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A Simple Implantable System for Delivery of Halothane

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A capsule for regulated halothane delivery after abdominal implantation in experimental animals is described. The capsule is constructed of readily available medical-grade polyethylene and Teflon® tubing. At 37 C linear halothane release rates of 0.4 to 15 mg/hour may be obtained. (Key words: Anesthetics, volatile: halothane. Equipment: anesthetic capsule.)

In the course of our *in-vivo* studies of halothane metabolism in experimental animals, we needed a method of controlled delivery of small quantities of radioactive halothane over periods ranging from hours to several days. Previously reported means of halothane administration to experimental animals have several disadvantages. Administration by inhalation is impractical, as this requires either immobilization or confinement of the animal in closely monitored chambers. Loss of radioactive halothane is also a considerable problem, as is decomposition of halothane during passage over soda lime in rebreathing circuits.[1] Administration of single doses by intragastric instillation or intraperitoneal injection does not provide for a slow and constant release rate and, in addition, results in tissue injury[2,3] and peritoneal inflammation.[4] Intraperitoneal injections of halothane dissolved in olive or corn oil slow the absorption rate, but the injected oils cause severe abdominal irritation and encapsulation. Continuous intravenous injection offers an ideal route of administration, but is impractical. A single intravenous halothane injection, again, does not provide a method of slow and controlled release. Commercially available drug infusion devices† have proved unsuitable for our purposes due to incompatibility of these devices with halocarbons.

In this communication we describe a conveniently assembled polyethylene capsule designed for the slow intraperitoneal release of halothane. The capsule is biologically inert and may be sterilized before implantation. It is not disruptive or toxic *in vivo*, and no tissue or organ necrosis or encapsulation of the device has been observed as long as five days after implantation.

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† Alzet Minipump, Alza Corporation, Palo Alto, California.

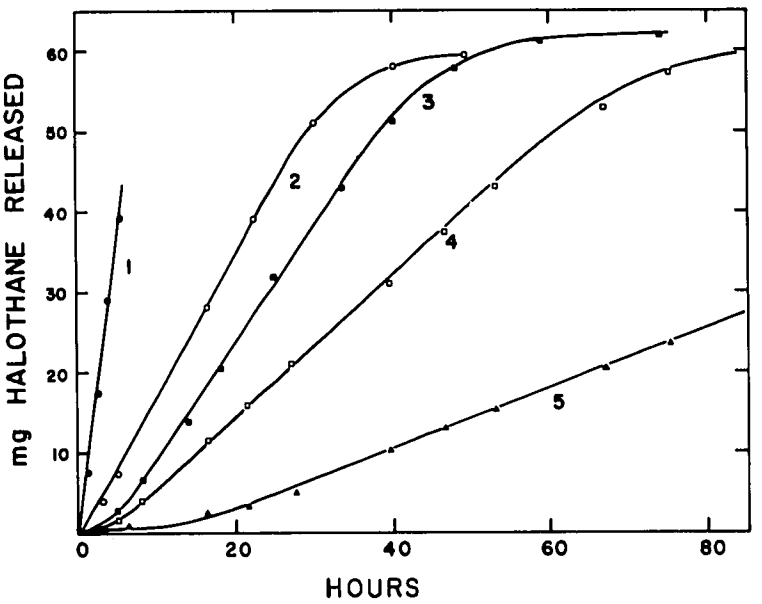

Fig. 1. Release of halothane from polyethylene capsules. Each capsule initially contained halothane, 25–35 μl (47–65 mg). Incubations were in water at 37 C. The capsule composition and halothane release rates were: 1) polyethylene 190, 7.8 mg/hour; 2) polyethylene 240, 2.2 mg/hour; 3) polyethylene 280 with an inner Teflon sleeve, 1.4 mg/hour; 4) polyethylene 280 with an inner Teflon sleeve plus propylene glycol at 10 per cent (v/v), 0.8 mg/hour; 5) same as 4 except propylene glycol at 30 per cent (v/v), 0.4 mg/hour.

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Halothane diffusion from the capsule is linear and is a function of temperature and capsule length and cross-sectional area, as already described for diffusion of gases from sealed Teflon® tubes.[5]

Materials, Methods and Results

A 2-cm piece of medical-grade 6452 standard-wall Teflon tubing,‡ stretched to 110 per cent of its initial length to 0.085 inch OD, was inserted into the center of a 3-cm section of Intramedic® PE 280 polyethylene tubing, 0.085 inch ID, 0.128 inch OD,§ and the polyethylene tubing was heat-sealed at one end using a soldering iron. The tube was cooled with a small piece of dry ice, halothane 25–35 μl (47–65 mg) was introduced with a microliter syringe, and the top end was heat-sealed as described above, leaving 3–5 mm air space between the halothane and the completed seal. The Teflon tubing was not sealed; each end of the Teflon tubing was 0.5 to 1 mm from the sealed end of the outer polyethlene sheath. The finished capsule is about 2.5 cm long and may be sterilized by rinsing with 70 per cent ethanol.

In preparation for implantation of the capsule, a rat was lightly anesthetized by administration of ketamine, 80 mg/kg, intramuscularly, supplemented by local abdominal infiltration of 1 per cent lidocaine, 1.0 ml/kg. A 1–2-cm abdominal incision was made, the capsule inserted into the lower abdominal cavity and sutured in place.

‡ Becton, Dickinson and Co., Rutherford, New Jersey.
§ Clay-Adams, Inc., New York, New York.

Release of halothane from the capsule may be conveniently monitored by weighing. The capsule described above delivers halothane at an approximate linear rate of 1.4 mg/hour, determined either *in vivo* after implantation or *in vitro* in water at 37 C. More rapid release rates may be obtained by decreasing the length of or omitting the inner Teflon sleeve and by using smaller-gauge and thinner-walled polyethylene tubing. For example, release rates in water at 37 C using 240-, 190-, and 90-gauge polyethylene tubing were 2.2, 7.5 and 9.8 mg/hour, respectively. Slower release rates were also obtained by adding propylene glycol to the halothane before heat-sealing the capsules. When propylene glycol was 10 and 30 per cent by volume, the linear release rates of halothane were 0.8 and 0.4 mg/hour at 37 C, respectively (fig. 1). The release of halothane is linear until approximately 90 per cent of the halothane has been released from the capsule. The ensuing release rate then slowly declines to zero over the next 15 hours.

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