Teachable Moments: When Potentially Fatal Side Effects of “Blockbuster” Drugs and Devices Unexpectedly Show Up

Charles L. Bennett, MD, PhD, MPP
Background

- sADRs account for 100,000 deaths annually
- sADRs reported late in the agents lifecycle
- Little empirical data for cancer drugs
- No study has systematically evaluated the timing and media to identify and disseminate information on sADRs for oncology drugs
Barriers to identifying sADRs

- Limited size of clinical trials
- Undetected toxicities at the time of FDA approval
- Many sADRs identified after several years on the market
Postmarket Pharmacovigilance

- sADRs account for 100,000 deaths annually

# Pharmacovigilance Organizations

<table>
<thead>
<tr>
<th></th>
<th>Academic Organizations</th>
<th>FDA</th>
<th>Pharmaceutical Manufacturers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Data</strong></td>
<td>Case assessments; Prospective data</td>
<td>MedWatch</td>
<td>Proprietary databases</td>
</tr>
<tr>
<td><strong>Science</strong></td>
<td>Pathology; histology</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td><strong>Timeliness</strong></td>
<td>1-2 years post approval</td>
<td>3 years or more</td>
<td>7-12 years</td>
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<tr>
<td><strong>Dissemination</strong></td>
<td>Manuscripts; presentations</td>
<td>Package inserts</td>
<td>Dear Doctor letters</td>
</tr>
<tr>
<td><strong>Network</strong></td>
<td>Broad; international</td>
<td>Mostly internal</td>
<td>Mostly internal</td>
</tr>
<tr>
<td><strong>Funding</strong></td>
<td>R01-based; CERTs</td>
<td>Internal</td>
<td>Not known</td>
</tr>
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</table>
### Major RADAR Publications

<table>
<thead>
<tr>
<th>Drug</th>
<th>ADR</th>
<th>N</th>
<th>Publication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonates</td>
<td>Osteonecrosis of the Jaw</td>
<td></td>
<td><em>Lancet Oncology</em> 2008</td>
</tr>
<tr>
<td>Epoetin/ darbepoetin</td>
<td>VTE and Mortality</td>
<td></td>
<td><em>JAMA</em> 2008</td>
</tr>
<tr>
<td>Sirolimus/paclitaxel coated cardiac stents</td>
<td>Thrombotic events</td>
<td>139</td>
<td><em>JAMA</em> 2007</td>
</tr>
<tr>
<td>Epoetin/ darbepoetin</td>
<td>Venous thromboembolism</td>
<td></td>
<td><em>J Natl Cancer Inst</em> 2006</td>
</tr>
<tr>
<td>Sirolimus/paclitaxel coated cardiac stents</td>
<td>Hypersensitivity reactions</td>
<td>6</td>
<td><em>J Am Coll Cardiol</em> 2006</td>
</tr>
<tr>
<td>Thalidomide/ lenalidomide</td>
<td>Venous thromboembolism</td>
<td></td>
<td><em>JAMA</em> 2006</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>Thrombotic thrombocytopenic purpura</td>
<td>21</td>
<td><em>Lancet</em> 1998</td>
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</tbody>
</table>
First Bite Syndrome: An interesting complication of carotid body paraglioma resection
Case Study

- 55-year old male
- Excision of asymptomatic left parapharangeal mass (carotid body paraganglioma)
- Transcervical incision
- Required ligation of the external carotid artery
- Postoperative pain in left jaw/ear with first bite of solid food.

- “Strong electrical jolt” in jaw with severe cramping
  - Initially very painful
  - Slowly dissipated after 5 to 15 minutes
- Pain returned a few minutes after eating and persisted up to 15 minutes
Case Study

• 3 months post surgery –
• First bite syndrome pain continues
  – Similar intensity and duration
• Acetaminophen and Ibuprofen - Ineffective
• Underlying etiology: interruption of parasympathetic and sympathetic nerves
• Occurs in 33% of persons undergoing external carotid artery ligation
Radiation overexposure following brain perfusion CT scans in California, Florida, and Alabama (2008–2009)
Introduction

• 69 million CT scans annually

• 2008-2009 --> 206 individuals at Cedars-Sinai Medical Center experienced 8x- greater irradiation following 64-slice brain perfusion CT scan during acute CVA evaluation

• ~40% reported clinical manifestations
  – Scalp hair loss; Confusion; skin allergies

Working diagnosis: not CT related.
Cases of CT scan exposure in hospitals nationwide

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Beds</th>
<th>Cases(^{a})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cedars-Sinai Medical Center, Los Angeles, CA</td>
<td>868</td>
<td>206–269</td>
</tr>
<tr>
<td>Providence Saint Joseph Medical Center, Burbank, CA</td>
<td>431</td>
<td>34–37</td>
</tr>
<tr>
<td>South Lake Hospital, Clermont, FL</td>
<td>104</td>
<td>40–77</td>
</tr>
<tr>
<td>Huntsville Hospital, Huntsville, AL</td>
<td>794</td>
<td>60–65</td>
</tr>
<tr>
<td>Bakersfield Memorial Hospital, Bakersfield, CA</td>
<td>340</td>
<td>16</td>
</tr>
<tr>
<td>UCSF Medical Center, San Francisco, CA</td>
<td>600</td>
<td>NA</td>
</tr>
<tr>
<td>Alta Bates Summit Medical Center, Berkley, CA</td>
<td>555</td>
<td>NA</td>
</tr>
<tr>
<td>Marin General Hospital, Greenbrae, CA</td>
<td>235</td>
<td>NA</td>
</tr>
<tr>
<td>California Pacific Medical Center, San Francisco, CA</td>
<td>1,300</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>5,227</strong></td>
<td><strong>356–464</strong></td>
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</tbody>
</table>

NA = not available

\(^{a}\) Multiple sources provided different numbers.

