Safety Pharmacology

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TOPRA MSc & Postgraduate Diploma in Regulatory Affairs
MODULE 2: REGULATORY STRATEGY FOR A NEW ACTIVE SUBSTANCE

De Vere Latimer Place, Chesham, Bucks
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Pharmacology

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AstraZeneca Drug Safety & Metabolism
Cambridge UK
In this presentation we will cover...
Safety Pharmacology

- What is it? How important is it?
- How do you do it?
- How do you use the data in risk assessment?
- Strategies to address the various Regulatory Guidance documents mentioning Safety Pharmacology
Safety Pharmacology

- What is it? How important is it?
- How do you do it?
- How do you use the data in risk assessment?
- Impact of other Regulatory Guidance documents mentioning Safety Pharmacology
Definitions

• **Primary Pharmacology Studies**
  • Investigate the mode of action and/or effects of a substance in relation to its desired therapeutic target

• **Secondary Pharmacology Studies**
  • Investigate the mode of action and/or effects of a substance not related to its desired therapeutic target

• **Safety Pharmacology Studies**
  • Investigate the potential undesirable pharmacodynamic effects of a substance on physiological functions in relation to exposure in the therapeutic range and above

*ICH S7A CPMP/ICH/539/00*
International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

“The purpose is to make recommendations on ways to achieve greater harmonisation in the interpretation and application of technical guidelines and requirements for product registration in order to obviate the need to duplicate the testing carried out during the research and development of new medicines”

“Topic S7: Safety Pharmacology Studies for Human Pharmaceuticals”.

• The committee on safety pharmacology brought together experts from safety assessment departments within the pharmaceutical industry, together with experts from regulatory authorities.

• The review of safety pharmacology began in 1999, with a desire to move away from prescribed lists and box-ticking, towards a more rational approach.

• Existing guidelines on safety pharmacology were superseded by the ICH guidelines.

• ICHS7A guideline adopted by all 3 territories in 2000.
ICH S7A stated objectives of Safety Pharmacology studies

1. To identify undesirable pharmacodynamic properties of a substance that may have relevance to its human safety; → → HAZARD IDENTIFICATION

2. To evaluate adverse pharmacodynamic and/or pathophysiological effects of a substance observed in toxicology and/or clinical studies; → → RISK ASSESSMENT

3. To investigate the mechanism of the adverse pharmacodynamic effects observed and/or suspected. → → RISK MANAGEMENT/MITIGATION
Implications of ICH S7A guidance document for safety pharmacology

- The core battery addresses effects on vital functions: CNS, CVS and respiratory system;
- If follow-up studies are required, these should be concluded before Phase I;
- The core battery should be conducted to GLP; any follow-up studies should be conducted in accordance with GLP ‘to the greatest extent feasible’.
Safety Pharmacology: How important is it?

• Safety pharmacology issues have a significant impact on CD attrition (both preclinically and during clinical development);
• Data are important for Phase I dose-setting;
• SP studies are a regulatory requirement for IND submissions prior to human exposure;
• There are 3 regulatory guidance documents focusing on safety pharmacology, and several others refer to it;
• The consequences of ‘getting it wrong’ can have dramatic implications.
Impact of Safety Pharmacology data

Discovery
- Target Identification
- Hit Identification
- Lead Identification
- Lead Optimisation
- Pre-nomination
- Pre-clinical Development

Development
- Principle Testing
- Concept Testing
- Dev. for Launch
- Launch
- Life Cycle Management

- Supporting Toxicology studies
- Resumption of clinical trial
- Drug interactions

- Predicting clinical outcome
- Influencing Phase I design
- Clinical biomarker
- Contributing to clinical plan

- In silico prediction
  - Pathway mapping
  - SAR

- Problem solving
- Influencing chemistry
Impact of adverse effects of drugs by organ system throughout the pharmaceutical life cycle

