic renal efferent nerve supply has not been blocked (Cousins and Mazze, 1973; Mazze, 1977). This may occur, for example, during operations under low spinal anaesthesia.

Mean renal vein oxygen tensions underwent no significant change from control values under spinal anaesthesia. The mean control value was 48 mm Hg, and that under spinal anaesthesia was 50 mm Hg.

During these studies the IOH extraction ratio was reduced under spinal anaesthesia to a mean of 93% of the mean control value; the decreases for each drug were within 2% of this value. These changes were not significant. IOH clearance for the pooled data was 98% of the mean control value; the IOH clearance values for each drug were within 7% of the mean control value for each drug.

Hepatic blood flow. This remained within 10% of the mean control value for each drug, except during lignocaine infusions when it was decreased to 73%. The hepatic fraction of cardiac output was decreased significantly under spinal anaesthesia to a mean of 86% of the mean control value. Decreases with each drug were within 10% of this value, except in the case of lignocaine, with which the hepatic fraction was decreased to 71% of mean lignocaine control value.

These findings are very similar to those of Kennedy and colleagues (1970) in a study on liver blood flow under spinal anaesthesia carried out in volunteers. Liver blood flow decreased initially to 15 or 20% below control values, but from 60 to 120 min was an average of about 10% below control values, in spite of cardiac output being maintained. It has been documented in man that liver blood flow decreased proportionally with decreases in mean arterial pressure (Strunin, 1980; Greene, 1981). However, in the sheep studies there was a 10% decrease in liver blood flow and hepatic fraction of cardiac output, even when cardiac output and mean arterial pressure were maintained at control values.

There were insufficient data in the sheep studies to comment on the relative contributions of the portal vein and hepatic artery to total hepatic blood flow under spinal anaesthesia. Hepatic and portal vein oxygen tensions were slightly increased under spinal anaesthesia; this may indicate that hepatic oxygen consumption was decreased to at least the same extent as hepatic flow.

GENERAL CONCLUSION

The i.v. infusion of the five test drugs chosen produced no significant effects of their own on haemodynamic variables, or on arterial or venous oxygen tensions in awake unrestrained animals. Under general anaesthesia (1.5% end-tidal halothane), haemodynamic changes occurred which were similar to those documented previously in man. Cardiac output and hepatic blood flow were decreased to 70%, and renal blood flow to 50% of control values; heart rate was unchanged, and mean arterial pressure decreased by an average of 10%. Hepatic and renal vein oxygen tensions were decreased significantly. Of particular note were the loss of renal autoregulation, the disproportionately great reduction in hepatic arterial flow, the significant desaturation of hepatic and renal venous blood, and the unchanged heart rate in the face of hypotension. It would seem that some important homeostatic mechanisms are compromised under general anaesthesia. Thus, a normal heart rate, a moderate decrease in arterial pressure, and normal arterial and mixed venous oxygen contents should not induce a state of complacency in the anaesthetist. Under spinal anaesthesia, apart from a 10% reduction in hepatic blood flow, there were no significant changes in any haemodynamic variables or in the arterial or in any of the venous oxygen tensions. The i.v. infusion of adequate volumes of saline at the time of the blockade probably contributed to the maintenance of these variables at their normal values. If these findings are confirmed in man, it would seem that well controlled regional anaesthesia may have much to commend it over general anaesthesia with halothane in patients with compromised hepato-renal function.

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ZUSAMMENFASSUNG
Es konnte gezeigt werden, daß bei wachen freilaufenden Tieren i.v. Infusionen von fünf Medikamenten (Cefoxitin, Pethidin, Chlormethiazol, Tocainid und Lignocain) mit potentiell durchblutungslimitierter Clearance von sich aus keine signifikanten hämodynamischen Effekte oder Effekte auf arterielle oder venöse Sauerstoffspannungen haben. In Vollnarkose (1,5% endexspiratorische Halothankonzentration) traten hämodynamische Veränderungen ähnlich denen auf, die früher am Menschen gefunden wurden. Herzfrequenz und Leberdurchblutung nahmen um 70%, die Nierendurchblutung um 50% gegenüber Kontrollwerten ab. Die Herzfrequenz blieb unverändert, der mittlere arterielle Druck fiel um durchschnittlich 10% ab. Die Sauerstoffspannungen in Leber- und Nierenvenen sanken signifikant. Unter Spinalanästhesie fand sich außer einer 10%igen Abnahme der Leberdurchblutung keine signifikante Veränderung irgendeines der hämodynamischen Parameter oder der arteriellen oder venösen Sauerstoffspannungen. Die intravenöse Infusion adäquater Volumina von Salzlösung während der Blockade hielt möglicherweise die Werte auf ihrer Ausgangshöhe.

UNA PREPARACION DE OVEJA PARA ESTUDiar LAS INTERACCIONES ENTRE LA CORRIENTE SANGUINEA Y LA ELIMINACION DE DROGAS. III

SUMARIO
En animales libres despiertos, les infusiones i.v. de cinco drogas (cefotaxima, petidina, clormetiazol, tocainida y lignocaina) con eliminación del flujo potencialmente limitada demostraron no tener efectos hemodinámicos significantes por sí solas, ni tampoco sobre las tensiones de oxígeno arterial o venoso. Bajo anestesia general (halotano respiratorio-terminal al 1,5%), se produjeron cambios hemodinámicos semejantes a los registrados en el hombre. El volumen-minuto y la corriente sanguínea hepática disminuyeron hasta un 70% y la corriente sanguínea renal hasta un 50% en comparación con los valores de control; el ritmo cardíaco no se alteró y la presión arterial promedia aumentó en un 10% más o menos. Las tensiones de oxígeno de las venas renales y hepáticas disminuyeron de manera significativa. Bajo anestesia espinal, fuera de una disminución de un 10% del flujo de la sangre hepática, no hubo cambios significantes en ninguna de las variables hemodinámicas ni en las tensiones de oxígeno arterial o en las de cualquiera de las venas. La infusión i.v. de volúmenes adecuados de solución salina al momento del bloqueo contribuyó probablemente a la mantención de dichos índices en sus valores de línea de base.