J. Physiol. (1968), **199**, *pp.* 253–265
With 3 text-figures
Printed in Great Britain

CIRCULATORY EFFECTS OF CHLORALOSE-URETHANE AND SODIUM PENTOBARBITONE ANAESTHESIA IN THE RABBIT

BY P. I. KORNER,* J. B. UTHER† AND S. W. WHITE‡
From the School of Physiology, University of New South Wales, Sydney, Australia

(*Received* 18 *March* 1968)

SUMMARY

1. The effects of chloralose-urethane and sodium pentobarbitone anaesthesia on heart rate, blood pressure and cardiac output were studied in normal rabbits, in animals given atropine and in animals without functioning autonomic effectors. The findings under anaesthesia were compared during spontaneous and artificial intermittent positive pressure respiration.

2. The circulatory effects of chloralose-urethane and sodium pentobarbitone anaesthesia differed significantly for the first hour after induction of anaesthesia. During the subsequent 3 hr of maintained anaesthesia differences in the circulatory effects of the two anaesthetics were small.

3. The direct local effects of these anaesthetics were assessed during the maintenance phase from the responses of animals without functioning autonomic effectors. With both anaesthetics there was peripheral vasodilatation and minimal effects on heart rate.

4. The autonomic activity in the normal animal was assessed by comparing the changes in normal, atropinized and 'de-efferented' rabbits without functioning autonomic effectors. During chloralose-urethane anaesthesia there was reduction in cardiac vagal efferent activity and no change in cardiac sympatho-adrenal activity. With both anaesthetics there was an increase in peripheral sympatho-adrenal constrictor activity, tending to minimize the local vasodilator effects.

* Present address: Cardiology Section, Department of Medicine, University of Sydney, Sydney, Australia 2006.

† Research Fellow of the Life Insurance Medical Research Fund of Australia and New Zealand.

‡ Research Fellow of the National Heart Foundation of Australia.

INTRODUCTION

The circulatory response of a normal animal to an anaesthetic results partly from the local effects of the drug on the heart and blood vessels, and partly from changes in autonomic activity. Different anaesthetics act on different sites along the neural pathways subserving the respiratory and circulatory control mechanisms, and may exert stimulating or depressant effects on various receptors, on different neurones in the central nervous system, and on the autonomic ganglia and adrenal medulla (Vincent & Thompson, 1928; Brooks & Eccles, 1947; Larrabee & Posternak, 1952; Landgren, Liljestrand & Zotterman, 1953; Exley, 1954; Redgate & Gellhorn, 1956, 1958; Whitteridge, 1958; Peiss & Manning, 1964; Millar & Biscoe, 1965). There are also significant differences in the direct cardiotoxic and peripheral vascular effects of different anaesthetics, which have been studied in the heart–lung preparation and in isolated vascular beds (Gruber, Gruber & Lee, 1952; Price, 1960; Bass & Buckley, 1966).

In the intact animal the circulatory responses produced by different anaesthetics have been studied extensively (Price, 1960; Heymans, 1964; Greisheimer, 1965; Dundee, 1967), but the relative contributions of reflex and local components have not been determined. In the present study the effects of chloralose-urethane and sodium pentobarbitone have been examined in the rabbit from this point of view. The 'local' (i.e. non-autonomic) effects have been studied in 'de-efferented' animals without functioning autonomic effectors. The reflex components of the response have been estimated from the differences in the responses of 'de-efferented' animals, normal animals and atropinized animals. The effects obtained during anaesthesia in the spontaneously breathing animal have also been contrasted with the findings during artificial ventilation.

METHODS

Conduct of experiments and groups. New Zealand White rabbits, cross-bred with the New Zealand Giant strain, were used in these experiments (mean body weight 2·6 kg, range 2·0–3·1 kg). Three groups of animals were studied: (1) normal animals with intact reflexes, (2) atropinized animals with vagal efferent block, (3) 'de-efferented' animals without functioning autonomic effectors, which had been subjected to bilateral adrenalectomy and placed on steroid maintenance, prolonged treatment with guanethidine, and administration of atropine (Korner & White, 1966; White, 1966; Chalmers, Korner & White, 1967*a*). In all animals a thermistor catheter was inserted into the upper abdominal aorta at a preliminary operation 3–12 days before an experiment (Korner, 1965), using sodium pentobarbitone anaesthesia (initial dose 30–40 mg/kg I.V., supplemented as necessary). Adrenalectomy was performed at this operation in the 'de-efferented' group (White, 1966). On the day of the experiment under local lignocaine anaesthesia the central ear artery and right atrium

were catheterized, and tracheotomy tube was inserted as described previously (Korner, 1965). The animal was then placed into a rabbit box where it rested for 1 hr before commencing the experiment.