<table>
<thead>
<tr>
<th>Phase</th>
<th>‘Nonclinical’</th>
<th>Phase I</th>
<th>Phase I-III</th>
<th>Phase III/Marketing</th>
<th>Post-Marketing</th>
<th>Post-Marketing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information:</td>
<td>Causes of attrition</td>
<td>Serious ADRs</td>
<td>Causes of attrition</td>
<td>ADRs on label</td>
<td>Serious ADRs</td>
<td>Withdrawal from sale</td>
</tr>
<tr>
<td>Sample size:</td>
<td>88 CDs stopped</td>
<td>1,015 subjects</td>
<td>82 CDs stopped</td>
<td>1,138 drugs</td>
<td>21,298 patients</td>
<td>47 drugs</td>
</tr>
<tr>
<td>CARDIOVASCULAR:</td>
<td>27%</td>
<td>9%</td>
<td>21%</td>
<td>36%</td>
<td>15%</td>
<td>45%</td>
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<tr>
<td>Hepatotoxicity:</td>
<td>8%</td>
<td>7%</td>
<td>21%</td>
<td>13%</td>
<td>0%</td>
<td>32%</td>
</tr>
<tr>
<td>Haematology/BM:</td>
<td>7%</td>
<td>2%</td>
<td>4%</td>
<td>16%</td>
<td>10%</td>
<td>9%</td>
</tr>
<tr>
<td>NERVOUS SYSTEM:</td>
<td>14%</td>
<td>28%</td>
<td>21%</td>
<td>67%</td>
<td>39%</td>
<td>2%</td>
</tr>
<tr>
<td>Immunotox; photosensitivity:</td>
<td>7%</td>
<td>16%</td>
<td>11%</td>
<td>25%</td>
<td>34%</td>
<td>2%</td>
</tr>
<tr>
<td>GASTROINTESTINAL:</td>
<td>3%</td>
<td>23%</td>
<td>5%</td>
<td>67%</td>
<td>14%</td>
<td>2%</td>
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<tr>
<td>Reprotox:</td>
<td>13%</td>
<td>0%</td>
<td>1%</td>
<td>10%</td>
<td>0%</td>
<td>2%</td>
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<tr>
<td>Musculoskeletal:</td>
<td>4%</td>
<td>0%</td>
<td>1%</td>
<td>28%</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>RESPIRATORY:</td>
<td>2%</td>
<td>0%</td>
<td>0%</td>
<td>32%</td>
<td>8%</td>
<td>2%</td>
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<tr>
<td>RENAL:</td>
<td>2%</td>
<td>0%</td>
<td>9%</td>
<td>19%</td>
<td>2%</td>
<td>0%</td>
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<tr>
<td>Genetic tox:</td>
<td>5%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Carcinogenicity:</td>
<td>3%</td>
<td>0%</td>
<td>0%</td>
<td>1%</td>
<td>0%</td>
<td>0%</td>
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<tr>
<td>Other:</td>
<td>0%</td>
<td>0%</td>
<td>4%</td>
<td>16%</td>
<td>2%</td>
<td>2%</td>
</tr>
</tbody>
</table>

The various toxicity domains have been ranked first by contribution to products withdrawn from sale, then by attrition during clinical development.

Adapted from Redfern WS et al. SOT 2010; 2011
What types of ADRs can safety pharmacology studies predict?

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Cause and Predictability</th>
</tr>
</thead>
<tbody>
<tr>
<td>type A</td>
<td>Dose-dependent; predictable from primary, secondary and safety pharmacology</td>
<td>Main cause of ADRs (~75%), rarely lethal</td>
</tr>
<tr>
<td>type B</td>
<td>Idiosyncratic response, not predictable, not dose-related</td>
<td>Responsible for ~25% of ADRs, but majority of lethal ones</td>
</tr>
<tr>
<td>type C</td>
<td>Long term adaptive changes</td>
<td>Commonly occurs with some class of drug</td>
</tr>
<tr>
<td>type D</td>
<td>Delayed effects e.g. carcinogenicity, teratogenicity</td>
<td>Low incidence</td>
</tr>
<tr>
<td>type E</td>
<td>Rebound effects following discontinuation of therapy</td>
<td>Commonly occurs with some class of drug</td>
</tr>
</tbody>
</table>

Causes of type A drug effects

1. Augmented (‘supratherapeutic’) effect of interaction with the primary target \( \textit{e.g. pronounced bradycardia with a beta-blocker} \);

2. Interactions with the primary target present in non-target tissues† \( \textit{e.g. sedation caused by antihistamines} \);

