OTOTOXICITY AND HEARING: Mechanisms and Measurement

Richard W. Danielson, Ph.D.
National Space Biomedical Research Institute
Baylor College of Medicine
NASA-Johnson Space Center

Danielson TAA 2007

Ototoxicity

… tendency of certain substances to cause functional impairment and cellular damage to the tissues of the inner ear

… especially to the end organs of the cochlear and vestibular divisions of N. VIII that can occur from systemic or topical administration.

Danielson TAA 2007 Rhatican, Mandel and Rutka. (2004) in Roland and Rutka,198-206

Roles of audiologists in assisting patients and monitoring ototoxicity

1. Reduce negative aspects of ototoxic hearing loss

"Ototoxic hearing loss, particularly in the pediatric population, may be tolerated in favor of survival"

Konrad-Martin et al. (2005) ASHA Leader, 1-14

"No one needs to lose his or her hearing in order to earn a living"

POSITION STATEMENT, AMER ACAD OF AUDIOLOGY, (Oct, 2003)

2. Help patients (based on their hearing loss) improve or maintain their quality of life
3. Communicate risks and patient status to other providers

Danielson TAA 2007

What is it that hearing-impaired people really want from their audiologist?

"We need to know about the many agents that can damage our ears"

"We need to be warned if we are now even more at risk from the effects of ototoxic drugs than the general population"

"We need to know how noise and certain drugs can team up to smash our remaining hearing"

http://hearinglosshelp.com/articles/audiologists.htm

Danielson TAA 2007

Objectives

- Recognize risks of common ototoxic agents
  - *Environmental* and *Occupational*
  - *Drugs*
- Describe common types of interactions that can increase risks of ototoxicity
- Identify ways that audiologists can assist and/or monitor patients exposed to ototoxic agents

Danielson TAA 2007

Assessing exposures to ototoxins

Drugs

Exposures in the workplace and environment

Danielson TAA 2007

TOXIC *Effects of Noise*

- Hearing Loss
  - *Sensitivity*
  - *Cochlear Tuning*
- Anatomical
  - *Cochlear damage (OHCs)*
- Mechanisms
  - *Mechanical Injury*
  - *Oxidative Stress*

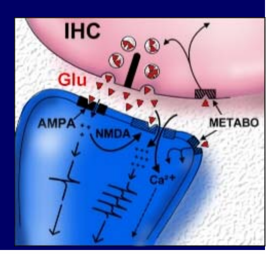
Danielson TAA 2007

TWO Mechanisms of Damage…

MECHANICAL

Hamernik, Turrentine and Roberto (1986)

METABOLIC (oxidative stress)



The Role of Oxidative Stress in Noise-Induced Hearing Loss

Henderson, Bielefeld, Harris and Hu (2006)
Ear and Hearing, 27(1):1-19.

Danielson TAA 2007

… yielding cell death

Necrosis

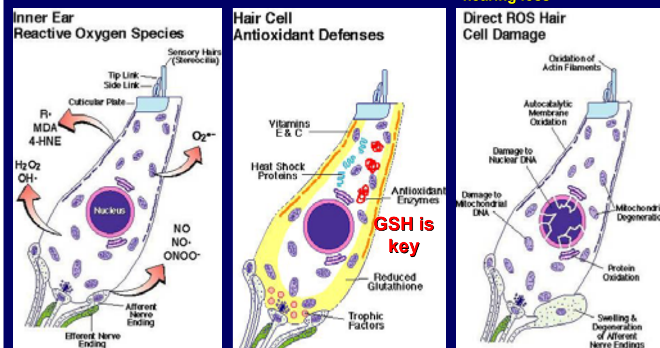
Death of a cell or group of cells as a result of injury, disease, or other pathologic state

Apoptosis

Programmed cell death

Danielson TAA 2007

Noise causes the release of free radicals | The inner ear's antioxidant defenses are overwhelmed | Cascade of events leading to cell death and permanent hearing loss



ROS and free radical damage
Increase inner ear antioxidants (GSH)

Danielson TAA 2007

Kopke and Danielson (2003) CAOHC Update 15(1):1,9

Over 30 compounds have been reported to have potential for
PROTECTING ear
or
OFFERING RESCUE
after excessive noise exposure