In the first series of experiments the time course of changes of various cardiorespiratory measurements was studied in two groups of rabbits during chloralose-urethane and sodium pentobarbitone anaesthesia, maintained for 4 hr. In each animal seven sets of measurements of respiratory minute volume, arterial pressure, heart rate and cardiac output were taken over a period of 25 min before anaesthesia. After giving the anaesthetic, the measurements were continued at 10 min intervals for 1 hr and at 30 min intervals for the next 3 hr, giving supplementary doses of anaesthetic every 20–50 min, as described below. In the second series of experiments each animal was studied before anaesthesia, 1 hr after induction of anaesthesia while breathing spontaneously, and 1 hr later under continuing anaesthesia whilst being ventilated by intermittent positive pressure using a Starling 'Ideal' respiratory pump. During each period four sets of measurements of cardiac output, arterial pressure, right atrial pressure, heart rate, respiratory rate and minute volume, and one set of measurements of arterial P_{O_2}, P_{CO_2} and pH was obtained. In a third series of experiments the effects of atropine were examined in a group of unanaesthetized rabbits and a group of animals anaesthetized with chloralose-urethane.

In each series of experiments the timing of the various measurements was the same in all the animals in each group. In the first series the mean value of each variable was obtained at the various selected time intervals (Fig. 2), and the standard error of the mean at a single time interval was calculated by analysis of variance, as described previously (Chalmers, Isbister, Korner & Mok, 1965). In the second and third series the differences between the mean values before and during anaesthesia, or before and after atropine were determined, and the standard error of the difference between the various treatments calculated from within-animal comparisons.

Anaesthesia. Chloralose-urethane anaesthesia was induced by first injecting urethane (ethyl carbamate, May and Baker, Ltd.), in a solution of 25 g/100 ml. saline (0·9 g NaCl/100 ml.) intravenously through the right atrial catheter in a dose of 400 mg/kg. The injection was made at a rate of about 2 ml./min without disturbing the animal in the box, and this dose of urethane induced hypnosis but not anaesthesia. Warm chloralose solution was next injected at a rate of about 2 ml./min through the catheter. This solution was prepared by dissolving 500 mg of α-chloralose (Roche Products Ltd.) in 50 ml. of NaCl (0·9 g/100 ml.) at 50–55° C, and filtering twice through no. 1 Whatman filter paper to remove excess sediment. The initial dose injected was 6 ml./kg of the above solution, which produced moderate surgical anaesthesia, with some responsiveness of the animal to strong superficial and deep painful stimuli (Bass & Buckley, 1966). With the chloralose prepared as described no myoclonic movements were observed in response to sudden noise, or while tapping the operating table (Kruger & Albe-Fessard, 1960; Balis & Monroe, 1964), even when urethane was not used to induce anaesthesia. Induction of sodium pentobarbitone (Veterinary Nembutal, Abbott) anaesthesia was performed by injecting 30–40 mg/kg I.V. This just stopped eye movements, but did not completely abolish reflex movements in response to deep paw pressure.

In the spontaneously breathing animals an approximately constant level of moderate surgical anaesthesia was maintained throughout the experiment. In the series of animals anaesthetized with chloralose-urethane this was done by injecting 1–3 ml. of chloralose every 30–50 min, the level of anaesthesia being judged by testing the animal's responses to painful stimuli, and by the depth and frequency of respiration. With sodium pentobarbitone the supplements were 4–12 mg/kg I.V. given every 20–50 min. In the series involving the use of decamethonium iodide, anaesthetic supplementation was continued at the same rate as in the same animal breathing spontaneously, in order to ensure adequate maintenance of anaesthesia in these experiments.

No premedication was given to the animals with either anaesthetic. We found it impossible

to maintain normal arterial blood gas tensions during anaesthesia in spontaneously breathing animals lying supine on the operating table, and it was necessary to support the animals in the normal, prone, crouching posture of an unanaesthetized rabbit (Fig. 1). They were wrapped in cotton wool to minimize heat loss, and also to reduce the amount of external heat required to maintain deep body temperature. An electric table heater was used to maintain the aortic temperature to $\pm 0{\cdot}5$ °C of the value before anaesthesia.

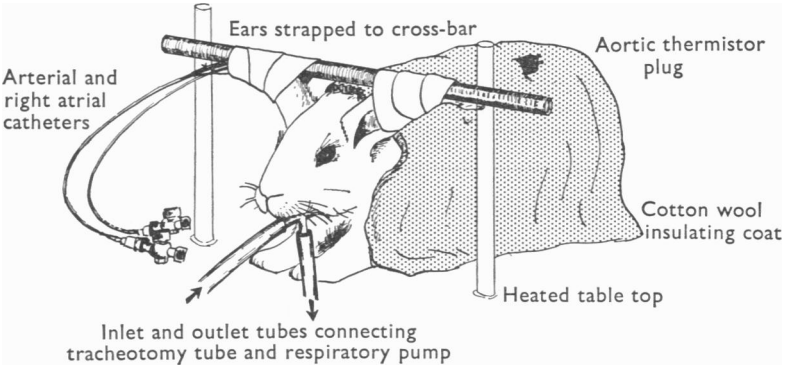

Fig. 1. Arrangement of anaesthetized rabbit in normal prone posture. The animal was maintained in this posture when breathing spontaneously and when ventilated artificially.