3. Interactions with non-target ‘receptors’† \( \textit{incl. cardiac ion channels} \);

4. Non-specific effects;

5. Pharmacologically-active metabolites.

† examples given in next 3 slides
Interactions with the primary target in non-target tissues

\(^{11}\text{C}-\text{doxepin labelling of } H_1 \text{ receptors in human forebrain (PET imaging)}\)

control

\begin{itemize}
\item terfenadine 60 mg (non-sedating antihistamine)
\item (+)-chlorpheniramine 2 mg (first generation antihistamine: sedating)
\end{itemize}

Importance of blood-brain barrier

![Diagram showing blood-brain barrier log BB values for 50 AZ 'non-CNS' compounds and 19 CNS drugs.]

Compounds readily cross the blood-brain barrier: expect increased CNS safety pharmacology ‘baggage’!

Compounds with relatively poor penetration across the blood-brain barrier: expect minimal CNS safety pharmacology ‘baggage’!

Interactions with non-target receptors (‘secondary pharmacology’)

<table>
<thead>
<tr>
<th>Receptors</th>
<th>1 nM</th>
<th>3</th>
<th>10</th>
<th>30</th>
<th>100</th>
<th>3</th>
<th>10</th>
<th>30</th>
<th>100</th>
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<tbody>
<tr>
<td>AZ5678 PRIMARY TARGET (Ki = 40 nM)</td>
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<td>Receptors</td>
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<td>α₂-adrenoceptor</td>
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<td>histamine H1</td>
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<td>muscarinic M₄</td>
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<tr>
<td>serotonin transporter</td>
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<td>5-HT₁B</td>
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<tr>
<td>glutamate AMPA</td>
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<tr>
<td>sigma α₂</td>
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<td>neurotensin</td>
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<tr>
<td>imidazoline I₂, central</td>
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<td>muscarinic M₃</td>
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<td>5-HT₂A</td>
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<td>opiate μ</td>
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<tr>
<td>κ₁₁A-adrenoceptor</td>
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<tr>
<td>choline transporter</td>
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<tr>
<td>dopamine transporter</td>
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<tr>
<td>noradrenaline transporter</td>
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<tr>
<td>OTHER RECEPTORS (94)</td>
<td></td>
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</tr>
</tbody>
</table>

No margin between potency at primary target and at non-target receptors: expect increased safety pharmacology ‘baggage’!
### Interactions with non-target receptors (‘secondary pharmacology’)

<table>
<thead>
<tr>
<th>Receptors</th>
<th>AZ1234 PRIMARY TARGET (Ki = 2.5 nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT₁B</td>
<td></td>
</tr>
<tr>
<td>dopamine D₄₋₇</td>
<td></td>
</tr>
<tr>
<td>muscarinic, non-selective</td>
<td></td>
</tr>
<tr>
<td>dopamine D3</td>
<td></td>
</tr>
<tr>
<td>dopamine transporter</td>
<td></td>
</tr>
<tr>
<td>sodium channel, site 2</td>
<td></td>
</tr>
<tr>
<td>monoamine transporter</td>
<td></td>
</tr>
<tr>
<td>β₁-adrenoceptor</td>
<td></td>
</tr>
<tr>
<td>5-HT₂₅</td>
<td></td>
</tr>
<tr>
<td>sigma σ₂</td>
<td></td>
</tr>
<tr>
<td>sigma, non-selective</td>
<td></td>
</tr>
<tr>
<td>OTHER RECEPTORS (128)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Enzymes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>acyl CoA-cholesterol acyltransferase, intestine phosphodiesterase PDE5</td>
<td></td>
</tr>
<tr>
<td>protein kinase, lck (pS6⁵⁰⁰) tyrosine kinase</td>
<td></td>
</tr>
<tr>
<td>protein kinase, PKA, non-selective</td>
<td></td>
</tr>
<tr>
<td>thromboxane synthetase</td>
<td></td>
</tr>
<tr>
<td>phosphodiesterase PDE6</td>
<td></td>
</tr>
<tr>
<td>protein kinase, Ca²⁺/calmodulin-dep. PKII</td>
<td></td>
</tr>
<tr>
<td>leukotriene C₄ synthetase</td>
<td></td>
</tr>
<tr>
<td>OTHER ENZYMES (63)</td>
<td></td>
</tr>
</tbody>
</table>

