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Safety Pharmacology

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ICH S7A
SAFETY PHARMACOLOGY STUDIES
FOR HUMAN PHARMACEUTICALS

ICH Step 5

NOTE FOR GUIDANCE ON SAFETY PHARMACOLOGY STUDIES
FOR HUMAN PHARMACEUTICALS
(CPMP/ICH/539/00)

| TRANSMISSION TO CPMP               | March 2000 |
| TRANSMISSION TO INTERESTED PARTIES | March 2000 |
| DEADLINE FOR COMMENTS             | November 2000 |
| APPROVAL BY CPMP                  | November 2000 |
| DATE FOR COMING INTO OPERATION    | June 2001   |
SAFETY PHARMACOLOGY
Scope

- Guideline is applied generally to
  - New chemical and biological entities, including biotechnology-derived products

- Guideline may be applied to
  - Marketed pharmaceuticals when appropriate (e.g. adverse clinical events, new patient population or route of administration)
Primary pharmacodynamic effects
- studies on the mode of action and/or effects of a substance in relation to its desired therapeutic target.

Secondary pharmacodynamic effects
- studies of the mode of action and/or effects of a substance not related to its desired therapeutic target.

Safety pharmacology
- studies that investigate the potential undesirable pharmacodynamic effects of a substance on physiological functions in relation to exposure in the therapeutic range and above.
Doses should include and exceed the primary pharmacodynamic or therapeutic range. In the absence of adverse effects on safety pharmacology parameters, the highest tested dose should produce moderate adverse effects in this or in other studies of similar route and duration. These adverse effects can include dose-limiting pharmacodynamic effects or other toxicity.
In practice, some effects in the toxic range (e.g. tremors or fasciculations during ECG recording) may confound the interpretation of the results and may also limit dose levels.
SAFETY PHARMACOLOGY Studies

- Core Battery of Safety Pharmacology Studies
- Safety Pharmacology Studies Conducted as Necessary
  - Follow-up Studies for Core Safety Pharmacology Battery
  - Supplemental Safety Pharmacology Studies
<table>
<thead>
<tr>
<th>SAFETY PHARMACOLOGY</th>
<th>Examples of adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Nervous System</td>
<td>Convulsion, disturbance of consciousness, etc.</td>
</tr>
<tr>
<td>Cardiovascular Functions</td>
<td>Arrhythmia, circulatory shock, etc.</td>
</tr>
<tr>
<td>Respiratory Functions</td>
<td>Bronchospasm, respiratory failure, etc.</td>
</tr>
</tbody>
</table>
Concerns may arise from:

- safety pharmacology core battery
- clinical trials
- pharmacovigilance
- experimental in vitro or in vivo studies
- literature reports
SAFETY PHARMACOLOGY
Conditions Under Which Studies are not necessary (1)

❖ SP studies may not be necessary for:
  • locally applied agents (e.g. dermal or ocular), where pharmacology well characterized and where systemic exposure low.
  • cytotoxic agents for treatment of end-stage cancer patients, but cytotoxic agents with novel mechanism of action: yes.
SAFETY PHARMACOLOGY
Conditions Under Which Studies are not necessary (2)

- biotechnology-derived products
  - achieve highly specific receptor targeting
  - SP endpoints in toxicology and/or
  - PD studies

- additional exception: e.g. new salt having similar pharmacokinetics and pharmacodynamics
SAFETY PHARMACOLOGY

Timing

🪤 Prior to First Administration in Humans
Core battery, follow-up or supplemental studies based on a cause for concern

🪤 During Clinical Development
To clarify observed or suspected undesirable effects in animals and humans.

🪤 Before Approval
- Supplemental studies unless not warranted
- SP endpoints covered in other studies
SAFETY PHARMACOLOGY

GLP

- **NOT GLP**
  - Primary PD studies
  - Secondary PD when not pivotal

- **Ordinary GLP**
  - Core battery
  - SP endpoints from toxicology studies
  - Secondary PD studies when pivotal

- **GLP to the greatest extent feasible**
  - Supplemental, follow-up
ICH S7B & E14 Guidelines
Step 4, May 12, 2005

S7B Guideline
The Non-clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals

E14 Guideline
The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs
**Risk factors:**
- Ion channel mutations
- Hypokalemia
- Bradycardia, etc

**Atrial Prolongation and Early Afterdepolarization (EAD)**

**QT Prolongation**

**Torsades de Pointes**
Objective of the Guideline S7B

• This guideline describes a nonclinical testing strategy for assessing the potential of a test substance to delay ventricular repolarization

