Review of Adverse Events Associated with Propoxyphene Containing Products

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Outline

• **Adverse Event Reporting System (AERS)**
  – Strengths and Limitations

• **AERS Reviews (1969-2005, 2006-07) and Literature Review of Cardiotoxicity**
  – Overall Summary
  – 1st AERS Review: Search Criteria and Findings
  – 2nd AERS Review: Search Criteria and Findings
  – Literature Review of cardiotoxicity
  – Conclusion
Adverse Event Reporting System (AERS)
AERS: Spontaneous Adverse Event Reporting

- Voluntary, “spontaneous” reporting
- Facilitated by the FDA MedWatch Program
- Reports are stored and retrieved via Adverse Event Reporting System (AERS) database
AERS Strengths

- Includes all U.S. marketed products
- Detection of events not seen in clinical trials
- Especially good for events with rare background rate, short latency
AERS Limitations

- Extensive underreporting
- Quality of reports is variable
- Reporting biases
- Actual numerator & denominator not known
- Causality of drug-event association often in question
Overall Summary
Summary: 1st AERS Review
Darvocet (1969 to 2005)

Deaths (n=91)

- Majority (90%) of deaths related to drug overdoses and suicides involving multiple drugs
- No other notable trends or characteristics
- A causal role of Darvocet could not be determined in any of the cases given the co-morbidities and polypharmacy
Summary: 2nd AERS Review (n=65)

- 40% Elderly (psychiatric notable)
- 18% Fatalities (accidental overdose)
- 17% Cardiac (82% confounded)

- Possible drug-event association
  - strong temporal relationship (16)
  - positive dechallenges (8)

- Causality questionable based on co-morbidities and multiple drug use
Summary: Literature Review (Cardiotoxicity)

- Mostly anecdotal reports
- Lacked sufficient scientific evidence to support an association between propoxyphene-containing products and cardiotoxicity
AERS Reviews
1st AERS Review

- Search Criteria
  - Search dates (1969 to 2/2/2005)
  - Trade Darvocet
  - Death as an outcome
  - US reports only

- Search Results (n=91)

- Main Finding
  - Causal role of Darvocet could not be determined given the co-morbidities and polypharmacy
### 2nd AERS Review: Crude Count (n=3038)

<table>
<thead>
<tr>
<th>Preferred Term (PT)</th>
<th>PT Counts</th>
<th>Preferred Term (PT)</th>
<th>PT Counts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed Suicide</td>
<td>433</td>
<td>Nausea</td>
<td>122</td>
</tr>
<tr>
<td>Intentional Overdose</td>
<td>341</td>
<td>Respiratory Arrest</td>
<td>109</td>
</tr>
<tr>
<td>Overdose</td>
<td>319</td>
<td>Vomiting</td>
<td>107</td>
</tr>
<tr>
<td>Multiple Drug Overdose</td>
<td>191</td>
<td>Cardio-Respiratory Arrest</td>
<td>104</td>
</tr>
<tr>
<td>Drug Dependence</td>
<td>168</td>
<td>Dizziness</td>
<td>98</td>
</tr>
<tr>
<td>Cardiac Arrest</td>
<td>161</td>
<td>Drug Interaction</td>
<td>94</td>
</tr>
<tr>
<td>Accidental Overdose</td>
<td>159</td>
<td>Convulsion</td>
<td>79</td>
</tr>
<tr>
<td>Coma</td>
<td>154</td>
<td>Confusional State</td>
<td>75</td>
</tr>
<tr>
<td>Drug Ineffective</td>
<td>130</td>
<td>Pulmonary Oedema</td>
<td>75</td>
</tr>
<tr>
<td>Drug Toxicity</td>
<td>126</td>
<td>Hypotension</td>
<td>74</td>
</tr>
</tbody>
</table>

Crude counts may contain duplicate reports and there is no certainty that the reported suspect product(s) caused the reported adverse event(s). Total Deaths (n=1452)
2nd AERS Review (2006-07)

Search Criteria

- Search dates (1/1/2006 – 12/31/2007)
- Drug names (all trade and generic single ingredient and combination products)
- Serious* outcomes only
- US cases only

Search Results

- 192 reports retrieved

*Serious per regulatory definition includes death, hospitalization or prolongation of hospitalization, life-threatening, disability, congenital anomaly, and other medically important events (CFR 314.80)
### Excluded Cases (n=127) (2006-07)