**Large margin** between potency at primary target and at non-target receptors: expect minimal safety pharmacology ‘baggage’!
Safety Pharmacology

- What is it? How important is it?
- How do you do it?
- How do you use the data in risk assessment?
- Strategies to address the various Regulatory Guidance documents mentioning Safety Pharmacology
“Every drug has two actions: the one you know about, and the one you don’t”

Sir John Gaddum, FRS

In Safety Pharmacology, we have to look out for the expected, and also any unanticipated adverse effects of a new active substance, prior to human exposure. Then use our collective experience to advise projects based on incomplete information.
Overall philosophy

Organ systems addressed in safety pharmacology studies

The 3 Vital Organ Functions:

- Cardiovascular System
- Nervous System
- Respiratory System

Also may study effects on:

- Gastrointestinal System
- Renal System
Cardiac action potential shape and duration are controlled by the complex interplay between a variety of ion channels…

The $I_{Kr}$ current is conducted via the hERG $K^+$ channel, and has a key role in repolarisation.
Relationship between increase in APD, QT prolongation and TdP

(schematic; not to scale)

Redfern & Wakefield (2006)
Consequences for Drugs Causing Torsade de Pointes

Withdrawn from market (1988-2009):
- Prenylamine (antianginal)
- Lidoflazine (antianginal)
- Terodiline (bladder incontinence)
- Astemizole (non-sedating antihistamine)
- Grepafloxacin (antibiotic)
- Terfenadine (non-sedating antihistamine)
- Cisapride (prokinetic)
- Sertindole (antipsychotic)*
- Droperidol (antipsychotic)
- Levomethadyl (heroin dependency)
- Dofetilide (antiarrhythmic)
- Thioridazine (antipsychotic)
- Clobutinol (antitussive)
- Dextropropoxyphene (analgesic)

Prescribing restriction/
Delays in regulatory approval/
Labelling implications:

Far too many examples to list!

*subsequently reinstated
erythromycin (iv)

flecainide

propafenone

sparfloxacin

bepridil

pimozide

haloperidol

aprindine

thioridazine

grepafloxacin

sertindole

astemizole

cisapride

terfenadine

amiodarone

tedisamil

procainamide

sematilide

D,L-sotalol

dofetilide

disopyramide

azimilide

almokalant

ibutilide

quinidine

Log margins of lowest published values for hERG IC₅₀ divided by 30-fold

GLP Core battery cardiovascular assessment: Manual hERG assay

- GLP-compliant, conventional, whole cell voltage clamp
- Recording of $K^+$ current from hERG-expressing CHO cell line
- Aims to generate full concentration-effect curve versus “tail current” or reach limit of solubility
- Data plotted against measured drug concentration
Front-loaded approach: IonWorks hERG screen

- Automated (e.g., IonWorks™; PatchXpress™) whole-cell voltage clamp screen
- Recording of K+ current from hERG-expressing CHO cell line
- Full curve or single concentration option
- Can be conducted for several key cardiac ion channels in addition to hERG

If you generate concentration-effect curves for a compound on several key cardiac ion channels (rather than just hERG) you can use computer modelling to predict the effects on the cardiac action potential...

Early (non-GLP) cardiovascular in vivo assessment: anaesthetised guinea-pig

Hemodynamics
Blood pressure
Heart rate
QA interval

Contractility
Left Ventricular pressure
dp/dt Max
dp/dt Min

ECG
PR, QRS, QT, QTc,
RR intervals

Closed chest surgery under sinusal rhythm
Sympathetic system not compromised apart from anesthesia
GLP core battery CVS assessment: dog telemetry

Receivers in floor

Remote monitoring room

CVS data in 4 dogs:
ECG; arterial blood pressure; left ventricular pressure; heart rate

Telemetry receiver
(inside sterile packaging)

QTc response to moxifloxacin
Potential changes to FDA QT Guidance
Comprehensive in vitro Proarrhythmia Assay (CiPA)

Current regulatory requirements
ICH S7B ICH E14

Dog QT data
hERG potency

Issues?
Pre-clinical data lack influence
Regulatory view of risk in late Ph2/Ph3
TQTS = $$$ + time
Not an assessment of arrhythmia risk

