Safety testing for antiarrhythmic drugs

Michael J. Curtis PhD

Cardiovascular Division, King’s College London,
The Rayne Institute, St Thomas’ Hospital
London, UK
Antiarrhythmic drug discovery was damaged by CAST and SWORD (1989-1992)

- Clinical trials of antiarrhythmic drugs: flecainide and D-sotalolol
- ‘Expectation’ of a reduction in sudden cardiac death (SCD)

These drugs caused a doubling of death rate

- Proarrhythmia from antiarrhythmic drugs?
  - Deeply unsettling, badly explained
Antiarrhythmic drug discovery was damaged by CAST and SWORD (1989-1992)

- Clinical trials of antiarrhythmic drugs: flecainide and D-sotalol
- 'Expectation' of a reduction in sudden cardiac death (SCD)
- These drugs caused a doubling of death rate
- Proarrhythmia from antiarrhythmic drugs?
  Deeply unsettling, badly explained
Antiarrhythmic drug discovery was damaged by CAST and SWORD (1989-1992)

- Clinical trials of antiarrhythmic drugs: flecainide and D-sotalolol
- ‘Expectation’ of a reduction in sudden cardiac death (SCD)

These drugs caused a doubling of death rate

- Proarrhythmia from antiarrhythmic drugs?
  Deeply unsettling, badly explained
Antiarrhythmic drug discovery was damaged by CAST and SWORD (1989-1992)

- Clinical trials of antiarrhythmic drugs: flecainide and D-sotalolol
- ‘Expectation’ of a reduction in sudden cardiac death (SCD)

These drugs caused a doubling of death rate
Background

Antiarrhythmic drug discovery was damaged by CAST and SWORD (1989-1992)

- Clinical trials of antiarrhythmic drugs: flecainide and D-sotalolol
- ‘Expectation’ of a reduction in sudden cardiac death (SCD)

These drugs caused a doubling of death rate

- Proarrhythmia from antiarrhythmic drugs?

Deeply unsettling, badly explained
Antiarrhythmic drug discovery was damaged by CAST and SWORD (1989-1992)

- Clinical trials of antiarrhythmic drugs: flecainide and D-sotalolol
- ‘Expectation’ of a reduction in sudden cardiac death (SCD)

These drugs caused a doubling of death rate

- Proarrhythmia from antiarrhythmic drugs?
- Deeply unsettling, badly explained
Drug-induced torsades de pointes (TDP)

Independently, by 1996

- Terfenadine recognised to be proarrhythmic
- Risk of TDP
- Responsible for at least 50 deaths
- Statistical association with QT prolongation
- Extremely rare
- ‘Unexpected’

QT prolongation went from ‘hallmark of class III antiarrhythmic activity’ to anathema
Drug-induced torsades de pointes (TDP)

Independently, by 1996

• Terfenadine recognised to be proarrhythmic
• Risk of TDP
• Responsible for at least 50 deaths
• Statistical association with QT prolongation
• Extremely rare
• ‘Unexpected’

QT prolongation went from ‘hallmark of class III antiarrhythmic activity’ to anathema
Drug-induced torsades de pointes (TDP)

Independently, by 1996

• Terfenadine recognised to be proarrhythmic
• Risk of TDP
• Responsible for at least 50 deaths
• Statistical association with QT prolongation
• Extremely rare
• ‘Unexpected’
• QT prolongation went from ‘hallmark of class III antiarrhythmic activity’ to anathema
Drug-induced torsades de pointes (TDP)

Independently, by 1996

- Terfenadine recognised to be proarrhythmic
- Risk of TDP
- Responsible for at least 50 deaths
- Statistical association with QT prolongation
- Extremely rare
- ‘Unexpected’

QT prolongation went from ‘hallmark of class III antiarrhythmic activity’ to anathema.
Drug-induced torsades de pointes (TDP)

Independently, by 1996

- Terfenadine recognised to be proarrhythmic
- Risk of TDP
- Responsible for at least 50 deaths
- Statistical association with QT prolongation
  - Extremely rare
  - ‘Unexpected’
- QT prolongation went from ‘hallmark of class III antiarrhythmic activity’ to anathema
Drug-induced torsades de pointes (TDP)

