*Brit. J. Pharmacol.* (1966), **26**, 482–493.

# THE ANALGESIC AND ANAESTHETIC ACTIONS OF TETRAFLUOROBENZENE

BY

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(*Received October* 29, 1965)

Many fluorinated compounds have been administered to various animal species in the hope of discovering new anaesthetics suitable for clinical use (Booth & Bixby, 1932; Brenner, 1937; Struck & Plattner, 1940; Robbins, 1946; Lester & Greenberg, 1950).

The first fluorinated anaesthetic to be used clinically was discovered by Lu, Johnson, Ling & Krantz (1953). They found that 2,2,2-trifluoroethyl vinyl ether was a good anaesthetic in dogs and this compound was later introduced clinically under the name Fluoromar (Krantz, Carr, Lu & Bell, 1953). Raventos (1956) demonstrated that 2-bromo-2-chloro-1,1,1-trifluoroethane (halothane) was an excellent nonflammable anaesthetic. Halothane is now used widely and extensive literature about its clinical use has accumulated. Methoxyflurane (2,2-dichloro-1,1-difluoroethyl methyl ether) is another fluorinated ether which has been used clinically. This compound was first investigated by Poznak & Artusio (1960) on dogs. Fabian, Dewitt & Carnes (1960) reported the effects of several fluorinated compounds on dogs. They considered that 3-chloro-1,1,2,2-tetrafluoropropane and 3-bromo-1,1,2,2-tetrafluoropropane were suitable for trial on man.

The anaesthetic action of aromatic fluorinated compounds was first reported by Burns, Hall, Bracken & Gouldstone (1961, 1964). These investigators found, rather unexpectedly, that hexafluorobenzene and pentafluorobenzene were good anaesthetics in mice. Neal & Robson (1965), in an attempt to discover a new potent inhalation analgesic, investigated the analgesic and anaesthetic actions of certain fluorinated aromatic compounds in mice. They found that although hexafluorobenzene and pentafluorobenzene were good anaesthetics they had little analgesic action when administered in subanaesthetic concentrations. However, 1,2,3,4-tetrafluorobenzene was an excellent analgesic but was hepatotoxic. The present paper describes results obtained with the 1,2,4,5- and 1,2,3,5-isomers of tetrafluorobenzene. These were investigated initially on mice and the most promising isomer (1,2,4,5-tetrafluorobenzene) was then investigated further on dogs.

## METHODS

### *Experiments on mice*

*Estimation of analgesia.* The analgesic action of the drugs administered in subanaesthetic concentrations was estimated using the method and apparatus described previously (Neal & Robson, 1964a). In outline the method consists of placing two mice at a time in a Perspex gas chamber. The mice are exposed to known concentrations of anaesthetic vapour in oxygen. To test for analgesia the mice are given a series of ten electric shocks at a previously determined voltage through a pair

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of electrodes attached to their tail. The number of times the mouse does not squeak out of ten shocks (negative response) is taken to be proportional to the degree of analgesia produced by the anaesthetic. When control mice are given shocks they squeak about nine times out of ten—that is, the negative response is about 1.

*Estimation of anaesthesia.* Mice were judged to be anaesthetized when they did not right themselves on shaking the gas chamber.

*Therapeutic index.* Groups of ten mice were placed in the gas chamber to estimate the concentrations of 1,2,4,5-tetrafluorobenzene that anaesthetized (AC50) or killed (LC50) half the mice after 30 min. The ratio LC50/AC50 was then calculated.

*Experiments on dogs*

Nine mongrel dogs weighing between 7 and 20 kg were used for experiments with the 1,2,4,5-isomer of tetrafluorobenzene.

Unless otherwise stated the dogs were not premedicated and anaesthesia was induced with thiopentone (30 to 50 mg/kg) injected intravenously. The dogs were then intubated with a cuffed Magill endotracheal tube and the cuff was inflated. While the dogs were anaesthetized with thiopentone, electrocardiogram leads were attached and a nylon intravenous cannula was inserted into a femoral artery using aseptic technique. The cannula was connected to a strain gauge transducer (Bell & Howell, type 4-326-L212) for the measurement of arterial blood pressure. The electrocardiogram (usually lead II) was recorded continuously on the same trace. Control recordings of blood pressure, respiration rate and electrocardiogram were taken until the dog started to recover from the effects of the thiopentone. When the animal began to show signs of consciousness tetrafluorobenzene was administered, usually for 1 hr. If the concentration of tetrafluorobenzene proved to be insufficient to maintain anaesthesia additional thiopentone was administered in small doses (5 to 10 mg/kg) as required.

The apparatus used to produce known concentrations of anaesthetic has been described (Neal & Robson, 1964a). The anaesthetic vapour in oxygen was led to polyethylene reservoir bags. The anaesthetic was drawn from these bags through a standard length of corrugated anaesthetic tubing. A Hooke & Tucker unidirectional valve was used to prevent rebreathing into the anaesthetic system.

