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Anaesthetic, cardiovascular and respiratory effects of a new steroidal agent CT 1341: a comparison with other intravenous anaesthetic drugs in the unrestrained cat

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Summary

1. The anaesthetic, cardiovascular, respiratory and adverse effects produced by the intravenous injection of CT 1341, thiopentone, methohexitone, pentobarbitone, propanidid and ketamine have been compared in unrestrained cats prepared with chronically implanted venous and arterial cannulae. Aortic blood pressure and heart rates were monitored before, during and after loss of consciousness.

2. CT 1341 produced rapid induction of anaesthesia followed by moderately rapid recovery, was active over a wide range of doses and caused minimal respiratory depression and few adverse effects. It caused an initial short-lasting tachycardia and fall in aortic blood pressure succeeded by a secondary depressor response.

3. The safety margin was narrower with the barbiturate drugs than with CT 1341, and large doses induced apnoea and respiratory depression. Small doses of methohexitone elicited excitatory effects and large doses caused severe respiratory and circulatory depression, and recovery from anaesthesia was protracted.

4. Propanidid induced short-lasting light anaesthesia. The safety margin was narrowest with this drug and induction was associated with adverse circulatory, respiratory and other effects.

5. Ketamine was active over a wide range of doses but exhibited qualitatively different properties from the other anaesthetics. Induction was slower after small doses and these produced circulatory stimulation, catatonia and bizarre behavioural effects. Large doses caused respiratory and circulatory depression and recovery was protracted.

6. It is concluded that CT 1341 has a wider therapeutic latitude, produces less respiratory depression and has other advantages over the currently used intravenous anaesthetics.

Introduction

The pharmacological properties of CT 1341 (Althesin), a new steroidal anaesthetic which contains as its active components 3α-hydroxy-5α-pregnane-11,20-dione (alphaxalone) and 21-acetoxy-3α-hydroxy-5α-pregnane-11,20-dione (alphadolone acetate), have recently been described (Child, Currie, Davis, Dodds, Pearce

& Twissell, 1971). It is a potent intravenous anaesthetic in animals, which produces rapid induction of anaesthesia without vascular irritation. The initial trials of CT 1341 in man (Campbell, Forrester, Miller, Hutton, Kennedy, Lawrie, Lorimer & McCall, 1971; Savege, Foley, Coultas, Walton, Strunin, Simpson & Scott, 1971; Clarke, Montgomery, Dundee & Bovill, 1971; Swerdlow, Chakraborty & Zahangir, 1971) appear to substantiate the findings in animals.

As cardiovascular disturbances such as changes in heart rate and blood pressure often occur during the induction of anaesthesia, we have measured these functions before, during and after loss of consciousness in intact unrestrained cats. The results with CT 1341 were compared with those obtained with thiopentone sodium, methohexitone sodium, pentobarbitone sodium, propanidid and ketamine hydrochloride.

Methods

Thirteen adult cats of either sex (1·8–3·9 kg) were used after an overnight fast. Polyvinyl cannulae had been implanted chronically in their right external jugular vein and descending aorta at least 4 days before the first experiment (Child *et al.*, 1971).

Blood pressure (1 mmHg≡1·33 mbar) and heart rate (derived from the blood pressure pulse using a Devices instantaneous ratemeter) were recorded on a Devices M8 recorder and on magnetic tape with an Ampex SP300 recorder, and displayed on an oscilloscope. The instruments were in a room separate from the cat. Recordings of blood pressure and heart rate were made for 15–30 min before drug injection with the cat in a quiet, resting condition. The cats were unaware of the start of the intravenous drug injection. Sodium chloride (0·9% w/v 1·5 ml) given routinely a few minutes before the anaesthetic drug, did not elicit any changes in behaviour, blood pressure or heart rate. After the injection of an anaesthetic drug the duration of loss of the corneal, flexor withdrawal and righting reflexes was measured. The character, rate and depth of the respiration, and any behavioural or adverse effects, were subjectively assessed until the cat was fully recovered. Artificial respiration was required on a few occasions.