"LEADING CANDIDATES"

- N-acetylcysteine or NAC (Kopke, Oklahoma)
- D-methionine (Campbell, SIU)
- Ebselen (Kyl, Seattle)
- JNK Inhibitors (Henderson, Buffalo)

Danielson TAA 2007 *Lynch and Kil (2005) Drug Discov Today (10:1291-1298*

Environmental and Occupational Risks
Noise, Solvents and Chemicals

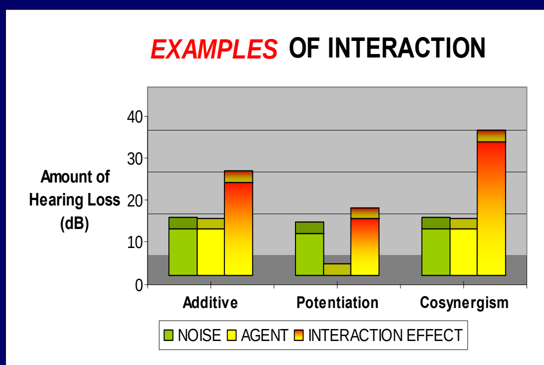
Clinicians evaluating cases of possible noise-induced hearing loss should keep in mind that co-exposure to ototoxic agents, such as solvents, heavy metals and tobacco smoke, may act in synergy with noise to cause hearing loss.

ACOEM EVIDENCE-BASED STATEMENT

J Occup Environ Med (2003) 45(6):579-81

Danielson TAA 2007

Synergy: What kinds are there?



Danielson TAA 2007

Activities Where Noise and Occupational / Environmental Ototoxins Often Interact

- **Painting**
- **Manufacturing of petroleum products**
- **Printing**
- **Boat building**
- **Furniture making**
- **Manufacturing of metal, leather**
- **Fueling vehicles and aircraft**
- **Firefighters**
- **Weapons firing**

AIHA Your Essential Connection AMERICAN INDUSTRIAL HYGIENE ASSOCIATION

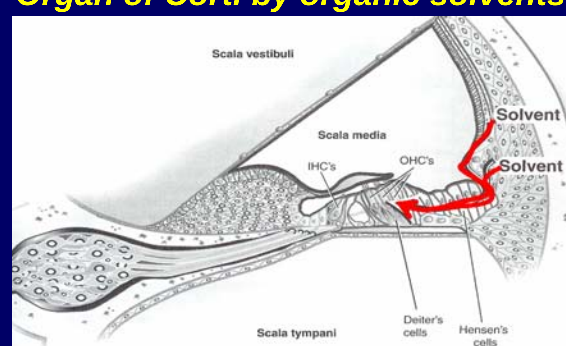
Danielson TAA 20

CHEMICAL OTOTOXINS

- **Heavy Metals**
  - ***Lead*** *(demyelination of N. VIII, but cochlea unharmed)*
  - ***Mercury Nitrate*** *(hatter's disease")*
- **Pesticides**
  - ***Organophosphates***
  - ***Paraquat***
- **Solvents**

Danielson TAA 2007

Hypothetical route of intoxication of Organ of Corti by organic solvents



Danielson TAA 2007 *Campo et al. (1999) Neurotox and Teratology 21:427-434*

How are Solvents Used?

Fuels, plastics, paints and paint thinners, wood stains and lacquers, coatings, dyes, inks, pesticides, resins,

How Do Solvent Exposures Occur?

Exposure typically by inhalation and through skin

Danielson TAA 2007

Which Organic Solvents Present a Risk?

- ***Styrene*** *(most prevalent, toxic)*
- ***Trichloroethylene*** *(degreaser, dry cleaning agent, "sniffer")*
- ***Carbon Disulfide***
- ***Toluene***

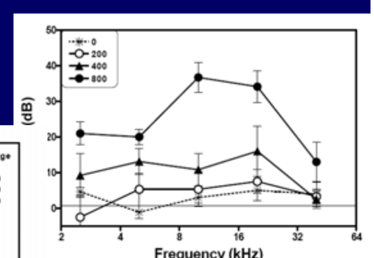
Danielson TAA 2007

Example: STYRENE

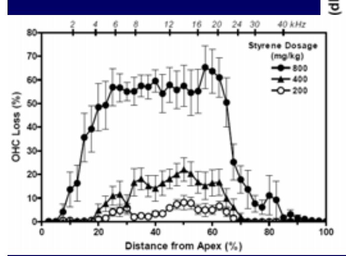
- Aromatic solvent
  - *Manufacture of reinforced plastics like glass-reinforced polyester (Boats)*
- 50,000 exposed in U.S.
- OSHA PEL: 100 ppm
- Destroys OHCs, supporting cells
- Can interact with noise