Other drugs. Before starting intermittent positive pressure ventilation, 1 mg/kg I.V. of decamethonium iodide (Eulissin A, Allen & Hanbury) was injected, which produced respiratory paralysis. The effect lasted approximately 40 min, and where necessary a supplementary dose of 0·3 mg/kg I.V. was given to the animal. This dose of relaxant has no significant vagolytic action in the rabbit (Korner, Langsford, Starr, Uther, Ward & White, 1968).

Atropine sulphate (British Drug Houses, Ltd.) was injected as a priming dose of 3 mg I.V. followed by doses of 1 mg I.V. every 5 min. The adequacy of block was tested in animals anaesthetized with chloralose-urethane by stimulating the cardiac end of the cut vagus with rectangular pulses of 10 V amplitude, 1 msec duration, and a frequency of 50 c/s. This stimulus failed to produce bradycardia (i.e. a fall in the heart rate of 10 beats/min or more) for about 7 min after injecting the drug. The doses of atropine were larger than those used in previous series (Chalmers *et al.* 1967*a*), probably reflecting a higher concentration of atropinesterase in this particular strain of rabbits (Goodman & Gilman, 1958). This dose of atropine did not disturb the unanaesthetized rabbits and they remained quietly in their box. There was, however, some respiratory stimulation both before and during anaesthesia (Table 3).

Cardiorespiratory measurements. The cardiac output was measured by recording thermodilution curves from the upper abdominal aorta after rapid injection of glucose in distilled water (5·5 g/100 ml.) into the right atrium (Korner, 1965). Mean central ear artery pressure, right atrial pressure and heart rate were measured as described previously (Korner, 1965). Total peripheral resistance was calculated as the ratio (ear artery pressure − right atrial pressure)/cardiac output. Ventilation was measured by collecting expired air, and expressed as l./min at ambient temperature. Respiration rate was counted by observing the animal's respiratory movements. Arterial P_{O_2}, P_{CO_2} and pH were measured once during each treatment using a Model 113 Instrumentation Laboratory Inc. Blood Gas Analyser and pH meter (Chalmers, Korner & White, 1967*b*).

RESULTS

Time course of changes during anaesthesia in normal animals

With chloralose-urethane the respiratory minute volume remained slightly below the control value observed before anaesthesia, the greatest depression occurring during the first hour (Fig. 2). With sodium pentobarbitone, ventilation remained depressed for about 40 min and then returned to the control value.

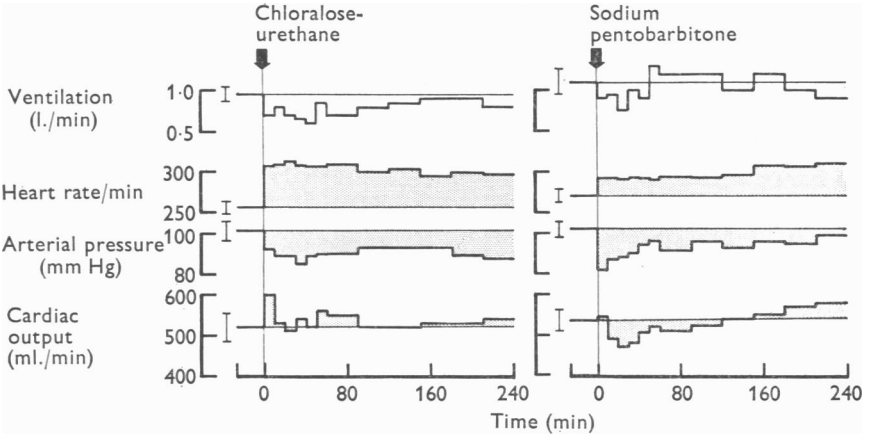

Fig. 2. Mean effects with respect to time in four rabbits of chloralose-urethane anaesthesia (left panel), and in four others of sodium pentobarbitone anaesthesia (right panel) on ventilation (l./min), heart rate (beats/min), arterial pressure (mm Hg) and cardiac output (ml./min). Anaesthesia was induced at the arrow. Supplementary doses were injected at somewhat different times in each animal in order to maintain an approximately constant level of anaesthesia. The height of the symbol to the left of each variable is twice the standard error of the mean at a single time interval.

