Infusion Technology Organization - ITO

Development and implementation of a new access button used in the rat self-administration design

September 15, 2011

Greet Teuns,
- Introduction to abuse potential/liability

- Nonclinical drug abuse liability testing

- The self-administration model:
  - technical requirements
  - development of the VAB
  - how did we move on
  - implementation of the VAB in the SA model
  - choice of catheters in the SA model
Introduction to Abuse Potential/Liability

Definition

Abuse potential refers to a drug that is used in nonmedical situations, repeatedly or even sporadically for the positive psychoactive effects it produces (US).

Abuse liability refers to the likelihood that a drug product could be subject to user-initiated, non-therapeutic self-administration (Canada).

Dependence potential of an active substance is the propensity of an active substance, as a consequence of its pharmacological effects on physiological or psychological functions, to give rise to a need for repeated doses of the active substance to “feel good” or to avoid “feeling bad” (Europe).
Introduction to Abuse Potential/Liability

Mesoaccumbens dopaminergic system: important modulator

Examples of neurotransmitter systems of interest include the following:

- Dopamine
- Norepinephrine
- Serotonin
- Gamma-aminobutyric acid (GABA)
- Acetylcholine
- Opioid
- N-methyl-D-aspartate (NMDA)
- Cannabinoid
• Importance of avoiding drug abuse
Non-clinical drug abuse liability testing

Out There

I'll try my best to be home for dinner honey... but it will depend on how well the experiment goes

The life of a lab rat
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Guidance documents

**EM(E)A: European Medicines Agency**
EMEA/CHMP/SWP/94227/2004:
Guideline on the non-clinical investigation of the dependence potential of medicinal products (23 maart 2006)

**ICH: International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use**
ICH M3 (R2): Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals (11 Juni 2009)

**FDA Guidance for Industry**
Assessment of Abuse Potential of Drugs (26 Jan 2010)
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Current regulatory guidelines

What products?

- All new CNS-active medicinal products
  - regardless of therapeutic indication
  - metabolites which enter the brain
    - at relevant concentrations
    - that interact as central targets
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**Two-tiered approach**

**First tier:** Pharmacology

**Second tier:** Behavioural pharmacology studies

1) Withdrawal
   - physical dependence

2) Conditioned Place Preference
   - conditioning, rewarding, reinforcing effects

3) Drug Discrimination Learning
   - drug profiling

4) Self-Administration
   - reinforcing effects
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IV self-administration
- animal model of human drug-taking behaviour
- experimental procedure for studying the reinforcing properties of drugs

Animals press a lever to obtain a drug or saline (self-administration).
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IV self-administration (IVSA)

Procedure:

a) Laboratory animals: surgically prepared with IV jugular catheters that permit automated drug injections.

b) training of the animals to press a lever to self-inject various known reinforcing drugs (i.e. Cocaine, amphetamine,…).

c) example study outline (per dose group):
   Training (non-GLP): minimum 6 weeks
   - lever press
   - training psycho-active drug versus saline

   GLP study: minimum 6 weeks
   Phase 1 - Phase 2 - Phase 3 - Phase 4 - Phase 5 - TK cocaine - saline - cocaine - TA - cocaine - TA
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IV self-administration

Technical requirements:

- System must be designed for long-term use
- System must be comfortable to the animal (i.e. rat)
- System includes:
  - internal catheter
  - fixing medium: harness
  - vascular access button
- swivel/tethering
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IV self-administration

Technical requirements:

- fixing medium: harness: - not very comfortable
  - easy to bite through
  - not in favour for use in SA model

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IV self-administration

Technical requirements:
fixing medium:
- Existing vascular access buttons (VABs) on the market:
  - not comfortable to the rat: too big, heavy, limiting movements
  - no ideal type available for use in SA model (long-term)
    (large tops, heavy material, …)
- some universities/companies construct VAB themselves
  (not to be used as a standard within a GLP environment)

Need for a commercial system:
- to be used in long-term studies
- comfortable to the rat
- to be used in a GLP environment
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IV self-administration

Technical requirements

- Instech Solomon and Drug Safety Sciences (DSSc) at Janssen Research & Development, Beerse, Belgium:

  close collaboration to develop a prototype of a vascular access button for use in (long-term) SA studies

- no use of harness
- comfortable to the rat
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IV self-administration

How did we move on

- Problem solving:
  - top VAB (tether connection) was reduced in height
    (from 2.7 cm to 1.2 cm): more comfortable to the rat
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IV self-administration

How did we move on:

- Problem solving:
  - a self-sealing septum was applied
    easy for flushing procedures
    easy to connect with the tether
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IV self-administration

How did we move on:

- Problem solving:
  - the gauze pad underneath was modified in shape, size and material
    easy to insert subcutaneously; no irritation
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IV self-administration

How did we move on:

- Problem solving:
  - the connection underneath between the VAB and the internal catheter was modified to avoid breaking loose
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IV self-administration

Implementation of the VAB in the SA model

-Result: a new prototype of a modified vascular access button™ that can be used for long-term studies as in the SA model
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**IV self-administration**

Using the right catheter in the SA model

- catheter: brought into the v. Jugularis with the tip located near the right atrium
- choice of catheter: to be used for long-term studies as in the SA model
  - PU uncoated catheter: regular flushing needed (heparin solution)
  - PU coated catheter: CBAS® heparin coated PU catheter
Thank you