The following drugs were tested: Thiopentone sodium ('Intraval', May & Baker), 2·5% w/v in water for injection (B.P.); methohexitone sodium ('Brietal', Lilly), 1% w/v in water for injection (B.P.); pentobarbitone sodium ('Sagatal', May & Baker) diluted to 3% w/v with 0·9% w/v sodium chloride; propanidid ('Epontol', Bayer), 5% w/v as dispensed; ketamine hydrochloride ('Ketalar', Parke-Davis), 1% w/v as dispensed; CT 1341 ('Althesin', Glaxo), 0·9% w/v 3α-hydroxy-5α-pregnane-11,20-dione, 0·3% w/v 21-acetoxy-3α-hydroxy-5α-pregnane-11,20-dione, 20% w/v polyoxyethylated castor oil (Cremophor EL), 0·25% w/v sodium chloride AR in water for injection B.P. (12 mg steroid/ml). The solvent mixture not containing the steroids ('vehicle', 20% w/v Cremophor EL, 0·25% w/v sodium chloride AR, water for injection B.P. to 100%) was also tested.

The drugs were injected intravenously through the implanted polyvinyl cannulae at a rate of 0·05 (ml/kg)/s and washed in with 1·5 ml 0·9% sodium chloride at the same rate. The quantities of each anaesthetic used are described in the **Results** section. The lowest dose of each anaesthetic drug (with the exception of pentobarbitone) was approximately the minimum amount required to produce loss of

the righting reflex in the cat. This dose was doubled after 2 or 3 days, and then doubled again every 2nd or 3rd day until the maximum dose was given. This 'maximum' dose was determined for each anaesthetic from preliminary experiments on other cats; double this dose was invariably lethal. Each cat received the anaesthetic drugs in a different order to minimize any interaction effects (e.g. induction of metabolizing enzymes in the liver). Some cats received all anaesthetic drugs, others only some of them.

Results

Anaesthetic activities of the intravenous induction agents

CT 1341, thiopentone, methohexitone, pentobarbitone and propanidid induced anaesthesia (i.e. loss of consciousness) in the cat 10–25 s from the start of the injection. Ketamine, in doses of 4, 8 and 16 mg/kg often elicited a startle response before loss of consciousness which occurred only after 25–50 seconds. The 30 mg/kg dose of pentobarbitone sodium produced maximal anaesthesia only 1–2 min after induction.

The depth and duration of the anaesthetic effects observed after a range of doses of the different drugs were assessed by the time required to recover the corneal, flexor withdrawal and righting reflexes (Table 1 and Fig. 2). After the minimum anaesthetic dose of CT 1341 (1·2 mg/kg) the corneal and flexor withdrawal reflexes were retained and the cats licked their lips, twitched their ears and began to make stirring movements within a few moments. Some stood up abruptly, others performed either a series of 'running movements' while lying on their sides or extended their fore-limbs and arched their necks before making attempts at standing. Then they walked with a high-stepping ataxic gait which quickly improved. The effects of larger doses are listed in Table 1 and Figure 2. The pupils

TABLE 1. *Recovery times of the corneal, flexor withdrawal and righting reflexes after the injection of anaesthetic drugs*

Drug	Dose mg/kg	Time to recovery of reflex (min after drug injection)		
		Corneal reflex	Flexor withdrawal reflex	Righting reflex
CT 1341	1·2	0 (7)	0 (7)	7± 1 (5)
	2·4	0 (7)	0 (7)	17± 3 (7)
	4·8	0·7± 0·7 (7)	4 ± 2 (7)	33± 3 (7)
	9·6	10 ± 3 (7)	20 ± 4 (7)	75± 21 (6)
	19·2	40 ±16 (7)	61 ±20 (6)	136± 21 (5)
Thiopentone	3	0 (6)	0 (6)	5± 2 (5)
	6	0 (6)	0 (6)	9± 2 (6)
	12	1 ± 1 (5)	2 ± 1 (5)	27± 8 (4)
	24	12 ± 3 (6)	17 ± 2 (6)	63± 6 (3)
Methohexitone	3	0 (5)	0 (5)	5± 1 (5)
	6	0 (5)	0 (5)	13± 2 (5)
	12	0·6± 0·6 (5)	3 ± 2 (5)	40± 5 (5)
	24	26 ± 4 (4)	32 ± 4 (4)	240± 52 (4)
Propanidid	8	0 (7)	0 (7)	4± 1 (7)
	16	0 (7)	0 (7)	12± 3 (7)
	32	0·1± 0·1 (7)	0·6± 0·4 (7)	12± 2 (7)
Ketamine	4	0 (5)	0 (5)	16± 5 (5)
	8	0 (5)	0 (5)	29± 8 (5)
	16	0 (5)	0 (5)	71± 12 (5)
	32	4 ± 4 (5)	16 ± 5 (5)	239± 36 (4)
	64	15 ±12 (3)	29 ± 9 (3)	All>300 (4)
Pentobarbitone	30	25 ± 8 (4)	31 ±11 (4)	270± 52 (3)

Values are means±S.E. Figure in parentheses: number of observations.

were moderately constricted and the nictitating membranes slightly relaxed during CT 1341 anaesthesia.