Independently, by 1996

- Terfenadine recognised to be proarrhythmic
- Risk of TDP
- Responsible for at least 50 deaths
- Statistical association with QT prolongation
- Extremely rare

‘Unexpected’

QT prolongation went from ‘hallmark of class III antiarrhythmic activity’ to anathema
Drug-induced torsades de pointes (TDP)

Independently, by 1996

- Terfenadine recognised to be proarrhythmic
- Risk of TDP
- Responsible for at least 50 deaths
- Statistical association with QT prolongation
- Extremely rare
- ‘Unexpected’

QT prolongation went from hallmark of class III antiarrhythmic activity to anathema.
Drug-induced torsades de pointes (TDP)

Independently, by 1996

- Terfenadine recognised to be proarrhythmic
- Risk of TDP
- Responsible for at least 50 deaths
- Statistical association with QT prolongation
- Extremely rare
- ‘Unexpected’
- QT prolongation went from ‘hallmark of class III antiarrhythmic activity’ to anathema
TDP in the ECG, and the underlying action potential (AP) abnormalities
Antiarrhythmic drugs can cause TDP

Dofetilide

DL-sotalol
How can it be that an antiarrhythmic drug can be proarrhythmic?

• There is no consensus view in the literature
How can it be that an antiarrhythmic drug can be proarrhythmic?

• There is no consensus view in the literature
Objective of webinar

- To explain how an antiarrhythmic can be proarrhythmic
- To suggest ways of minimising risk
Objective of webinar

- To explain how an antiarrhythmic can be proarrhythmic
- To suggest ways of minimising risk
Objective of webinar

• To explain how an antiarrhythmic can be proarrhythmic

• To suggest ways of minimising risk
Key issues

• Arrhythmias are caused by electrophysiology changes, caused in turn by biochemical changes.

• Injury current, re-entry and abnormal automaticity are the electrophysiological mechanisms.

• Accumulation and depletion of biochemicals ‘mediate’ the electrophysiological changes.

• Electrophysiological mechanisms and mediator identities differ according to pathology: ischaemia vs infarction vs heart failure etc.
Key issues

• Arrhythmias are caused by electrophysiology changes, caused in turn by biochemical changes

• Injury current, re-entry and abnormal automaticity are the electrophysiological mechanisms

• Accumulation and depletion of biochemicals ‘mediate’ the electrophysiological changes

• Electrophysiological mechanisms and mediator identities differ according to pathology: ischaemia vs infarction vs heart failure etc.
Key issues

• Arrhythmias are caused by electrophysiology changes, caused in turn by biochemical changes

• Injury current, re-entry and abnormal automaticity are the electrophysiological mechanisms

• Accumulation and depletion of biochemicals ‘mediate’ the electrophysiological changes

• Electrophysiological mechanisms and mediator identities differ according to pathology: ischaemia vs infarction vs heart failure etc.
Key issues

- Arrhythmias are caused by electrophysiology changes, caused in turn by biochemical changes

- Injury current, re-entry and abnormal automaticity are the electrophysiological mechanisms

- Accumulation and depeletion of biochemicals ‘mediate’ the electrophysiological changes
Key issues

• Arrhythmias are caused by electrophysiology changes, caused in turn by biochemical changes.

• Injury current, re-entry and abnormal automaticity are the electrophysiological mechanisms.

• Accumulation and depletion of biochemicals ‘mediate’ the electrophysiological changes.

