“Use of animal models with disease in Safety Pharmacology”

or

“You don’t give drugs to normal people!”

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Which animal is the best surrogate for man?

We must develop safe and efficacious drugs for all!

Is it likely that these animals possess polymorphisms suitable for extrapolation?
Clear FDA Guidelines, June 18th, 2007:
“….recommend you conduct pre-clinical testing, where appropriate and feasible, in an environment that simulates actual clinical conditions.” Clinical conditions seldom refer to healthy persons!
For those of you who balk at using diseased (not “naïve”) animals…

you already are!!
“Good” for the mouse

AALAS/NIH/USDA

Heavy viscera, lighter brains, immune-compromised, clotting activated

You study 80 to 100 million per year.

The LD50’s for both IP ephedrine and salicylic acid are ~50% lower at 20° than at 30°.

“It’s always been that way!”

Gerhard Zbinden: Don’t do something just because it’s always been done that way, because you can, or because others do!
“…..experiments conducted under highly standardized conditions (eg., on normal animals) may reveal local ‘truths’ with little external validity (to patients with disease).”

S Helene Richter, Joseph P Garner & Hanno Würbel, 2009
I know what a diseased animal is, but what is a naïve animal?

Is it gnotobiotic?
Is it vaccinated?
Are all parameters of the CBC and SMA normal?
Has it ever been used in a previous study?
Does it behave “normally“?
Is it not diseased (i.e., not showing signs/symptoms)…not absent from health (i.e., asymptomatic but will not live life span determined by apoptosis)?

Does it make a difference (more/less predictive) if it is naïve/diseased?
We should savor and exploit (not shy away from) genetic, epigenetic, and developmental heterogeneities in our surrogate populations in the hope of achieving greater statistical power or control. (i.e., Make statisticians happy!) Everybody knows that toxicity occurs much more ubiquitously in patients with multiple risk factors.

You can search for torsadogenicity in the best-controlled study on a million “identical” rats and never get the correct answer for man. You can ligate the left main coronary artery of a million guinea pigs and never learn anything about myocardial ischemia for man. You can give doses of atropine (lethal to man) to most rabbits and not get toxicity. Digitalis, ACE inhibitors, antiarrhythmics, beta blockers, and diuretics have profoundly different pharmacology/toxicology in normals than in subjects with heart failure....and on and on!
“The primary goals of preclinical safety evaluation are:

(1) to identify an initial safe dose and subsequent dose escalation schemes in humans (Do they mean healthy humans (yes in phase I, no in phases II and III?)�;
(2) to identify potential target organs for toxicity and for the study of whether such toxicity is reversible (Do they mean normal target organs?)�;
(3) to identify safety parameters for clinical monitoring (Do you monitor normal patients?)�.

Is there anybody who does not know that adverse events to drugs occur more commonly in patients because they are sick?
“Preclinical safety testing should consider:

(1) Selection of the relevant animal species;
(2) age;
(3) **physiological state**;
(4) the manner of delivery, including dose, route of administration, and treatment regimen; and
(5) stability of the test material under the conditions of use.”
“In recent years, there has been much progress in the development of animal models that are thought to be similar to the human disease. These models may provide further insight, not only in determining the pharmacological action of the product, pharmacokinetics, and dosimetry, but may also be useful in the determination of safety (e.g., evaluation of undesirable promotion of disease progression). In certain cases, studies performed in animal models of disease may be used as an acceptable alternative to toxicity studies in normal animals. The scientific justification for the use of these animal models of disease to support safety should be provided.”

What about providing the scientific justification for the use of healthy animals? Do we have knowledge of sensitivity and specificity of our present paradigms?
Issues for animal models with disease (for later discussion):

- Cost
- Availability
- Necessity/Demand
- Sensitivity (usually 1/specificity)
- Which diseases? Which conditions?
- Data supporting or refuting.
- Acceptability
- Interpretability
Examples of the value of using animal models with disease (not to be restricted to electrophysiology, but to all parameters that, if affected, translate to morbidity and/or mortality.
While not a model of disease? This model demonstrates the value of altered physiology/pharmacology for enhancing sensitivity to detect toxicity.

