J. Pharm. Pharmacol. 1990, 42: 693–697
Received March 3, 1990

Differential Influence of Laboratory Anaesthetic Regimens upon Renal and Hepatosplanchnic Haemodynamics in the Rat

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Abstract—Renal blood flow in rats anaesthetized with the combination alphaxolone/alphadolone (3·90 mL min^{-1} (g tissue)$^{-1}$) was significantly ($P < 0.05$) greater than in rats anaesthetized with ketamine/midazolam (3·24 mL min^{-1} (g tissue)$^{-1}$), pentobarbitone (3·19 mL min^{-1} (g tissue)$^{-1}$), fentanyl/fluanisone/midazolam (2·84 mL min^{-1} (g tissue)$^{-1}$) or urethane (1·99 mL min^{-1} (g tissue)$^{-1}$). Renal blood flow in the urethane anaesthetized rats was significantly ($P < 0.05$) lower than in animals anaesthetized with the other anaesthetic regimens, and is consistent with literature reports of a depressive effect of urethane anaesthesia upon xenobiotic renal clearance in the rat. Hepatosplanchnic blood flow was highest in the alphaxolone/alphadolone anaesthetized animals (71·7 mL min^{-1} kg^{-1}), with the urethane anaesthetized animals demonstrating a significantly ($P < 0.05$) lower (33·4 mL min^{-1} kg^{-1}) blood flow. The fentanyl/fluanisone/midazolam (65·4 mL min^{-1} kg^{-1}), pentobarbitone (61·1 mL min^{-1} kg^{-1}), and ketamine/midazolam (51·4 mL min^{-1} kg^{-1}) regimens resulted in hepatosplanchnic blood flows of intermediate magnitude. The observed marked differential effects of the anaesthetic regimens upon renal and hepatosplanchnic blood flows may dramatically influence drug disposition in the experimental animal, and be of significance to laboratory pharmacokinetic studies in which anaesthesia is used.

An examination between February and August 1989 of seven journals publishing pharmacological papers revealed that the number of pharmacokinetic studies using the rat was 51 and in studies performed in the acute surgically-prepared anaesthetized rat, 48% were under pentobarbitone anaesthesia and 26% under urethane anaesthesia. Despite generalized depression of the central and autonomic nervous systems, and the sometimes marked endocrine responses following anaesthesia induction (Pettinger et al 1975; Parker & Adams 1978; Carruba et al 1987), limited attention has been given to the possible influence that anaesthetic regimens may have upon regional haemodynamics. This is of particular significance given the wide range of anaesthetic agents available to an investigator, and the implications that a change in regional haemodynamics may have upon xenobiotic disposition (Wilkinson & Shand 1975; Duchin & Schrier 1978).

Some reports of the differential effect of laboratory anaesthetics upon drug disposition in the rat have appeared. Pipkin & Stella (1982) reported that urethane anaesthesia resulted in dose-dependent pharmacokinetics of i.v. thiamine. The total clearance of thiamine, after doses of 12 and 36 mg kg^{-1} was respectively 53 and 70% lower under urethane anaesthesia compared with the dose-independent clearance seen under ether anaesthesia. The clearance of carboxyfluorescein has been reported to be 40% lower in rats anaesthetized with urethane compared with those anaesthetized with pentobarbitone (Woolfrey et al 1985). Additionally, Gumbleton et al (1987) reported that urethane anaesthesia resulted in a total blood clearance for *p*-aminohippurate that was only 54 and 64% of the respective clearances in pentobarbitone and fentanyl/fluanisone/midazolam anaesthetized rats. Recently, significant differential effects of some laboratory anaesthetic regimens upon the clearance of gentamicin in the rat were found (Gumbleton et al 1990). Urethane anaesthesia was observed to result in a clearance for gentamicin that was 40% of the clearance in pentobarbitone anaesthetized animals, and 32% of the clearance in the conscious chronically-catheterized animal.

The implication of anaesthetic-induced changes in haemodynamics upon drug disposition is clearly demonstrated in the chronically-catheterized sheep studies of Runciman et al (1986) and Mather et al (1986), who reported a relation between halothane-induced reductions in hepatic blood flow and the clearance of the high hepatically-extracted compounds chlormethiazole and pethidine. Runciman et al (1985) also demonstrated a significant relation between halothane-induced reductions in renal blood flow and in the clearance of cefoxitin.