Polyethylene bags are not impermeable to either oxygen or fluorinated compounds and for this reason the anaesthetic mixtures were retained in the reservoir bags for only a short time. This was achieved by filling the reservoir bags with anaesthetic at about the same rate as that of removal by the dog. This ensured that any given sample of anaesthetic mixture remained in the bag for only a matter of minutes (never more than 20 min).

At the end of the experiment the arterial cannula was removed and the incision closed. Before the dogs completely regained consciousness, pethidine (100 mg) and Crystamycin (sodium benzylpenicillin 500,000 units, and streptomycin 0.5 g) were injected intramuscularly. The dogs were kept for an observation period of 10 days. In one experiment anaesthesia was not induced with thiopentone. The dog was premedicated with an intramuscular injection of morphine sulphate (2 mg/kg) and an attempt was then made to induce anaesthesia by allowing the animal to inhale tetrafluorobenzene vapour (8%) through a mask.

To investigate the effect of tetrafluorobenzene on bronchial secretion, bronchoscopy was performed on two nonpremedicated dogs after inhalation of tetrafluorobenzene for 1 hr.

## RESULTS

### *Mice*

*1,2,3,4-Tetrafluorobenzene.* The excellent analgesic properties of various concentrations of this compound in oxygen and with nitrous oxide have already been described in detail (Neal & Robson, 1965). However, for the sake of comparison the analgesic effect of 1,2,3,4-tetrafluorobenzene (0.5%) is shown in Fig. 1. Unfortunately this compound produces centrilobular coagulative necrosis of liver parenchymal cells (Fig. 2,*a*). The appearance of liver from a control mouse is shown in Fig. 2,*b*.

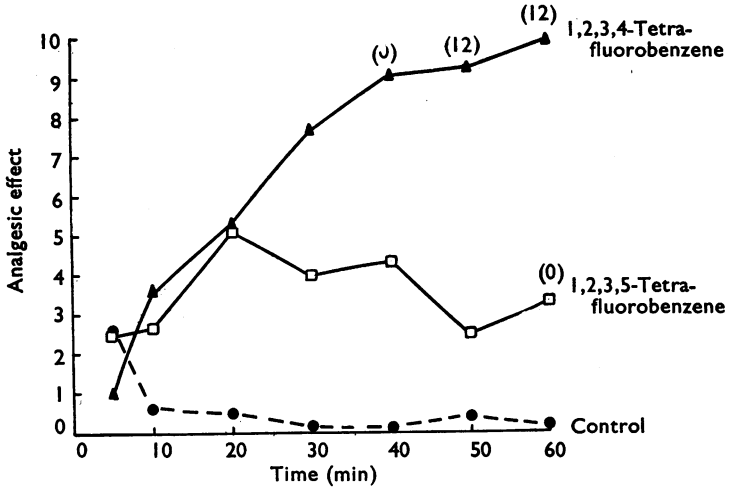


Fig. 1. Analgesia produced by 1,2,3,5-tetrafluorobenzene (0.5%) and 1,2,3,4-tetrafluorobenzene (0.5%). The ordinate is the analgesic effect (mean negative response) and is the number of times the mice did not squeak out of ten shocks. Numbers in parentheses show percentages of mice anaesthetized. After 10 min all the results are significantly greater than the control ($P<0.05$).

*1,2,3,5-Tetrafluorobenzene.* The analgesic effect produced by a subanaesthetic concentration of 1,2,3,5-tetrafluorobenzene (0.5%) is illustrated in Fig. 1. The analgesic activity of this compound is poor compared with that of the other two isomers of tetrafluorobenzene. 1,2,3,5-Tetrafluorobenzene was also the most toxic of the three isomers, killing 80% of mice after 24 to 48 hr. Histological examination showed necrosis in both the liver and kidneys of mice killed 24 hr after 60 min exposure to 0.5% 1,2,3,5-tetrafluorobenzene. The hepatic lesions closely resembled those produced by 1,2,3,4-tetrafluorobenzene (Fig. 2,*a*).