Future regulatory requirements?
CiPA
Updated ICH S7B

Dog QT data
Detailed assessment of all key ion channels

Benefits
Pre-clinical data centre stage
Regulatory view of risk by end Ph1
No TQTS! (less $$$ + less time)
Increased focus on arrhythmia risk

Thorough QT Study
High quality QT data in Phase 1

Computer modelling
Assessment of respiratory function: options

**Forced Manoeuvres**
- Anaesthetised
- Accurate determination of lung volumes, resistance and compliance
- Clinically translatable

**Head-out plethysmography**
- Animals restrained
- Direct determination of tidal volume
- No compensation

**Whole-body plethysmography**
- No restraint
- Indirect determination of tidal volume
- Compensation required

---

Invasiveness →

Accuracy

- Forced manoeuvres
- Whole-body plethysmography
- Head-out plethysmography
Ventilatory Patterns Measurement

- Whole Body Plethysmograph Chambers
  - Indirect Volume Measurement
    - pressure change = inhaled gas expansion

Individual chamber

Inspiration

Expiration

8-chamber set-up
Recordings via whole body plethysmography in a rat

Core battery tests for evaluating effects on the nervous system

- The principal core battery test should assess multiple behavioural, neurological and autonomic parameters in the same animals.
- The collective name for such tests is ‘neurobehavioural assessment’\(^1\).
- The 2 main tests used are either the Irwin test\(^2\) or the Functional Observational Battery (FOB\(^3\)). Both are systematic evaluations of nervous system function.

# FOB cf. Irwin Test

<table>
<thead>
<tr>
<th></th>
<th>FOB</th>
<th>Irwin test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Species originally developed for</strong></td>
<td>Rat</td>
<td>Mouse (subsequently adapted for rats)</td>
</tr>
<tr>
<td><strong>Original purpose</strong></td>
<td>First-tier neurotoxicity evaluation (non-pharmaceuticals)</td>
<td>Screening for psychoactive compounds</td>
</tr>
<tr>
<td><strong>Speed</strong></td>
<td>Slow; one rat at a time</td>
<td>Fast; one cage at a time</td>
</tr>
<tr>
<td><strong>Time points post-dose</strong></td>
<td>Usually 1 to 3</td>
<td>Usually &gt;3</td>
</tr>
<tr>
<td><strong>Main application</strong></td>
<td>In-depth assessment of both CNS and non-CNS targeted compounds; for the latter, this may be the only CNS functional evaluation performed</td>
<td>Rapid screening of multiple CNS-targeted compounds, to aid compound selection</td>
</tr>
</tbody>
</table>
GLP ‘Core battery’ nervous system assessment: The Irwin test/FOB
A multi-parameter assessment of nervous system function in rodents

**AUTONOMIC**
- salivation
- lacrimation
- piloerection
- abnormal urination
- abnormal defaecation
- abnormal respiration
- pupil size
- rectal temperature

**SENSORIMOTOR**
- touch response
- palpebral reflex
- startle reflex
- pinna reflex
- righting reflex

**NEUROMUSCULAR**
- posture
- gait
- Straub tail
- body tone
- ptosis
- exophthalmos
- grip strength
- traction response
- tremor
- twitches
- convulsions

**BEHAVIOURAL**
- arousal
- spontaneous activity level
- vocalisation
- aggressiveness
- sniffing
- grooming
- scratching
- rearing
- stereotypy
- bizarre behaviour
- activity

Plus: any miscellaneous observations; body weight gain overnight post-dose
Limitations of the FOB (and Irwin test)

• No single evaluation within the FOB/Irwin test is definitive for establishing effects on that particular variable – the FOB/Irwin test would take several hours per rat if this were the case, and exposure to one test could affect performance in some others.

• Some assessments are less-sensitive than others, and can only detect marked effects.

• Some aspects of brain function - e.g. special senses (apart from overt deafness or blindness), cognition, anxiety - are not detectable in the FOB/Irwin test.

• Some neurological effects may not appear until after repeat dosing.