• Electrophysiological mechanisms and mediator identities differ according to pathology: ischaemia vs infarction vs heart failure etc.
Pathology: consider ischaemic phase 1 and 2

(Data for conscious rat, Curtis, 1993)
Pathology: consider ischaemic phase 1 and 2

(Data for conscious rat, Curtis, 1993)
Phase 1 and 2 VF respond differently to drugs e.g., Conscious rat 20 mg/kg i.v. verapamil:

(Curtis et al., 1984)
Phase 1 and 2 VF respond differently to drugs e.g., Conscious rat 20 mg/kg i.v. verapamil:

(Curtis et al., 1984)
Phase 1 and 2 VF respond differently to drugs, e.g., Conscious rat 20 mg/kg i.v. verapamil:

Phase 1 VF

Control | Verapamil

Incidence (%)

Phase 2 VF

Control | Verapamil

Incidence (%)
Phase 1 and 2 VF respond differently to drugs e.g., Conscious rat 20 mg/kg i.v. verapamil:

(Curtis et al., 1984)
Antiarrhythmic mechanisms & proarrhythmia

• Ion channels are targets for antiarrhythmic drugs:
  • $I_{K_r}$ for class III
  • $I_{Na}$ for class I
  • $I_{CaL}$ for class IV

• Mechanisms by which targeting leads to effects on rhythm are not well understood

• Even these antiarrhythmic drugs can be proarrhythmic
Antiarrhythmic mechanisms & proarrhythmia

• Ion channels are targets for antiarrhythmic drugs:
  • $I_{Kr}$ for class III
  • $I_{Na}$ for class I
  • $I_{CaL}$ for class IV

• Mechanisms by which targeting leads to effects on rhythm are not well understood

• Even these antiarrhythmic drugs can be proarrhythmic
Antiarrhythmic mechanisms & proarrhythmia

- Ion channels are targets for antiarrhythmic drugs:
  - $I_{Kr}$ for class III
  - $I_{Na}$ for class I
  - $I_{CaL}$ for class IV

- Mechanisms by which targeting leads to effects on rhythm are not well understood

- Even these antiarrhythmic drugs can be proarrhythmic.
Antiarythmic mechanisms & proarrhythmia

- Ion channels are targets for antiarythmic drugs:
  - $I_{K_r}$ for class III
  - $I_{Na}$ for class I
  - $I_{CaL}$ for class IV

- Mechanisms by which targeting leads to effects on rhythm are not well understood

- Even these antiarythmic drugs can be proarythmic
Antiarrhythmic mechanisms & proarrhythmia

- Ion channels are targets for antiarrhythmic drugs:
  - $I_{Kr}$ for class III
  - $I_{Na}$ for class I
  - $I_{CaL}$ for class IV

- Mechanisms by which targeting leads to effects on rhythm are not well understood

- Unfortunately all antiarrhythmic mechanisms can be proarrhythmic.
Antiarrhythmic mechanisms & proarrhythmia

• Ion channels are targets for antiarrhythmic drugs:
  • $I_{K_r}$ for class III
  • $I_{Na}$ for class I
  • $I_{Ca_L}$ for class IV

• Mechanisms by which targeting leads to effects on rhythm are not well understood

• Unfortunately all antiarrhythmic mechanisms can be proarrhythmic: 
Antiarrhythmic mechanisms can be proarrhythmic

- IK_r block by class III drugs inhibits re-entry
- BUT IK_r block facilitates abnormal automaticity
  - TDP
- I_Na block by class I drugs can block re-entry
  - This requires total local block in damaged region
  - Partial block will facilitate re-entry
  - Ventricular fibrillation (VF)
- I_CaL block by class IV can block AV node re-entry
- Excess block, AV dissociation
Antiarrhythmic mechanisms can be proarrhythmic

- $I_{Kr}$ block by class III drugs inhibits re-entry
- BUT $I_{Kr}$ block facilitates abnormal automaticity
  - TDP
- $I_{Na}$ block by class I drugs can block re-entry
  - This requires total local block in damaged region
  - Partial block will facilitate re-entry
  - Ventricular fibrillation (VF)
- $I_{CaL}$ block by class IV can block AV node re-entry
  - Excess block, AV dissociation
Antiarrhythmic mechanisms can be proarrhythmic

- $\text{IK}_r$ block by class III drugs inhibits re-entry
- BUT $\text{IK}_r$ block facilitates abnormal automaticity
  - TDP
- $I_{Na}$ block by class I drugs can block re-entry
  - This requires total local block in damaged region
  - Partial block will facilitate re-entry
- Ventricular fibrillation (VF)
- $I_{CaL}$ block by class IV can block AV node re-entry
  - Excess block, AV dissociation
Antiarrhythmic mechanisms can be proarrhythmic

