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SOME EFFECTS OF HEXAFLUOROBENZENE IN CATS

BY

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Hexafluorobenzene is one of the fluorinated compounds screened for possible use in anaesthesia by Burns, Hall, Bracken & Gouldstone (1961). Their preliminary studies indicated that the compound possessed anaesthetic properties in mice in a concentration of 1.25–3.5% v/v. Lapik (1965) found, however, an LD_{50} in mice of only 1.1% v/v, but the incomplete description of the experimental details makes it impossible to comment on this result.

Because of the promising anaesthetic qualities of hexafluorobenzene reported by Burns *et al.* (1961) it was decided to study the effects of this compound in cats.

Physical properties

Hexafluorobenzene, C_6F_6, is a clear, colourless liquid with a characteristic odour. Some of its more important physical properties are given in Table 1, together with those of halothane, methoxyflurane and trichloroethylene for comparison. Hexafluorobenzene does not react with soda lime heated at 70° C for three hours (Burns *et al.*, 1961).

TABLE 1

SOME PHYSICAL PROPERTIES OF HEXAFLUOROBENZENE, HALOTHANE, METHOXYFLURANE AND TRICHLOROETHYLENE

Figures within parentheses signify that these concentrations cannot be obtained in unheated vaporizers at normal room temperature. The hexafluorobenzene data were supplied by the Imperial Smelting Corporation Ltd. The flammability limits of the other agents are from *A Practice of Anaesthesia* (Wylie & Churchill-Davidson, 1966)

	Hexafluorobenzene	Halothane	Methoxyflurane	Trichloroethylene
Molecular weight	186	197	165	131
Boiling point (°C)	80	50	105	87
Density (g/ml.)	1·62	1·86	1·42	1·46
Latent heat of vaporization (cal/g)	46	35	49	58
Oil/water solubility	470	330	400	400
Vapour pressure at 20° C (mm Hg)	66	241	25	57
Lower limit of flammability (%)				
in air	nonflam.	nonflam.	(9)	nonflam.
in oxygen	6	nonflam.	(5·2)	(10)
in nitrous oxide	4	4–5	4	2–2·5

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METHODS

Samples of anaesthetic grade hexafluorobenzene for this work were supplied by the Imperial Smelting Corporation Ltd., Bristol.

Vaporization of anaesthetic agents

Hexafluorobenzene was vaporized in a copper kettle (Morris, 1952) by a separately metered oxygen stream and mixed with the main gas stream in a glass reservoir bottle before being delivered to the cat.

Halothane was vaporized in a Fluotec vaporizer (Cyprane Ltd.).

Experiments performed

In these experiments 24 cats were used, of which 14 were anaesthetized with hexafluorobenzene, 4 with halothane and 6 (see below) with both agents.

Comparative studies of the induction characteristics of hexafluorobenzene and halothane were carried out in an observation chamber, through which the anaesthetic vapours were passed. Anaesthesia was discontinued as soon as the pedal reflex was lost. This spinal withdrawal reflex, elicited by pinching an interdigital web, is sluggish in plane 2 and lost in plane 3 of surgical anaesthesia (Hall, 1966). Induction time, recovery time and any associated phenomena were compared. For this purpose 6 unpremedicated cats were anaesthetized with each agent on successive days; 3 cats were given hexafluorobenzene first, the other 3 halothane first.

During anaesthesia with different concentrations of the anaesthetics the following were studied: (1) general cardiovascular and respiratory effects, (2) the effect of rapid intravenous injections of adrenaline and noradrenaline on cardiac excitability and cardiovascular reactivity, (3) the effect of vagal and splanchnic nerve stimulation on autonomic cardiovascular responses.

No premedication was given in these experiments. Anaesthesia was induced with thiopentone sodium in the majority of the cats, but pentobarbitone sodium was used when long surgical preparation was necessary. These drugs were given intravenously in a dose of 20–30 mg/kg. Endotracheal intubation was performed after intravenous injection of 3–5 mg suxamethonium.

The anaesthetic mixture was delivered to the cat *via* a T-piece system. The main gas flow was 3 l./min and consisted of nitrous oxide/oxygen (2:1) during surgical preparation and oxygen alone during control and experimental observations.

During the course of the experiments the cats were allowed to breathe spontaneously. When breathing was depressed by high concentration of the anaesthetic compounds ventilation was performed by intermittent occlusion of the T-piece reservoir limb.

Catecholamine solutions were administered in a concentration of 10 μg/ml. *via* a femoral vein catheter and followed by a 1 ml. normal saline flush.

Faradic stimulation was applied to the vagus and splanchnic nerves from an induction coil using a constant coil setting for each experiment.

The following recordings were obtained on a three-channel recorder (Cambridge Instrument Co. Ltd.): (1) intra-arterial blood pressure from a femoral or carotid artery catheter using a pressure transducer (N.E.P. 1025), (2) one-lead electrocardiogram from subcutaneous needle electrodes, (3) ventilation rate from a needle inserted into the endotracheal tube using a gas pressure transducer (Type 73428-Cambridge Instrument Co. Ltd.).