The heart rate rose immediately after induction of anaesthesia, the rise being greater with chloralose-urethane than with sodium pentobarbitone. During the first hour after induction there was a significantly different effect on arterial pressure and cardiac output with each anaesthetic. With chloralose-urethane the cardiac output increased transiently, and the pressure fell to about 90 % of the value before anaesthesia (Fig. 2, left panel). During sodium pentobarbitone anaesthesia there was significant reduction in cardiac output during the first 40–50 min after induction, and the fall in blood pressure to 80 % of control was greater than with chloralose-urethane. With each anaesthetic the circulatory variables become stable about 1 hr after induction, and further changes during the next 3 hr were relatively slight. During this anaesthetic maintenance phase there was an increase in heart rate above pre-anaesthetic control values, little change in cardiac output, but some reduction in arterial pressure.

Effects in normal, atropinized and 'de-efferented' animals during the maintenance phase

The results of the second and third series of experiments are shown in Tables 1–3. In the 'de-efferented' animals the anaesthetics were administered at about half the rate used in normal rabbits, since otherwise the

TABLE 1. Mean resting values in six normal rabbits before and during chloralose-urethane anaesthesia, and in four normal rabbits before and during sodium pentobarbitone anaesthesia. U, unanaesthetized animal; AS, same animal anaesthetized and breathing spontaneously; AC, same animal anaesthetized with controlled ventilation. Results from each animal during each period are based on the mean of four measurements of each cardiorespiratory variable and one measurement of arterial blood composition. S.E. = standard error of difference of the appropriate means, calculated from within-animal comparisons

	U	AS	AC	± S.E. (U–AS)	± S.E. (AS–AC)
Before and during chloralose-urethane					
Cardiac output (ml./min)	541	598	546	±33	±14
Arterial pressure (mm Hg)	98	93	94	±3·8	±3·6
R. atrial pressure (mm. Hg)	−0·2	+0·2	+2·4	±0·6	±0·5
Heart rate (beats/min)	269	321	331	±9·2	±5·2
Ventilation (l./min)	1·03	0·81	0·95	±0·05	—
Respiration rate (breaths/min)	62	40	60	±5·9	—
Arterial P_{O_2} (mm Hg)	95	92	102	±3·0	±2·1
Arterial P_{CO_2} (mm Hg)	36	32	32	±2·4	±2·2
Arterial pH	7·35	7·37	7·39	±0·02	±0·02
Before and during sodium pentobarbitone					
Cardiac output (ml./min)	576	592	518	±24	±17
Arterial pressure (mm Hg)	95	89	85	±6·5	±2·7
R. atrial pressure (mm. Hg)	0	+0·5	+2·7	±0·7	±0·2
Heart rate (beats/min)	275	302	296	±6·5	±6·9
Ventilation (l./min)	0·84	0·61	0·95	±0·08	—
Respiration rate (breaths/min)	56	38	60	±7·5	—
Arterial P_{O_2} (mm Hg)	89	89	98	±1·3	±4·6
Arterial P_{CO_2} (mm Hg)	38	37	34	±1·0	±1·1
Arterial pH	7·34	7·39	7·37	±0·01	±0·06

animals were liable to cardiac arrest. However, the total dose of anaesthetic given to the 'de-efferented' animals was the same as in normal rabbits, and the levels of anaesthesia were similar in both groups.

Respiration. In normal animals, with intact reflexes, both anaesthetics significantly depressed the respiratory minute volume in this series of experiments (Table 1). The effect was entirely due to reduction in respira-

tion rate, and the tidal volume actually increased. The changes in arterial P_{O_2}, P_{CO_2} and pH during anaesthesia were minimal. In 'de-efferented' animals without functioning autonomic effectors the reduction in respiratory minute volume and rate was approximately the same as in normal rabbits (Table 2), but the arterial P_{O_2} was about 10 mm Hg lower than before anaesthesia. This reduction can probably be explained by the rise in cardiac output observed during anaesthesia, in the 'de-efferented' animals (Table 2).

TABLE 2. Mean resting values in three 'de-efferented' rabbits before and during chloralose urethane anaesthesia, and in three 'de-efferented' animals before and during sodium pentobarbitone anaesthesia. Notation as in Table 1

	U	AS	AC	± S.E. (U–AS)	± S.E. (AS–AC)
Before and during chloralose-urethane					
Cardiac output (ml./min)	506	655	573	±24	±29
Arterial pressure (mm Hg)	74	68	63	±4·1	±2·3
R. Atrial pressure (mm Hg)	+0·6	+0·5	+1·9	±0·6	±0·5
Heart rate (beats/min)	221	230	231	±3·9	±2·0
Ventilation (l./min)	1·0	0·80	0·95	±0·07	—
Respiration rate (breaths/min)	84	50	60	±8·5	—
Arterial P_{O_2} (mm Hg)	104	91	90	±3·5	±1·9
Aterial P_{CO_2} (mm Hg)	37	35	38	±2·0	±1·2
Arterial pH	7·49	7·42	7·45	±0·03	±0·02
Before and during sodium pentobarbitone					
Cardiac output (ml./min)	484	642	500	±34	±33
Arterial pressure (mm Hg)	72	65	57	±6·7	±5·1
R. Atrial pressure (mm Hg)	+0·8	+1·1	+2·7	±0·4	±0·3
Heart rate (beats/min)	224	220	218	±2·2	±2·8
Ventilation (l./min)	0·97	0·78	0·95	±0·05	—
Respiration rate (breaths/min)	78	64	60	±13	—
Arterial P_{O_2} (mm Hg)	101	89	89	±2·0	±1·0
Arterial P_{CO_2} (mm Hg)	30	34	28	±1·2	±4·0
Arterial pH	7·47	7·39	7·38	±0·04	±0·01