• Therefore the FOB/Irwin test is useful as a first-tier test to flag-up possible effects that may require follow-up in a specific, sensitive test, and it may have to be supplemented when effects on special senses, cognition or anxiety are anticipated.
## Potential CNS follow-up studies

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Evaluation of gastrointestinal transit & gastric emptying

- ICH S7A GLP-compliant supplemental study in rats or mice
  - Terminal study, measures taken at Cmax
  - Charcoal suspension given by oral gavage post-dose
  - Gastric emptying = weight of stomach contents;
  - Intestinal transit = distance travelled by charcoal meal as a % of total small intestinal length

![Graphs showing stomach contents and intestinal transit](image)

- 4 increasing doses of Compound X
- Vehicle control
- Positive control Atropine
Safety Pharmacology

- What is it? How important is it?
- How do you do it?
- How do you use the data in risk assessment?
- Strategies to address the various Regulatory Guidance documents mentioning Safety Pharmacology
How to maximise detection of acute side-effects whilst minimising false positives

1. Validate all tests with a reference substance(s);
2. Optimise conditions before testing NCEs;
3. Use adequate group sizes to detect ‘biologically-significant’ effects (from power calculations based on validation data);
4. Incorporate a positive control group (reference substance) where appropriate;
5. Always use experienced, trained staff;
6. Test multiples of the therapeutic dose up to the MTD - solubility and toxicity permitting.
Predicting clinical outcome

- QT-liability detected in integrated pre-clinical assays with compound Z

- Liability confirmed in man, compound discontinued
- Data valuable as evidence of translation – for next time!
Negative inotropic effect detected \textit{in vitro} and \textit{in vivo} with compound A

- Influenced Phase I design - inclusion of echocardiograms for monitoring ejection fraction
Compound affecting pupil diameter/light reflex in rats

**RAT pupil proforma**

<table>
<thead>
<tr>
<th>Rat ID</th>
<th>Pupil diameter (mm)</th>
<th>Speed (reflex)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ambient</td>
<td>0.5 1.0 1.5 2.0 2.5 3.0 3.5 mm</td>
</tr>
<tr>
<td>1</td>
<td>reflex</td>
<td>*************</td>
</tr>
</tbody>
</table>

Effects of AZ compound B (with secondary M<sub>3</sub> blocking properties):

Storey S et al. (2007) J Pharmacol Toxicol Methods

- Influenced Phase I design - inclusion of pupillometry
Safety Pharmacology

- What is it? How important is it?
- How do you do it?
- How do you use the data in risk assessment?
- Strategies to address the various Regulatory Guidance documents mentioning Safety Pharmacology
Principal regulatory guidance documents impacting on safety pharmacology

  Outlines the requirements for assessment of vital organ functions (GLP Core Battery), any follow-up studies, and supplemental studies on other organ functions (esp. Renal; GI).

- **ICH S7B  The nonclinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals (2005)**
  Superseded CPMP/986/96.

  Outlines the requirements for assessing abuse-dependence liability of NCEs.
Other regulatory guidance documents impacting on safety pharmacology

• **ICH S6 Biotechnology-derived pharmaceuticals: nonclinical evaluations** (1997)
  Safety pharmacology endpoints required either as separate studies (in vivo and/or in vitro) or incorporated into the toxicity studies.

• **ICH M3(M) Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals** (2000)
  Safety pharmacology evaluations required prior to human exposure; may be additions to toxicity studies or as separate studies.

• **CPMP/SWP/2599/02/Rev 1 Position paper on non-clinical safety studies to support clinical trials with a single microdose** (2004)
  Safety pharmacology studies may be replaced by an extended single dose toxicity study in one species.

• **ICH E14 Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs** (2005)
  All NAS’s to undergo a “Thorough Phase I QT/QTc Study” – regardless of preclinical risk assessment.

• **G:\7086fnl.doc Guidance for industry, investigators and reviewers: exploratory IND studies** (2006)
  Safety pharmacology endpoints incorporated into toxicology studies will suffice.

