Introduction

Internationally, miniature swine have become a definitive translational research and preclinical pharmacology model. Many if not most of the scientific protocols require the administration of test substances or therapeutic agents and the collection of samples of bodily fluids for assays. It is preferable to administer test substances via non-surgical routes however this is not always possible due to both technical and pharmacological factors. Methods of delivery of drugs and collection of test samples for assays have been described in detail. This manuscript provides an overview of those methodologies.

Non-Surgical Methodologies

Oral Administration

Swine can be induced to eat many test substances provided they do not have a noxious taste or odor. Capsules, pills and powders can be mixed with palatable substances and fed in small amounts if they will not consume it in their primary food ration. The primary food substances utilized by the author are dog and/or cat food meatballs, chocolate or strawberry syrup and fruit jelly. (Figure 1)

Injectable Administration

Intramuscular injections (IM) are painful in swine because of their dense muscle mass. They should be avoided if another route of injection such as subcutaneous (SC) is acceptable. Repeated injections, especially im, will create an avoidance reaction in swine when approached by personnel. SC injections in the side of the neck are the least objectionable sites for swine. They can either be restrained in slings or a butterfly catheter technique can be utilized. For that technique manual restraint is not necessary.

First a butterfly catheter is placed in the neck and the pig allowed to accommodate to the slight pain from the placement of the catheter. The end of the catheter is picked up, attached to a syringe and the injection is administered. (Figure 2)
IV injections are typically performed with indwelling catheters. If single IV injections need to be made without a catheter then sedation of the pig would be required and typically the injection is made into a marginal ear vein. The cephalic vein on the cranial surface of the radius can also be utilized for a one time IV injection.

Indwelling catheters may be placed using light sedation for short term use of < 3 days. The short term catheters are usually placed in a marginal ear vein or the precava. It is possible with an Intracath (Intracath® Central Venous Catheter, BD Worldwide, 16-22 g, 8-24 in long) to pass a catheter from the auricular vein into the external jugular catheter. This method provides the most security for a short term catheter. Shorter catheters of various types (14-24 g, 0.75-2.25 in long) can be utilized as well but the shorter catheters make it more likely that the catheter can be displaced from the vein by the pig. (Figure 3)

If the auricular veins are used then a gauze roll is placed inside the fold of the ear and taped in place with the catheter. If the precava is used then the catheter entry site is protected with gauze and a iodine impregnated sticky drape (3M™ Ioban™, St. Paul, MN). The surgical drape will stick to the skin after it is shaved and cleaned with alcohol. The alcohol must be dried off the skin prior to the application.

It can be further secured by circumferential taping around the neck. All short term catheters need to be filled with a premeasured amount of heparin or catheter lock solution. (Figure 4)

**Surgical Methodologies**

**Chronic Intravenous (iv) Implantations**

If catheters are expected to be functional for > 3 days then they should be
surgically implanted using methodologies to ensure security of the implant and to protect against sepsis. The catheters can be externalized though an exit on the dorsum of the pig or implanted subcutaneously. Any blood vessel in the periphery or abdomen can be catheterized. For example, catheterization of the portal vein may be indicated in some pharmaceutical metabolism studies. The most common peripheral veins that are catheterized are the external and internal jugular, the cephalic as it crosses the neck (subclavian area) and the portal vein. The femoral and ventral abdominal vessels provide less security and are utilized only if there is specific interest in the areas which they drain.

Externalized catheters are used for short term <14 days of access, especially if frequent vascular access is required. It is difficult to maintain sterility beyond that time. Silicone is the most common material used for these catheters and the tips of the catheter should be rounded not square or angular to prevent thrombus formation at the tip. IV catheters should be secured with circumferential sutures at the site of entry and exit of the catheter from the vessel. A loop of the catheter should be left in the internal incision to allow for movement to prevent dislodgement of the catheter.

At the exit site though the skin the catheter should have a cuff in the subcutaneous region to allow ingrowth of fibrous connective tissue, which acts as a seal on the catheter exit site. If the catheter is allowed to move in and out of the skin at that site it is highly likely that the catheter tract will become infected in a few days. (Figure 5)

Vascular access ports (VAP) should be utilized if the catheterization is expected to be patent for longer periods of time.1,7 (Figure 6) In the author’s experience this may be as long as a year. These ports are implanted subcutaneously with the IV catheter attached. Ports have to be accessed with Huber point needles in order to prevent coring of the silicone injection port. It is advisable to have suture retention beads attached to the catheter to increase security at the site of insertion into the vessel. The VAP must be implanted in a subcutaneous pocket distant from the skin incision to prevent erosion. Typically the sites of VAP implantation are along the dorsum of the pig behind the ear or over the rib cage. There are many different designs of ports and readers are encouraged to read the reference material for in depth descriptions of the implantation procedure prior to performing the procedure in a pig. 1,7

Figure 6. Vascular Access Port.

Gastrointestinal (GI) Access1,6

Various areas of the GI tract may need to be accessed for both administration of test substances and for collection of samples. Endoscopic techniques may
be used for some of these procedures if the equipment is available and access is limited to a few times under anesthesia. However, it is common for there to be a requirement for access of the various areas of the GI tract to determine the best site of absorption of a drug. Areas which are frequently catheterized are the stomach, duodenum, jejunum, ileum and colon.

Specialized catheters have been designed for implantation into these areas of the GI tract. (Figure 7) These catheters are attached to a VAP device. The catheter that is inserted into the intestine must have a closed tip and have small slits cut into the distal sides of the catheter. This prevents the catheter from being plugged by ingesta; however, these catheters can only be utilized for infusion of substances not withdrawal of samples. The VAP body is implanted subcutaneously into a pocket along the dorsal flank of the pig. At the site of insertion into the intestine a fixed suture bead is implanted inside a stab incision into the intestine and closed with a purse string suture. A silicone disc is sutured to the outer serosa to provide for a secure attachment to the intestine which prevents dislodgement during peristalsis. These catheters have remained patent for a year in the experience of the author.

If sampling of intestinal contents is required then a fistula must be created using cannulas specially designed for the study. (Figure 8) These cannulas should be secured inside the GI tract with a purse string suture leaving a retention disc inside the structure. They should also be sutured to the interior of the abdominal wall and in the subcutaneous tissue at the exit site. The exit site should be in the dependent portion of the intestine in the lateral flank. As the pig grows it is useful to have a device which can be loosened to accommodate the increase width of the abdominal muscles. This growth is minimized in the ventral section of the abdomen. In the authors experience these fistulas may be maintained for as long as a year. 6

**Discussion**

This manuscript is meant to provide an overview of the possible methods of delivery of test substances, such as pharmaceuticals, and the collection of samples for these studies. Surgeons should read the in depth descriptions of the surgical procedures and the perioperative care methods in the selected references prior to proceeding. In all of the catheterization methods the IV catheters should be filled with a pre-measured amount of heparin of taurolidine citrate solution to prevent clotting. Asepsis should be utilized for every access of these sites by cleaning with an antiseptic solution and wearing of sterile gloves. The same degree of asepsis should be utilized for the GI catheters and fistula devices.
Miniature pigs would be preferred over farm pigs for these types of studies because of their slower growth rate and smaller size which would require a lesser amount of test substance. They can also be selected at a reasonable size at sexual maturity in order to study the effects of the drug on a sexually mature animal. Farm pigs would not be manageable at sexual maturity for such studies. There is also a large body of literature available to study the effects of drugs on the various miniature breeds.2-4

Selected References