Heart rate. The heart rate increased with both anaesthetics in the spontaneously breathing normal animals, and the increase was greater with chloralose-urethane than with sodium pentobarbitone (Table 1). There was no additional significant change in rate when the animals were ventilated artificially, at the mean respiration rate and minute volume of normal unanaesthetized rabbits. Although the spontaneously breathing 'de-efferented' animals have a higher respiration rate than normal animals,

the respiratory rate and minute volume were maintained at the same level during artificial ventilation in both groups in order to have identical mechanical effects. In the group of 'de-efferented' animals the heart rate did not change significantly during anaesthesia from the pre-anaesthetic control value. The heart rate before anaesthesia, and the changes during spontaneous and artificial ventilation under anaesthesia, are shown for each agent in Fig. 3.

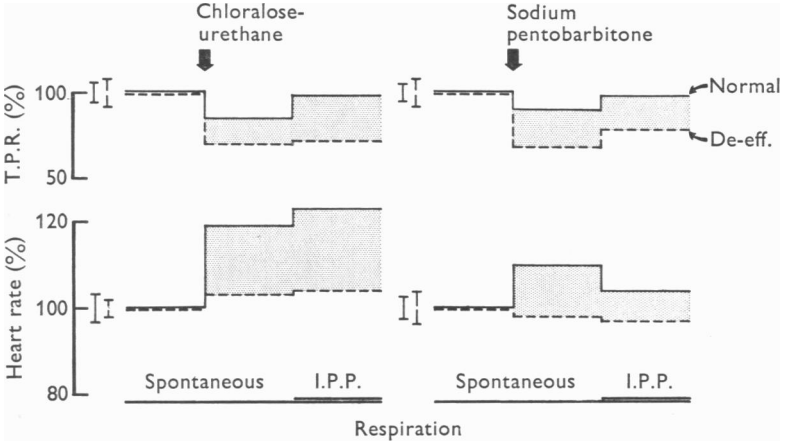

Fig. 3. Mean effects of anaesthesia on changes in total peripheral resistance (T.P.R.) and heart rate, expressed as percentage of the pre-anaesthetic control value, in six normal (continuous line) and three 'de-efferented' rabbits (dashed line) given chloralose-urethane (at arrow), and in four normal and three 'de-efferented' animals given sodium pentobarbitone. The effects shown are the mean findings 1 hr after induction of anaesthesia with the animals breathing spontaneously, and 10–15 min after commencing intermittent positive pressure respiration (I.P.P.). The symbol on the left is twice the standard error of the mean of one period and is shown in the order (from left) normal and 'de-efferented' preparation.

The vagal component of the heart rate change was assessed by comparing the effects of atropine in a group of unanaesthetized rabbits, with the effects in another group anaesthetized with chloralose-urethane (Table 3). Before administration of atropine the mean heart rate of animals anaesthetized with chloralose-urethane (298/min) was significantly higher than in the unanaesthetized group (277/min). After atropine the heart rate increased to approximately the same value in each group (Table 3). The change was smaller in the anaesthetized rabbits (16 beats/min) than in the unanaesthetized animal (32 beats/min), suggesting that there was less cardiac vagal activity present during anaesthesia. An approximate estimate of the sympatho-adrenal activity to the heart can be made by subtracting the heart rate of the 'de-efferented' animals studied either before or during anaesthesia from the corresponding group of atropinized

animals. This difference averaged 88 beats/min in unanaesthetized animals, and 84 beats/min during chloralose-urethane anaesthesia and indicates that cardiac sympatho-adrenal activity is not greatly altered by this anaesthetic.

