Important Tools in Determining Whether a Signal Warrants Further Investigation

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Tools for Signal Assessment

- Published case reports
- Elements of biologic plausibility
Published Cases


Elements of Biologic Plausibility

- Same adverse event with pharmacologically related substances that bind to the same physiologic receptor

- Dose effect

- Temporal association that is consistent with the pharmacokinetics of the drug

- Retinoids and the central nervous system
**Biologic Plausibility**

Occurrence of psychiatric adverse events with distinct substances that bind the same physiologic receptors:

- High-dose vitamin A (acne)
  
  RM Restak 1972; EF McCance-Katz and LH Price, 1992

- Etretinate (psoriasis)
  
  Martinez et al 1987; CA Henderson and AS Highet, 1989

- All-trans-retinoic acid (leukemia)
  
  Sacchi et al. 1999 Leukemia & Lymphoma

**All-trans retinoic acid (ATRA)**

- Unexpected high incidence of severe toxicities when ATRA added to IFN-alpha and low-dose ara C for leukemia

- Possible synergistic toxicity between IFN and ATRA
  
  » Sacchi et al. 1999 Leukemia & Lymphoma
All-trans retinoic acid (ATRA)
(Sacchi et al. 1999 Leukemia & Lymphoma)

<table>
<thead>
<tr>
<th></th>
<th>+ ATRA (n = 42)</th>
<th>No ATRA (n = 134)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>31%</td>
<td>13%</td>
</tr>
<tr>
<td>Psychosis</td>
<td>5%</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>62% (36% severe)</td>
<td>0</td>
</tr>
<tr>
<td>Pseudotumor</td>
<td>5%</td>
<td>0</td>
</tr>
<tr>
<td>Overall CNS</td>
<td>84%</td>
<td>27%</td>
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Dose Effect

- Dose effect is clear for Vitamin A
- For isotretinoin and etretinate
  - there are isolated case reports that suggest a possible dose response
  - a dose threshold cannot be ascertained from spontaneous reports
Biologic Plausibility: Pharmacokinetics

- The terminal elimination half-life of isotretinoin is 10-20 hours
- The pharmacokinetics of isotretinoin are consistent with observed time to resolution of psychiatric adverse events in many patients upon drug discontinuation

Temporal Pattern in Sponsor Analysis of Adverse Events

- A majority of substantive mood disorder cases had off-set within 30 days, most of those within 15 days
- For 25 cases with both on-set and off-set within 15 days:
  - 23 had resolution within 7 days
  - 17 of those had resolution within 4 days
## Temporal Pattern in Published Cases

- Depression in 7 of 700 patients
  - Symptoms resolved within 1 week of stopping Accutane; one patient had positive re-challenge
    » Sheinman et al. JAAD 1990

- Depression in 6 of 110 patients
  - Five continued drug despite depression, which “rapidly” resolved upon discontinuation of Accutane
    » Hazen et al. JAAD 1983

## Retinoids and Central Nervous System

- Retinoids enter the central nervous system
- Retinoid receptors are present in adult brain
- Of all organ system categories, the nervous system ranks second only to “psychiatric” in the highest percentage of serious adverse events in the HLR post-marketing database for Accutane
Overall Assessment

- No mechanism is known for the psychiatric adverse events observed with retinoids
- An association is not biologically implausible
- None of these elements of adverse event assessment, nor their totality, proves that isotretinoin causes psychiatric disease

"Thus, be vigilant"

- Isotretinoin and Depression: Care is Needed

  » Bravard, Krug, and Rzeznick
Risk Management and Assessment

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Labeled Warnings:
21 CFR 201.57

- The labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur.
- The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug.
- A causal relationship need not have been proved.
Current Labeled Warning

“Accutane may cause depression, psychosis and rarely, suicidal ideation, suicide attempts and suicide. Discontinuation of Accutane therapy may be insufficient; further evaluation may be necessary. No mechanism of action has been established for these events”.

Risk Management and Assessment

- Short-term goal
  - Management of uncertain risk

- Long-term goal
  - Resolution of uncertainty
Management of Uncertain Risk

- Information and Education
- Intervention

Management of Uncertain Risk: Information and Education

- Information for Health Care Professionals
  - CME programs
  - Professional labeling
- Information for Patients
  - Patient Package Insert (optional)
  - Brochure (optional)
  - Medication Guide (required distribution)
- Informed Consent
Management of Uncertain Risk: Intervention

- Monitoring of Patients
- Management of Events
- Drug Distribution

Resolution of Uncertainty: Formal Studies

- Basic science research
- Open cohort study
- Retrospective epidemiologic cohort study
- Prospective controlled trial
Formal Studies Might Answer Clinically Important Questions

- Is there a dose threshold that is within the minimum effective dose for acne?
- Is there an identifiable subset of patients at increased risk?
- Once symptoms occur, is dose adjustment/treatment with anti-depressants safe or must Accutane® be discontinued?

Options

- **Education & Information**
  - Information for Health Care Professionals
    - CME programs
    - Professional labeling
  - Information for Patients
    - Patient Package Insert (optional)
    - Brochure (optional)
    - Medication Guide (required distribution)
    - Informed Consent

- **Intervention**
  - Monitoring of Patients
  - Management of Events
  - Drug Distribution

- **Formal Studies**
  - Basic science research
  - Open cohort study (survey)
  - Retrospective epidemiologic cohort study
  - Prospective controlled trial