- $I_{K_r}$ block by class III drugs inhibits re-entry
- BUT $I_{K_r}$ block facilitates abnormal automaticity
  - TDP
- $I_{Na}$ block by class I drugs can block re-entry
  - This requires total local block in damaged region
  - Partial block will facilitate re-entry
- Ventricular fibrillation (VF)
- $I_{Ca_L}$ block by class IV can block AV node re-entry
  - Excess block, AV dissociation
Antiarrhythmic mechanisms can be proarrhythmic

- $\text{IK}_r$ block by class III drugs inhibits re-entry
- BUT $\text{IK}_r$ block facilitates abnormal automaticity
  - TDP
- $\text{INa}$ block by class I drugs can block re-entry
  - This requires total local block in damaged region
  - Partial block will facilitate re-entry
  - Ventricular fibrillation (VF)
- $\text{ICaL}$ block by class IV can block AV node re-entry
  - Excess block, AV dissociation
Antiarrhythmic mechanisms can be proarrhythmic

- $I_{K_r}$ block by class III drugs inhibits re-entry
- BUT $I_{K_r}$ block facilitates abnormal automaticity
  - TDP

- $I_{Na}$ block by class I drugs can block re-entry
  - This requires total local block in damaged region
    - Partial block will facilitate re-entry
  - Ventricular fibrillation (VF)

- $I_{CaL}$ block by class IV can block AV node re-entry
  - Excess block, AV dissociation
Antiarrhythmic mechanisms can be proarrhythmic

- $\text{IK}_r$ block by class III drugs inhibits re-entry
- **BUT** $\text{IK}_r$ block facilitates abnormal automaticity
  - TDP
- $\text{INa}$ block by class I drugs can block re-entry
  - This requires total local block in damaged region
  - Partial block will facilitate re-entry
  - Ventricular fibrillation (VF)
- $\text{ICaL}$ block by class IV can block AV node re-entry
  - Excess block, AV dissociation
Antiarrhythmic mechanisms can be proarrhythmic

- $I_{Kr}$ block by class III drugs inhibits re-entry
- BUT $I_{Kr}$ block facilitates abnormal automaticity
  - TDP
- $I_{Na}$ block by class I drugs can block re-entry
  - This requires total local block in damaged region
  - Partial block will facilitate re-entry
    - Ventricular fibrillation (VF)

- $I_{CaL}$ block by class IV can block AV node re-entry
  - Excess block, AV dissociation
Antiarrhythmic mechanisms can be proarrhythmic

- $I_{Kr}$ block by class III drugs inhibits re-entry
- BUT $I_{Kr}$ block facilitates abnormal automaticity
  - TDP
- $I_{Na}$ block by class I drugs can block re-entry
  - This requires total local block in damaged region
  - Partial block will facilitate re-entry
    - Ventricular fibrillation (VF)
- $I_{CaL}$ block by class IV can block AV node re-entry
  - Excess block, AV dissociation
Antiarrhythmic mechanisms can be proarrhythmic

- $I_{K_r}$ block by class III drugs inhibits re-entry
- BUT $I_{K_r}$ block facilitates abnormal automaticity
  - TDP
- $I_{Na}$ block by class I drugs can block re-entry
  - This requires total local block in damaged region
  - Partial block will facilitate re-entry
  - Ventricular fibrillation (VF)
- $I_{CaL}$ block by class IV can block AV node re-entry
  - Excess block, AV dissociation
Arrhythmia mechanisms themselves vary according to pathology

- In acute ischaemia two mechanisms operate
- These are flow of injury current and re-entry
- During infarct evolution the mechanisms differ
- Abnormal automaticity and re-entry are important
- Heart failure, hypertrophy, different again
- No reason to expect proarrhythmia risk is the same in each setting
Arrhythmia mechanisms themselves vary according to pathology

