A Central Venous Catheter for Long-term Studies on Drug Effects and Pharmacokinetics in Munich Minipigs

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SUMMARY

We have developed an implantable venous catheter for repeated blood sampling in the Munich minipig. The catheter consists of silicone tubing, with a polyesterfibre net for fixation in the subcutaneous tissue of the neck. It was introduced into the right jugular vein, and its tip was positioned in the right atrium. The extravascular part of the catheter was tunnelled subcutaneously to the exit point in the subscapular region. In order to avoid contamination of the silicone tubing by drugs, intravenous administrations were performed via a second polyethylene catheter inserted into the implanted catheter. In 9 minipigs, the catheter remained patent for an average of 200 days (maximum 515 days). The animals did not show any signs of discomfort or impaired health.

INTRODUCTION

In animal studies on drug effects and pharmacokinetics, blood samples have to be taken for the determination of drug plasma levels, the analysis of metabolites or the assessment of drug action. In small laboratory animals blood samples can be collected by puncture of the orbital venous plexus, the tail vein or the heart. In dogs, blood samples are routinely obtained from a forelimb vein. In pigs, blood samples have been obtained from various sites. Single blood samples can be taken by puncture of the cranial vena cava (1), the orbital venous plexus (2) or the femoral vessels (3). In pigs with large ears, the earveins can be used for collecting blood (4). Blood sampling from piglets can be performed by cardiac puncture (5) or tail cut (6). The animals have to be restrained to perform these techniques, which are timeconsuming and accompanied by stress and discomfort for the animal. In addition, some of these techniques require a blind approach to the target vessel, which may result in vessel injury.

In the serum of small laboratory animals, Friedel et al. (7) observed higher enzyme activity in samples from the retroorbital venous plexus as compared to samples taken from the jugular vein or by cardiac puncture. Döhler et al. (8) discussed the site of blood sampling as a possible source of error in hormone determination. They compared cardiac puncture, retrobulbar puncture and decapitation in rats. Van der Wal et al. (9) showed that the acid-base status of porcine blood is affected by severe stress associated with vena cava puncture, as opposed to sampling via an indwelling catheter. Therefore, it would be useful to have venous access for parenteral drug administration and for repeated blood sampling without adverse effects.

To solve this problem, a number of indwelling catheters have been developed for implantation in pigs. Some of these catheters are complex, and made of various materials. Since their patency is short, some can be used for one experiment only.
The purpose of this study was to develop a central venous catheter which would be easy to assemble, to handle and to maintain. The catheter should remain patent for 6 months or longer. In addition, there should be a minimal risk of thrombosis and no adverse effects on the health of the animal. For our studies we chose the Munich minipig, Troll®, because it is small, sturdy, learns quickly and is easily tamed (10, 11).

MATERIALS AND METHODS

Animals

Nine castrated male Munich miniature pigs (Troll, MSM, Munich, FRG) were trained until they accepted handling and experimental conditions without requiring restraint. The minipigs were maintained singly on a heated tile floor and were fed a total of 425 g Altromin 9023 in two meals per day (Altromin, Lage, FRG). Water was available ad libitum. At the time of surgery, the pigs weighed 9-12 kg and were 100-140 days old. The last feed prior to surgery was given 20 hours before induction of anesthesia.

Catheters

The catheters were made of medical grade silicone tubing (Dow Corning, Midland, USA). They had an inner diameter of 1.02 mm, an outer diameter of 2.16 mm and were 400 mm long. The volume of the catheter was approximately 0.5 ml (Figure 1). To allow the catheter to be fixed in the subcutaneous tissue, a mersilene net 20 mm in diameter was mounted 70 mm from the proximal end of the catheter (RM-54, Ethicon, Norderstedt, FRG). The proximal end was reinforced with two silicone rings. In addition, two silicone cuffs were added to the catheter 240 mm behind the mersilene net 20 mm apart. These allowed fixation of the catheter within the jugular vein. Attachment of the cuffs and smoothing of the distal tip of the catheter was carried out using silicone glue (Silcoset 151 RTV, Ambersil, Basingstoke, UK). The proximal end of the catheter was closed using a stainless steel pin, 10 mm long and 1.6 mm in diameter (Henke-Sass Wolf, Tuttingen, FRG). The catheters were sterilized by an autoclave (FOH/70 - Z 2 Tecnorama, Fernwald, FRG).

Anesthesia

Before premedication, the animals were shaved around the neck and washed (Esemtan Lotion, Schülke & Mayr, Norderstedt, FRG). A depilatory cream was used to remove the bristles at the operation site (Depilan, Hamol, Köln, FRG). The pigs were premedicated with 0.2 mg of atropine sulfate (Braun Melsungen, Melsungen, FRG) and 80 mg of azaperone (Janssen, Neuss, FRG), both administered intramuscularly simultaneously in unrestrained animals. This was accomplished by interposing a 500 mm catheter extension filled with atropine between a syringe and a 23-gauge needle (Venofix, Braun Melsungen, Melsungen, FRG). The syringe was filled with azaperone. Anesthesia was then induced with 250 mg of metomidate i.p. and continued as requi-