*1,2,4,5-Tetrafluorobenzene.* Of all the fluorinated compounds investigated (Neal, 1965), this isomer of tetrafluorobenzene was the most potent inhalation analgesic discovered. The degree of analgesia produced by 1,2,4,5-tetrafluorobenzene (0.5%) after inhalation for 20 min was about ten times that produced by the same concentration of trichlorethylene. The analgesic effect produced by 1,2,4,5-tetrafluorobenzene (0.25%) is shown in Fig. 3. This concentration of drug produced an analgesic effect which was not significantly different from that produced by 1,2,3,4-tetrafluorobenzene (0.5%). Increasing the concentration of 1,2,4,5-tetrafluorobenzene to 0.5% rapidly produced an almost maximal analgesic effect (Fig. 3). Thus at 5 min the analgesic effect was slightly greater than that produced by methadone hydrochloride (8 mg/kg) injected intraperitoneally. The excellent analgesia produced by 1,2,4,5-tetrafluorobenzene was obtained without loss of consciousness in any mice. Results on the AC50 and LC50 of 1,2,4,5-tetrafluorobenzene are summarized in Table 1, together with some results obtained with other anaesthetics. The ratio of concentrations for 1,2,4,5-tetrafluorobenzene in mice is 5.5. This is considerably higher than the ratio for halothane and is more than three times the ratio for ether and cyclopropane.

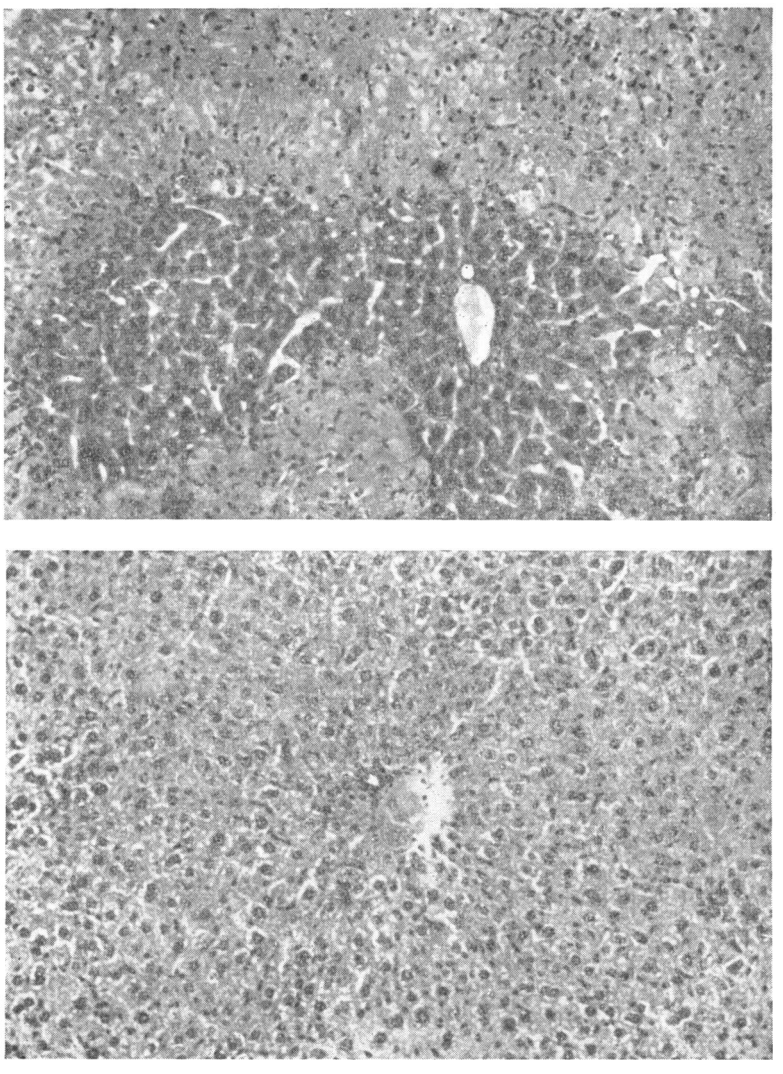


Fig. 2. (*a*) Appearance of liver removed from mouse 24 hr after exposure for 60 min to 1,2,3,4-tetrafluorobenzene (0.5%). Massive areas of coagulative necrosis are evident. Haemotoxylin and eosin ; × 100. (*b*) Appearance of liver from control mouse. Haemotoxylin and eosin × 100.

*Histological pathology.* None of the mice exposed to 1,2,4,5-tetrafluorobenzene died within 2 months. A group of ten mice was exposed to 1,2,4,5-tetrafluorobenzene (1%) for 30 min on five successive days. The animals were killed on the sixth day and their liver, kidneys, lungs and heart were removed for examination. The histological sections were kindly examined by Dr G. A. K. Missen, who found no abnormalities in the tissues taken from eight of the ten test animals. In one mouse, sections of the lung showed purulent bronchitis and bronchiolitis with severe and extensive acute bronchopneumonia, which occurs occasionally in our colony. Sections of liver from the remaining mouse