Table 1
Influence of $\alpha_1$-adrenoceptor stimulation by methoxamine on the induction of torsades de pointes (TdP) by class III antiarrhythmic agents in the anaesthetised rabbit

<table>
<thead>
<tr>
<th>Agent</th>
<th>No methoxamine</th>
<th>Methoxamine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># of rabbits with TdP</td>
<td>Dose at TdP</td>
</tr>
<tr>
<td>Clofilium</td>
<td>3/10 (30%)</td>
<td>2.2 mg/kg</td>
</tr>
<tr>
<td>Clofilium</td>
<td>4/6 (67%)</td>
<td>4.6 mg/kg</td>
</tr>
<tr>
<td>Clofilium</td>
<td>0/10 (0%)</td>
<td>34.7 mg/kg</td>
</tr>
<tr>
<td>Almokalant</td>
<td>1/6 (17%)</td>
<td>0.5 mg/kg</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>1/6 (16%)</td>
<td>0.5 mg/kg</td>
</tr>
<tr>
<td>E-4031</td>
<td>0/6 (0%)</td>
<td>0.5 mg/kg</td>
</tr>
<tr>
<td>β-sotalol</td>
<td>0/6 (0%)</td>
<td>0.5 mg/kg</td>
</tr>
<tr>
<td>Ibutilide</td>
<td>0/6 (0%)</td>
<td>0.5 mg/kg</td>
</tr>
</tbody>
</table>

*: J Matz, personal communication.
Example 1.
Example 2.

A Kijtawornrat/R Hamlin (OSU/QTest)
Example 3.

Incidence of TdP (%)

Control 2/8
RVH 6/7
LVH 2/9
BVH 7/9

*p < 0.01
*p < 0.05

Yaowalok Panyasing
Y Panyasing/A Kijtawornrat/R Hamlin (OSU/QTest)
Example 4.

Induction of Torsades de Pointes after HMR1556 (1.5 mg/kg IV) and Isoproterenol (2.5 μg/kg IV) in the anaesthetised beagle dog model.

**Baseline**

- **ECG:**
  - QT interval:
  - EMw = +89 ms

- **LVP:**
  - EMw = +89 ms

**HMR1556**

- **ECG:**
  - QT interval:
  - EMw = -39 ms

- **LVP:**
  - EMw = -39 ms

**HMR1556 + ISO**

- **ECG:**
  - QT interval:
  - EMw = -141 ms

- **LVP:**
  - EMw = -141 ms

**Example 5.**

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Exercise</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>C+E Decrease</td>
<td>C and C+E Decrease</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Graphs:**

- **Left Graph:**
  - **X-axis:** Time following start of treadmill (minutes)
  - **Y-axis:** Baseline-adjusted LV heart rate (mmHg)
  - **Legend:**
    - Placebo (5 mg/kg)
    - Esmolol (0.0 mg/kg)
    - Ceredistil (0.0 mg/kg)
    - Esmolol/Ceredistil (1.0 mg/kg)

- **Right Graph:**
  - **X-axis:** Time following start of treadmill (minutes)
  - **Y-axis:** Baseline-adjusted LV heart rate (mmHg)
  - **Legend:**
    - Placebo (5 mg/kg)
    - Esmolol (0.0 mg/kg)
    - Ceredistil (0.0 mg/kg)
    - Esmolol/Ceredistil (1.0 mg/kg)
Models to consider:
- Aged…costly and simple
- Diabetes…type I, but we’re interested in type II
- Obesity…relatively expensive
- Hypertension…inexpensive and facile depending upon type
- Heart failure…inexpensive and facile depending on type
- Hypertrophy…inexpensive and facile
- Concomitant drugs…least expensive and facile

Studies for exploitation of those models:
- General toxicology…No!
- To evaluate efficacy and mechanisms….Yes and yes!
- All Safety Pharmacology….No!
- “Lead” compounds….Yes!
- “Lead” compound….Yes, yes!

Why?
- to increase sensitivity (decrease specificity minimally?)
- to comply with FDA suggestion
- it “sounds reasonable”
- not costly
- requires moderate surgical skill
- humane
However, don’t even consider animal models with disease if you are satisfied with the Toxicology/Safety Pharmacology paradigm as it exists! Don’t do something just because you can! (GZ) It must make a difference! (GZ) The FDA seems to think it does!

Clear FDA Guidelines, June 18th, 2007:
“….recommend you conduct pre-clinical testing, where appropriate and feasible, in an environment that simulates actual clinical conditions.”
Thanks for your kind attention, and I look forward to stimulating criticisms, questions/answers and discussion. Mackenzie deserves safe and efficacious drugs!
QUESTIONS

We will now open the phone lines for discussion. If you would like to speak click the hand icon below the participants list.

Reminders:

Continue discussion on the SPS Blog

THANK YOU FOR ATTENDING.