Minipigs in the safety assessment of drugs

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Outline

• Regulatory requirements
• Choice of Non-rodent species
• Pigs and minipigs
• The Göttingen minipig
• Similarities to humans
• Dose routes, study types and experimental procedures
• Conclusion
Regulatory requirements

• A rodent and a non-rodent species should be used in safety assessment of new pharmaceutical products
• Dogs or non-human primates traditionally used
• Focus on the minipig significantly increased
Choice of non-rodent species

• Pharmacological responsiveness similar to man
• Metabolic similarity
• Physical or anatomical similarity
• Comparative reasons (species previously used for same class of compound)
Pigs and minipigs

• 13 species of pigs worldwide (suidae)

• At least 11 strains of minipigs exist
Why use minipigs?

- Size
- Similarity to man
- Growth in background data
- Regulatory acceptability
- Availability of high quality animals
- Concerns about primates (availability, handling, health status, zoonosis, emotive, costs)
- Concerns about use of dogs (emotive, vomiting)
Types of minipigs

- "Natural", ex. The Yucatan minipig
- Purposely bred, ex. The Göttingen minipig

- Weight ranges
  35-55 kg: Yucatan micropig, Göttingen minipigs
  50-60 kg: Sinclair, Hanford
  70-90 kg: Yucatan minipig, Hormel minipig
The Göttingen minipig I

- Bred in Germany (Göttingen) from the 1960’s
- Purposely bred entirely for use in biomedical research
- Breeding ”goals”:
  - small size – easier to handle, less test item
  - ”non-pigmented” – use for dermal research
- Crossbred
  - Minnesota minipig
  - Vietnamese pot belly pig
  - German landrace
- Well defined health status
The Göttingen minipig II

• Age up to 20 years?
• Body weight at birth: 0.45 kg
  Body weight at weaning: 2-3 kg
• Sexual maturity
  - males: 3-4 months (7-9 kg)
  - females: 4-5 months (9-11 kg)
• Body weight at age of 1 year: 25 kg
• Fully grown body weight: 35 kg
  - older boars up to 50 kg
  - older sows after multiple litter up to 60 kg
Similarity to humans

- Structure of the skin
- Gastrointestinal tracts
- Cardiovascular system
- Metabolism
- Teratogenic sensitivity
- Urogenital system (size, number of lobes)
- Nasal cavity (two sides separated)
Göttingen minipig skin
Gastrointestinal tract

- Pigs and humans are omnivorous
- Pigs have similar gastric cell types, villi and secretions to humans
- pH changes and transit time in the small intestine similar to humans
- Colon arranged in series of coils
Cardiovascular system

- Heart and great vessels similar to man (except left azygos vein)
- Coronary arterial blood supply to heart almost identical to humans
- Induction of myocardial infarction
- Hypercholesterolaemia and artherosclerosis
Metabolism

- Minipig CYP 1A, CYP 2A and CYP 3A metabolise same test substrates as in humans
- 75% identical cDNA sequences
- The minipig is a good model if these enzymes are involved in the metabolism of the test compound
Housing of minipigs
Routes of dosing/study types

- Oral (gavage/capsule/tablet)
- Dietary
- Inhalation/intranasal
- Dermal
- Injection (sc, im, iv, ip)
- Continuous iv infusion
- Intravesical
- Intravaginal

- Single dose studies
- Repeat dose studies
- Teratology studies
- ADME studies
- Telemetri
- Disease models
  - diabetes
  - wound healing
  - parkinsonism
  - transgenic minipigs
Dermal dosing II
Local tolerance studies
Oral gavage
Subcutaneous dosing
Intramuscular dosing
Blood sampling
Ophthalmoscopy
Urine collection
Electrocardiography

Normal sinus rhythm

Slight sinus arrhythmia

Occasionally wandering pace maker

Heart rate 90-164
Anaesthesia and surgery

• Rapid gastric emptying
  - short fasting period
• Injectable anaesthetics
  for surgery of short duration
• Inhalation anaesthetics recommended
  for longer procedures
• Endotracheal intubation requires
  special laryngoscope
• Anatomical differences
  (intestinal system, azygos veins)
• Post-surgical analgetic treatment
  (opoids, NSAIDs)
Intravenous dosing techniques

- Sparse peripheral veins
- Ear veins for single dosing
- Surgical intravenous access recommended for repeated i.v. dosing
  - Vascular Access Ports
- Infusion pumps connected to i.v. catheters used for continuous infusion
VAP implantation
Wound healing techniques

- Skin and wound healing of minipigs similar to humans
- Adult animals can be used
- Two models generally used
  - split-thickness wounds
  - full-thickness wounds
- Studies individually designed (limited regulatory guidance)
- Models of acute wound healing, not chronic
Juvenile studies

- Paediatric development in focus
- Age dependent pharmacokinetic, pharmacodynamic or toxicological differences may exist
- Development of main organ systems have important structural and functional differences with age
- Many practical aspects to be considered for each individual species
What is a juvenile pig?

- **Humans**
  - neonate: from birth to 1 month
  - infant: 1 month to 2 years
  - child: 2-12 years
  - adolescent: 12-16 years

- **Minipigs**
  - neonate: from birth to 4 weeks
  - infant: 4-8 weeks
  - child: 8 weeks to 3 months
  - adolescent: 3-5 months
Juvenile studies, study design

- Time mated sows
- Considerations for group establishment
  - one litter = one group (genetic bias)
  - all groups represented in one litter (contamination risk)
  - cross fostering (time mating, induced farrowing)
- Study procedures starting from Day 7
Teratology studies

• Minipig useful alternative to rabbits
• First choice when metabolism is similar to man
• Susceptible to human teratogens (thalidomide, hydroxyurea, ethanol and others)
• Large litter size as compared to primates
• Gestational period shorter than primates
• Regulatory acceptance
Uterus with fetuses
Alizarin stained fetus
Telemetria

- Cardiovascular safety pharmacology
- Animal handling at dosing only
- Transmitter placed s.c. in flank
- Blood pressure transducer placed in a. femoralis
- Wires for ECG placed s.c. over thorax
- Battery life time of transmitter
Conclusion

• The minipig shows many similarities to man
• The minipig constitutes a suitable model for a wide range of non-clinical studies
• All general routes of dosing can be used
• Anaesthesia of minipigs is a non-complicated procedure
• Many surgical procedures are practically feasible
• The minipig is accepted by regulatory authorities worldwide as a useful non-rodent species
The end...