THE ABSORPTION AND DISTRIBUTION OF HALOTHANE

By W. A. M. Duncan

From Imperial Chemical Industries Limited, Pharmaceuticals Division, Alderley Park, Macclesfield, Cheshire

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Halothane (Fluothane), 1, 1, 1-trifluoro-2-chloro-2-bromoethane, the pharmacology of which was studied by Raventos[1], is a non-explosive volatile anaesthetic which was first used clinically by Johnstone[2].

The absorption and excretion of ether and chloroform were studied early in this century, and since then similar studies have been carried out on the other volatile anaesthetics. These studies showed that the depth of anaesthesia is dependent upon the concentration of the anaesthetic in the arterial blood and in the central nervous system, and that this is controlled by the concentration of the agent in the inspired gas mixture.

Goodall[3] described a method for the analysis of halothane in which a light petroleum extract of blood from an anaesthetised animal was heated with sodium amoxide at an increased pressure for 2 hours. Some 60–80 per cent of the bromine of halothane was liberated. It was later found that halothane could be degraded at room temperature with an ether solution of lithium aluminium hydride which, in 20 minutes, liberated 85 per cent of the bromine and 30 per cent of the chlorine[4]. The liberated halide was then extracted and estimated nephelometrically by the addition of silver nitrate. This method was suitable for routine use in the estimation of halothane in blood and tissues.

Mice and rats were anaesthetised in an atmosphere of usually 1·5 per cent v/v halothane in oxygen, without any premedication, using the apparatus which has been described by Raventos[1]. The kinetics of halothane anaesthesia and the distribution of the agent in the tissues were studied by exposing the mice, or rats, for varying lengths of time to the anaesthetic after which the animal was killed and the halothane content of the whole mouse or the separate tissues of the rat determined. In a similar way the concentration of halothane in the whole animal, or in the tissues, at different times after the cessation of inhalation of the agent was examined.

It was found that in the mouse halothane was rapidly absorbed during the first 10 minutes of inhalation of the anaesthetic; after 10 minutes, a 20 g. mouse contained about 6 mg. of halothane. As the duration of anaesthesia increased the absorption of the agent continued more slowly so that after 180 minutes anaesthesia a 20 g. mouse contained about 35 mg. of halothane. This was the longest period of anaesthesia studied in the mouse but, as there was no decrease in the rate of absorption it is obvious that the tissues would be able to absorb considerably more halothane. On recovery from anaesthesia with halothane, which had been administered for 2 hours, it was found that the total amount of

anaesthetic in the animal decreased rapidly; the half-clearance time was about 30 minutes.

In the rat, the rates of absorption of halothane by the arterial blood, the brain, the liver and the perirenal fat were examined and several unexpected facts observed (Fig. 1). All of these tissues showed an initial rapid absorption of the agent, similar to that found in the whole mouse. The perirenal fat was found to have the greatest affinity for the agent, which was not surprising as halothane has a high oil:water partition coefficient. However, even after 6 hours anaesthesia, at which time the fat contained about 1 per cent by weight of halothane, there was no indication of the saturation of this tissue with the agent. The liver and brain gave identical results; this was attributed to the poor solubility of halothane in phospholipids and to the difference in the blood supply in the two tissues. The concentration of halothane in the brain was about 45 mg./100 g. after 6 hours. This slow increase in the concentration of halothane in the brain contributes to the small influence which the duration of anaesthesia has on the time taken to recover after anaesthesia. The arterial blood was observed to reach a state of equilibrium with the inhaled gas concentration in about 90 minutes, when the concentration of halothane was about 20 mg./100 ml. of blood. This is quite different from what has been observed with ether and chloroform where the concentration of the agent in the blood increases with continued anaesthesia.