- In acute ischaemia two mechanisms operate
- These are flow of injury current and re-entry
- During infarct evolution the mechanisms differ
- Abnormal automaticity and re-entry are important
- Heart failure, hypertrophy, different again
- No reason to expect proarrhythmia risk is the same in each setting
Arrhythmia mechanisms themselves vary according to pathology

- In acute ischaemia two mechanisms operate
- These are flow of injury current and re-entry
- During infarct evolution the mechanisms differ
- Abnormal automaticity and re-entry are important
- Heart failure, hypertrophy, different again
- No reason to expect proarrhythmia risk is the same in each setting
Arrhythmia mechanisms themselves vary according to pathology

- In acute ischaemia two mechanisms operate
- These are flow of injury current and re-entry
- During infarct evolution the mechanisms differ
- Abnormal automaticity and re-entry are important
- Heart failure, hypertrophy, different again
- No reason to expect proarrhythmia risk is the same in each setting
Arrhythmia mechanisms themselves vary according to pathology

- In acute ischaemia two mechanisms operate
  - These are flow of injury current and re-entry
- During infarct evolution the mechanisms differ
- Abnormalautomaticity and re-entry are important
- No reason to expect proarrhythmia risk is the same in each setting
Arrhythmia mechanisms themselves vary according to pathology

- In acute ischaemia two mechanisms operate
- These are flow of injury current and re-entry
- During infarct evolution the mechanisms differ
- Abnormal automaticity and re-entry are important
- Heart failure, hypertrophy, different again
- No reason to expect proarrhythmia risk is the same in each setting
Arrhythmia mechanisms themselves vary according to pathology

- In acute ischaemia two mechanisms operate
- These are flow of injury current and re-entry
- During infarct evolution the mechanisms differ
- Abnormal automaticity and re-entry are important
- Heart failure, hypertrophy, different again
- No reason to expect proarrhythmia risk is the same in each setting
Example of complexity, consider acute ischaemia

- In acute ischaemia two mechanisms operate
- These are flow of injury current and re-entry
- Underlying these mechanisms are complex changes in Em, APD and conduction velocity
Example of complexity, consider acute ischaemia

- In acute ischaemia two mechanisms operate
- These are flow of injury current and re-entry
- Underlying these mechanisms are complex changes in $E_m$, APD and conduction velocity
Example of complexity, consider acute ischaemia

- In acute ischaemia two mechanisms operate
- These are flow of injury current and re-entry
- Underlying these mechanisms are complex changes in Em, APD and conduction velocity
Example of complexity, consider acute ischaemia

- In acute ischaemia two mechanisms operate
- These are flow of injury current and re-entry
- Underlying these mechanisms are complex changes in Em, APD and conduction velocity
Potential for flow of injury current

Ischaemic

Normal adjacent
Potential for flow of injury current

Ischaemic → Normal adjacent

Flow of current between regions initiates VPB
Potential for flow of injury current

Potential for flow of injury current

Caused by APD shortening

And by diastolic depolarization

Facilitated by ischaemic conduction delay

Facilitated by ischaemic conduction delay

Ischaemic AP also facilitates re-entry

Re-entry occurs when wavelength of a propagating VBP is smaller than available pathlength

• Wavelength equals conduction velocity times refractory period \((\omega = \theta \times RP)\)

• Slowing \(\theta\) (m/s) and reducing \(RP\) (s) reduces \(\omega\) (m) and so facilitates re-entry
Ischaemic AP also facilitates re-entry

Re-entry occurs when wavelength of a propagating VPB is smaller than available pathlength

- Wavelength equals conduction velocity times refractory period ($\omega = \theta \times RP$)
- Slowing $\theta$ (m/s) and reducing $RP$ (s) reduces $\omega$ (m) and so facilitates re-entry
Ischaemic AP also facilitates re-entry

Re-entry occurs when wavelength of a propagating VBP is smaller than available pathlength

• Wavelength equals conduction velocity times refractory period ($\omega = \theta \times RP$)

• Slowing $\theta$ (m/s) and reducing $RP$ (s) reduces $\omega$ (m) and so facilitates re-entry
Ischaemic AP also facilitates re-entry