• **ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals** (2009)
  Stand-alone safety pharmacology studies need not be conducted to support studies in patients with late stage cancer or advanced disease. In case of concern appropriate safety pharmacology studies, core battery described in ICH S7A and/or follow up or supplemental studies should be considered.
Drug abuse-dependence liability
EMEA: issued 2006; FDA: 2010 draft

EMEA: All putative medicines which have a CNS effect need to be assessed for their ability to cause dependence

FDA…“Likelihood that a drug with anabolic, psychoactive or CNS effects will sustain patterns of non-medical self-administration that results in disruptive or undesirable consequences”
17 QUESTIONS - Abuse Potential Assessment Roadmap

1. Target?
2. Chemistry?
3. Pharmacology?
4. PK in animals?
5. AEs in animals?
6. CNS-active?
7. Reward effects in animals?
8. Physical dependence in animals?
10. Abuse signals in patients? Phase II
11. Physical dependence in humans?
12. Human abuse potential study?
13. Abuse Study 3
14. Reward effects in humans?
15. Abuse AEs in Phase III?
16. NDA info shows abuse?
17. Reports of actual human abuse?

IN VITRO  ANIMAL  HUMAN  REGULATORY
Safety pharmacology endpoints in repeat-dose toxicity studies

Scientific drivers

Doing it in addition to standalone safety pharmacology studies

Rationale:

• To provide early warning flags well ahead of the regulatory GLP SP core battery studies (by incorporating into MTD studies).
• To assess whether findings in acute SP studies persist, intensify, or diminish after repeated dosing, and to demonstrate recovery after cessation of dosing.
• To provide functional correlates of histopathological findings in previous tox studies.
• To assess potential effects that may only develop after prolonged exposure.

Regulatory drivers

Doing it instead of standalone safety pharmacology studies

Rationale:

To opt for the minimum regulatory requirement for FTIM:

  ICHS6 (Biologics)
  ICHS9 (Oncology Products)
  FDA Guidance on Exploratory IND Studies

by incorporating SP core battery assessments into the 1-month regulatory tox studies.
## Changes in response with repeat-dosing

### DECREASE in response/clinical efficacy with repeat-dosing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Therapeutic target</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opiate analgesics</td>
<td>Pain</td>
<td>Rapid tolerance to most effects develops on repeat-dosing</td>
</tr>
<tr>
<td>Baclofen</td>
<td>Spasticity</td>
<td>Tolerance develops to muscle relaxant effects due to down-regulation of GABA-B receptors</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Anxiety</td>
<td>Tolerance develops to initial sedative effect</td>
</tr>
<tr>
<td>L-DOPA; bromocriptine</td>
<td>Parkinson's</td>
<td>Reduced efficacy</td>
</tr>
<tr>
<td>SSRI’s</td>
<td>Depression</td>
<td>Reduced efficacy</td>
</tr>
<tr>
<td>Haloperidol; chlorpromazine</td>
<td>Schizophrenia</td>
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</tr>
<tr>
<td>Anticonvulsants</td>
<td>Epilepsy</td>
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</tr>
<tr>
<td>Nitrates</td>
<td>Hypertension</td>
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</tr>
<tr>
<td>Beta-blockers</td>
<td>Hypertension</td>
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“Some form of adaptive syndrome is the inevitable consequence of the reciprocal interaction between most or all classes of drugs and the organism”.

W Haefely (1986)

### INCREASE in response/clinical efficacy with repeat-dosing

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<th>Therapeutic target</th>
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<td>Amiodarone</td>
<td>Class III antiarrhythmic</td>
<td>Requires several days’ administration before clinical efficacy (incl. QT prolongation) is achieved.</td>
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<tr>
<td>Antidepressants</td>
<td>Depression</td>
<td>Require ~2 weeks before clinical efficacy is achieved.</td>
</tr>
<tr>
<td>Clonidine</td>
<td>Hypertension</td>
<td>Initial hypertensive response followed by hypotension, losing the initial hypertensive response on repeat-dosing.</td>
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### SLOW/Delayed development of adverse effect

- Neuropathy (e.g. paclitaxel);
- Cardiomyopathy (e.g. doxorubicin);
- Retinopathy (e.g. quinine).
Note of caution:

If you choose to go down this route, it is vitally important to conduct functional measurements on Day 1 of the repeat-dose toxicity studies (in addition to later time points), for the reasons outlined earlier (ie, you may miss an acute response).

But Day 1 of a tox study is usually mayhem, with timed TK bleeds etc...