During the recovery from anaesthesia, irrespective of the dose or drug, a fine, generalized muscle tremor occurred, extending over the trunk and limbs, sometimes accompanied by a moderate degree of piloerection.

Cardiovascular effects

The control values of the mean aortic blood pressure and the heart rate in the 13 conscious resting cats were consistent on 130 occasions over several months (115 ± 1 (S.E.)/80 ± 1 mmHg (systolic/diastolic) and 92 ± 1 mmHg (mean) with a heart rate of 160 ± 3 beats/min). The cardiovascular and respiratory effects associated with induction of anaesthesia were usually fully developed in the first few min after drug injection.

CT 1341. As can be seen in Fig. 1, the immediate response to the injection of CT 1341 was similar after each dose level of the drug and consisted of a transient tachycardia that usually preceded and persisted during a short-lasting fall in mean aortic blood pressure. These changes occurred during and just after loss of consciousness. They were followed by a secondary depressor response approximately 2·5–5 min after the start of the injection. After the two highest doses the

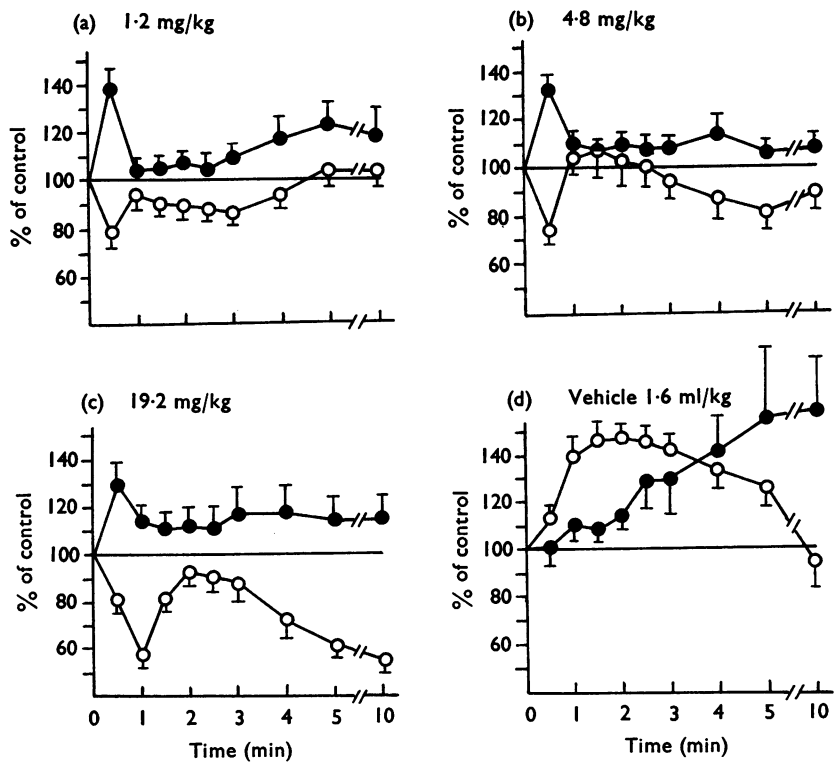

FIG. 1. The effect of intravenous injections of CT 1341 or the vehicle alone on the mean aortic blood pressure (○——○) and heart rate (●——●) in cats. Blood pressure and heart rate are expressed as percentages of the control values before the start of the injection at time 0. Values are group means ($n=7$). Vertical bars: S.E. of the mean (only one bar shown for clarity). Only 4 of the cats received the vehicle alone.

secondary hypotensive response was greater and more prolonged, recovery occurring gradually over about 30 and 60 min respectively.

