Drug-Induced Recurrent Acute Pancreatitis:

Does It Exist?

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Does It Exist?

Yes
No
Maybe

A 55 year old woman with diabetes presents for consultation in search of identifying her cause of acute pancreatitis. She was discharged after a 5 day stay for mild acute pancreatitis. This was her 3rd attack in 2 years.

Past Medical History: Acute Pancreatitis, DM, HTN
Medications: Metformin, Byetta (exenatide), ASA, Bystolic, Enalapril
No Family History of Pancreatic Disease
No Alcohol Use, Triglycerides Normal, US negative
MRCP negative

When to Blame the Drug for Acute Pancreatitis?

• Enalapril
• Byetta
• Asprin
• Bystolic

By the way, what is the etiology?

• Diverticulitis?
• Appendicitis?
• Ulcerative Colitis?
• Crohn’s Disease?
• Cholecystitis (considering most patients with gallstones never develop gallbladder disease)
Drug Induced Acute Pancreatitis

• According to PDR, 1800 meds implicated
• In peer reviewed literature, >120 drugs have been implicated in causing acute pancreatitis
• However, many case reports are poorly written:
  – inadequate criteria for the diagnosis of acute pancreatitis.
  – failure to rule out more common etiologies.

Levels of Evidence

• Randomized Controlled Clinical Trials:
  – 6 MP, Azathioprine, DDI
• Large Pharmaco-epidemiologic Databases
  – None
• Case Control Studies
  – None
• Case Reports
  – Complex Story

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Classification System of Drug Induced Acute Pancreatitis

Class Ia drug
At least one case report with positive rechallenge, excluding all other etiologies, such as alcohol, hypertriglyceridemia, gallstones, and other drugs.

Class Ib drug
At least one case report with positive rechallenge, however, other etiologies, such as alcohol, hypertriglyceridemia, gallstones, and other drugs were not ruled out.

Class II drug

1 At least four cases in literature
2 Consistent latency (>75% of cases)
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**Class II drug**
1. At least four cases in literature
2. Consistent latency (>75% of cases)

**Class III drug**
1. At least two cases in literature
2. No consistent latency among cases
3. No rechallenge

**Class IV drug**
Drugs not fitting into the above classes, single case report published in medical literature, without rechallenge.

Mechanism of Action?
- Hypersensitivity Reaction
- Idiosyncratic Reaction vs Intrinsic Toxin
- Toxic Metabolites – Dose Dependent/Time Dependent
- Toxic Intermediaries
- Mechanical Effects

GLP – 1 Agonist Story
- Exenatide (Byetta) marketed in 2007.
- Case Reports of AP – Poorly Written.
- Multiple Phase 3b Studies – FDA noted increase in Medwatch Reports/AERS.
- FDA Compared Expected to Reported.
- Despite Pancreatologists Explaining that background increase likely due to Diabetic Population compared to Normal Population Incidence, FDA Issued Warning – Black Box
- Surge in FDA Medwatch Reports/AERS.

GLP – 1 Agonist Story - Continued
- Multi-district/State litigation begins
- UCLA Group (Endocrinologists) proposes hypothesis of causation based on limited science.
- Multiple randomized controlled trials and large pharmacoepidemiologic studies show no evidence of causation.
- By 2013, almost 1000 law suits are pending, settled or tried.
- Pancreatologists pulled from research to participate in the legal follies.
- Almost all suits refer to . . . . .
Moving Forward

- Focus on the Scientific Evidence
- Be careful of our use of Language

Considering Scientific Causation


- **Strength**: randomized trials and large epidemiologic studies show only a few drugs cause acute pancreatitis (host factors also exist)
- **Consistency**: Results from clinical trials, epidemiology, case reports, and animal studies are inconsistent.

- **Temporality** exists only for a handful of drugs attributed as causing acute pancreatitis.
- **Biologic plausibility** does not exist for any drug except by speculation.
- **Dose/Response** does not exist. There is no linear increased risk by the drugs attributed as causing acute pancreatitis.

- **Experimental data**, in both animals and humans, do not establish that any drug causes acute pancreatitis.
- The only **Coherence/Analogy** that exists for drugs causing acute pancreatitis is between 6 MP and Azathioprine.

Legal Definitions of Causation

- Criminal Law – Beyond a Reasonable Doubt
- Civil Law – The Preponderance of Evidence
- Malpractice – More Likely Than Not
- Circumstantial Evidence – Evidence that can be inferred by a reasonable person (physician)

Summary

There is almost no evidence that the vast majority of drugs claimed by authors and the FDA as causing acute pancreatitis actually cause acute pancreatitis.