The aim of the present investigation was to examine the differential effect of five laboratory injectable anaesthetic regimens upon regional haemodynamics in the acute surgically-prepared rat, a protocol commonly adopted in laboratory pharmacokinetic studies. The microsphere 'reference sample technique' of McDevitt & Nies (1976) was used to examine regional haemodynamics; of particular interest were the blood flows associated with the renal and hepatosplanchnic tissues. The microsphere technique allows the simultaneous assessment of cardiac output, and, by measurements of the regional distribution of cardiac output, an examination of organ vascular resistance. Injectable anaesthetic regimens were chosen, as pharmacokinetic investigations in the acute surgically-prepared anaesthetized rat almost exclusively adopt the parenteral rather than inhalation route for anaesthetic induction and maintenance. Seyde & Longnecker (1984) and Miller et al (1980) have previously

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examined the effect of some inhalation anaesthetics upon cardiovascular and haemodynamic status in the rat.

Materials and Methods

The study was performed in male Wistar rats, 270 ± 19 g, allowed free access to water until the time of the experiment, and laboratory rat chow (Grain Harvesters Ltd, Canterbury, UK) until 4 h before experimentation.

Anaesthetic regimens

The anaesthetic regimens were:

A. Alphaxolone and alphadolone mixture, (9 and 3 mg kg^{-1}, respectively), (Saffan; Glaxovet Ltd, Harefield, UK) was administered i.v. for induction of anaesthesia. Maintenance doses (3 and 1 mg kg^{-1}) were given every 15 min.

F. Fentanyl and fluanisone mixture, (0·26 and 8·3 mg kg^{-1}, respectively), (Hypnorm; Janssen Pharmaceuticals, Wantage, UK) was administered i.p. with midazolam, (4·16 mg kg^{-1} i.p.) (Hypnovel; Roche Pharmaceuticals, Welwyn Garden City, UK), for induction of anaesthesia, which was maintained by fentanyl and fluanisone (0·08 and 2·5 mg kg^{-1}) given every 30 min.

K. Ketamine, (80 mg kg^{-1}), (Vetalar; Parke Davis, Pontypool, UK) was administered i.p. with midazolam (5 mg kg^{-1} i.p.) for induction of anaesthesia and ketamine (20 mg kg^{-1}) was given every 30 min for maintenance.

P. Pentobarbitone sodium, (67 mg kg^{-1}) (Sigma Chemical Co., Poole, UK) was administered i.p. for induction of anaesthesia with 7 mg kg^{-1} given every 60 min for maintenance.

U. Urethane, (1·75 g kg^{-1}) (Sigma Chemical Co., Poole, UK) was administered i.p. as a single dose.

The doses were the minimum required to produce surgical anaesthesia, and are within the range commonly employed for laboratory anaesthesia in the rat (Green 1979; Green et al 1981; Wixson et al 1987). The required depth of anaesthesia was adjudged to have been attained when the corneal reflex and response to painful stimuli were no longer present.

Assessment of cardiac output and regional haemodynamics

Once anaesthetized, the animal's right carotid artery was exposed, separated from the vagus nerve, and catheterized (polythene tubing; i.d., 0·58 mm; o.d., 0·96 mm; code 800/100/200/100; Portex, Hythe, UK). With the aid of pressure monitoring, the tip of the catheter was manipulated into the left ventricle; the correct position of the catheter tip was confirmed at autopsy. Blood pressure measurements were monitored before and for 90 s after microsphere injection, via a polythene catheter in the right femoral artery and connected via a fixed volume pressure transducer (no 3552CA, Lectromed Ltd, Letchworth, UK) to an MX 2 Devices recorder (Lectromed) with internal calibration.

Approximately 2 μCi (60 000–80 000 counts min^{-1}) of ^{113}Sn-labelled microspheres for injection (15 ± 1·5 μm; stored in 0·9% NaCl (saline), with a specific activity of 63 d min^{-1}/microsphere (code NEM-062A; Nen-Trac, Dupont Ltd, Stevenage, UK), were dispersed homogeneously in 0·3 mL of 0·01% Tween 80/saline at 37°C. After 60 min of stable anaesthesia microspheres were injected into the left ventricle over 5 s, the syringes used having been stored overnight in a solution of 0·03% Tween 80/saline, to minimize adsorption of microspheres to the syringe wall.

