After-Event Medical Monitoring: Pros and Cons

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Faculty Disclosure

• Faculty: Charles McKay MD
  – Relationships with commercial interests:
    • Principal Investigator for clinical trial (Alere)
  – Speakers Bureau/Honoraria: none
  – Consulting Fees:
    • Member, Science Advisory Council, Environmental Health Research Foundation
  – Other: none
Medical Monitoring: Session Outline

• What is medical monitoring?
• Should it be done?
• If so, when and how?
• Can it be done in a mass casualty situation?
Medical Monitoring

Ongoing or serial evaluation (clinical and/or laboratory) of individuals in order to identify adverse effects following their exposure to some substance.
Medical Monitoring

• Divisive, emotional concept or term
• Often claimed and maligned in the toxic tort system
  – Federal Employer’s Liability Act of 1909
  – Metro North Commuter Railroad vs. Buckley (1997)
  – Silicone breast implants, Phen-Fen, Vioxx,…?
Example: Clinical Monitoring

- Methylisocyanate-induced reactive airways disease
  - Peak flow measurements
  - ?Methacholine challenge testing
  - ? removal of those with previous/underlying asthma or atopic conditions
Example: Laboratory Monitoring

• Using cholinesterase measurements as rule-out tests for nerve agent or organophosphate exposure
  – Population norms for plasma cholinesterase
  – Confirmatory testing by RBC Cholinesterase or serial plasma cholinesterase
# Medical Monitoring in Biopreparedness

## POTENTIAL AGENTS

<table>
<thead>
<tr>
<th>Agent</th>
<th>Clinical Monitoring</th>
<th>Laboratory Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyanide</td>
<td>Rapid knock-down</td>
<td>Slow</td>
</tr>
<tr>
<td>Incapacitating Agents</td>
<td></td>
<td></td>
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<tr>
<td>Volatile Organic Compounds</td>
<td></td>
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<tr>
<td>Industrial Contaminants</td>
<td></td>
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<tr>
<td>Industrial Solvents</td>
<td></td>
<td></td>
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<tr>
<td>Heavy Metals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nerve Agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mustard Agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritants/Sedatives</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>CNS depressants</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Variable organ effects</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>CNS/other organs</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>CNS/other organs</td>
<td>Slow</td>
<td></td>
</tr>
<tr>
<td>Cholinergic crisis</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Skin/Pulmonary</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>
Medical Monitoring

• Presumes an injury may or will occur
• Presumes an exam or test will identify:
  – Those at risk
  – The injury itself, hopefully at an early stage
• Best utilized when an effective treatment or mitigation can be done
The Existence of a Test Does Not Mean We Know What To Do With The Results

• CA Prop 65
  – The Safe Drinking Water and Toxic Enforcement Act of 1986
• Currently over 700 substances on list
• No dose/response consideration
• http://www.oehha.org/prop65/prop65_list/files/070904list.html
The Future of Biomonitoring: National Academy of Science Report 2006

- The relative value of biomonitoring efforts is dependant on what is communicated
- Is the sample population representative?
- Are the methods and analysis sound?
- Descriptive vs. Risk-based communication?

Interpretation and Communication of Biomonitoring Information

• Many groups have biomonitoring initiatives
  – CDC/NCEH National Report on Human Exposure to Environmental Chemicals
    http://www.cdc.gov/exposurereport/
    • Stringent laboratory science with descriptive and some risk-based interpretation
  – California Environmental Contaminant Biomonitoring Program
    http://www.calepa.ca.gov/Legislation/2006/SB1379.pdf
    • Revised to incorporate risk communication
  – Environmental Working Group
    http://www.ewg.org/bodyburden/
    • “Nice” website; no information for comparison/interpretation
Interpretation and Communication

• Descriptive vs. Risk-Based Interpretation
  – Descriptive
    • Presence and concentration of a compound in the 50th, 95th percentiles of population
      – How well does the sample population mimic the population of interest?
      – How well do the exposure settings match?
        » Acute vs. chronic
    – Are the matrices (e.g. blood, urine) the same or are there conversion estimates available?
Interpretation and Communication

- Risk-based interpretation
  - Good data only available for some compounds
  - Usually requires modeling and extrapolation
    - Does the primary literature (animal, human epidemiologic) adequately address dose range and potential confounders?
    - For any postulated low-level exposures, difficult to sort out confounders from genetically “sensitive population”
      - Mostly speculation
Applying Medical Monitoring To A Terrorist or HazMat Event