Discussion

• Root Cause Analysis by hospital safety employees
  – Lack of familiarity of radiation personnel with modifications of computer software on the CT
  – Presentation of dosimetry levels in nonstandard units
  – Reliance of technicians on the package for calibration of dosages
  – Difficulty comparing planned with delivered dosing levels

• Emergency Care Research Institute (ECRI): RT therapy overdose was the #1 technology hazard for 2011

• 2010: FDA officials disseminated a communication identifying operator error as the cause of the overexposure
X-Rays and Unshielded Infants
The Radiation Boom

- Premature Baby over-radiated at State University of New York Downstate Medical Center, Brooklyn
- Newborn irradiated from head to toe
- According to the technologists association
  - Radiation therapists are unregulated in 15 states,
  - Imaging technologists in 11 states
  - Medical physicists in 18 states
- Michigan, Nuclear Regulatory Commission reported – healthy tissue of 4 cancer patients irradiated – 3 suffered burns
A probable serotonin syndrome complicating a routine screening colonoscopy procedure
Case Study

- Serotonin syndrome - adverse event associated with various classes of medications

- 1984 - Libby Zion died shortly after receiving meperidine in combination with phenelzine, a monoamine oxidase inhibitor.

- 52-year-old Caucasian woman underwent a routine colonoscopy screening

- Medical history significant for mild depression; on SNRI duloxetine, 60 mg/d (discontinued 2 days prior to the procedure)

- Patient medicated with IV midazolam (1 mg), meperidine (80 mg), and hyoscyamine sulfate (0.5 mg), not intubated

- No polyps identified and no biopsies performed
• Follow-up to the colonoscopy
• Experienced confusion in the recovery setting
• Patient did not recall the car ride home
• Slept much of the afternoon
• That evening: a severe headache
• Over next 5 days – patient bed-bound
• Symptoms- Mental confusion, Nausea, Severe headaches, Dizziness, Agitation, Shivering, Diaphoresis, Amnesia, Myoclonus.
Case Study

• One-week follow-up

• 6 days after the colonoscopy, the abnormal clinical findings resolved spontaneously, and the patient resumed taking duloxetine

• No recurrence

• Diagnosis: Serotonin syndrome- resulting from interaction between SNRI and demarol

• GI and anesthesiology were unaware of the possibility of the Serotonin syndrome
Nephrogenic Systemic Fibrosis
Introduction

• NSF:

• The first cases of nephrogenic systemic sclerosis were identified in 1997

• Fifteen patients on hemodialysis with thickening and hardening of the skin and scleromyxedema-like features.
Clinical Appearance of NSF

FIG. 1. The forearm of a patient manifesting the thickened, brawny plaques of NFD. The surface can appear “cobblestoned” or have a “peau d’ orange” texture.
Clinical Appearance of NSF
Systemic Involvement in NSF
Number of Cases in FDA database of GBCA-associated NSF by Year (With Confirmed Event Date)

Key Events (US):
- Grobner’s report (2005)
- First FDA report: summarizes Danish findings and indicates that the FDA is investigating (2006)
- FDA advisory warns of GBCA administration to persons with CKD stage 4-5 (2007)
- Black-box warnings issued (2008)
Results of Advisories

• Swift but uncoordinated efforts led to identifying and disseminating information GBCA-associated NSF

• Nearly a 70% drop in US cases from 2006 to 2008

• Key effort: Danish physicians recognized 20 CKD patients with NSF in 2006; all had recently undergone NSF with gadodiamide (Omniscan)

• Following the diffusion of this information by regulatory authorities, responses were quick and uncoordinated; yet successful
Epoetin-associated pure red cell aplasia

- Similar graph to the NSF cases - found that production defected with one of the epoetin formulations caused the problem. Underlying cause was “mad-cow” disease concerns in Europe.


HSA denotes human serum albumin. Epogen is also marketed as Procrit, and Neorecormon as Recormon.

% of anemic cancer pts with ESA, blood transfusion or VTE (Stafkey-Mailey data (SCTA pilot grant)
Lessons learned

• Adverse side effect identification of popular drugs is not a popular hobby-

• To date: 50 potentially fatal sADRs have been identified by our group

• Companies account for trillions in market cap, tens of billions in sales, and tens of millions in users
Radiology-associated sADRs

- in the US, few radiologists will publicly discuss the issues (medicolegal)

- In Denmark, the leading radiologist and nephrologist published the cases

- Result: temporary removal from jobs, two national inquiries, and one libel suit
Blockbuster drugs- EPO

• first response– hope that it is the other manufacturer
• Second response- hope that the data are wrong
• Third response- lobby and motivate patients and clinicians
• Fourth- use the drug more rationally (sales down, safety up, Medicare and Medicaid budgets better)
Plavix and Rituxan

• Rare side effects, but fatal

• Manufacturers- outline the side effects prominently on the medical and Direct-to-Consumer marketing

• Next step: collaborative scientific research evaluating causality—lip-service generally
Bisphosphonates

• Safety information disseminated to patients, dentists, and physicians

• Collaborative research: again- not agree to

• Very serious side effect- not so rare

• In cancer, marked pull-back
Overall conclusion

• Detecting sADRs is an art;

• Single case reports are essential

• Pharma, FDA, and MDs- not in favor

• Collaborative projects: unlikely

• Ultimate benefits: accrue to patients
QUESTIONS?!?!