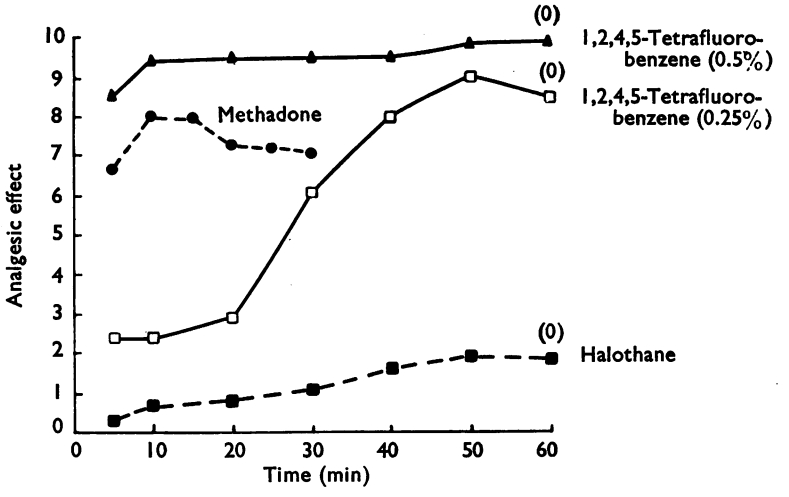


Fig. 3. Analgesic effect of 1,2,4,5-tetrafluorobenzene (0.25 and 0.5%). For comparison the analgesic effects of methadone (8 mg/kg, intraperitoneally) and halothane (0.75%) are included. The analgesic effect of halothane is significant only after 50 min. Numbers in parentheses show proportions of mice anaesthetized.

TABLE 1

EFFECT OF INHALATION OF ANAESTHETICS ON MICE AFTER 30 MIN EXPOSURE

All results are from our own experiments except those marked by an asterisk, which are from Raventos (1956). Concentrations are vapour percentages

| Compound | AC50 (%) | LC50 (%) | Ratio LC50/AC50 |
|---|---|---|---|
| 1,2,4,5-Tetrafluorobenzene | 0·82 | 4·5 | 5·5 |
| Halothane | 1·0 | 3·8 | 3·8 |
| Halothane* | 0·86 | 2·8 | 3·3 |
| Trichlorethylene* | 0·82 | 4·9 | 6·0 |
| Chloroform* | 1·3 | 2·0 | 1·5 |
| Diethyl ether* | 4·3 | 7·3 | 1·7 |
| Cyclopropane* | 17·4 | 25·8 | 1·5 |

showed considerably more cytoplasmic vacuolation than was present in any of the controls. However, no necrosis or inflammatory cellular infiltration was seen. It was thought likely that the appearance described was due to physiological glycogenic vacuolation as seen in man.

Thus of the three isomeric tetrafluorobenzenes only the 1,2,4,5-isomer was free from obvious toxic effects in mice. As this compound was an excellent inhalation analgesic it was thought of interest to investigate its actions further using larger animals.

*Dogs*

In mice 1,2,4,5-tetrafluorobenzene is a slightly more potent anaesthetic than halothane and it was expected that 4% tetrafluorobenzene would be more than adequate to maintain anaesthesia in dogs. Surprisingly, even concentrations of 8 to 10% were insufficient to maintain anaesthesia in nonpremedicated dogs. However, it was possible to produce light anaesthesia in one dog premedicated with morphine (2 mg/kg) by allowing it to

inhale 8% tetrafluorobenzene through a mask. The depth of anaesthesia produced in this manner was not sufficient to permit intubation. Three dogs were exposed to 12% tetrafluorobenzene after induction with thiopentone. For practical reasons one of these dogs was premedicated with morphine (1.7 mg/kg) and atropine (0.05 mg/kg). Tetrafluorobenzene (12%) was sufficient to maintain surgical anaesthesia in two of the dogs for the 60 min of the experiment. However, inhalation of this concentration of tetrafluorobenzene caused ventricular fibrillation in one nonpremedicated dog after only 15 min.

Four dogs were allowed to survive after inhaling tetrafluorobenzene (2, 8, 10 and 12% respectively). Three recovered rapidly, but one dog, which had been exposed to only 2% tetrafluorobenzene, had a flaccid paralysis and possible sensory loss which affected all four limbs 24 hr after the experiment. After 48 hr the dog had recovered completely. This effect was seen only once out of four experiments. It is possible that this paralysis was due to a peripheral neuropathy caused by a direct toxic action of tetrafluorobenzene. This point has not been investigated further.

*Effect on blood pressure.* 1,2,4,5-Tetrafluorobenzene causes a fall in blood pressure which is roughly proportional to the concentration of drug administered. The results with nonpremedicated dogs are summarized in Table 2. It should be remembered that with the lower concentrations of tetrafluorobenzene unconsciousness was maintained with thiopentone. However, the doses of thiopentone used were small and control experiments showed that the amounts used had little effect on blood pressure although they did depress respiration.