In the conscious cat, injections of the vehicle alone (1·6 ml/kg, the volume used in the administration of CT 1341 19·2 mg/kg) produced a statistically significant ($P<0·05$) rise in the mean aortic blood pressure during the first 5 min after the injection (Fig. 1). The heart rate increased as blood pressure returned towards normal. This stimulant effect may be related to perception of the injected material by the animal. The behaviour of conscious cats suggested that large volumes may sometimes be associated with irritant effects; the latter manifested by scratching, flushing of the ears and oedema of the paws, ears and facial skin.

Thiopentone. During induction of anaesthesia with thiopentone, only small, variable blood pressure changes occurred. Emergence was accompanied by statistically significant rises in the blood pressure from 88 ± 3 to 98 ± 3 and 104 ± 4 mmHg, 5 and 10 min after the 6 mg/kg dose. Heart rate was slightly increased after 3, 6 and 12 mg/kg but only to a significant extent 0·5 min after 24 mg/kg. The mean aortic blood pressure fell slightly during the first minute after the injection of 24 mg/kg. This was followed by a secondary depressor response 10 min after the injection, the blood pressure falling significantly to 77 ± 6 mmHg (79% of control).

Methohexitone. The induction of anaesthesia with low and intermediate doses of methohexitone was associated with tachycardia. One minute after the injection of 3, 6 or 12 mg/kg the heart rate had increased by 60, 77 and 82 beats/min respectively above the resting control values, and after 12 mg/kg the heart rate was still significantly elevated 10 min after the injection (197 ± 6 beats/min, 118% of control). Blood pressure usually increased 1 to 5 min after injection of these doses. The group mean aortic blood pressure was only significantly elevated 2 and 2·5 min after 12 mg/kg methohexitone. The individual variations were large: 1·5 min after an injection of 6 mg/kg one cat's blood pressure had increased from 109/75 mmHg (control) to 250/158 mmHg while in another cat it had fallen from 110/80 mmHg (control) to 67/48 mmHg.

Methohexitone 24 mg/kg induced apnoea and severe respiratory depression (see below) accompanied by a profound fall in blood pressure and a significant increase in heart rate. The mean aortic blood pressure had fallen to 39 ± 16 mmHg (41% of control) 1·5 min after the injection and artificial respiration was then instituted for several min until adequate spontaneous respiration returned. Ten min after injection, when the cats were again breathing spontaneously, the mean aortic blood pressure was 52 ± 4 mmHg (54% of control). One cat died a few min after the intravenous injection of this dose despite attempts at resuscitation.

Propanidid. This drug caused only a slight tachycardia which was preceded in some cats by a slowing and irregularity of the pulse 10–20 s after the start of the injection. The blood pressure fell during the loss of consciousness and 0·5 min after 32 mg/kg it was significantly lower than the control value. This initial depressor response was followed by a pressor response. The mean blood pressure was increased to 125 and 135% of control from 1·5 to 2·5 min after 8 and 16 mg/kg and to 140% of control from 2 to 10 min after 32 mg/kg. In some cats the blood pressure increased while the heart rate fell slightly; e.g. in one cat the blood pressure increased from 112/76 mmHg (control) to 185/128 mmHg 2 min after

the injection, at which time heart rate had fallen from 129 beats/min (control) to 122 beats/min.

Ketamine. The induction of anaesthesia with ketamine in doses of 4, 8 and 16 mg/kg was associated with a rise in blood pressure to 125–135% of the control values within 1·5 min of the start of injection. This effect occurred after each of the doses used but with the small number of animals in each group was only statistically significant 1 and 1·5 min after the 4 mg/kg dose. The heart rate increased also but not to a significant extent. After 32 mg/kg the mean aortic blood pressure was usually first depressed and then increased, but there were wide individual variations in the response to the drug. Thus in one cat (control blood pressure 90/52 mmHg, heart rate 145 beats/min) the blood pressure fell to 54/25 mmHg, and the heart rate fell to 119 beats/min, whereas in another cat (control 117/79 mmHg, 120 beats/min) they rose to 186/128 mmHg and 195 beats/min, 1·5 min after injection. The maximum dose of ketamine (64 mg/kg) induced profound respiratory and circulatory depression. Two minutes after the start of the injection the mean aortic blood pressure had fallen significantly to 47 ± 6 mmHg (57% of control) when artificial respiration was instituted. One cat died after this dose despite attempts at resuscitation.