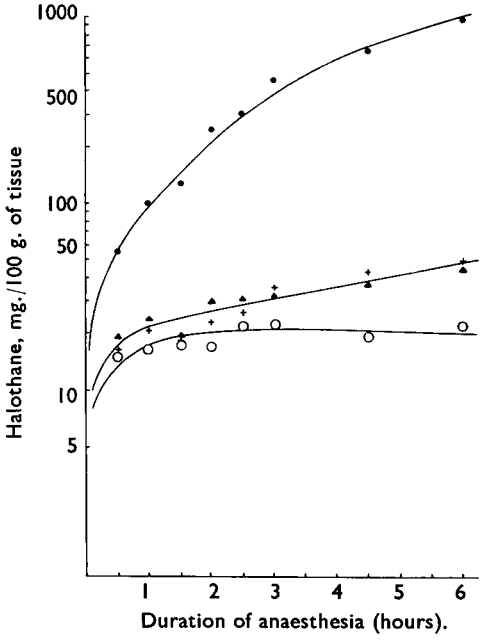

FIG. 1. The absorption of halothane by the tissues of rats during anaesthesia with 1·5 per cent v/v halothane in oxygen. ○—○ Arterial blood; +—+ liver; ▲—▲ brain; ●—● perirenal fat.

During the period following cessation of inhalation of halothane a very marked difference was observed between the arterial and venous blood systems in the rates of elimination of the anaesthetic (Fig. 2). The agent was cleared rapidly from the arterial blood, the half-clearance time being about 15 minutes, whereas the rate of clearance from the fat and the venous blood was slower with a half-clearance time for both of 45 minutes.

In man it was observed that for anaesthesias lasting more than 30–60 minutes, the half-clearance time of halothane from the venous blood was about 25 minutes.

The half-clearance time of an inert gas from the body is a function of the blood: gas partition coefficient of the gas. Butler[5] derived the following expression:—

$$\text{Half-clearance time (min.)} = 1n.2 \frac{V_D(V_P + \lambda C_P)}{V_P \cdot C_P}$$

Where V_D = volume of distribution of the drug in litres
V_P = pulmonary ventilation in litres per minute
C_P = pulmonary circulation in litres per minute
and λ = blood: gas partition coefficient.

With the following values $V_D = 70$ litres, $V_P = 8$ litres per minute, $C_P = 5$ litres per minute and with the appropriate blood: gas partition coefficient (halothane 3·6, chloroform 7·3, and ether 15) it can be calculated that the half-clearance time of halothane is 31, of chloroform 54 and of ether 100 minutes.

The calculated value for halothane is in close agreement with those reported above and thus substantiates the view that the blood: gas partition coefficient is one of the main controlling factors in the exhalation of a volatile anaesthetic. Halothane has a low blood: gas partition coefficient and therefore during recovery the anaesthetic is almost completely cleared from the venous blood during its passage through the lungs so that no "reanaesthetisation" of the patient, or animal takes place; this does occur with ether which has a much higher blood: gas partition coefficient. The gas or volatile anaesthetic which is rapidly exhaled during recovery is also readily absorbed during induction so that the onset of anaesthesia with halothane is quick.

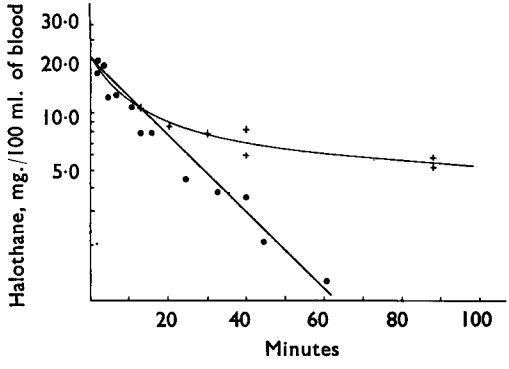

FIG. 2. The elimination of halothane from the arterial and venous blood of rats after anaesthesia with halothane. ●—● Arterial blood; +—+ venous blood.

The correlation of the calculated and experimentally determined half-clearance times of halothane indicate that it is not extensively metabolised. Several different experiments were carried out to determine whether halothane was metabolised; all gave negative results.

REFERENCES

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2. Johnstone, *Brit. J. Anaesthesia*, 1957, **29**, 135.
3. Goodall, *Brit. J. Pharmacol.*, 1956, **11**, 409.
4. Duncan, *Brit. J. Anaesthesia*, In the press.
5. Butler, *Fed. Proc.*, 1958, **17**, 1158.

After Dr. Duncan presented the communication there was a DISCUSSION.