Haemodynamic findings. The results in Table 1 indicate that in the second series of experiments there were in the normal group no statistically significant changes in arterial pressure, right atrial pressure and cardiac output after administration of each anaesthetic whilst the animals were breathing spontaneously. During artificial ventilation under anaesthesia the right atrial pressure increased significantly by 2·2 mm Hg, and there was also a significant reduction in cardiac output from the mean value

TABLE 3. Mean circulatory and respiratory effects of atropinizing six normal unanaesthetized rabbits, and of atropinizing four rabbits anaesthetized with chloralose-urethane. Control: mean value before atropine; atropine: mean value after atropine. Results during each period from each animal are based on four measurements of each cardiorespiratory variable, and one set of measurements of arterial blood composition. S.E. = standard error of the difference of means calculated from within-animal comparisons

	Unanaesthetized			Chloralose-urethane		
	Control	Atropine	±S.E.	Control	Atropine	±S.E.
Cardiac output (ml./min)	596	585	±24·8	526	480	±27·0
Arterial pressure (mm Hg)	110	102	±4·8	97	88	±3·8
R. atrial pressure (mm Hg)	−0·9	−1·6	±0·5	−1·5	−1·6	±0·3
Heart rate (beats/min)	277	309	±8·0	298	314	±5·0
Ventilation (l./min)	0·88	1·10	±0·11	0·46	0·57	±0·03
Respiration rate (breaths/min)	64	84	±7·0	35	41	±2·1
Arterial P_{O_2} (mm Hg)	97	101	±2·8	87	95	±3·7
Arterial P_{CO_2} (mm Hg)	37	34	±2·1	43	39	±3·0
Arterial pH	7·41	7·44	±0·03	7·37	7·35	±0·02

observed during anaesthesia whilst breathing spontaneously. In the spontaneously breathing 'de-efferented' animals (Table 2) the changes in arterial pressure and right atrial pressure during anaesthesia were again not significantly different from the control values before anaesthesia, but the cardiac output rose to 130 % of control ($P = 0·02$). When these animals were ventilated artificially the rise in right atrial pressure was 1·5 mm Hg, and the cardiac output was again reduced significantly from the value observed during spontaneous respiration under anaesthesia. The reduction in cardiac output in 'de-efferented' animals was greater with sodium pentobarbitone 23 % than with chloralose-urethane 12 %, but the difference was not statistically significant.

Although the total peripheral resistance before anaesthesia was lower in the 'de-efferented' animals than in the normal group (i.e. was 85 % of

normal), it was more markedly reduced in the 'de-efferented' animal during anaesthesia. The difference between the response of the normal and 'de-efferented' groups was approximately the same during spontaneous and artificial ventilation (Fig. 3). Using the pooled data from both anaesthetics during spontaneous and artificial ventilation the total peripheral resistance fell to 72 % of the value before anaesthesia in the 'de-efferented' animals, but only to 94 % of this value in the normal group, the difference being statistically significant ($P = 0{\cdot}01$).

DISCUSSION

The experiments demonstrate significant differences in circulatory response to chloralose-urethane and sodium pentobarbitone during the first hour of anaesthesia, but closely similar effects during the next 3 hr of anaesthesia. The greater concentration of drug present soon after induction in some organs before attainment of equilibrium distribution probably accounts for the initial differences in responses. The transient elevation of cardiac output after giving chloralose-urethane contrasts with the reduction in cardiac output and greater arterial hypotension after administration of sodium pentobarbitone. The stimulating effect of urethane on adrenal catecholamine secretion may account for the rise in cardiac output with the former anaesthetic (Spriggs, 1965), and the transient nature of the effect may be due to lack of this property with the chloralose, used in these experiments to maintain anaesthesia (Malmejac, Chardon & Naverre, 1950). The greater reduction in blood pressure and cardiac output during the early phase of pentobarbitone anaesthesia is probably related to the cardiotoxic and ganglion-blocking properties of the barbiturates (Daniel, Fulton, Hiddleston, Martin & Foulks, 1956; Price, 1960; Larrabee & Posternak, 1952, Exley, 1954). Compared with the results in the dog, the effects of sodium pentobarbitone and chloralose-urethane anaesthesia are similar with respect to the rise in heart rate, and absence of significant changes in cardiac output during the maintenance phase (Van Citters, Franklin & Rushmer, 1964; Bass & Buckley, 1966; Olmsted & Page, 1966). However, whilst in the dog there is usually some elevation in arterial pressure, in the rabbit the blood pressure tends to fall.

The 'local' (i.e. non-autonomic) effects on heart rate have been assessed from the changes observed in 'de-efferented' animals without functioning autonomic effectors. The common occurrence of cardiac arrest following administration of each anaesthetic at a normal rate suggests that these agents have a direct myocardial depressant effect in high concentrations. Absence in these animals of significant heart rate changes during the maintenance phase does not exclude the possibility of some depression of myocardial contractility, but the degree of depression is probably small.

A comparison of the heart rate changes in normal and 'de-efferented' animals allows assessment of the net autonomic chronotropic effects during the maintenance phase. Since the local chronotropic effects in the 'de-efferented' group are minimal, the changes in heart rate in normal animals are entirely the result of autonomic activity. As seen in Fig. 3, the net change in autonomic activity is greater with chloralose-urethane anaesthesia than with sodium pentobarbitone. More detailed analysis during chloralose-urethane anaesthesia indicates that with this anaesthetic the rise in heart rate is largely the result of reduction in vagal efferent activity, with little change in estimated cardiac sympatho-adrenal activity.

