Challenges in data collection for HABP/VABP trials: Investigator’s Perspective

Richard G. Wunderink MD, FCCP
Northwestern University Feinberg School of Medicine
Chicago, IL
Challenges in data collection for HABP/VABP trials

- Excessive amount of irrelevant data collection
- ICU is unique environment
  - Expected complications/abnormalities
  - Rapid monitoring of therapeutic interventions
  - Excess of testing
16 episodes of hypokalemia, 7 episodes of hyperchloremia
Sepsis with DKA

Bedside Glucose

New VAP
Challenges in data collection for HABP/VABP trials

- Excessive amount of irrelevant data collection
- ICU is unique environment
- Esoteric testing – external EKG analysis
  - Short term, no-cost lease agreement
  - Biomedical clearance
  - Collection of additional concomitant meds
  - Investigator review and sign offs
Azithromycin and the Risk of Cardiovascular Death

Wayne A. Ray, Ph.D., Katherine T. Murray, M.D., Kathi Hall, B.S., Patrick G. Arbogast, Ph.D., and C. Michael Stein, M.B., Ch.B.

A Cardiovascular Death

Entire 10 days: Hazard ratio, 1.86 (95% CI, 1.27–2.73) P=0.002

Days 1–5:
Hazard ratio, 2.88
(95% CI, 1.79–4.63)
P<0.001

Days 6–10:
Hazard ratio, 0.88
(95% CI, 0.43–1.80)
P=0.72
Azithromycin and the Risk of Cardiovascular Death

Wayne A. Ray, Ph.D., Katherine T. Murray, M.D., Kathi Hall, B.A., Patrick G. Arbogast, Ph.D., and C. Michael Stein, M.B., Ch.B.

A Cardiovascular Death
Entire 10 days: Hazard ratio, 1.86 (95% CI, 1.27–2.71); P=0.002

---

Use of Azithromycin and Death from Cardiovascular Causes

Henrik Svanström, M.Sc., Björn Pasternak, M.D., Ph.D., and Anders Hviid, Dr.Med.Sci.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Azithromycin (N=1,102,419)</th>
<th>Penicillin V (N=7,364,292)</th>
<th>Rate Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of events</td>
<td>no./1000 patient-yr</td>
<td>no. of events</td>
<td>no./1000 patient-yr</td>
</tr>
<tr>
<td>Primary analysis</td>
<td>17</td>
<td>1.1</td>
<td>146</td>
<td>1.5</td>
</tr>
<tr>
<td>Subgroup analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9</td>
<td>1.7</td>
<td>87</td>
<td>2.3</td>
</tr>
<tr>
<td>Female</td>
<td>8</td>
<td>0.8</td>
<td>59</td>
<td>1.0</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–44 yr</td>
<td>3</td>
<td>0.3</td>
<td>17</td>
<td>0.3</td>
</tr>
<tr>
<td>45–64 yr</td>
<td>14</td>
<td>2.5</td>
<td>129</td>
<td>3.1</td>
</tr>
<tr>
<td>History of cardiovascular disease‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10</td>
<td>9.7</td>
<td>62</td>
<td>8.0</td>
</tr>
<tr>
<td>No</td>
<td>7</td>
<td>0.5</td>
<td>84</td>
<td>0.9</td>
</tr>
</tbody>
</table>
Challenges in data collection for HABP/VABP trials

- Excessive amount of irrelevant data collection
- ICU is unique environment
- Esoteric testing – external EKG analysis
- **Excessive regulatory documentation**
  - Lot number, expiration date, signature of pharmacy preparer and saved vials/infusion bags for FDA-approved drugs taken from hospital stock
  - Training in general and drug-specific GCP for all RNs who may potentially infuse study drug
- Inadequate HIPPA standards
Clinical Response in Carbapenem VAP Trial
Kollef, Crit Care, 2012

Doripenem overall clinical cure rate difference was -11.2%, 95% CI of difference -26.3 to 3.8%
Pseudomonas Pneumonia Cases

$p = 0.04$
Mortality: 0% imipenem vs. 35.3% doripenem
95% CI of difference: 12.6% to 58.0%

N = 274 Overall
Dori = 115
Imi = 112
Poor GCP = 41

Pseudomonas
N = 27
Dori = 17
Imi = 10

Kollef, Crit Care, 2012
Results

- Excess time = excess cost
- Fatigue = loss of sites/patients
  - Investigator/ Research coordinator fatigue
  - Monitor fatigue = lose the forest for the trees
- Audit risk
- No clear patient benefit
  - ? unexpected side effects detected by extensive data collection in Phase III trials
  - Most unusual side effects detected by post marketing surveillance
Humanity has but three great enemies: Fever, famine, and war. Of these, by far the greatest, By far the most terrible, is fever.

**Sir William Osler**