• This guideline includes information concerning nonclinical assays and an integrated risk assessment
Scope of the Guideline S7B

- This guideline extends and complements the “ICH Guideline on Safety Pharmacology Studies for Human Pharmaceuticals” (ICH S7A)
- This guideline applies to new chemical entities for human use and marketed pharmaceuticals
  - when appropriate (e.g., when adverse clinical events, a new patient population, or a new route of administration raises concerns not previously addressed).
- Pharmaceuticals for which testing is not called for are described in ICH S7A.
General Principles

• Principles and recommendations described in ICH S7A also apply to the studies conducted in accordance with the present guideline.

• *In vitro and in vivo* assays are complementary approaches; therefore, according to current understanding, both assay types should be conducted.

• The investigational approach and evidence of risk should be *individualized* for the test substance, depending on its pharmacodynamic, pharmacokinetic and safety profiles.
Nonclinical Testing Strategy

- In Vitro \( I_{kr} \) assay
- In Vivo QT assay
- Chemical/Pharmacological Class
- Follow-up Studies
- Integrated Risk Assessment
- Evidence of Risk
- Relevant Nonclinical and Clinical Information

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Nonclinical Testing Strategy

**In vitro I\textsubscript{kr} assay**
- Effects on $I_{Kr}$ or the ionic current through a native or expressed $I_{Kr}$ channel protein, such as that encoded by hERG

**In vivo QT assay**
- Measures indices of ventricular repolarization such as QT interval

**Chemical/pharmacological class**
- Consideration should be given to whether the test substance belongs to a chemical/pharmacological class in which some members have been shown to induce QT interval prolongation in humans (e.g., antipsychotics, histamine H-1 receptor antagonists, fluoroquinolones). This should, where appropriate, influence the choice of reference compound(s) and be included in the integrated risk assessment.
Relevant nonclinical and clinical Information

• Additional information for the integrated risk assessment can include results from:
  • Pharmacodynamic studies,
  • Toxicology/safety studies,
  • Pharmacokinetic studies, including plasma levels of parent substance and metabolites (including human data if available),
  • Drug interaction studies,
  • Tissue distribution and accumulation studies,
  • Post-marketing surveillance.
Follow-up Studies

Follow-up studies are intended to provide greater depth of understanding or additional knowledge regarding the potential of test substance for delayed ventricular repolarization and QT interval prolongation in humans.

Such studies can provide additional information concerning potency, mechanism of action, slope of the dose-response curve, or magnitude of the response.

Follow-up studies are designed to address specific issues, and, as a result, various in vivo or in vitro study designs can be applicable.
Evidence of Risk

Evidence of risk is the overall conclusion from the integrated risk assessment for a test substance to delay ventricular repolarization and to prolong QT interval in humans.
S7B Timing

- Conduct of S7B non-clinical studies assessing the risk for delayed ventricular repolarization and QT interval prolongation prior to administration to humans should be considered.
- These results, as part of an integrated risk assessment, can support the planning and interpretation of subsequent clinical studies.
S7B  Safety Margin

- Relationship between the exposures associated with an effect on repolarization and those eliciting the primary pharmacodynamic effect in the non-clinical test species or the proposed therapeutic effect in humans
### Implications of ICH S7B study results (non-negative / positive)-1

<table>
<thead>
<tr>
<th>Conditions</th>
<th>hERG assay and/or in vivo QT assay</th>
<th>Consequences</th>
</tr>
</thead>
</table>
| Human therapeutic plasma concentration not known | Ratio of IC50 hERG / EC50 of primary pharmacological effect: 30 -100 (non-negative) | In vivo QT assay shows < 10% QTc increase (negative) | 1) Proceed to nonclinical follow-up studies.  
2) Proceed to first into man study with careful dose escalation and monitoring of ECG in early human studies  
3) Routine monitoring of ECG in all subsequent clinical studies |
| Human therapeutic plasma concentration not known | Ratio of IC50 hERG / EC50 of primary pharmacological effect: 30 -100 (non-negative) | In vivo QT assay shows ≥ 10% QTc increase (positive) | 1) Proceed to nonclinical follow-up studies.  
2) Proceed to first into man study with careful dose escalation and monitoring of ECG in early human studies  
3) Proceed to thorough QT/QTc study |
Implications of ICH S7B study results (non-negative / positive)-2