The local effects of the two anaesthetics on the systemic circulation estimated from the responses of the 'de-efferented' animals, consist mainly of peripheral vasodilatation, as suggested by the reduction to approximately 70% of control in the total peripheral resistance (Guyton, 1963). Such a direct peripheral vasodilator action is in agreement with the findings in isolated vascular beds and blood vessels (Gruber *et al.* 1952; Price, 1960). The reduction in arterial P_{O_2} of about 10 mm Hg probably does not contribute to an important degree to this vasodilatation (Korner, 1959; Ross, Fairchild, Weldy & Guyton, 1962).

A comparison of the differences in the response during anaesthesia in normal and 'de-efferented' animals shows the approximate magnitude of the autonomic effects in the normal animal as discussed in detail in an accompanying paper (Korner *et al.* 1968). The present results indicate that the reduction in total peripheral resistance during anaesthesia is considerably smaller in the normal than in the 'de-efferented' rabbit (Fig. 3). Assuming that as with hypoxia (cf. Korner *et al.* 1968) the local effects of anaesthesia are the same in both preparations, the difference in the change in total peripheral resistance reflects an increase in peripheral constrictor activity in the normal animal.

Thus during the maintenance phase of chloralose-urethane anaesthesia there is some reduction in resting efferent vagal activity, little effect on cardiac sympatho-adrenal activity and an increase in total systemic sympatho-adrenal constrictor activity. With sodium pentobarbitone the net cardiac effects and change in total systemic sympatho-adrenal constrictor activity was similar, but the cardiac effects have not been subdivided into vagal and sympatho-adrenal components. These changes in autonomic activity could result from the effect of anaesthesia on the central nervous system, but it is probable that part of the effect is the result of reflex activity (e.g. through the arterial baroreceptors), which minimizes the circulatory disturbance produced by the direct local effects of anaesthesia on the heart and blood vessels.

The present findings indicate that when the circulation becomes stable some time after induction of anaesthesia there is little difference between either the local or autonomic effects of sodium pentobarbitone and chloralose-urethane. This finding is surprising in view of the marked differences in reputation of these anaesthetics regarding their suitability for the study of cardiovascular reflexes (Heymans, 1964). In the present experiments blood loss and tissue trauma were avoided almost completely, and this probably contributed to the small difference in effects. It seems possible that if these factors were present their depressant effects on the circulation (Chalmers *et al.* 1967*a*) could enhance the difference in local depressant effects of these drugs, e.g. the slight difference in depressant action of sodium pentobarbitone and chloralose-urethane might become exaggerated. Local factors could thus become of primary importance in modifying the circulatory responsiveness to a test stimulus during experimental cardiovascular studies with different anaesthetics.

This study was supported by grants from the Life Insurance Medical Research Fund of Australia and New Zealand, and by the National Heart Foundation of Australia as well as by the Australian Research Grants Committee. We are grateful to Miss J. Oliver, Mrs R. Mather and Mrs S. Pajor for their assistance with the experiments.

REFERENCES

BALIS, G. U. & MONROE, R. R. (1964). The pharmacology of chloralose. *Psychopharmacologica* **6**, 1–30.

BASS, B. G. & BUCKLEY, N. M. (1966). Chloralose anaesthesia in the dog–a study of drug action and analytical methodology. *Am. J. Physiol.* **210**, 854–862.

BROOKS, C. McC. & ECCLES, J. C. (1947). A study of the effects of anaesthesia and asphyxia on the monosynaptic pathway through the spinal cord. *J. Neurophysiol.* **10**, 349–360.

CHALMERS, J. P., ISBISTER, J. P., KORNER, P. I. & MOK, H. Y. I. (1965). The role of the sympathetic nervous system in the circulatory response of the rabbit to arterial hypoxia. *J. Physiol.* **181**, 175–191.

CHALMERS, J. P., KORNER, P. I. & WHITE, S. W. (1967*a*). The effects of haemorrhage in the unanaesthetized rabbit. *J. Physiol.* **189**, 367–391.

CHALMERS, J. P., KORNER, P. I. & WHITE, S. W. (1967*b*). Local and reflex factors affecting the distribution of the peripheral blood flow during arterial hypoxia in the rabbit. *J. Physiol.* **192**, 537–548.

DANIEL, E. E., FULTON, J. B., HIDDLESTON, M., MARTIN, W. & FOULKS, J. G. (1956). An analysis of the mechanism of barbiturate induced cardiovascular depression and its antagonism by sympathomimetic amines. *Archs int. Pharmacodyn. Thér.* **58**, 457–472.

DUNDEE, J. W. (1967). Clinical pharmacology of general anaesthetics. *Clin. Pharmac. Thér.* **8**, 91–123.

EXLEY, K. A. (1954). Depression of autonomic ganglia by barbiturates. *Br. J. Pharmac. Chemother.* **9**, 170–181.