The carbon dioxide tension of arterial blood was calculated using the interpolation method of Siggaard Andersen & Engel (1960). The pH values were obtained on an Astrup Micro Equipment, type AME 1 (Radiometer, Copenhagen). Arterial samples of 0.6 ml. were withdrawn into heparinized syringes from a three-way tap in the arterial catheter. No temperature correction was necessary as the rectal temperature did not fall more than 1° C below the operating temperature of the apparatus (38° C).

Control studies were carried out before the volatile agent was introduced.

RESULTS

In these experiments the concentration of hexafluorobenzene required for maintenance of anaesthesia was 1.5–2.5% v/v. This was judged by the absence of a cough reflex on moving the endotracheal tube and the presence of a sluggish pedal reflex. Above these limits the pedal reflex was lost. In the cats given halothane the corresponding concentration was 1.0–1.5% v/v.

For the induction and recovery studies 4% hexafluorobenzene was compared with 2.5% halothane. Induction with hexafluorobenzene was more than twice as long as with halothane and was accompanied by salivation and retching or vomiting. Recovery was likewise longer after hexafluorobenzene anaesthesia and there were signs of a "hangover," manifested by reluctance to move spontaneously and by ataxia. These effects lasted at least 30 min and were not seen after halothane anaesthesia. One cat showed evidence of skin irritation after hexafluorobenzene anaesthesia, scratching its ears and face continually. This animal developed facial oedema and conjunctival hyperaemia lasting for 2 hr.

The respiratory studies showed that hexafluorobenzene in concentrations up to 4% did not cause a rise in $Paco_2$, although above 2.5% a decrease in ventilation rate was observed. Above 4% there was significant respiratory depression as shown by a rising $Paco_2$. This depression was observed as a very slow and shallow ventilation and respiratory arrest occurred in most cats at a concentration of 5%. Halothane produced a progressive respiratory depression above 1% as shown by a continuous rise in $Paco_2$.

Hexafluorobenzene always caused hypotension and bradycardia, but less so than did halothane (Fig. 1), and when spontaneous ventilation ceased the mean blood pressure was between 70 and 90 mm Hg. Artificial ventilation with high concentrations of hexafluorobenzene (6–8%) caused a severe fall in blood pressure, but this soon returned to control values when ventilation was performed with oxygen alone.

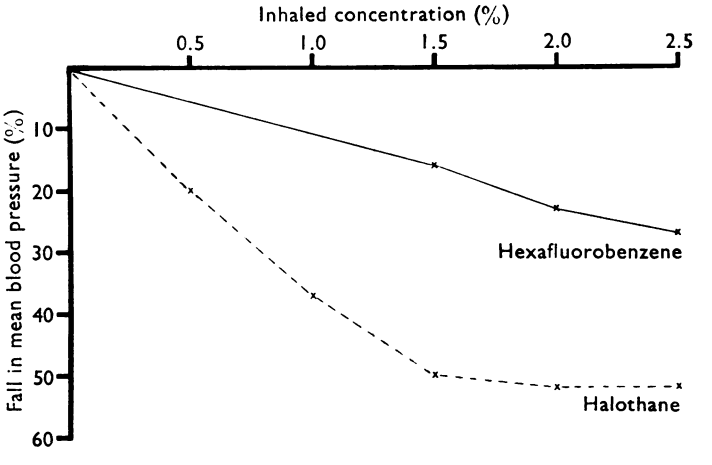

Fig. 1. Per cent decrease of mean blood pressure at different inhaled concentrations of hexafluorobenzene and halothane. ——=average of 7 cats given hexafluorobenzene. – – –=average of 4 cats given halothane.

An unexpected finding was that all cats, in which blood gas analysis was performed, appeared to have an initial metabolic acidosis. The mean values obtained in the control period from the 8 cats used were: pH 7.29, $Paco_2$ 31.5 mm Hg, and standard bicarbonate 14.6 m-equiv/l.

No spontaneous cardiac arrhythmias were observed in any cat in this study.

The rapid intravenous injection of 10 μg adrenaline or noradrenaline in the control periods produced no arrhythmias. When this procedure was repeated during inhalation of halothane multifocal ventricular extrasystoles always occurred for 2–3 min, after which sinus rhythm returned spontaneously, usually with an intervening period of nodal rhythm. However, in no cat given hexafluorobenzene did any kind of arrhythmia develop, not even when the catecholamine dosage was doubled.