<table>
<thead>
<tr>
<th>Reasons for exclusion</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed suicides</td>
<td>43</td>
</tr>
<tr>
<td>Intentional overdose/suicide attempt</td>
<td>11</td>
</tr>
<tr>
<td>Drug dependence/abuse/misuse</td>
<td>17</td>
</tr>
<tr>
<td>Duplicate reports</td>
<td>44</td>
</tr>
<tr>
<td>Others*</td>
<td>12</td>
</tr>
</tbody>
</table>

*Event unlikely related to propoxyphene products (9), medication error (1), miscoded (1), homicide case (1)
### Demographics, Indication and Dose (2006-07)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>65</td>
</tr>
<tr>
<td>Gender (n=63):</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>21</td>
</tr>
<tr>
<td>Female</td>
<td>42</td>
</tr>
<tr>
<td>Age:</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>62 years (n=53)</td>
</tr>
<tr>
<td>Range</td>
<td>19-92 years</td>
</tr>
<tr>
<td>Indication (n=31)</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>13</td>
</tr>
<tr>
<td>back pain</td>
<td>6</td>
</tr>
<tr>
<td>dental/surgical pain</td>
<td>3</td>
</tr>
<tr>
<td>joint/hip pain</td>
<td>3</td>
</tr>
<tr>
<td>leg/knee pain</td>
<td>2</td>
</tr>
<tr>
<td>osteoarthritis</td>
<td>2</td>
</tr>
<tr>
<td>ankle pain</td>
<td>1</td>
</tr>
<tr>
<td>nerve pain</td>
<td>1</td>
</tr>
<tr>
<td>Total daily dose:</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>200 mg (n=13)</td>
</tr>
<tr>
<td>Range</td>
<td>100 mg to 800 mg</td>
</tr>
</tbody>
</table>
# Time to Onset, Duration and Outcome (2006-07)

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Estimated time to onset:</strong></td>
<td>1 day (n=18)</td>
<td>1 dose to 4 years</td>
</tr>
<tr>
<td><strong>Estimated duration of therapy:</strong></td>
<td>15 days (n=16)</td>
<td>1 day to 16 years</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Death (12), Hospitalization (29), Life Threatening (5), Other {med significant} (38)</td>
<td></td>
</tr>
</tbody>
</table>
2nd AERS Review 2006-07 (n=65)

- 45% of the cases reported confounding factors
  - contributing medical history
  - use of labeled concomitant medications
2nd AERS Review 2006-07 (n=65)

- 18% (12/65) Psychiatric related disorders
  - mental status changes-6, hallucination-5, confusional state-3, abnormal behavior-1

- 17% (11/65) Cardiac related events
  - bradycardia-4, cardio-resp arrest-2, tachycardia-2, arrhythmia-1, CHF-1, MI-1
2nd AERS Review 2006-07 (n=65)

- 15% (10/65) Drug ineffective
- 14% (9/65) Accidental multiple drug overdose
- 35% (23/65) Other adverse events
  - majority (78%) of cases reported another drug as the primary suspect drug
Cardiotoxicity Literature Review
Literature Review Search Results

PubMed and EMBASE (1960 – 2008)

- 16 publications
  - 3 epidemiology studies
    - 2 randomized trials and
    - 1 observational study
  - 12 case reports
  - 1 case series
Study Findings - Mixed

- Changes in cardiac conduction not related to study medications
- Observed significant changes in cardiac conduction AND
- Correlation between conduction changes and estimated propoxyphene dose
- Cardiac Output changes not clinically significant
Limitations of Studies

- Small sample sizes
- Patients on multiple medications
- Difficulty measuring propoxyphene concentrations
- Sample populations may not represent typical users
- Negative finding DOES NOT EQUATE TO no association between propoxyphene and cardiotoxicity
Conclusion

- 1st AERS Review: causal role of propoxyphene products could not be established
- 2nd AERS Review: potential drug to event association in some cases
  - Reports were qualitatively similar to the prior AERS review
  - Causal role of propoxyphene was questionable
- Literature lacked sufficient data to establish cardiotoxicity with use of propoxyphene products
- Despite current propoxyphene label warnings, narcotic pain relievers and CNS related drugs continue to be prescribed and used with propoxyphene containing products resulting in accidental and intentional deaths.