Commencing 15 s before, and continuing for 90 s after, microsphere injection, a reference blood sample was withdrawn from a left femoral artery catheter directly into a 1·5 m length of silicone-rubber tubing (i.d., 0·6 mm; o.d. 1·6 mm; code 915-0008-016, Watson Marlow, UK), at a constant withdrawal rate of 0·43 mL min^{-1} (modified slow infusion pump; Scientific and Research Instruments Ltd, Sheerness, UK). To maintain catheter patency, the left femoral catheter, silicone-rubber tubing and the withdrawal syringe contained 500 i.u. mL^{-1} of sodium heparin (Sigma Chemical Co, Poole, UK) in saline. The right carotid and femoral artery catheters contained 100 i.u. mL^{-1} sodium heparin in saline. All surgical wounds were covered with cotton gauze, kept moist with saline to minimize tissue fluid loss. To ensure against hypothermic-induced haemodynamic changes (Ballard 1974), rectal temperatures were monitored and maintained at 38 ± 1°C using an incandescent lamp and heated surgical tray. Tracheostomies were performed as an aid to respiration throughout anaesthesia.

At the end of the experiment the anaesthetized animals were killed by cervical dislocation, and the splanchnic organs and tissues removed, washed in saline and blotted dry. The alimentary tract was cleared of undigested material and all organ weights recorded. The organs and tissues, together with the reference blood sample, were analysed for radioactivity using an LKB 1275 Minigamma counter (window setting, 100–450 keV; counting efficiency for ^{113}Sn, 20%). The exact radioactive dose reaching the left ventricle, was assessed by reference to all possible sources of radioactive microsphere loss from the initial dose, e.g. microsphere injection syringe, left ventricular catheter.

Cardiac output and regional blood flows were calculated as described by McDevitt & Nies (1976). The radioactivity located in the liver is a measure of hepatic arterial supply, whilst hepatic portal venous flow was calculated from the radioactivity in spleen, stomach, small intestine, large intestine, pancreas and mesentery. Total hepatosplanchnic blood flow is the sum of hepatic arterial and hepatic portal blood flows.

The criteria used for a successful microsphere injection were: i) that less than 15% of the injected microspheres remained in the heart, and that their distribution between left and right kidneys differed by less than 15%, indicating correct ventricular catheter placement and efficient mixing in the aorta; ii) that no change in mean arterial pressure occurred following microsphere injection; (iii) that less than 3% of the microspheres appeared in the lungs, indicating total entrapment by the proximal organs in the first circulation; iv) that a minimum of 400 microspheres were distributed to each organ of interest, enabling statistical validity.

Results are presented as mean ± s.d. Statistical comparisons between groups was accomplished by one-way analysis of variance and Duncan's multiple range test (Duncan 1955).

Results

The results of the cardiac output and regional blood flow assessments are presented in Table 1. The assessment of the

Table 1. Anaesthetic regimens and regional haemodynamics in the rat (mean ± s.d.; n = 8).