GOODMAN, L. S. & GILMAN, A. (1958). *The Pharmacological Basis of Therapeutics*, p. 551. New York: Macmillan.

GREISHEIMER, E. M. (1965). The circulatory effects of anaesthetics. In *Handbook of Physiology*, Section 2: Circulation. Ed. HAMILTON, W. F. & DOW, P., vol. III, pp. 2477–2510. Washington: American Physiological Society.

GRUBER, C. M., GRUBER, C. M. JR. & LEE, K. S. (1952). A study of the thiobarbiturates on the cardiovascular system. *Archs int. Pharmacodynam. Thér.* **41**, 461–488.

GUYTON, A. C. (1963). *Circulatory Physiology: Cardiac Output and its Regulation.* Philadelphia: Saunders.

HEYMANS, C. (1964). Action of drugs on blood pressure homeostasis. *Acta anaesth. scand.* suppl. **15**, 60–65.

KORNER, P. I. (1959). Circulatory adaptations in hypoxia. *Physiol. Rev.* **39**, 687–730.

KORNER, P. I. (1965). The effect of section of the carotid sinus and aortic nerves on the cardiac output of the rabbit. *J. Physiol.* **180**, 266–278.

KORNER, P. I., LANGSFORD, G., STARR, D., UTHER, J. B., WARD, W. & WHITE, S. W. (1968). The effects of chloralose-urethane and sodium pentobarbitone anaesthesia on the local and autonomic components of the circulatory response to arterial hypoxia. *J. Physiol.* **199**, 283–302.

KORNER, P. I. & WHITE, S. W. (1966). Circulatory control in hypoxia by the sympathetic nerves and adrenal medulla. *J. Physiol.* **184**, 272–290.

KRUGER, L. & ALBE-FESSARD, D. (1960). Distribution of responses to somatic afferent stimuli in the diencephalon of the cat under chloralose anaesthesia. *Expl Neurol.* **2**, 442–467.

LANDGREN, S., LILJESTRAND, G. & ZOTTERMAN, Y. (1953). Wirkung von Alkohol, Aceton, Äther u. Chloroform auf die Chemozeptoren des Glomus Caroticum. *Arch. exp. Path. Pharmak.* **219**, 185–191.

LARRABEE, M. G. & POSTERNAK, J. M. (1952). Selective action of anaesthetics on synapses and axons in mammalian sympathetic ganglia. *J. Neurophysiol.* **15**, 91–114.

MALMEJAC, J., CHARDON, G. & NEVERRE, G. (1950). A propos de l'action de chloralose sur l'adrenaline-secretion. *C. r. Séanc. Soc. Biol.* **144**, 1034–1035.

MILLAR, R. A. & BISCOE, T. J. (1965). Preganglionic sympathetic activity and the effects of anaesthetics. *Br. J. Anaesth.* **37**, 804–832.

OLMSTED, F. & PAGE, I. H. (1966). Haemodynamic changes in dogs caused by sodium pentobarbital anaesthesia. *Am. J. Physiol.* **210**, 817–820.

PEISS, C. N. & MANNING, J. W. (1964). Effects of sodium pentobarbital on electrical and reflex activation of the cardiovascular system. *Circulation Res.* **14**, 228–235.

PRICE, H. L. (1960). General anaesthesia and circulatory homeostasis. *Physiol. Rev.* **40**, 187–217.

REDGATE, E. S. & GELLHORN, E. (1956). The tonic effects of the posterior hypothalamus on blood pressure and pulse rate as disclosed by the action of intrahypothalamically injected drugs. *Archs int. Pharmacodyn. Thér.* **55**, 193–198.

REDGATE, E. S. & GELLHORN, E. (1958). Respiratory activity and the hypothalamus. *Am. J. Physiol.* **193**, 189–194.

ROSS, J. M., FAIRCHILD, H. M., WELDY, J. & GUYTON, A. C. (1962). Autoregulation of blood flow by oxygen lack. *Am. J. Physiol.* **202**, 21–24.

SPRIGGS, T. L. B. (1965). The effects of anaesthesia induced by urethane or phenobarbitone upon the distribution of peripheral catecholamines in the rat. *Br. J. Pharmac. Chemother.* **24**, 752–758.

VAN CITTERS, R. L., FRANKLIN, D. L. & RUSHMER, R. F. (1964). Left ventricular dynamics in dogs during anaesthesia with alpha-chloralose and sodium pentobarbital. *Am. J. Cardiol.* **13**, 349–354.

VINCENT, S. & THOMPSON, J. H. (1928). The pharmacodynamical action of chloralose. *J. Physiol.* **65**, 449–455.

WHITE, S. W. (1966). Adrenalectomy in the rabbit. *Aust. J. exp. Biol. med. Sci.* **44**, 447–450.

WHITTERIDGE, D. (1958). Effects of anaesthetics on mechanical receptors. *Br. med. Bull.* **14**, 5–7.