Pentobarbitone. Intravenous injection of pentobarbitone (30 mg/kg) produced hypotension and tachycardia. The mean aortic blood pressure fell significantly to 47 ± 9 mmHg (51% of control) 1 min after the start of the injection and was still significantly depressed at 10 min (64 ± 5 mmHg, 70% of control). The heart rate increased significantly during induction of anaesthesia from a control value of 160 ± 18 beats/min to 243 ± 14 beats/min at 0·5 min, then gradually returned towards the control rate.

Respiratory effects

The respiratory effects of the anaesthetic drugs used are shown in Figure 2b.

CT 1341 produced the least respiratory depression. One to 5 min after 2·4 and 4·8 mg/kg there were small increases in the respiratory rate. Regular, thoraco-abdominal respiration was observed in the cats after CT 1341 9·6 mg/kg. All the cats continued to breathe spontaneously after the maximum dose of CT 1341 (19·2 mg/kg), usually with a pronounced diaphragmatic movement. In 3 out of 7 cats the respiration became shallow, irregular or slow for a few min after induction.

Apnoea and respiratory depression occurred after high doses of the barbiturate drugs. The injection of thiopentone (12 mg/kg) depressed the respiration in 5 out of 6 cats (in 2 the rate was reduced, in 2 the respiration became irregular and depressed and in another apnoea occurred for 45 s after the injection). The maximum dose of thiopentone (24 mg/kg) induced apnoea for 30–90 s in every cat and the respiration was depressed for several min. One of these cats was given intermittent positive pressure ventilation during a circulatory collapse. After methohexitone 12 mg/kg apnoea occurred in 3 cats for 30–45 s after the end of the injection and this was followed by a period of gasping, irregular, depressed respiration. In one cat respiration was arrested after every dose. The maximum dose (24 mg/kg) produced apnoea and severe respiratory depression in every animal and 3 cats required artificial respiration for a few min. Pentobarbitone 30 mg/kg induced apnoea in 2 cats and respiration was depressed for several minutes.

Propanidid administration was associated with a brief period of hyperventilation. This effect occurred in 3 of the 7 cats approximately 0·5–1 min after the start of injection of the 8 mg/kg dose and in 3 cats it was very marked after the 16 and 32 mg/kg doses. After the maximum dose (32 mg/kg) hyperventilation occurred immediately in one cat succeeded by depressed respiration for 1–2 min, and in another animal the respiratory rate fell briefly to 5–10 breaths/minute. In two other cats propanidid 16 and 32 mg/kg induced bizarre, violent respiratory efforts 0·5–1 min after injection; 'retching' in one cat and 'pumping' and 'gasping' in the other. A tachypnoea developed 5–12 min after injection in two cats of 16 and 32 mg/kg.

