Exercise 1 – RISK-Benefit ASSESSMENT

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Ground Rules for Problem-Based Discussions

1. The purpose is to apply material from the lectures.
2. Use brainstorming, any information can be valuable.
3. All should agree before moving to the next page.
4. Have someone read the material aloud.
5. Record basic information for presentation later
6. All members should participate,
RISK-BENEFIT ASSESSMENT EXERCISE

You have just become Director of Safety and Risk-Benefit Management for a company that markets GerdAway. GerdAway is a new medication for treatment of night-time GERD that has been on the market for 12 months. Over the past year, your department received three confirmed reports of deaths due to arrhythmias in patients who were treated with GerdAway.

Pre-clinical evidence (printed in GerdAway label)
“GerdAway is associated with an increase in the QTc interval. In the GERD trials, GerdAway was associated with a mean increase in the heart rate of 1.4 beats per minute compared to a 0.2 beats per minute decrease among placebo patients.”

Effect of other drugs on GerdAway
“Ketoconazole – Ketoconazole, a potent inhibitor of CYP3A4, at a dose of 400 mg QD for 5 days, increased the AUC and Cmax of GerdAway by about 35-40%. Other inhibitors of CYP3A4 would be expected to have similar effects.”

Clinical trials
In a 6 month study, GerdAway was shown to significantly decrease symptoms of GERD among 82% of patients versus 48% of patients on placebo. In a comparative efficacy trial of 250 patients over 3 months, the symptom reduction from GerdAway was 78% versus 73% from the top selling product in the same therapeutic class (not statistically significant).
No arrhythmia events were found in clinical trials.

Product label
GerdAway label in the US has warning language about increases in the QTc interval but does not have a black box warning.

What is the nature of the concern? What are the possible causes?

Using this information, discuss at least three different risk-benefit assessment techniques presented in this workshop.
1. 
2. 
3. 

Which technique might be best? Why?

After discussing the above, turn the page together.
Additional Information
The results of an epidemiologic study performed prior to product launch found the background incidence rates shown in the table below.

Background incidence rates computed using a retrospective database prior to GerdAway’s launch*

<table>
<thead>
<tr>
<th></th>
<th>Events per 1,000 Py</th>
<th>Events per 1,000 Py</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients with GERD*</td>
<td>-Matched comparison group</td>
<td></td>
</tr>
<tr>
<td>Ventricular arrhythmias</td>
<td>1.7</td>
<td>0.8</td>
<td>2.0 (1.1 to 3.8)</td>
</tr>
<tr>
<td>Any arrhythmias per 1000</td>
<td>16.5</td>
<td>14.2</td>
<td>1.2 (1.0 to 1.4)</td>
</tr>
</tbody>
</table>

*Note, this is fictitious data created for purposes of the example

Discuss this information in conjunction with the 3 Risk-Benefit Assessment techniques you reviewed on the previous page.

How does this information apply?

Are there other techniques that would be more relevant, in light of this information?
Exercise 2 – RISK-BENEFIT ASSESSMENT

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Cureallia is an agent developed to treat 7 out of 10 types of bioterrorist attacks. Efficacy data are overwhelmingly positive, especially for anthrax spores. [Any benefit data? Say risk reduction was 10%.] It currently has a safety database of 600 subjects.

Results:
- 4 cases of severe localized skin reactions
- 2 cases of severe flu-like syndrome
- 1 pregnancy recorded

What is the nature of the concern? What are the possible causes?

Using this information, discuss at least three different risk-benefit assessment techniques presented in this workshop.
1.
2.
3.

Which technique might be best? Why?
A confirmed bioterrorist attack occurred on the Washington DC Metro Subway. The agent was thought to be anthrax, with over 100,000 persons exposed within 12 hours. Thousands of patients with symptoms of respiratory distress appeared at emergency rooms throughout the area within 24 hours. Many expired. Within 3 days after the first case Cureallia was widely distributed throughout the metropolitan area, using public venues and health care centers. It was estimated that at the end of one week over 1/2 million persons had received the drug.

Within 3 more days the following events were suspected to have been caused by the drug due to exposure timing and lack of previous medical history:

- 70 myocardial infarctions (21 fatal)
- 120 strokes (30 fatal)
- 25 pulmonary embolisms (19 fatal)

Furthermore, of 10,000 people receiving Cureallia who were exposed to patients with anthrax or exposed to the spores, 367 developed anthrax, 39 expired.

Of 10,000 people not receiving Cureallia, who were exposed to patients or the spores, 2,721 developed anthrax, 178 expired.

**Discuss this information in conjunction with the 3 Risk-Benefit Asssessment techniques you reviewed on the previous page.**

**How does this information apply?**

**Are there other techniques that would be more relevant, in light of this information?**