Re-entry occurs when wavelength of a propagating VBP is smaller than available pathlength

• Wavelength equals conduction velocity times refractory period ($\omega = \theta \times RP$)

• Slowing $\theta$ (m/s) and reducing $RP$ (s) reduces $\omega$ (m) and so facilitates re-entry
Ischaemic AP facilitates re-entry

Diastolic depolarisation causes partial inactivation of iNa

AP upstroke slowed

$\theta$ slowed

Ischaemia

$\omega$ therefore reduced

VPB more likely to initiate VF

APD shortened due to $\uparrow I_{K,ATP}$ and $\Delta I_{Na/Ca}$

RP reduced
Ischaemic AP facilitates re-entry

Diastolic depolarisation causes partial inactivation of iNa

AP upstroke slowed

$\theta$ slowed

$\omega$ therefore reduced

VPB more likely to initiate VF

APD shortened due to $\uparrow$IK$_{ATP}$ and $\Delta$I$_{Na}$/Ca

Ischaemia

Diastolic depolarisation causes partial inactivation of iNa

AP upstroke slowed

$\theta$ slowed

$\omega$ therefore reduced

VPB more likely to initiate VF

APD shortened due to $\uparrow$IK$_{ATP}$ and $\Delta$I$_{Na}$/Ca

Ischaemia
Ischaemic AP facilitates re-entry

Diastolic depolarisation causes partial inactivation of iNa

$\theta$ slowed

$\omega$ therefore reduced

VPB more likely to initiate VF

AP upstroke slowed

APD shortened due to $\uparrow I_{K_{ATP}}$ and $\Delta I_{Na/Ca}$

Ischaemia

$RP$ reduced
Complexity increased by molecular pathology: consider acute ischaemia again

- Numerous chemicals accumulate or are depleted in the ischaemic region
- Some are proarrhythmic, some antiarrhythmic
- They have independent effects, and interact
- A drug may be proarrhythmic by blocking or facilitating generation or actions of these ‘mediators’
Complexity increased by molecular pathology: consider acute ischaemia again

- Numerous chemicals accumulate or are depleted in the ischaemic region
- Some are proarrhythmic, some antiarrhythmic
- They have independent effects, and interact
- A drug may be proarrhythmic by blocking or facilitating generation or actions of these ‘mediators’
Complexity increased by molecular pathology: consider acute ischaemia again

• Numerous chemicals accumulate or are depleted in the ischaemic region

• Some are proarrhythmic, some antiarrhythmic

• They have independent effects, and interact

• A drug may be proarrhythmic by blocking or facilitating generation or actions of these ‘mediators’
Complexity increased by molecular pathology: consider acute ischaemia again

- Numerous chemicals accumulate or are depleted in the ischaemic region
- Some are proarrhythmic, some antiarrhythmic
- They have independent effects, and interact
- A drug may be proarrhythmic by blocking or facilitating generation or actions of these ‘mediators’
Complexity increased by molecular pathology: consider acute ischaemia again

• Numerous chemicals accumulate or are depleted in the ischaemic region

• Some are proarrhythmic, some antiarrhythmic

• They have independent effects, and interact

• A drug may be proarrhythmic by blocking or facilitating generation or actions of these ‘mediators’
Mediators may act in series, and in parallel, and may interact

Mediators may act in series, and in parallel, and may interact

And the role of a mediator may change as ischaemia progresses to infarction

And the role of a mediator may change as ischaemia progresses to infarction.

Putative proarrhythmic mediators

- Endothelin
- K^+
- Angiotensin-II
- Leukotrienes
- Thromboxane A_2
- Other prostaglandins
- Other lipids
- PAF
- Palmitoylcarnitine
- 5-HT
- Histamine
- Noradrenaline
- Aldosterone
- "X"
- Opioids
- H^+
- VF

Clements-Jewery et al., Current Opinions in Pharmacology 9:81-83, 2009
And some protective mediators

- Prostacyclin
- Nitric oxide
- cGMP
- Blood K+ (acts in uninvolved region)
- Magnesium
- Endocannabinoids
- Adenosine
- "X"

