DRUG-INDUCED PANCREATITIS …OR NOT?

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Objectives

- Present a step-wise approach for recognition and diagnosis of drug-induced pancreatitis (DIP)
- Classify drugs associated with pancreatitis based on evidence from available literature
- Discuss the pattern of clinical presentation for select drugs

Disclosure Statement

- Disclosure statement: these individuals have the following to disclose concerning possible financial or personal relationships with commercial entities (or their competitors) that may be referenced in this presentation.
  - Resident: Amanda Guffey, PharmD (nothing to disclose)

Patient Case

- AB is a 19 y.o. AAF admitted 11/7/11 with polymicrobial abdominal abscess s/p C-Section
- PMH: Bipolar disorder, mild mental retardation, congenital solitary kidney
- Social History: denies tobacco, alcohol, illicit drugs
- Home Meds: Olanzapine 10 mg qam, 15 mg qpm

Inpatient Treatments

- TPN (11/11 – 11/19)
- Propofol (11/11 – 11/14)
- Dilaudid (11/7 – 11/25)
- Acetaminophen (11/7 – 11/16)
- Tigecycline (11/14 – 11/22)
- Ondansetron (11/8 – 11/19)

Inpatient Treatments

- Pertinent Labs
  - Triglycerides = 1386 (11/14/11)
  - AST = 117, ALT = 120 (11/21/11)
  - Calcium = 7.4 (11/21/11)
  - Amylase = 220 (11/22/11)
  - Lipase = 831 (11/22/11)

Diagnosis of Acute Pancreatitis

- Gallstones or alcohol?
- Test for metabolic changes (hypercalcemia, hypertriglyceridemia)
- Rule out duct obstruction, pancreatic cancer, or autoimmune pancreatitis
- Patient taking medications associated with pancreatitis?

Diagnosis of DIP

- Rare incidence
  - Estimated 0.1% - 2% of all acute pancreatitis cases

- Diagnosis of elimination
  - No specific clinical or laboratory evidence

- Limited adequate studies

Classification System of DIP

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class Ia</td>
<td>At least 1 case report with positive rechallenge, excluding all other causes</td>
</tr>
<tr>
<td>Class Ib</td>
<td>At least 1 case report with positive rechallenge, but other causes cannot be ruled out</td>
</tr>
<tr>
<td>Class II</td>
<td>At least 4 cases in literature and consistent latency (&gt;75% of cases)</td>
</tr>
<tr>
<td>Class III</td>
<td>At least 2 cases in literature with no consistent latency and no rechallenge</td>
</tr>
<tr>
<td>Class IV</td>
<td>Drugs not fitting into previous classes, including single case reports with no rechallenge</td>
</tr>
</tbody>
</table>

Enalapril

- Angioedema of pancreatic duct
- Appears dose-dependent
  - 5 of 7 cases taking 20 mg/day
- Higher risk if taking < 6 months
- Also reported with lisinopril (6), captopril (2), benazepril (1), and ramipril (1)

Drug Classification

<table>
<thead>
<tr>
<th>Class Ia</th>
<th>Class Ib</th>
<th>Class II</th>
<th>Class III</th>
<th>Class IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enalapril</td>
<td>Carisoprodol</td>
<td>Furosemide</td>
<td>Losartan</td>
<td>Metoprolol</td>
</tr>
</tbody>
</table>

Furosemide

- Proposed mechanisms
  - Increased pancreatic secretions and increased amylase
  - Extracellular volume contraction decreasing pancreatic circulation
- Other case reports without rechallenge showed initial latency < 1 week
**Metronidazole**
- Diffusion into pancreas
  - Direct toxic effect
- Spanier et al → increased risk with concomitant use of drugs associated with pancreatitis
- Helicobacter pylori regimen → 8-fold increase
- Incidence 4.6 per 10,000 patients treated
  - Discharge data

<table>
<thead>
<tr>
<th>Author</th>
<th>Age/Sex</th>
<th>Initial Latency</th>
<th>Repeat Latency</th>
<th>Severity</th>
<th>Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanford et al 1998</td>
<td>F 63</td>
<td>3 days</td>
<td>3 days</td>
<td>Mild</td>
<td>Definite</td>
</tr>
<tr>
<td>California et al 1999</td>
<td>F 22</td>
<td>12 hours</td>
<td>1 day</td>
<td>Mild</td>
<td>Definite</td>
</tr>
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**Valproic Acid**
- Direct toxin effect
  - Free radical formation
- Estimated ½ occur in pediatric population
- Estimated ¼ cases severe (pseudocyst, necrosis, death)