Blood flows	F	P	U	K	A	Statistical comparisons[a]
Cardiac output (mL min^{-1} kg^{-1})	324 ± 65	228 ± 29	174 ± 14	193 ± 38	244 ± 25	$F\ A^1\ P^{1,2}\ K^{2,3}\ U^3$
Renal (mL min^{-1} (g tissue)$^{-1}$)	2·84 ± 0·54	3·19 ± 0·41	1·99 ± 0·26	3·24 ± 0·56	3·90 ± 0·58	$A\ K^1\ P^1\ F^1\ U$
Renal (mL min^{-1} kg^{-1})	28·2 ± 4·6	31·2 ± 3·6	17·0 ± 2·9	31·3 ± 4·3	36·6 ± 2·5	$A\ K^1\ P^1\ F^1\ U$
Spleen (mL min^{-1} (g tissue)$^{-1}$)	1·77 ± 0·57	1·11 ± 0·43	0·54 ± 0·08	1·17 ± 0·32	1·72 ± 0·60	$F^1\ A^1\ K^2\ P^2\ U$
Stomach (mL min^{-1} (g tissue)$^{-1}$)	0·41 ± 0·10	0·4 ± 0·12	0·23 ± 0·06	0·43 ± 0·13	0·53 ± 0·31	$A^1\ K^1\ F^1\ P^1\ U$
Small intestine (mL min^{-1} (g tissue)$^{-1}$)	1·21 ± 0·31	1·34 ± 0·34	0·87 ± 0·30	1·66 ± 0·32	1·91 ± 0·45	$A^1\ K^{1,2}\ P^{2,3}\ F^3\ U$
Large intestine (mL min^{-1} (g tissue)$^{-1}$)	0·85 ± 0·28	0·92 ± 0·29	0·63 ± 0·21	1·04 ± 0·37	1·26 ± 0·20	$A^1\ K^{1,2}\ P^{1,2}\ F^2\ U$
Pancreas & mesentery (mL min^{-1} (g tissue)$^{-1}$)	0·62 ± 0·11	0·45 ± 0·08	0·24 ± 0·06	0·41 ± 0·20	0·76 ± 0·29	$A^1\ F^{1,2}\ P^2\ K\ U$
Liver (hepatic artery) (mL min^{-1} (g liver)$^{-1}$)	0·06 ± 0·02	0·13 ± 0·03	0·11 ± 0·01	0·11 ± 0·03	0·12 ± 0·03	$P^1\ A^1\ K^1\ U^1\ F$
Hepatosplanchnic (mL min^{-1} (g liver)$^{-1}$)	1·23 ± 0·15	1·11 ± 0·17	0·65 ± 0·19	0·95 ± 0·15	1·26 ± 0·28	$A^1\ F^1\ P^{1,2}\ K^2\ U$
Hepatosplanchnic (mL min kg^{-1})	65·4 ± 13·2	61·1 ± 11·4	33·4 ± 10·5	51·4 ± 8·8	71·7 ± 15·3	$A^1\ F^1\ P^{1,2}\ K^2\ U$

[a] Statistical comparisons: anaesthetics are arranged left to right in the order of descending magnitude for the parameter. Anaesthetics given the same superscript number are not significantly different ($P > 0·05$) from each other.
Key: F—fentanyl/fluanisone/midazolam; P—pentobarbitone; U—urethane; K—ketamine/midazolam; A—alphaxolone/alphadolone.

Table 2. Anaesthetic regimens and distribution of cardiac output in the rat (mean ± s.d.; n = 8).

% Cardiac output	F	P	U	K	A	Statistical comparisons[a]
Renal	8·81 ± 0·41	13·91 ± 2·71	9·75 ± 1·35	15·85 ± 3·19	16·23 ± 1·19	$A^1\ K^1\ P^1\ U\ F$
Spleen	1·81 ± 0·49	1·38 ± 0·48	0·72 ± 0·09	1·40 ± 0·38	1·77 ± 0·40	$F^1\ A^1\ K^1\ P^1\ U$
Stomach	0·72 ± 0·21	0·99 ± 0·29	0·62 ± 0·12	1·07 ± 0·20	1·06 ± 0·44	$K^1\ A^1\ P^{1,2}\ F^2\ U$
Small intestine	11·15 ± 3·20	14·39 ± 1·57	9·85 ± 4·08	14·29 ± 2·54	15·43 ± 3·03	$A^1\ P^{1,2}\ K^{1,2}\ F^2\ U$
Large intestine	3·38 ± 1·15	4·28 ± 0·82	3·34 ± 1·23	4·57 ± 0·61	5·18 ± 0·55	$A^1\ K^1\ P^1\ F\ U$
Pancreas & mesentery	2·61 ± 0·64	2·51 ± 0·58	1·51 ± 0·44	2·34 ± 0·68	2·97 ± 0·86	$A^1\ F^1\ P^1\ K^1\ U$
Liver (hepatic artery)	0·98 ± 0·45	3·15 ± 0·92	3·19 ± 0·61	3·31 ± 1·12	2·84 ± 0·75	$K^1\ U^1\ P^1\ A^1\ F$
Hepatosplanchnic	20·7 ± 5·03	26·7 ± 2·70	19·2 ± 5·8	27 ± 3·3	29·3 ± 4·30	$A^1\ K^1\ P^1\ F\ U$

[a] Statistical comparisons: anaesthetics are arranged left to right in the order of descending magnitude for the parameter. Anaesthetics given the same superscript number are not significantly different ($P > 0·05$) from each other.
Key: F—fentanyl/fluanisone/midazolam; P—pentobarbitone; U—urethane; K—ketamine/midazolam; A—alphaxolone/alphadolone.

fractional distribution of cardiac output, a measure of organ vascular resistance, is presented in Table 2.

