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Patency of chronic jugular cannulae with systematically varied outer diameter and length

R. F. MUCHA*, C. VOLKOWSKIS, *Department of Pharmacology, University of Toronto and *Addiction Research Foundation, 33 Russell Street, Toronto, Ontario, Canada M5S 2S1*

Chronic intrajugular cannulation has a variety of applications in biological investigations of the rat since it allows for repeated administration of substances to freely moving, and relatively stressfree subjects (Davis & Campbell 1974). There are a number of cannulation procedures differing in the dimensions of the tubing inserted into the vein. The tubing, typically silicone because of its reduced tendency to cause tissue irritation (Stewart & Sanislow 1961), has its termination ranging from a point in the heart (Weeks 1972) to one a few cm from the heart (Davis & Campbell 1974), and its diameter varied between 0.064 cm (Weeks 1972) and 0.1 cm (Steffens 1969).

The problem is that none of the procedures are entirely problem-free. For example, we have found in preliminary work that cannulae constructed and implanted according to Davis & Campbell (1974) often failed within 1 week of surgery. Similarly, Terkel & Urback (1974) noted problems with Week's cannula, although the implication was that the patency lasted longer than in Davis and Campbells' procedure. However, except that in many reports Week's cannula has been used, there are almost no reasons for choosing one cannula over another. Thus, the question to be answered in the present experiment was whether any particular cannula has a higher probability of remaining patent.

Fifty-four adult male Wistar rats (Canadian Breeding Laboratories), housed individually in stainless steel cages, were divided into six equal groups. Under sodium pentobarbitone anaesthesia (60 mg kg⁻¹) each rat received one of six different cannulae, implanted into the right jugular vein. The cannulae varied over two lengths and three diameters. They were constructed by swelling silicone tubing on to the end of 15 cm of polyethylene tubing. A 10 cm length of cotton

suture was secured with a knot over the joint of the connection and the silicone tubing portion of the cannula was cut to a length of 25 mm according to Davis & Campbell (1974), or 40 mm to rest just inside the right atrium as recommended by Weeks (1972). The cut end of the silicone tubing was then plugged with cement (Dow Corning Silastic No 891) and after curing, pin holes (1 mm²) were punched over the final 0.75 cm. The three diameters of the cannulae, 0.064, 0.094, and 0.119 cm, were constructed of Silastic tubing No 602-101 and Clay Adams Intramedic PE 10, Silastic No 602-135 and PE 50, and Silastic No 602-151 and PE 60, respectively. The tubing diameters were the three sizes of silicone tubing available to us which were capable of easily fitting into the jugular vein.

Surgery was similar to the methods of Weeks (1972) and of Davis & Campbell (1974). The right jugular vein was exposed through a 3 cm skin incision following the separation of the fat and connective tissue. The cannula was inserted into the blood vessel about 1 mm rostral to the cephalic vein and was gently pushed until the aforementioned knot came in contact with the opening into the vein. The cannula was secured, once to the pectoral muscle and twice to one of the adjacent neck muscles. The cannula was then passed subcutaneously to an exit site 2 cm behind the ears where the tube was sutured once to the outside of a stab wound. Each rat received no systematic post-

Table 1. Proportion of rats with patent cannulae in groups implanted with cannulae having one of three diameters and two lengths.

Cannula outer diameter (mm)	0.064	0.094	0.119
25 mm length	5/9	0/8	0/7
40 mm length	9/9	6/6	3/9

* Correspondence.

operative care except 30 000 units of long-acting penicillin G (i.m.) every 2 days for 8 days.

Patency of each cannula was tested 14 to 17 days after surgery. Under light ether anaesthesia each rat was connected to an infusion pump. Following a 5 min period required to regain normal ambulatory activity, the rat was infused with 0.5 ml min⁻¹ of physiological saline (0.9% NaCl) containing 60 mg ml⁻¹ of pentobarbitone. The latency between the start of the infusion and loss of righting reflex was measured. Rats with patent cannulae responded with loss of righting reflex between 20 and 42 s after start of the infusion. Rats with non-functional cannulae did not show a loss of righting reflex even after 60 s and the infusion was accompanied by seepage of fluid at the point of entry into the rat.

The results of the test for patency carried out on 48 rats that did not dislodge their cannulae are summarized in Table 1. Chi square statistical tests indicated a significant effect of length ($P < 0.01$) and outer diameter ($P < 0.05$). Cannulae consisting of the two smaller diameters and the 40 mm length were all functional, whereas none of those consisting of the two larger diameters and 25 mm length were. Dissection of four to five animals in each group revealed that all cannulae regardless of dimensions were encapsulated in a sheath of dense tissue between the

vessel wall and the cannula, and in the case of cannulae that did not work the tissue completely enclosed the open end of the cannula. Thus, as the fluid was infused it was forced along a pathway between the silicone tubing and the vessel wall and out of the vein. The functioning cannulae were also completely covered over, but the tissue was not as dense and therefore not impervious to the fluid.

Thus, it was concluded that jugular cannulae constructed of small diameter silicone tubing and terminating in the heart have the greatest probability of remaining patent.

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Further consideration of the existence of an optimal partition coefficient for intestinal absorption of foreign compounds

S. G. WOOD*, D. G. UPSHALL, J. W. BRIDGEST†, *Chemical Defence Establishment, Porton Down, Salisbury, Wilts., and †Department of Biochemistry, and Institute of Industrial and Environmental Health and Safety, University of Surrey, Guildford, U.K.*

A number of workers have reported that a linear relationship exists between the rate of absorption from the small intestine and partition coefficient of foreign compounds (Schanker 1960; Kakemi et al 1967; Bates & Gibaldi 1970). Houston et al (1974, 1975) using a homologous series of aliphatic carbamates, covering a much wider span of partition coefficients than investigated by previous workers, have proposed that the true relationship between rate of absorption and partition coefficient is a parabolic one.

The findings of Houston et al are not directly comparable with those of other workers for the following reasons: fed rather than starved animals were used and although the intestines were rinsed thoroughly before use intestinal absorption characteristics could vary between the fed and starved states. Because of the lack of sensitivity of the g.l.c. procedure for measuring the carbamates, relatively high concentrations (10 mM) were used for the higher homologues, these concentrations are greater than the water solubility of these

compounds. To keep these compounds in solution small amounts of Tween-80 were added and although the detergent did not appear to alter the rate of absorption of the lower carbamates (in which its addition was not required for solubilization purposes) it might have influenced the absorption of the higher homologues thus contributing to the parabolic relationship between absorption rate and partition coefficient.

In view of the fact that the relationship of rate of absorption to the partition coefficient may be an important consideration in drug design we have re-investigated the absorption characteristics of the carbamates studied by Houston et al at concentrations well below their water solubility limits (i.e. 0.1 mM) with and without added detergent in both fed and starved animals.

[¹⁴C-carbonyl] Ethyl carbamate (specific activity 31.4 mCi mm⁻³) was supplied by Fluorechem Ltd., Glossop, Derby. [¹⁴C-carbonyl]n-Butyl, n-hexyl and n-octyl carbamates (specific activity 1.5 mCi mm⁻³) were synthesized by the Chemistry Division, Chemical Defence Establishment. Techniques for studying absorption were those described by Houston et al (1974) unless otherwise stated.

* Present address: Huntingdon Research Centre, Wooley, Nr. Huntingdon.

† Correspondence.