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</thead>
<tbody>
<tr>
<td>Coulter and Allen 1980</td>
<td>M 8</td>
<td>6 months</td>
<td>3 months</td>
<td>Mild</td>
<td>Definite</td>
</tr>
<tr>
<td>Camfield 1979</td>
<td>F 11</td>
<td>3 months</td>
<td>6 weeks</td>
<td>Severe</td>
<td>Definite</td>
</tr>
<tr>
<td>Fecik et al 1999</td>
<td>M 57</td>
<td>17 months</td>
<td>2 months</td>
<td>Mild</td>
<td>Definite</td>
</tr>
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**Azathioprine**
- Mechanism unknown
- Particularly in Inflammatory Bowel Syndrome
  - Crohn’s disease

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<tr>
<td>Guillaume P 1984</td>
<td>M 22</td>
<td>27 days</td>
<td>2 days</td>
<td>Mild</td>
<td>Definite</td>
</tr>
<tr>
<td>Paloyan D 1977</td>
<td>M 19</td>
<td>20 days</td>
<td>1 day</td>
<td>Mild</td>
<td>Definite</td>
</tr>
<tr>
<td>Nogueira JR 1972</td>
<td>F 57</td>
<td>21 days</td>
<td>2 hours</td>
<td>Mild</td>
<td>Probable</td>
</tr>
</tbody>
</table>

**Statins**
- Mechanism unknown
- Likely class effect
  - Singh et al demonstrated recurrence after atorvastatin → rosuvastatin
  - Case reports with atorvastatin, simvastatin, lovastatin, and fluvastatin

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<tr>
<td>Castells et al 2004</td>
<td>M 56</td>
<td>6 months</td>
<td>3 days</td>
<td>Mild</td>
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**Amiodarone**
- Mechanism unknown
- Likely dose-related
  - Loading dose

<table>
<thead>
<tr>
<th>Author</th>
<th>Age/Sex</th>
<th>Dosage</th>
<th>Initial Latency</th>
<th>Repeat Latency</th>
<th>Severity</th>
<th>Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosch and Berndt 1997</td>
<td>F 46</td>
<td>800 mg</td>
<td>4 days</td>
<td>3 days</td>
<td>Mild</td>
<td>Definite</td>
</tr>
<tr>
<td>Famularo et al 2004</td>
<td>M 80</td>
<td>600 mg</td>
<td>5 days</td>
<td>---</td>
<td>Mild</td>
<td>Possible</td>
</tr>
</tbody>
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**Trimethoprim/Sulfamethoxazole**
- Sulfa component
  - DIP reports with sulfamethazole and sulfamethoxazole
  - No DIP reports with trimethoprim alone
- Allergic reaction?

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<tr>
<td>Park TY et al 2010</td>
<td>M 32</td>
<td>2 weeks</td>
<td>3 days</td>
<td>Mild</td>
<td>Definite</td>
</tr>
<tr>
<td>Antanow 1986</td>
<td>M 33</td>
<td>7 days</td>
<td>3 days</td>
<td>Mild</td>
<td>Definite</td>
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Exenatide (Byetta)

- Class II (no rechallenges)
- Gila monster venom
- FDA alert
- Case reports of hemorrhagic or necrotizing pancreatitis

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<td>Tripathy et al 2008</td>
<td>52/F</td>
<td>8 days</td>
<td>Mild</td>
<td>Possible</td>
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<tr>
<td>Denker and Dimitrova 2006</td>
<td>49/F</td>
<td>5 days</td>
<td>Mild</td>
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Gila monster venom

FDA alert

Case reports of hemorrhagic or necrotizing pancreatitis

Tigecycline (Tygacil)

- Class II (no rechallenges)
- Tetracycline, minocycline, oxytetracycline also associated with DIP (Class I)
- Toxic metabolite
- Hypertriglyceridemia
- High biliary concentration

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<td>Gilson et al 2008</td>
<td>35/M</td>
<td>13 days</td>
<td>Mild</td>
<td>Possible</td>
</tr>
<tr>
<td>Lipshitz et al 2009</td>
<td>64/F</td>
<td>14 days</td>
<td>Mild</td>
<td>Possible</td>
</tr>
<tr>
<td>Marshall 2009</td>
<td>55/F</td>
<td>10 days</td>
<td>Mild</td>
<td>Possible</td>
</tr>
<tr>
<td>Hung et al 2009</td>
<td>65/F</td>
<td>7 days</td>
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Patient Case

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Summary

- Diagnosis of DIP is difficult due to rare incidence and limited study data
- DIP should be considered in differential diagnosis for acute pancreatitis
- Pharmacist have the ability to identify and be a knowledgeable source regarding DIP

References


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March 25, 2012
SCSHP Clinical Pearls