↓ VF

Evidence for mediator involvement: potassium
Very rapid local increase during ischaemia

Hirche et al., 1980
Evidence for mediator involvement: potassium

Local (intracoronary) injection of potassium: arrhythmogenic

Concentration dependence studies

• Isolated rabbit heart (Langendorff perfusion)
• Epicardial cannulation of LAD
• Independent perfusion of LAD
• Local infusion of $K^+$-supplemented Krebs (*no ischaemia*)
• Electrogram recorded from LAD and RV territory
Evidence for mediator involvement: potassium
Local (intracoronary) injection of potassium: arrhythmogenic

Concentration dependence studies

• Isolated rabbit heart (Langendorff perfusion)
• Epicardial cannulation of LAD
• Independent perfusion of LAD
• Local infusion of $K^+$-supplemented Krebs (no ischaemia)
• Electrogram recorded from LAD and RV territory
Evidence for mediator involvement: potassium
Local (intracoronary) injection of potassium: arrhythmogenic

Concentration dependence studies

• Isolated rabbit heart (Langendorff perfusion)
• Epicardial cannulation of LAD
• Independent perfusion of LAD
• Local infusion of $K^+$-supplemented Krebs (no ischaemia)
• Electrogram recorded from LAD and RV territory
Evidence for mediator involvement: potassium
Local (intracoronary) injection of potassium: arrhythmogenic

Concentration dependence studies

• Isolated rabbit heart (Langendorff perfusion)
• Epicardial cannulation of LAD
• Independent perfusion of LAD
• Local infusion of K⁺- supplemented Krebs (*no ischaemia*)
• Electrogram recorded from LAD and RV territory
Evidence for mediator involvement: potassium
Local (intracoronary) injection of potassium: arrhythmogenic

Concentration dependence studies

• Isolated rabbit heart (Langendorff perfusion)
• Epicardial cannulation of LAD
• Independent perfusion of LAD
• Local infusion of K\(^+\)-supplemented Krebs (*no ischaemia*)
• Electrogram recorded from LAD and RV territory

Regional K+ elevation can cause VF.
Arrhythmias most severe with 15 mM K+ and reduced by small K+ increase in adjacent bed.

Curtis, 1991
How can you anticipate how a drug will affect rhythm?

• Test

• Test in all conditions in which the drug will be used

• Ischaemia, infarction, heart failure .etc.
How can you anticipate how a drug will affect rhythm?

- Test
- Test in all conditions in which the drug will be used
- Ischaemia, infarction, heart failure etc.
How can you anticipate how a drug will affect rhythm?

- Test
- Test in all conditions in which the drug will be used
How can you anticipate how a drug will affect rhythm?

- Test
- Test in all conditions in which the drug will be used
- Ischaemia, infarction, heart failure etc.
If you are not sure your drug is safe

• Then you don’t know that it is safe....
If you are not sure your drug is safe

• Then you don’t know that it is safe….
Data required for *Pharma* decision making: the risk benefit continuum

<table>
<thead>
<tr>
<th>Basis for decision to proceed to man</th>
<th>Basis for decision to not proceed to man</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug for lethal indication</strong></td>
<td><strong>Drug for lethal indication</strong></td>
</tr>
<tr>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td><strong>Drug for innocuous indication</strong></td>
<td><strong>Drug for innocuous indication</strong></td>
</tr>
<tr>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

**Key:**
- ‘Good’ discovery data
- ‘Bad’ safety data
- Data threshold for decision to proceed
- Data threshold for decision to not proceed

**Brit J Pharmacol**
154:1282, 2008
Reading

Pugsley MK, Authier S, MJ Curtis
Principles of Safety Pharmacology

Pugsley MK, Hancox JC, MJ Curtis
Perception of validity of clinical and preclinical methods
for assessment of torsades de pointes liability
Pharmacology and Therapeutics 119: 115-117, 2008

Shah RR
If a drug deemed ‘safe’ in nonclinical tests
subsequently prolongs QT in phase 1 studies, how can
its sponsor convince regulators to allow development