TABLE 2

EFFECT OF 1,2,4,5-TETRAFLUOROBENZENE ON THE MEAN BLOOD PRESSURE OF DOGS

Mean blood pressure = diastolic pressure + one-third of pulse pressure

| Dog No. | Concentration of tetrafluorobenzene (%) | Fall in blood pressure (mm Hg) | Onset of blood pressure fall (min) |
|---|---|---|---|
| 1 | 2 | 10 | 60 |
| 2 | 4 | 32 | 30 |
| 4 | 8 | 60 | 45 |
| 5 | 10 | 70 | 40 |
| 6 | 12 | 92 | 15 |
| 8 | 12 | 83 | 20 |

*Effect on heart rate and the electrocardiogram.* The electrocardiograms of all the nonpremedicated dogs which were exposed to 1,2,4,5-tetrafluorobenzene (2 to 12%) showed various types of changes. These ranged from relatively trivial ectopic ventricular rhythms (Fig. 4, second panel) to ominous multifocal ventricular tachycardia (Fig. 5). One dog which was treated with 8% tetrafluorobenzene showed ventricular tachycardia for 30 min but after this time the heart reverted to normal sinus rhythm for the remainder of the experiment. In some experiments tetrafluorobenzene had little effect on the heart rate and electrocardiogram, but in others tachycardia together with irregularities in the electrocardiogram were produced. In the two nonpremedicated dogs in which anaesthesia was successfully maintained with 12% tetrafluorobenzene no cardiac irregularities were observed after the first 10 min. However, the myocardium of these

dogs was seriously depressed. This was shown by the rapid decrease which occurred in the voltage of the QRS complex (Fig. 4). The inhalation of 12% tetrafluorobenzene by one dog depressed the QRS voltage from 1.75 to 0.25 mV in 15 min. In this period the blood pressure fell from a mean of 127 to 35 mm Hg. After 15 min ventricular fibrillation occurred.

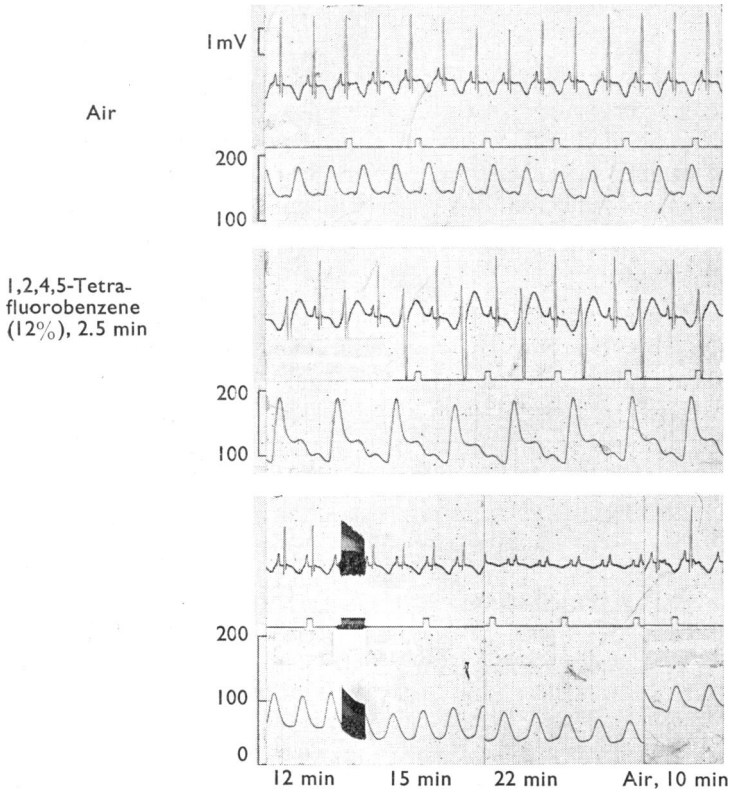


Fig. 4. Effect on blood pressure (mm Hg, lower trace) and electrocardiogram (upper trace) of a dog exposed to 12% 1,2,4,5-tetrafluorobenzene. The bigeminal rhythm apparent at 2.5 min has disappeared by 12 min. After 22 min the blood pressure and QRS voltage are severely depressed ; however, these rapidly recover on breathing air. Time marks, seconds.

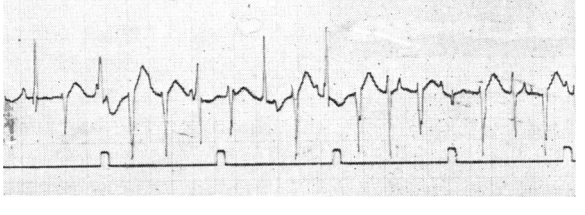

Fig. 5. Multifocal ventricular tachycardia produced in a dog inhaling 4% 1,2,4,5-tetrafluorobenzene for 15 min. Time marks, seconds.

