Comparing Audiometric Threshold Shift Definitions for Ototoxicity Detection

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Learning Objectives

- Describe rationale for early detection of ototoxic hearing loss
- Outline benefits of using Clinical Decision Theory for examining test performance
- Discuss implications of this study for various ototoxicity monitoring methods
  - Criteria for hearing threshold shifts
  - Test-frequency step sizes
  - Testing above 8 kHz
Background

- Patients may not notice hearing change until speech frequencies affected
- Serum levels are not good indicators of cochleotoxicity
- The only way to know if a person is losing their hearing is direct assessment of auditory function
Attributes of Screening Test

- **High sensitivity** (sensitivity rate = hit rate)
  - High hit rate in exposed ears

- **High specificity** (1 - specificity = false positive rate)
  - Low false alarm rate in unexposed ears

- **Most tests are imperfect, so that some clinical errors are made. There is a trade off between sensitivity and specificity**
  - Make cutoff more stringent, reduce false positives, but also reduce hit rate
  - Make cutoff more lax, increases hit rate, but also increases false positives

- **Time efficiency**
Ototoxicity Monitoring

"Now just relax and we'll begin your hearing test."
Benefits of Ototoxicity Monitoring

- Early detection may prevent hearing damage that requires rehabilitation
- If change observed, treatment modification can prevent further hearing loss; if no change observed, continued treatment warranted
- Ototoxicity monitoring program
  - educates patients, care givers and physicians about ototoxic symptoms (hearing loss, tinnitus, and balance problems)
  - raises awareness of synergistic effects of toxins and noise
  - ensures audiology work up and rehabilitation plan are implemented if and when appropriate
Sensitive Range of Ototoxicity (SRO) Principle

- Most initial changes seen in a limited range near the highest audible frequency
- Range for each individual is unique and specific to their hearing configuration
- Frequencies with thresholds > 100 dB SPL usually remain unchanged
- A sensitive range for ototoxicity (SRO) can be defined as a one octave range near the upper-frequency limit of hearing (i.e., frequency with a threshold ≤100 dB SPL)
Example SRO

Threshold (dB SPL)

F-1  F-2  F-3  F-4  F-5  F-6

Behavioral SRO
# Sensitivity: SRO 1/6th Octave

<table>
<thead>
<tr>
<th></th>
<th>Total (Ears)</th>
<th>Hit</th>
<th>Miss</th>
<th>Initial Change in SRO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AMG</strong></td>
<td>54</td>
<td>46</td>
<td>8</td>
<td>85%</td>
</tr>
<tr>
<td><strong>Cisplatin</strong></td>
<td>226</td>
<td>207</td>
<td>19</td>
<td>92%</td>
</tr>
<tr>
<td><strong>Carboplatin</strong></td>
<td>59</td>
<td>50</td>
<td>9</td>
<td>85%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>339</td>
<td>303</td>
<td>36</td>
<td>89%</td>
</tr>
</tbody>
</table>
Few studies have compared audiometric methods and hearing loss change criteria.

Methods vary for monitoring hearing in patients receiving ototoxic drugs:
- frequencies tested
- frequency step sizes used
- decision variables (number frequencies affected)
- magnitude of threshold shifts
Case Study: SRO 7.13 - 14 kHz

Threshold (dB SPL)

Frequency (kHz)

- 19 July Baseline
- 17 August Monitor
- 18 August Retest
- 5 October 1 Month
- 20 March 6 Month

F-1, F-2, F-3, F-4, F-5, F-6
Case Study

- Conventional audiometric testing (<8 kHz) would have identified hearing change later
- Hearing continued to decline after treatment ended (black line: 1 month post-drug; and light blue line: 6 month post-drug)
  - ultimately, 20-dB change at 3 kHz; 40-dB change at 4 kHz; 65-dB change at 8 kHz
- Greatest changes at the conventional frequencies occurred after treatment ended!
- Information used to counsel patient about aural rehab options and necessity of follow up with audiologist
Background

- Challenge is to quantify ototoxic changes in a group of adults.
- Different frequencies may be affected in a given person, so averaging across all frequencies tested tends to wash out ototoxic changes.
- 90% of changes occur within an octave of highest audible frequency (Fausti et al., 1993).
- Therefore, can average threshold shifts across individuals, normalizing to the highest frequency able to be heard.
Study Objectives

1. Examine ability of individually-tailored threshold monitoring to detect ototoxic hearing loss using various (significant threshold shift) STS definitions.

2. Determine whether evidence supports use of ASHA-recommended STS definitions.

3. Determine whether testing in 1/3- or 1/6-octave steps improves test performance when compared to use of 1/2-octave steps.
Methods

- **All subjects**
  - at least 3 audiograms, one audio ~1.5 months, one audio ~6.5 months after initial dose
  - baseline within 2 days of first dose (some controls were within 3 days)

- **Cisplatin-exposed Group**
  - used for hit or true positive (TP) rates
  - 78 ears of 41 patients receiving cisplatin
  - cumulative dose at least 350 mg
  - mean age 59.4 years (SD 10.2)

- **Control Group**
  - used for false positive (FP) rates
  - 53 ears of 28 hospitalized patients receiving non-ototoxic antibiotics
  - mean age 56.0 (SD 10.5)
Example: Frequencies Tested in One Subject