The mean arterial pressures (MAP) (mean ± s.d.) for the different anaesthetic regimens were as follows; U, 90 ± 6 mmHg; F, 104 ± 6 mmHg; A, 116 ± 4 mmHg; K, 126 ± 8 mmHg and P, 128 ± 8 mmHg. Analysis of variance and Duncan's multiple range test revealed that MAP during U anaesthesia was significantly lower than in any of the other anaesthetic regimens. MAP was observed not to alter between pre- and post-microsphere injection in any of the groups. The mean microsphere count remaining in the heart was 5·8 ± 1·5% of the injected dose. The mean microsphere count found in the lungs was 1·9 ± 1·3% of the dose. The mean difference in microsphere counts between left and right kidney was 7·7 ± 4·6%.

Discussion

The results of this study demonstrate marked differential effects of the anaesthetic regimens upon cardiac output. U anaesthesia resulted in a cardiac output value approximately 50% of that recorded with F anaesthesia. In the present report the cardiac output values recorded for the different anaesthetic regimens are in close agreement with the results of the microsphere study performed by Bell et al (1977), examining the effects of A, P and K anaesthesia upon cardiovascular haemodynamics in the rat, and reporting values for cardiac output (mL min^{-1} kg^{-1} body wt) of 250, 220 and 200, respectively.

The F and A anaesthetic combinations are not generally associated with any significant cardiovascular depression (Green 1979), although reports of A anaesthetic-induced reductions in cardiac output in laboratory animals do exist (Thomson et al 1986; Dyson et al 1987). The cardiovascular response to anaesthetic doses of pentobarbitone is usually characterized by depression of myocardial contractility, with a decreased cardiac output compared with the conscious animal (Kawaue & Iriuchijima 1984). In contrast to the anaesthetic state produced by barbiturates, ketamine anaesthesia is not usually associated with cardiovascular depression. Indeed, following ketamine anaesthesia cardiovascular haemodynamics are usually considered to be well maintained, if not stimulated (Haskins et al 1985; Idvall et al 1980). However, dose-dependent myocardial depressor responses have also been reported for ketamine (Chen et al 1984). Miller et al (1980) have reported that a high anaesthetic dose of ketamine (125 mg kg^{-1} i.m.) administered to the rat, results in a significant depression in cardiac output compared with the conscious animal. With equivocal literature reports of the effect of ketamine anaesthesia upon cardiovascular haemodynamics that are complicated by dose, route of administration and species, it should be noted that the ketamine dosage used in the present study, i.e. 80 mg

kg^{-1} i.p. administered in conjunction with a benzodiazepine, is a recommended dosage regimen for the laboratory anaesthesia of the rat (Green 1979; Green et al 1981; Wixson et al 1987). The co-administration of a benzodiazepine may further attenuate any cardio-stimulatory action of ketamine. Such differential effects between the anaesthetic regimens upon cardiac output, may be of significance in the performance of in-vivo cardiovascular studies, when anaesthesia is a component part of the experiment.

In the rat P-induced reductions in renal blood flow and glomerular filtration rate are recognized (Walker et al 1983, 1986), with reductions to approximately 75% of the values recorded in the conscious animal. Thus, in the present investigation, the lower renal blood flow recorded with U anaesthesia must represent a significant reduction relative to the other anaesthetic regimens. It is recognized that U anaesthesia results in activation of the pituitary-adrenal axis, with elevated circulating levels of catecholamines (Spriggs & Stockham 1964; Carruba et al 1987), and in activation of the renin-angiotensin system (Pettinger et al 1975), with resultant systemic elevations in angiotensin II. The systemic vasopressor responses arising from these endocrine changes may be expected to increase renal vascular resistance, reducing the fractional distribution of cardiac output to the kidneys and, in conjunction with a reduced systemic perfusion pressure, result in the inability to maintain renal blood flow. In rats, the autoregulation of renal blood flow and glomerular filtration rate is impaired below a mean arterial pressure of 80 mmHg (Arendshorst et al 1975).