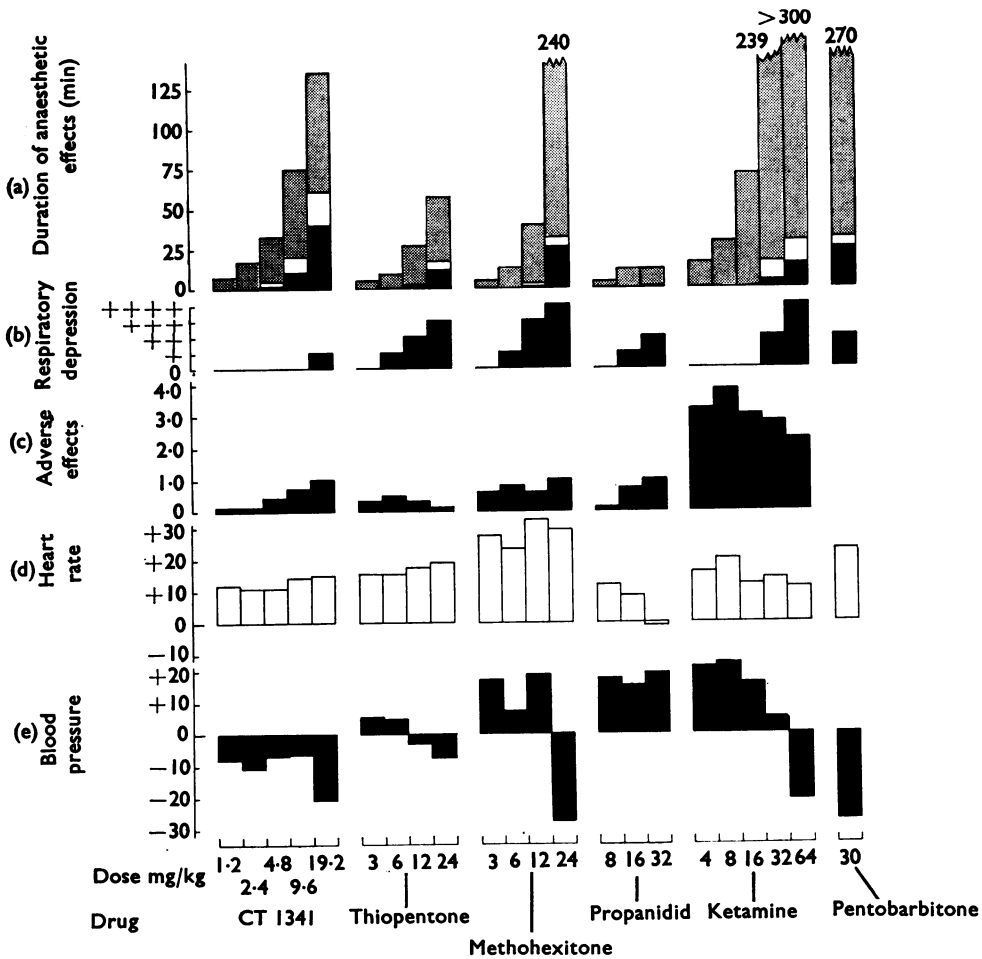

FIG. 2. Comparison of the anaesthetic, cardiovascular, respiratory and adverse effects of various intravenous anaesthetics in the cat. All histograms represent mean values. (a) Duration of the anaesthetic effects: time (min) elapsed between the drug injection and the recovery of the corneal (black columns), flexor withdrawal (white columns) and righting reflex (hatched columns). (b) Respiratory depressant effects in arbitrary units: 0=no effect, +=minimal, ++=moderate, +++=severe and ++++=very severe (artificial respiration required). (c) Adverse effects: calculated for each dose level of each anaesthetic drug by dividing the total number of all adverse effects observed (see Table 2) by the number of cats tested. (d) Heart rate and (e) blood pressure: percentage changes from control values which occurred during the first 5 min after the drug injection.

Ketamine (32 mg/kg) always reduced the respiratory rate and in one cat the depression was severe and prolonged. It developed gradually over 5 min and in the most severely affected animal the respiratory rate fell to 2–4/min 10–15 min after the injection. After 64 mg/kg apnoea occurred 1–2 min after the injection in each cat. This was followed by very slow depressed respiration in two cats and another required prolonged artificial respiration. One cat suffered respiratory and cardiac arrest after the maximum dose of ketamine and attempts at resuscitation were ineffective.

Adverse effects

A list of adverse effects that occurred in cats after the various drugs is given in Table 2. No attempt has been made to grade their severity or interpret their relative importance. In Figure 2 histograms were plotted for each dose level of each drug by dividing the total number of adverse effects observed by the total number of cats tested.

CT 1341 produced only a few adverse effects. The flushing of the ear skin and the oedema of the paws and face that occurred in the cat after 9·6 and 19·2 mg/kg were probably caused by the vehicle for CT 1341, as subsequent experiments showed that the equivalent volumes of vehicle elicited the same effects. The exceptionally prolonged recovery of one cat after CT 1341 19·2 mg/kg led to hypostatic pneumonia and it died 32 h after receiving the drug. Thiopentone also caused few adverse effects except intense emergence excitement in some animals.

TABLE 2. *Adverse effects following the intravenous injection of anaesthetic drugs*

Drug	Dose mg/kg	No. of cats	Adverse effects
CT 1341	1·2	7	Def (1)
	2·4	7	Def (1)
	4·8	7	Def (1) Irr (1) Flu (1)
	9·6	7	Def (1) Flu (1) Oed (1) Pro (1) Exc (1)
	19·2	7	Def (2) Flu (2) Oed (2) Pro; died at +32 h (1)
Thiopentone sodium	3	6	Def (1) Exc (1)
	6	6	Def (1) Exc (1) Flu (1)
	12	6	Exc (1) Flu (1)
	24	6	Flu (1)
Methohexitone sodium	3	5	Con* (3)
	6	5	Con* (3) Exc (1)
	12	5	Con* (2) Con (1)
	24	5	Con (1) Pro (2) Ano (1) Died (1)
Propanidid	8	7	Sal (1)
	16	7	Def (1) Sal (1) Uri (1) Irr (1) 'Unwell' (1)
	32	7	Def (1) Uri+Def (2) Sal (1) Flu (1) Pup (1) Vom (1)
Ketamine hydrochloride	4	5	Pup (4) Sal (2) Nys (1) Hyp (1) Cat (2) Con (2) Biz (3)
	8	5	Pup (4) Sal (2) Nys (1) Hyp (2) Cat (3) Con (4) Biz (3)
	16	5	Pup (4) Sal (2) Nys (1) Hyp (1) Cat (1) Con (3) Biz (3)
	32	5	Pup (4) Sal (4) Nys (2) Hyp (2) Flu (1) Ano (1)
	64	4	Pup (3) Pro (3) Ano (2) Died (1)