<table>
<thead>
<tr>
<th>Baseline Test Frequencies (kHz)</th>
<th>0.50</th>
<th>1.00</th>
<th>2.00</th>
<th>3.00</th>
<th>4.00</th>
<th>6.00</th>
<th>6.35</th>
<th>7.13</th>
<th>8.00</th>
<th>9.00</th>
<th>10.00</th>
<th>11.20</th>
<th>12.50</th>
<th>14.00</th>
<th>16.00</th>
<th>18.00</th>
<th>20.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Hearing Thresholds</td>
<td>25</td>
<td>25</td>
<td>35</td>
<td>40</td>
<td>55</td>
<td>55</td>
<td>55</td>
<td>60</td>
<td>70</td>
<td>75</td>
<td>85</td>
<td>90</td>
<td>100</td>
<td>110</td>
<td>12.50</td>
<td>14.00</td>
<td>16.00</td>
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<tr>
<td>Comparison Test Frequencies</td>
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<td></td>
</tr>
<tr>
<td>1/6-octave</td>
<td>F-6</td>
<td>F-5</td>
<td>F-4</td>
<td>F-3</td>
<td>F-2</td>
<td>F-1</td>
<td>F</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/3-octave</td>
<td>F-3</td>
<td>F-2</td>
<td>F-1</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>F</td>
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</tr>
<tr>
<td>1/2-octave</td>
<td>F-2</td>
<td>F-1</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>F</td>
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</table>
Mean data underestimate effect because some subjects have hearing loss at a given frequency, but others do not.
Methods

- Hearing changes calculated for frequencies within an octave of high-frequency hearing limit
- Compared initial audiogram to tests obtained 1.5 and 6.7 months later
- Determined if changes met STS criteria
  - based on magnitudes of positive threshold shifts (worsening of thresholds by 5, 10, 15, or 20 dB)
  - and numbers of frequencies affected (threshold shifts at a minimum of 1, 2, or 3 adjacent frequencies)
- Test performance evaluated using CDT
Clinical Decision Theory (CDT)

- Can go beyond asking ‘Does the test work or not?’, to the more useful question, ‘How well does it work in this context?’
- Can estimate test performance for all values of the experimental variable, in this case dB of hearing change
  - in this case 5, 10, 15, or 20 dB of threshold shift
- Can compare various different decision variables
  - in this case, numbers of frequencies affected (1, 2, 3 or more adjacent)
- Note absence of true “gold standard”
- Compared STS rates for cisplatin-exposed group (“true” positive rates) to non-exposed group (false positive rates) following Dobie 2005
  - Underestimates true positive rates
  - Accurately estimates false positive rates
  - Accurately estimates rankings of competing STS criteria
Methods

- Compared test performance 2 ways

1. Examined receiver operating characteristic (ROC) curves
   - Plots of true positive rate or sensitivity as a function of false positive rate or 1 minus specificity
   - Compared relative position of curves and areas under the curves

2. Determined STS definitions with the highest true positive rates for a fixed false positive rate near 5%
   - Chosen to minimize the number of patients incorrectly diagnosed with ototoxic hearing loss
ROC Curves

Receiver Operating Characteristic (ROC) Curves

Each point in ROC curve represents a particular criterion cutoff (dB shift)

Sensitivity (true positive rate) is plotted vs false positive rate

Criterion cutoffs range from stringent (20-dB change) to lax (5-dB change) as curve progresses from left to right

Relative position of curves and area beneath them is used to compare them
AUCs

28-63 days into treatment

1/6-oct
1/3-oct
1/2-oct

Area Under ROC Curve

Consecutive Frequencies

1 or more
2 or more
3 or more

final test

1/6-oct
1/3-oct
1/2-oct

Area Under ROC Curve

Consecutive Frequencies

1 or more
2 or more
3 or more
Final Test

The diagram illustrates the percent distribution of different frequency stepsizes across various magnitudes of change (dB) for different categories of frequencies:

- One or more frequencies
- Two or more frequencies
- Three or more frequencies

The categories are further differentiated by frequency step-size:

- 1/2 Octave
- 1/3 Octave
- 1/6 Octave

The chart includes bars representing True Positives (Cisplatin) and False Positives (Control) at different frequency stepsizes and magnitudes of change.
ASHA Criteria for Hearing Change

- 20 dB change at any 1 test frequency
- 10 dB change at any 2 adjacent test frequencies
- Loss of responses (as little as 5 dB change) at 3 consecutive frequencies, where responses were previously obtained close to the limit of the audiometer
- Changes confirmed by repeat testing
Results

- For the 1/2-octave step size used clinically, best performance was achieved for threshold losses of 15 dB at a single frequency, a change present in 50% of ears by completion of cisplatin therapy.
- Use of smaller frequency step sizes consistently increased test performance; (improvements were significant when threshold shifts were required to occur at 2 or 3 adjacent frequencies)
- Best overall test performance was obtained using 1/6-octave steps and a criterion cut-off of 10 dB at 2 or more frequencies
Results

- Certain ASHA-recommended criteria performed well
  - threshold shifts > 20 dB at 1 frequency
  - > 10-dB at 2 or more adjacent frequencies)

- For ½-octave step size, these STS definitions resulted in TP rates of 36% and 39%, respectively, at the final test date.

- 5-dB at three frequencies performed less well due to increased FP rate
Conclusions & Clinical Implications

- Monitoring protocol that uses a tailored, patient-specific one octave range of frequencies is a clinically effective protocol for detecting early ototoxic changes with an acceptable false positive rate.

- In general, using smaller frequency step sizes increases false positives only slightly, while increasing sensitivity significantly.
High Frequency Audiometers

**Interacoustics AC40**
- High-frequency to 20 kHz, multi-frequency, 1/6 octave (1 octave up to 1/24)
- With boost feature, 115-120 dB output
- HL ≤ 8 kHz; SPL > 8 kHz
- Approximately $6200.

Decos Systems Audiology Workstation
- High-frequency to 20 kHz, multi-frequency, 1/6 octave
- 120 dB HL output at all frequencies-Computer based
- Programmable option for testing in HL & SPL at all frequencies
- Approximately $12,800.
References