*Effect of adrenaline.* In view of the electrocardiographic changes produced by 1,2,4,5-tetrafluorobenzene it was thought of interest to investigate whether tetrafluorobenzene " sensitized " the heart to adrenaline. This was done by determining the dose of adrenaline which produced ventricular tachycardia or ventricular fibrillation. Each dose of adrenaline was dissolved in 5 ml. of 0.9% saline and injected at a rate of 1 ml. in 10 sec. The injections were continued until the dose was found that produced either ventricular tachycardia or ventricular fibrillation. The results are summarized in Table 3. The effect of adrenaline (2 $\mu$g/kg, intravenously) on the electrocardiogram of a dog inhaling tetrafluorobenzene (8%) is illustrated in Fig. 6. This small dose of adrenaline produced ventricular fibrillation. From the results of these experiments it is clear that tetrafluorobenzene greatly increases the sensitivity of the myocardium to adrenaline.

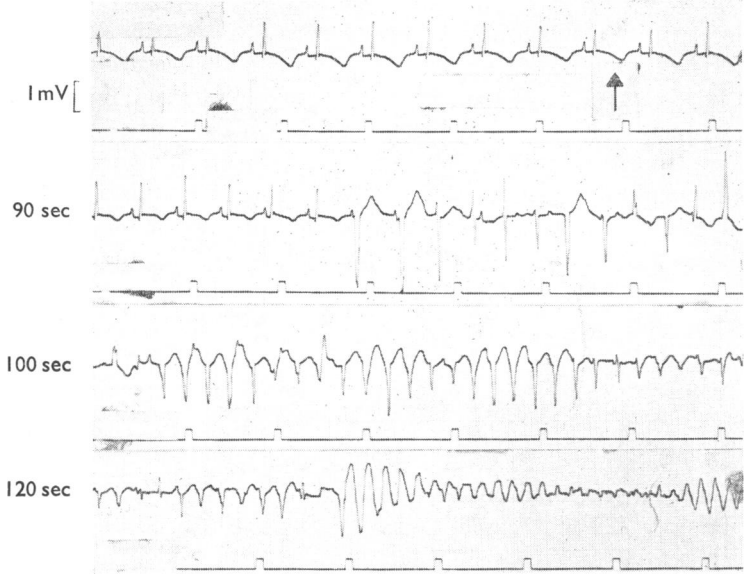


Fig. 6. Ventricular fibrillation produced by a small intravenous dose of adrenaline (2 $\mu$g/kg, at arrow) in a dog inhaling 8% 1,2,4,5-tetrafluorobenzene. Time marks, seconds.

*Respiration.* The effect of tetrafluorobenzene on respiration was difficult to assess due to the fact that in all the experiments, except those in which the dogs were treated with 12% tetrafluorobenzene, additional thiopentone was required to maintain anaesthesia.

TABLE 3

DOSES OF ADRENALINE THAT PRODUCE VENTRICULAR TACHYCARDIA AND/OR VENTRICULAR FIBRILLATION IN NONPREMEDICATED DOGS

* Results from Raventos (1956). Doses, except for the chloroform experiments, are ranges

| Anaesthetic | Number of dogs | Dose of adrenaline ($\mu$g/kg) | Number of deaths |
|---|---|---|---|
| Thiopentone (controls) | 4 | 16–30 | Nil |
| 1,2,4,5-Tetrafluorobenzene | 3 | 1·1–3·5 | 2 |
| Chloroform | 1 | 5·2 | |
| Halothane* | 13 | 7–11 | 1 |

In the three dogs which were treated with 12% tetrafluorobenzene and did not require additional thiopentone the respiration rate was slightly depressed.

Tetrafluorobenzene did not seem to irritate the tracheobronchial tree, even at concentrations of 12%. Thus at bronchoscopy the trachea and bronchi of two dogs were found to be remarkably free from secretions.

## DISCUSSION

The tetrafluorobenzenes were investigated in the hope that one of them might prove to be a more satisfactory inhalation analgesic than trichlorethylene and nitrous oxide. The main difficulty with these established drugs is that patients vary considerably in their responses and since nitrous oxide and trichlorethylene are rather weak analgesics many patients derive little benefit from their administration in subanaesthetic doses. Thus 50% nitrous oxide may produce unconsciousness in one patient and yet barely affect a more resistant subject. A disadvantage of trichlorethylene is that it tends to be cumulative and if administration is prolonged the patient may become drowsy and uncooperative.

Apart from lack of toxicity and unpleasant side-effects, three important factors must be considered in assessing inhalation analgesic agents for possible clinical use: analgesic potency, length of time before analgesia is produced and anaesthetic potency of the drug. Ideally a drug is required which produces complete analgesia after a short time and yet after prolonged administration does not produce anaesthesia.