Glossary of abbreviations: Def=Defaecation; Irr=Irritant effects; Flu=Flushing of ear skin; Oed=Oedema of paws, facial skin; Exc=Emergence excitement; Pro=Protracted recovery; Con=Convulsive twitching; Con*=Violent convulsive movements; Ano=Anorexia; Sal=Salivation; Uri=Urination; Nys=Nystagmus; Hyp=Hypertonus; Cat=Catatonia; Vom=Vomiting; Biz=Bizarre behavioural effects; Pup=Pupillary dilatation. The figures in parentheses are the number of cats in which the effect was observed.

Convulsive twitching or jerking movements, sometimes of a violent character, were a feature during anaesthesia produced by methohexitone. Recovery from the maximum dose (24 mg/kg) was very protracted and one animal became anorexic. After propanidid (16 and 32 mg/kg) pupillary dilatation, salivation, urination and defaecation were observed on a number of occasions a few moments before or just after recovery of the righting reflex.

In cats anaesthetized with ketamine movements of the mouth, tongue and limbs were commonly observed while the cats were still lying down, and sometimes there was marked hypertonus of the muscles or convulsive twitching. Pupillary dilatation and salivation occurred very frequently. Catatonia and bizarre patterns of behaviour were consistently observed during recovery from 4 and 8 mg/kg. The central nervous depressant properties of the drug were predominant after the larger doses (32 and 64 mg/kg) but recovery was extremely protracted and 2 cats were anorexic for a few days afterwards. This was an uncommon finding; the cats were fasted overnight before the experiment and almost invariably ate their food voraciously when it was presented to them after recovery irrespective of the dose or drug they had received.

Discussion

In the present experiments the arterial blood pressure and the heart rate were continuously monitored in untreated, resting cats and the drugs were injected without disturbing the animal. There have been few studies in which the effects of anaesthetic drugs were monitored in conscious intact animals that had completely recovered from preparative treatments. These include studies of 5-ethyl-6-phenyl-*m*-thiazine-2,4-dione and thiopentone (Cotten & Bay, 1956); α-chloralose and pentobarbitone (Van Citters, Franklin & Rushmer, 1964); pentobarbitone (Olmsted & Page, 1966) and thiamylal and pentobarbitone (Goldberg, Linde, Gaal, Momma, Takahashi & Sarna, 1968).

The testing of intravenous anaesthetic drugs in chloralose or pentobarbitone-anaesthetized animals is unsatisfactory as the injection of a second drug which depresses the central nervous system may induce severe respiratory and circulatory depression in doses much smaller than those required to induce anaesthesia in a conscious animal. Lerman & Paton (1960) described such an interaction when hydroxydione was injected into chloralose-anaesthetized cats, Payne & Wright (1962) reported that the eugenol derivative G 29505 and chloralose apparently enhanced each other's effects in cats and Chen, Ensor, Russell & Bohner (1959) commented on the great sensitivity of the respiratory centre of the cat to the combined depressant action of phenobarbitone and phencyclidine. McCarthy, Chen, Kaump & Ensor (1965) reported similar effects with ketamine in dogs anaesthetized with pentobarbitone or chloralose. The 'mutual potentiation' between hydroxydione and chloralose in cats was confirmed by Davis (unpublished observations), who further observed potentiation between the steroid anaesthetic 3α-hydroxy-5β-pregnane-11,20-dione 3-disodium phosphate (Atkinson, Davis, Pratt, Sharpe & Tomich, 1965) and chloralose. More recently we have observed a similar potentiation of the depressant actions of CT 1341 in cats anaesthetized with chloralose, pentobarbitone or inhalational anaesthetics.