- Sarin Tokyo Event
  - Cholinesterase monitoring of patients
  - Serial exams of exposed healthcare providers
- Radiation workers
  - External/Internal Contamination vs. “radiated”
- Seveso, Italy
  - Acute and chronic effects
- South Wales, 1995
  - Perception
5500 people “sick”
~500 admitted
17 critically ill
12 dead
## Nerve Agent vs. Anxiety/Stress Response

<table>
<thead>
<tr>
<th>Nerve Agent Poisoning</th>
<th>Anxiety/Stress Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest Tightness</td>
<td>Chest Tightness</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>Dyspnea</td>
</tr>
<tr>
<td>Brady or Tachycardia</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>Nausea/Vomiting</td>
</tr>
<tr>
<td>Abdominal Cramps</td>
<td>Abdominal Cramps</td>
</tr>
<tr>
<td>Involuntary Urination</td>
<td>Involuntary Urination</td>
</tr>
<tr>
<td>Fasciculations</td>
<td>Tremor</td>
</tr>
<tr>
<td>Headache</td>
<td>Headache</td>
</tr>
<tr>
<td>Coma</td>
<td>Syncope</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>Diaphoresis</td>
</tr>
<tr>
<td>Pinpoint Pupils</td>
<td>Dilated Pupils</td>
</tr>
</tbody>
</table>
Chemical attack victims go to area hospitals. Hospitals are categorized into three tiers:

- **Tier I**
  - Local Hospitals
  - TAT: 1-4 h

- **Tier II**
  - Regional
  - DPHL
  - TAT: <24 h

- **Tier III**
  - National
  - CDC, FBI, etc.
  - TAT 1-7 d
Radiation Medical Monitoring

• Goiania, Brazil: Sept 1987
  – Dismantling of an abandoned Cs-137 radiotherapy source results in dispersal and distribution of radioactive cesium
    • Over 100,000 people surveyed for contamination
    • 249 identified; 4 deaths
  – “Radioactive” biomonitoring tool would be the Geiger counter
And more recently: Polonium-210

• UNITED KINGDOM: 100 test positive for polonium exposure

More than 100 people have tested positive for polonium-210 exposure during investigations into the death of the former Russian agent Alexander Litvinenko, the Health Protection Agency (HPA) revealed yesterday. Thirteen have been told they received a dose above six millisieverts, which increases the lifetime risk of cancer by 0.005%. The HPA has tested almost 600 people in the vicinity of the hotels and restaurants where radioactive traces were found. Of these, 73 received doses of less than one millisievert and 30 received up to six millisieverts - levels the HPA said posed no public health risk. Alok Jha

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Radiation Medical Monitoring

• Exposure to source of ionizing radiation
  – Iridium 192 gamma radiation emitter
    • 0.5 x 0.5 mm core with 1 Ci of activity
• Irradiated NOT radioactive
• Absolute lymphocyte count as a prognostic tool
Seveso, Italy 1976

- Worst environmental exposure to TCDD
- Early rise in induced abortions and circulatory deaths
- Late statistically significant rise in non-Hodgkin’s lymphoma (Relative Risk 2.8, with CI: 1.1, 7)
- Significance of lymphoma risk?
  - Baseline incidence 10/100,000 or so
- Risk communication?
  - U.S. <10 ppt (vs >200 ppt in Seveso-exposed)

Sea Empress Oil Spill 1996

- 70,000 tonnes of oil spilled into an environmentally sensitive area
- 39% of residents near the spill complained of persistent headaches, irritive, or psychological symptoms
- 20% of people in unaffected, but nearby areas, complained of similar symptoms, with 1 of 5 thinking their symptoms were related to the oil spill
Degree of Outrage

“Unfamiliarity” factor

Severity of Effect

Involuntary nature of exposure
Should Medical Monitoring Be Considered?

• Only in larger context of risk communication

• Clinical Monitoring: Only if a clinical measurement is demonstrated to have good correlation
  – Problem of screening and specificity/sensitivity

• Laboratory Monitoring: Only if a reference measurement is available
  – E.g. population measurements by NHANES
Example: Response to Community Concern

• “Everyone is being poisoned by <fill in the blank>”

• Let’s use mercury as an example
  – Good population data
  – Good clinical harm data for overt effects
  – Data for “low-level” or “special population” effects?
Common Example

• School custodian is cleaning a science room
• Notes silver globules over floor and in hallway
• Notifies...
• School evacuated – 300 children
• Shoes evaluated for mercury contamination
• Children sent home, some wrapped in blankets
• Parents ask...
  what happened?
  what should I do?
  are my children safe?
What plan do you want to implement?