The 1,2,3,4- and 1,2,4,5-isomers of tetrafluorobenzene both produced excellent analgesia in mice. Analgesia was rapidly obtained particularly with the 1,2,4,5-isomer. The concentration of 1,2,4,5-tetrafluorobenzene that produced almost maximal analgesia (0.5%) did not anaesthetize any mice after administration for 1 hr. This was not true for the same concentration of 1,2,3,4-tetrafluorobenzene which anaesthetized 12% of mice after 50 min. The 1,2,3,5-isomer of tetrafluorobenzene (0.5%) surprisingly proved to be a poor analgesic.

Thus, considering these three tetrafluorobenzenes purely from the point of view of inhalation analgesics, only the 1,2,4,5-isomer approaches the "ideal." It was fortunate that this isomer proved to be the only tetrafluorobenzene which is not toxic to mice. Thus, while the 1,2,3,4- and 1,2,3,5-tetrafluorobenzenes are hepatotoxic and nephrotoxic in mice, the 1,2,4,5-isomer does not produce histologically detectable lesions in these organs. It is not clear why the tetrafluorobenzenes should vary in toxicity. It is possible but unlikely that this variation is due to a difference in purity of the isomers, as all three tetrafluorobenzenes were found to be 99.9% pure by gas chromatography. The toxicity of fluorinated benzene compounds appears to have an inverse relationship to the degree of fluorination. Thus, while hexafluorobenzene and pentafluorobenzene are nontoxic (Burns *et al.*, 1961, 1964; Neal & Robson, 1965), 1,3,5-trifluorobenzene is extremely toxic and rapidly kills most mice exposed to it (Neal, 1965). The tetrafluorobenzenes may be regarded as being in an intermediate position, two of the isomers being toxic and one being nontoxic. Although the purity of these compounds may not be identical, the general trend of increasing toxicity with decrease in fluorine atoms in the benzene ring does seem to be apparent.

In mice there appears to be no clear correlation between analgesic potency and degree of fluorination in the benzene ring. Neither hexafluorobenze nor pentafluorobenzene

has much analgesic action in subanaesthetic doses but it may be significant that nitrous oxide, which has no action on its own in mice, potentiates markedly the analgesic action of pentafluorobenzene but not that of hexafluorobenzene (Neal & Robson, 1965). Of the three tetrafluorobenzenes two are powerful analgesics when administered in subanaesthetic doses. The analgesic effect of 1,2,3,4- and 1,2,4,5-tetrafluorobenzene was remarkable in that it persisted for several minutes after removal of the mice from the gas chamber. Squeezing the tails of mice with a pair of Rampley's sponge forceps tightened to the last rachet did not elicit any response from mice just removed from the gas chamber having been exposed to 1,2,3,4- or 1,2,4,5-tetrafluorobenzene. In contrast the same procedure applied to mice treated with other fluorinated compounds (Neal & Robson, 1965; Neal, 1965) or to the established anaesthetics including trichlorethylene (Neal & Robson, 1964b) immediately elicited squeaks and vigorous escape manœuvres.

While 1,2,4,5-tetrafluorobenzene seems to be an ideal inhalation analgesic in mice, man does not necessarily respond to anaesthetics in the same way. For example mice are unaffected by inhalation of 90% nitrous oxide for 60 min (Neal & Robson, 1964b). Such prolonged inhalation of 90% nitrous oxide would produce loss of consciousness in most subjects.

The importance of species variation in anaesthetic studies is emphasized by the fact that, although mice were anaesthetized by 2% 1,2,4,5-tetrafluorobenzene, the concentration needed to maintain anaesthesia in dogs after thiopentone induction was 12%. This concentration of 1,2,4,5-tetrafluorobenzene caused a rapid and severe fall in blood pressure. The mechanism of this effect was not analysed but it seems likely to be due, in part at least, to direct myocardial depression since 1,2,4,5-tetrafluorobenzene rapidly caused a reduction in the voltage of the QRS complex. In the experiment illustrated (Fig. 4) the amplitude of the QRS complex was reduced to less than 5 mm in all three standard leads. In man such a small amplitude is generally regarded as unsatisfactory since such low voltage is seen in cardiac failure and in any conditions producing widespread myocardial damage. In one dog 12% 1,2,4,5-tetrafluorobenzene did in fact produce cardiac failure. After only 15 min the blood pressure of this animal had fallen to 55/25 mm Hg, and the heart rate from 140 to 80 beats/min; the amplitude of QRS complex was depressed from 18 to 5 mm. At this stage ventricular fibrillation occurred. Clearly anaesthetic concentrations of 1,2,4,5-tetrafluorobenzene have a serious effect on the heart. It seems likely that the action of tetrafluorobenzene on the heart is one of myocardial depression and is not simply due to damage produced by a toxic compound. This is supported by two facts: no lesions were discovered histologically in the hearts of mice treated repeatedly with tetrafluorobenzene, and the depression of the QRS voltage in dogs was quickly reversed. Thus in the experiment cited (Fig. 4) the amplitude of the QRS complex on changing from tetrafluorobenzene (12%) to air increased from 5 to 25 mm in 10 min. The latter amplitude is only 5 mm less than that observed during the initial control period. At the present time it is not clear whether the depressant action of anaesthetics on the myocardium is due to changes in permeability of the cell membrane or to an action inside the cell.