Despite the recognition that U anaesthesia results in marked changes in the renin-angiotensin system and in systemic catecholamine levels, the blood pressure and cardiac output reported in this study remained significantly depressed in comparison with the other anaesthetic regimens, indicating a dramatic effect of the U regimen upon cardiovascular homeostasis. Previous studies have observed a depressive effect of U upon cardiac dynamics (Van der Meer et al 1975; DeWildt et al 1983; Maggi et al 1984), although equivocal conclusions regarding the effects of urethane upon the cardiovascular system do exist (Maggi & Meli 1986).

That intraperitoneal toxicity occurs, following the i.p. administration of anaesthetic doses of urethane to the rat, appears to be unequivocal (Van der Meer et al 1975; Severs et al 1981; Gumbleton et al 1988). This condition, characterized by mesenteric vascular damage with leakage of plasma albumin and plasma water into the peritoneal cavity, may be expected to have a deleterious effect upon the maintenance of cardiovascular homeostasis under U anaesthesia.

The results of this study in demonstrating a much lower renal blood flow in the U anaesthetized animals is consistent with a haemodynamic basis to the previously mentioned reports of Pipkin & Stella (1982), Woolfrey et al (1985) and Gumbleton et al (1987, 1990) demonstrating a deleterious effect of urethane upon xenobiotic renal clearance. The elimination of *p*-aminohippurate, like that of carboxyfluorescein, thiamine and gentamicin, is highly dependent upon renal excretion mechanisms, and the influence of renal haemodynamics. Deleterious effects of an anaesthetic upon renal blood flow will perturb glomerular and peritubular haemodynamics, influencing both the filtration rate at the glomerulus and the rate of delivery of a xenobiotic to the active secretory mechanisms within the proximal tubule.

U anaesthesia resulted in a hepatosplanchnic blood flow significantly lower than any other anaesthetic regimen, being approximately 50% of that obtained with A anaesthesia. U anaesthesia in the rat has previously been reported to result in a lower hepatosplanchnic blood flow that was approximately 68% of the value recorded in animals anaesthetized with P (Hiley et al 1978). Such differences in hepatosplanchnic blood flow may be expected to influence the systemic clearance of compounds with high hepatic extraction ratios, but may also influence the clearance of low hepatically extracted compounds, through changes in the rate of hepatic oxygen delivery. A reduction in the rate of oxygen delivery to rat isolated perfused liver (to $\approx 30\%$ of the control value) has been shown to significantly reduce the intrinsic clearance of antipyrine (Brouwer & Vore 1985), a compound with a low hepatic extraction ratio.

The relative effects of anaesthetic agents upon cardiovascular and regional haemodynamics is of obvious significance to laboratory investigators, especially when cardiac ouput, and renal and hepatosplanchnic blood flows, can vary by as much as 100%. A further perspective upon the differential haemodynamic effects of the anaesthetic regimens, may be gained by comparison with microsphere studies that have examined haemodynamics in the conscious chronically-catheterized rat. Values of cardiac output ranging from 280 to 424 mL min^{-1} kg^{-1}, renal blood flow ranging from 4·2 to 7·5 mL min^{-1} (g tissue)$^{-1}$ and hepatosplanchnic blood flow ranging from 65·5 to 90 mL min^{-1} kg^{-1} have been reported (Idvall et al 1980; Miller et al 1980; Cerini et al 1989; Ozier et al 1989; Roulet et al 1989). Comparison of the haemodynamic data from the present investigation, performed in the acute surgically-prepared anaesthetized rat, with the range of literature values reported for the conscious chronically-catheterized rat, substantiates the marked differential effects between anaesthetic regimens.

Acknowledgement

The authors are grateful to Drs C. R. Hiley and M. Maclean, Department of Pharmacology, University of Cambridge, for demonstration of the microsphere technique.

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