**Good luck!**

In this presentation we have covered...
Safety Pharmacology

- What is it? How important is it?
- How do you do it?
- How do you use the data in risk assessment?
- Strategies to address the various Regulatory Guidance documents mentioning Safety Pharmacology
Summary of lecture

- Safety pharmacology is an integral component of the preclinical safety evaluation of new active substances;
- The intense focus on the ‘QT issue’ over recent years must not deflect attention away from other aspects of safety pharmacology;
- The assessment of new active substances should be science-driven, rather than doing the bare minimum to address regulatory guidelines.
Further information

PUBLICATIONS


Synopsis of lecture

The aim of this lecture was to provide illustrations of the types of studies undertaken in safety pharmacology, when they are done, and what they hope to achieve. The regulatory requirements and the impact of doing/not doing adequate safety pharmacology studies are also illustrated with examples.

The underlying causes of acute adverse drug effects are the key to how we would go about trying to detect them preclinically. In addition to a set of core battery studies that are ‘blind’ to the pharmacological profile of the test compound, we would also build-in tests to address potential effects suspected from the known pharmacology. This combination therefore addresses both the ‘expected’ and the ‘unexpected’.

Prediction of effects in humans by safety pharmacology studies has never been studied systematically. Indications are that we are improving, and prediction of proarrhythmic potential is a good example. The key is to base risk assessment on reliable data.
QUESTIONS?
BACK-UP SLIDES:
Details on CNS methods
## Potential CNS follow-up studies

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Methods to assess motor inco-ordination in rats

• Accelerating rotarod
• Beam walking
• Gait analysis?

Vrinten & Hamers (2003)
Validation of the accelerating rotarod test with clonidine

- The accelerating rotarod test detects the effects of drugs on motor co-ordination in rats.
- This test was validated in-house with clonidine (iv and po), a drug which impairs motor performance in man (Frith et al., 1989).
- Male Sprague-Dawley rats, n = 8 per group.
- Clonidine doses of 0.1 mg/kg iv or 1 mg/kg po are suitable for routine inclusion in safety pharmacology studies on NCEs.

Spontaneous locomotor activity in a novel environment can be measured by videotracking, or by an array of photocell beams.

Several rats can be monitored simultaneously.

Usually measured over a 30-minute period.
Spontaneous Locomotor Activity

Spontaneous Locomotor Activity in a novel arena provides 2 levels of baseline activity: initial high exploratory-related locomotor activity followed by low baseline activity due to habituation.

Novelty Phase - from 0 to 10 min of assessment
Habituation Phase - from 10 to 30 min of assessment

Spontaneous Locomotor Activity Profiles

Novelty Phase - sedative effects detectable

Spontaneous Locomotor Activity Profiles

Novelty Phase - sedative effects detectable
Habituation Phase - stimulant effects detectable

Methods to assess visual function in rodents

- **Visual acuity**
  Generally uses gratings of different frequencies, either static (2-choice paradigm) or moving (optometry).

- **Visual threshold (signal detection)**
  Visual stimuli of differing luminance are presented, usually in a 2-lever operant paradigm. Rat has to select the lever in front of the stimulus to obtain a food reward.

- **Electroretinography (ERG)**
  Electrophysiological recording from corneal surface in response to flash stimuli. Usually requires terminal anaesthesia.
Methods to assess visual function in rodents

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• **Electroretinography (ERG)**
  Electrophysiological recording from corneal surface in response to flash stimuli. Usually requires terminal anaesthesia.
Diagram of *OptoMotry* System

Observer View on PC

Low frequency grating

High frequency grating

Rat at start of testing
Dose-response relationship of quinine on visual acuity

*(N.B. Quinine causes loss of visual acuity and even blindness in humans)*

Dose-response relationship of quinine on visual acuity

*Vehicle Control (n=13)*
*Quinine 10 mg/kg oral (n=6)*
*Quinine 30 mg/kg oral (n=6)*
*Quinine 100 mg/kg oral (n=6)*
*Quinine 300 mg/kg oral (n=8)*

•P<0.05; **P<0.01; ***P<0.001
Draper et al. (2008) EPHAR Proceedings
Pupil diameter/reflex in dogs

Effects of an AZ compound (with secondary M_3 blocking properties):

Storey S et al. (2007) J Pharmacol Toxicol Methods