In one experiment adrenaline was first given during inhalation of 1% halothane, and then, after a wash-out period of 30 min, during inhalation of 2% hexafluorobenzene. In the halothane period 10 μg adrenaline produced the usual sequence of multifocal

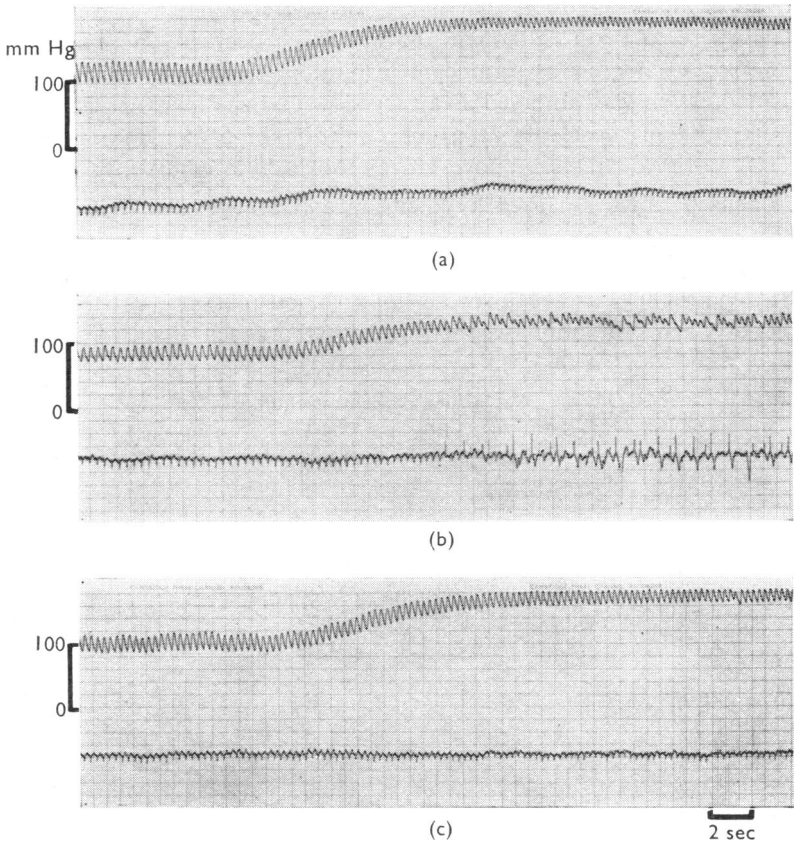

Fig. 2. The effect in one cat (weight 2.5 kg) of: (a) 10 μg adrenaline during inhalation of oxygen; (b) 10 μg adrenaline during inhalation of 1% halothane; (c) 20 μg adrenaline during inhalation of 2% hexafluorobenzene. Upper trace: blood pressure; lower trace: electrocardiogram.

ventricular extrasystoles, but in the hexafluorobenzene period no arrhythmias were produced even with 20 μg adrenaline (Fig. 2).

The pressor response to injection of noradrenaline and stimulation of the splanchnic nerves decreased as the concentration of hexafluorobenzene and halothane was increased. The pressor response to adrenaline was similarly decreased. The effect of vagal stimulation was unchanged by both agents.

DISCUSSION

These experiments indicate that, at equal inhaled concentrations, hexafluorobenzene has one-third to one-half of the depressant action of halothane on the blood pressure; also hexafluorobenzene produces less bradycardia. Even though the anaesthetic range of hexafluorobenzene is 1.5–2.5% and that of halothane 1.0–1.5%, this still represents an increase in safety. Added to this, the complete lack of cardiac arrhythmias, even in the presence of high doses of adrenaline and noradrenaline, makes hexafluorobenzene superior to halothane in its cardiovascular effects.

As suggested by the normal $Paco_2$ there seems to be no respiratory depression in the clinical range of hexafluorobenzene anaesthesia. However, the consistent finding of initial metabolic acidosis with a presumed effect of respiratory stimulation may tend to conceal the possible respiratory depressant effects of hexafluorobenzene. This finding of metabolic acidosis needs further investigation in order to ascertain the value of using cats for respiratory studies. Nevertheless, the results obtained indicate that hexafluorobenzene causes less respiratory depression than does halothane.

The experiments performed to investigate the cardiovascular responses indicate that both hexafluorobenzene and halothane have similar actions, but there is not enough evidence to show that the hypotension is due to any predominant factor in either case.

While the longer induction period of hexafluorobenzene could be acceptable, the incidence of salivation and retching during induction and the prolonged "hang-over" effects, if they occur in other species of animals, would be considerable disadvantages. These phenomena have not been observed in mice (Burns *et al.*, 1961). The facial oedema and conjunctival hyperaemia observed in one cat, uneventfully anaesthetized with halothane the day before, suggest that the compound may possess local irritating effects.

The flammability of hexafluorobenzene (Table 1) is another disadvantage. It is flammable in oxygen in concentrations which can be obtained under normal operating theatre conditions, unlike halothane, methoxyflurane and trichloroethylene.

SUMMARY

1. The effects of hexafluorobenzene anaesthesia were studied in cats and compared with those of halothane anaesthesia.

2. Hexafluorobenzene caused less hypotension and respiratory depression than did halothane.

3. No cardiac arrhythmias were observed during inhalation of hexafluorobenzene even in the presence of exogenous catecholamines.

4. Induction of anaesthesia with hexafluorobenzene was slower than with halothane and was accompanied by salivation and retching; also, recovery was prolonged and appeared to be associated with "hang-over" effects.

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