The Minipig in Toxicology

As a laboratory animal, the minipig offers many advantages compared to other non-rodent species. Although non-human primates may seem to be the best candidates as non-rodent models for toxicity testing, the Beagle dog has important characteristics which make the dog a well established non-rodent species. However, the present world-wide recognition of the dog as a non-rodent model is highly influenced by tradition and conservatism among decision makers in industry.

The minipig performs well as an alternative animal model. The skin, the gastrointestinal tract and the cardiovascular and urogenital systems of the minipig are in many ways similar to those of man. Besides a similarity of anatomy and physiology, the minipig also has a drug metabolism similar to man's.

Techniques such as blood and excreta sampling, including urine sampling from metabolism cages, routine dosing and continuous infusion are easily performed in the minipig.

While rabbits are commonly used for the assessment of primary dermal irritation, pigs and minipigs have been considered a good model for dermal absorption and toxicity studies. Human and porcine skin are similar with regard to sparsity of the pelage, thickness and general morphology, epidermal cell turnover time and size, and orientation and distribution of blood vessels. The particularly thin haircoat and the lack of pigment of the minipig make it ideal for dermal studies.

Besides being used in general toxicity testing, the minipig is a model for teratogenesis and immunotoxicity. In addition, the minipig develops parkinsonism after treatment with MPT, diabetes after treatment with streptozotocin and hypercholesterolaemia and atherosclerosis after treatment with atherogenic diets.

References:

Satellite symposium to Eurotox'97

The Minipig in Toxicology is organized on 24-25 June 1997 at the Scandinavian Congress Centre in Aarhus, Denmark, as a satellite symposium to Eurotox'97. The aim of the symposium is to exchange information on the use of minipigs in toxicity testing, and to discuss regulatory aspects of minipigs in toxicology during a workshop with representatives of EMEA, FDA and OECD. It is our hope that the importance of the minipig as an alternative model in toxicology will be mediated through the symposium.
CONTINUOUS INFUSION IN THE GÖTTINGEN MINI-PIG

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Introduction

A description is given of continuous intravenous infusion with an ambulatory infusion pump in the mini-pig at Scantox. Scantox is a contract research laboratory specialized in toxicology, pharmacology and bioassays. Within the last ten years, Scantox has used the mini-pig extensively as a model in toxicology and pharmacokinetics. Thus the mini-pig has become part of the profile of Scantox.

Continuous intravenous infusion is an alternative method of dosing for compounds where other dosing methods would turn out to be inadequate - often because of either low adsorption after oral administration or the short halflife of the compound. The short halflife of the compound may be due to extensive local degradation after subcutaneous or intramuscular administration or to fast systemic clearance after intravenous bolus injection.

Preclinical testing of such drugs therefore necessitates continuous intravenous supply of the compound to ensure stable plasma concentrations during the dosing period.

Catheter insertion and infusion

Using aseptical surgical procedures incisions are made on the neck over the jugular vein and on the back between the scapula and the spine. A catheter is tunnelled subcutaneously between the incisions, inserted into the jugular vein, and the tip of the catheter is advanced into the vein until a position just in front of the heart. The catheter is fixed in this position by sutures.

The free end of the catheter is connected to the tubing of an ambulatory infusion pump. A plastic bag containing the test article solution to be infused is placed in the pump. The pump is placed in a pocket in a jacket carried by the mini-pig. Immediately after connection of the catheter to the pump, the infusion is started with sterile physiological saline at a flow rate of 1.0 ml/hour. After a recovery period of at least one week the mini-pig is ready for dosing with the compound.

Ambulatory continuous infusion at Scantox allows the mini-pigs to move freely in the cage and the method is generally very well accepted by the animals.

Continuous infusion in toxicology

There is no indication that continuous intravenous infusion per se causes any change of clinical signs, body weight, food consumption, electrocardiography, ophthalmoscopy, haematology, clinical chemical parameters or urinalysis. Minor macroscopic and microscopic findings of scar tissue associated with the area of surgery and minimal irritation in the vein accommodating the tip of the catheter are the only adverse effects caused by this method of dosing.

Continuous infusion using this model can be performed for up to three months and is offered on a routine basis at Scantox.

Continuous infusion in pharmacology

In pharmacodynamic and pharmacokinetic studies continuous infusion (by intravenous, subcutaneous, intrathecal or epidural route) may be especially useful as stable, measurable plasma concentrations are easily obtained. Blood sampling, urine sampling and other methods employed in these studies are not affected by this method of dosing.

Conclusion

Continuous infusion is a reliable and safe method for dosing and can be performed in mini-pigs when needed for testing in toxicological and pharmacological studies.
Glutathione S-transferases (GSTs) comprise a ubiquitous multi-gene family of proteins consisting mainly of α, μ, π and θ-class isoforms as defined by isoelectric point and are responsible for the detoxification of a range of xenobiotics, mainly via conjugation to glutathione. Alpha glutathione S-transferase (αGST) is predominantly found in the liver and kidney and has been conclusively shown to be an excellent indicator of hepatic damage in humans, when released into the circulatory system, by virtue of a high tissue concentration (3-5% hepatic soluble protein) and a short plasma half-life (1.5-2 hours). Porcine GST isoenzymes have been extensively described in the literature and this has facilitated both the purification of porcine αGST and the identification of a highly specific monoclonal IgG (anti-porcine αGST). Given that the porcine model is often used to predict hepatotoxicity and non-hepatoxin related damage in humans (e.g. post-transplantation ischemic damage), an enzyme immunoassay based on the aforementioned reagents has been developed for the quantitative detection of porcine αGST in various biological matrices. More specifically, αGST purified from porcine liver was used to generate a specific anti-porcine αGST antiserum. This antiserum, in combination with a highly specific anti-porcine αGST monoclonal antibody was used to format the immunoassay, which has a dynamic range of 0-100μg/L (extendable by sample dilution) and facilitates simultaneous multiple sample analysis (n=40) (Figure 1). The use of enzyme immunodetection offers several advantages over conventional enzyme activity measurements, including the reduced likelihood of assay interferences (e.g., bilirubin), analyte stability and no system artifacts due to enzyme inhibition/activation unrelated to organ damage.

The enzyme immunoassay has been utilised in a number of biological test systems to evaluate organ damage. For instance, the viability of porcine hepatocytes in culture has been evaluated whereby increased release of αGST is observed with extended culture periods. Additionally, the presence of foetal calf serum appears to be beneficial to in vitro hepatocyte viability as measured by reduced αGST release. Endotoxin hepatotoxicity has also been investigated using αGST detection whereby a ninefold increase in plasma enzyme levels was detectable nine hours after exposure to an experimental hepatotoxin. Measurement and quantitation of porcine αGST levels have also been applied to the field of experimental surgery for the investigation of damage caused by warm and cold ischemia, respectively during organ retrieval and storage. Here, it has been demonstrated that αGST release correlated with the extent of hepatocellular damage following ischemia and that enzyme release was more dynamic, peaking faster and returning to control values earlier, than corresponding markers such as ALT. In fact, these authors concluded that αGST quantitation is the most useful technique currently available when close monitoring of hepatic damage is required.

In summary, the quantitative determination of porcine αGST, in either in vivo or in vitro model systems, is an excellent indicator of hepatocellular damage and offers the evaluator a useful tool to investigate organ damage.

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References:

Selected references on the use of minipigs
Below you will find a selection from recent papers on the use of minipigs. If you have special inquiries of literature for your project, please let us help you with abstracts from our database.

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