1. Obtain blood and urine Hg on all
2. Obtain blood and urine Hg on some
3. Obtain urine protein determinations
4. Begin immediate chelation of all
5. Begin immediate chelation of some
6. Work with the school and FD to develop response/cleanup system
School Mercury Exposure

• Risk Assessment
  – Environmental mercury contamination
    • Duration and extent must be defined
  – Environmental measurements
    • Air and shoes/clothing

• Risk Communication
  – “There is no health risk from this event”
  – “There is no need for medical monitoring in this situation”
  – “We are taking extra precautions to prevent tracking of the mercury elsewhere”
However, each Situation Needs To Be Evaluated…

- Day care center housed in previous thermometer factory
  - Exposed group: children
  - Duration: hours/daily
  - Dose: ???

NEW JERSEY
INQUIRY PLANNED INTO DAY-CARE MERCURY LEVELS

FRANKLINVILLE, N.J. — New Jersey’s attorney general has ordered an investigation into why a day-care center where dozens of children were exposed to toxic mercury fumes was allowed to operate in a former thermometer factory. Attorney General Zulima Farber called the situation at Kiddie Kollege “outrageous.” The center closed July 28 after owners were told of the mercury fumes, and officials said more than 30 children were exposed to toxic mercury vapors at the center.
Legislation and Lawsuits: Best Answer?

- Governor signs law for air-quality checks at day care centers
  Angela Delli Santi / Associated Press Writer  Thu January 11, 2007 13:36 EST

FRANKLIN TOWNSHIP, N.J. (AP) _ The air quality of new day-care centers in New Jersey will have to be monitored under a measure signed into law by Gov. Jon S. Corzine on Thursday in a Gloucester County town where children attending one facility were contaminated by high levels of mercury…

The bill was signed in Franklin Township, the same small southern New Jersey community where more than 30 children were exposed to toxic mercury vapors while attending Kiddie Kollege, a day care on the site of a former thermometer factory. A second center, also closed, was atop a former fuel company. A third sits at a former gas station that has leaking underground tanks.

The state Department of Environmental Protection found mercury levels at Kiddie Kollege were 25 times the allowable limit during a random check of the site in July, prompting the building to be shut. Subsequent tests showed the preschool students had elevated levels of mercury, but officials said the effects of the exposure should not be long-term.

The state filed a lawsuit against the current and former owners of the site last month, claiming that environmental officials have been denied access to the site since Kiddie Kollege closed in August. The families of several children enrolled at Kiddie Kollege have filed their own lawsuits…

The state Attorney General's office is looking into how the center, which opened in 2004, was allowed to operate without a cleanup of the mercury.

Wolf Skacel, assistant DEP commissioner for compliance and enforcement, said the agency has thus far inspected 142 of the 1,400 day cares located within 400 feet of a site that DEP regulates. Those include dry cleaners and other businesses for which the environmental agency issues permits, as well as contaminated sites, Skacel said.

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Summary

• Post-event medical monitoring may be indicated in the assessment of an exposure
• Medical monitoring is only one component of risk assessment and communication
• If performed, medical monitoring requires defined clinical and/or laboratory parameters and must be done with an appropriate control group
• Healthy skepticism is important in interpreting reported medical monitoring data
Appendix

• Sorting out screening from ‘rule-in’ and ‘rule-out’ testing
• Importance of recognizing role of disease prevalence when evaluating ‘positive’ tests (even with high sensitivity and specificity)
Testing Paradigm

• Therapeutic monitoring
  – High pre-test likelihood, looking for high precision

• Screening
  – Low pre-test likelihood, looking for high sensitivity

• Diagnostic Testing
  – Rule-out [SnNout]
    • Low to moderate pre-test likelihood, high sensitivity test negative  (few false negatives)
  – Rule-in [SpPin]
    • Moderate pre-test likelihood, high specificity test positive  (few false positives)
Interplay of Sn and Sp

- Even very specific tests will have low positive predictive value if sensitivity is low
- Even very sensitive tests will have low negative predictive value if specificity is low
# The Influence of Prevalence on Drug Testing Assays

10,000 subjects

<table>
<thead>
<tr>
<th></th>
<th>Nonusers</th>
<th>Users</th>
</tr>
</thead>
<tbody>
<tr>
<td>True negative</td>
<td>9801</td>
<td>99</td>
</tr>
<tr>
<td>False positive</td>
<td>99</td>
<td>1</td>
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<tr>
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<tbody>
<tr>
<td>True positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>False negative</td>
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Prevalence: 1%

Test accuracy: 99%