| Only estimate of human therapeutic plasma concentration known | Ratio of IC50 hERG / (estimated) free human plasma concentration: < 30 (positive) | In vivo QT assay shows ≥10% QTc increase with high safety margin (positive). | Make go/no-go decision OR  
1) Proceed to nonclinical follow-up studies.  
2) Proceed to first into man study with careful dose escalation and monitoring of ECG in early human studies  
3) Proceed to thorough QT/QTc study |
|---|---|---|---|
| Human therapeutic plasma concentration known | Ratio of IC50 hERG / free human plasma concentration: < 30 (positive) | In vivo QT assay shows ≥10% QTc increase with low safety margin (positive). | Make go/no-go decision OR  
1) Proceed to nonclinical follow-up studies  
2) Proceed to first into man study with careful dose escalation and monitoring of ECG in early human studies  
3) Robust monitoring of ECG in all subsequent clinical studies |

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# HERG / Antipsychotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>HERG (IC$_{50}$, nM)</th>
</tr>
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<tbody>
<tr>
<td>Drug 1</td>
<td>12</td>
</tr>
<tr>
<td>Drug 2</td>
<td>28</td>
</tr>
<tr>
<td>Drug 3</td>
<td>152</td>
</tr>
<tr>
<td>Drug 4</td>
<td>163</td>
</tr>
<tr>
<td>Drug 5</td>
<td>181</td>
</tr>
<tr>
<td>Drug 6</td>
<td>191</td>
</tr>
</tbody>
</table>

- All antipsychotics display HERG (I$_{kr}$) blocking affinity
- It is a therapeutic class effect
Other Human Cardiac Ion Channels

<table>
<thead>
<tr>
<th>Ion Channel</th>
<th>Drug 1 (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-type Ca^{2+}</td>
<td>8.5</td>
</tr>
<tr>
<td>T-type Ca^{2+}</td>
<td>13.4</td>
</tr>
<tr>
<td>SCN5A (I_{Na})</td>
<td>2.3</td>
</tr>
</tbody>
</table>

- **Drug 1** displays an affinity for calcium and sodium channels
- This effect will balance the risk associated with the HERG blockade
OTHER CHANNELS

Drug 1

hERG blocking effects: \( n/\text{Mol range} \)

Ca + Na effects: \( \mu/\text{Mol range} \)

Will this balance the risk?
Purkinje Fibers (APD)
Drug 1 increases APD but the effect reaches a plateau
### Purkinje Fibres (EAD)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Frequency of EAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug 1</td>
<td>0/7 (0 %)</td>
</tr>
<tr>
<td>Drug 5</td>
<td>1/7 (14 %)</td>
</tr>
<tr>
<td>Drug 2</td>
<td>3/7 (43 %)</td>
</tr>
<tr>
<td>Drug 4</td>
<td>7/7 (100 %)</td>
</tr>
</tbody>
</table>

**Drug 1** does not induce EADs
Protective Actions in Purkinje Fibres

Control fiber  + 3 μM dofetilide  + 3 μM dofetilide

+ 10 μM Drug 1

EAD

Drug 1 restores dofetilide-induced EADs.
Protective Actions in Purkinje Fibres

Dofetilide is a strong $I_{kr}$ blocker with a proarrhythmic potential.

Drug 1 reversed dofetilide effect on APD.
Carlsson Model

- Rabbits are sensitised to TdP using a $\alpha_1$-agonist methoxamine.
- The model induces TdP in 80% of the cases.
- Antipsychotics were tested for ability to reduce the rate of TdP.
Carlsson Model

<table>
<thead>
<tr>
<th>Treatment</th>
<th>TdP arrhythmia</th>
<th>$\alpha_1$-affinity (Ki, nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>8/10</td>
<td>-</td>
</tr>
<tr>
<td>Drug 5</td>
<td>5/10</td>
<td>19</td>
</tr>
<tr>
<td>Drug 3</td>
<td>4/10</td>
<td>7.3</td>
</tr>
<tr>
<td><strong>Drug 1</strong></td>
<td><strong>2/10</strong></td>
<td><strong>1.4</strong></td>
</tr>
<tr>
<td>Drug 2</td>
<td>0/10</td>
<td>0.69</td>
</tr>
</tbody>
</table>

**Drug 1** and Drug 2 markedly reduce occurrence of TdP in this model.
The inherent alpha$_1$-antagonistic profile protects against pharmacological induced TdP.
CONCLUSION

Drug 1

Potent hERG blocking effects but no EADs and reduced TdP in the Carlsson Model