Lower concentrations of 1,2,4,5-tetrafluorobenzene, which might have been used for the production of analgesia, frequently produced cardiac irregularities. These effects usually continued for the whole experiment but sometimes they disappeared after a

variable period of drug administration. 1,2,4,5-Tetrafluorobenzene resembled cyclopropane in that the type of cardiac irregularities produced were of ventricular origin. These varied from ventricular bigeminy or trigeminy to ominous multifocal ventricular tachycardia.

1,2,4,5-Tetrafluorobenzene greatly increases the sensitiveness of the heart to adrenaline and, although other anaesthetics sensitize the heart to adrenaline, none do so to the extent of 1,2,4,5-tetrafluorobenzene. Even at a quarter of the concentration required to produce anaesthesia (3%), tetrafluorobenzene sensitizes the heart to a greater extent than anaesthetic concentrations of halothane.

In two premedicated dogs no spontaneous cardiac irregularities were observed. One dog received morphine (20 mg ; 2.2 mg/kg) the other atropine (0.05 mg/kg) and morphine (1.7 mg/kg). This finding is not altogether unexpected as it has been shown experimentally that in cyclopropane anaesthesia morphine affords protection against spontaneous ventricular arrhythmias (Allen, Stutzman, Slocum & Orth, 1941 ; Nickerson & Smith, 1949). Atropine affords partial protection against cyclopropane-induced cardiac irregularities in dogs. This effect is due to nonspecific myocardial depression. Although large doses of morphine prevent arrhythmias in dogs under cyclopropane anaesthesia, the doses of morphine used clinically in man do not afford any protection. Thus there is no reason to suppose that in man the doses of morphine used clinically would prevent cardiac irregularities produced by 1,2,4,5-tetrafluorobenzene.

No attempt was made to investigate the effect of adrenergic-blocking drugs on the arrhythmias produced by 1,2,4,5-tetrafluorobenzene but it is quite possible that they could be prevented by a $\beta$-receptor blocking drug such as pronethalol.

The significance of the flaccid paralysis observed in one dog after exposure to tetrafluorobenzene is not clear. This effect was not seen in the other three dogs which were allowed to recover after inhalation of tetrafluorobenzene or in control animals which had been anaesthetized with thiopentone and/or halothane. As great care was taken in arranging the dogs on the operating table it is unlikely that the paralysis was due to nerve damage produced by prolonged maintenance of an unnatural posture. Thus on the basis of the small number of experiments in which dogs were allowed to recover it must be concluded for the time being that the paralysis seen in one dog was due to a toxic effect of tetrafluorobenzene.

The number of experiments performed on dogs was limited by the small quantity of 1,2,4,5-tetrafluorobenzene available. However, it seems clear that, although 1,2,4,5-tetrafluorobenze is an excellent inhalation analgesic in mice, it has a serious depressant action on the myocardium and a great liability to produce ventricular irregularities. These unfortunate actions together with a possible neuropathic action indicate that 1,2,4,5-tetrafluorobenzene is probably not suitable for further investigation in relation to clinical use.

## SUMMARY

1. The three isomers of tetrafluorobenzene all produce anaesthesia in mice when given in concentrations of 1 to 2%.

2. Subanaesthetic concentrations of the 1,2,4,5-tetrafluorobenzene produce excellent analgesia in mice, this isomer being about twice as potent as the 1,2,3,4-isomer in this

respect. The 1,2,3,5-tetrafluorobenzene has relatively little analgesic activity in the mouse.

3. 1,2,4,5-Tetrafluorobenzene is apparently nontoxic in mice but the other two isomers kill about half the mice exposed to their vapour. The main lesion found in mice treated with these compounds is hepatic coagulative necrosis.

4. In the dog 1,2,4,5-tetrafluorobenzene produces anaesthesia but a higher concentration (12%) is required than for mice.

5. 1,2,4,5-Tetrafluorobenzene in dogs causes ventricular arrythmias and in anaesthetic concentrations severely depresses the myocardium and the blood pressure.

6. It is concluded that, although 1,2,4,5-tetrafluorobenzene might prove to be a good inhalation analgesic in man, its action on the heart makes it unsuitable for clinical use.

We are grateful to Dr G. A. K. Missen, of Guy's Hospital Medical School for examining the histological sections, to the Medical Research Council for personal grants and expenses to one of us (M. J. N.), and to Imperial Smelting Ltd. (Avonmouth) for a gift of the tetrafluorobenzenes.

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