Most complete haemodynamic studies in intact unanaesthetized animals have been performed in dogs (e.g. Gregg, Khouri & Rayford, 1965; Vatner, Franklin,

Van Citters & Braunwauld, 1970 ; Bache, McHale, Curry, Alexander & Greenfield, 1970). However, cats were used in these experiments because the dog is exceptional in exhibiting an anaphylactoid reaction to the polymeric constituent of the vehicle used in the formulation of both propanidid (Wirth & Hoffmeister, 1965) and CT 1341 (Child *et al.*, 1971). Some haemodynamic studies have been undertaken in the dog with propanidid (Conway, Ellis & King, 1968) but this species would seem an inappropriate choice for a comparison of the circulatory effects of intravenous anaesthetic drugs as the response to both propanidid and CT 1341 are masked by the circulatory depression that accompanies the injection of very small amounts of Cremophor EL.

The results presented here show that induction of anaesthesia in cats with CT 1341 is accompanied by tachycardia and a fall in arterial blood pressure. The net increase in heart rate in the first 5 min after intravenous injection of CT 1341 was similar to that observed after thiopentone and ketamine (Fig. 2) ; propanidid produced a lesser and methohexitone a greater increase in heart rate during this period. The net changes in mean aortic blood pressure observed after CT 1341 and the other anaesthetic drugs were widely different in both direction and magnitude (Fig. 2). CT 1341 was solely depressor, whereas thiopentone, methohexitone and ketamine exerted varying pressor effects on arterial blood pressure that changed to depression on increasing the dose ; propanidid was solely pressor. CT 1341 in a dose of 9·6 mg/kg exerted a similar net depression on arterial blood pressure 0–5 min after the injection of the drug to that produced by a comparable anaesthetic dose of thiopentone (24 mg/kg). This dose of CT 1341 produced less change in arterial blood pressure than that occasioned by comparable doses of methohexitone or ketamine. Propanidid failed to provide comparable conditions of anaesthesia but its pressor effects were marked.

The circulatory effects of methohexitone and propanidid have been well defined in human anaesthesia, both drugs exerting a hypotensive effect (Dundee & Clarke, 1964 ; Wynands & Fox, 1966 ; Johnstone & Barron, 1968). In intact animals their effects are less well understood and statements to the contrary by Conway & Ellis (1970) do not take sufficient account of the relevance of the species used and the methods employed in investigation. The pressor effects observed in cats after small doses of ketamine are similar to those obtained in intact unanaesthetized dogs (McCarthy *et al.*, 1965) and unpremedicated human volunteers (Corssen & Domino, 1966). Although no exact comparison is possible, reports suggest that hydroxydione exerted similar effects to CT 1341 on the arterial blood pressure of the cat. In cats partially recovered from ether anaesthesia the slow intravenous injection of a 5% solution of hydroxydione in a dose of 100 mg/kg caused a fall in arterial blood pressure that usually returned to normal within 10 min after completion of the injection (P'an, Gardocki, Hutcheon, Rudel, Kodet & Laubach, 1955).

The therapeutic index of these intravenous anaesthetics in the cat can be derived from the number of doubling doses used. The margin of safety with propanidid was small (3 doses) compared with the barbiturates (4 doses), and greatest with CT 1341 and ketamine (5 doses). The latter two drugs differ in their anaesthetic properties: CT 1341 is similar to the barbiturates, whereas ketamine resembles phencyclidine (Chen *et al.*, 1959) to which it is structurally related. The large number of ' adverse effects ' described here after ketamine exemplify the qualitatively different properties of the drug, which has been described as a ' dissociative '

anaesthetic (Corssen & Domino, 1966) producing a cataleptic state rather than true hypnosis (McCarthy *et al.*, 1965).

Although in general agreement with the animal results the clinical studies with CT 1341 have revealed two actions of the drug in man which were not observed in cats; a consistent, marked dilatation of the pupils following induction, and the occurrence of involuntary muscle movements in some patients. No movements or other excitatory phenomena were observed in cats after CT 1341 although convulsive activity had been seen in cats given methohexitone and ketamine.

These studies in cats suggest that CT 1341 may afford a wider therapeutic latitude, less respiratory depressant action and other advantages when compared with thiopentone or the other drugs more recently introduced into clinical anaesthesia.

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