Danielson TAA 2007

Effects of STYRENE exposure at different doses for 3 weeks



Averaged PTS

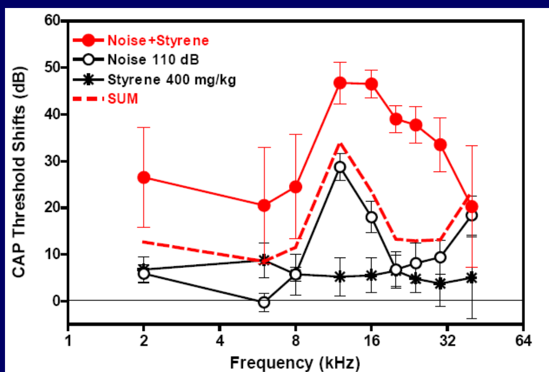


Cochlear Damage

Danielson TAA 2007

Chen et al. (2007) Toxicol Sci. 2007 98(1):167-77

STYRENE SYNERGISTIC INTERACATIONS WITH NIHL



Danielson TAA 2007

Chen et al. (2007) Toxicol Sci. 2007 98(1):167-77

SOLVENT OTOTOXICITY

- **Industrial solvents are ototoxic**
- **Solvent-induced cochlear injury starts from the middle turn, involves supporting cells and hair cells**
- **Main cell death pathway: Caspase-dependent apoptotic cell death**
- **Solvent exposures can interact with noise**

Danielson TAA 2007

Ototoxic Drugs

- **Aminoglycosides (antibiotics)**
- **Anti-Neoplastics (anti-cancer drugs)**
- **Salicylates**
- **Quinines**
- **Loop Diuretics**

Danielson TAA 2007

Ototoxic Drugs by Risk Class

(Based on frequency and severity of side effects; impact on daily living)

RISK OF OTOTOXICITY	NUMBER OF DRUGS REVIEWED*	PER CENT OF DRUGS REVIEWED
(high)	**17**	**3%**
	33	5%
(moderate)	52	8%
	186	28%
(low)	265	40%
(inadequate data, not rated)	*110*	*16%*

** Bauman NG (2002) Ototoxic Drugs Exposed*

Danielson TAA 2007

Underlying mechanisms of inner ear damage

- Require uptake of drug into cells
- Permanent SNHL
  - (can be reversible, loop diuretics)
- Ototoxicity risks increase with renal impairment, premature infants, and those receiving aminoglycoside antibiotics.

Danielson TAA 2007

Examples of Ototoxic Drugs Anti-neoplastic agents

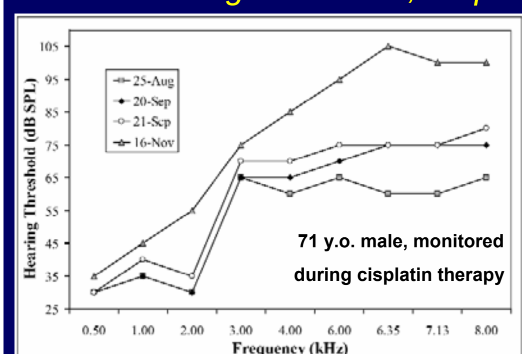
CISPLATIN TARGETS
- Outer hair cells of the organ of Corti
- Spiral ganglion neurons
- Stria vascularis
- Spiral ligament

CARBOPLATIN TARGETS
- Outer hair cell loss
- Inner hair cell loss (chinchilla only)

VINKA ALKALOIDS TARGETS
- Outer hair cells of the organ of Corti
- Spiral ganglion neurons

Danielson TAA 2007

Issues of Ototoxic Pathophysiology: Shift in hearing thresholds, Cisplatin



Danielson TAA 2007

Fausti et al. JAAA 19: 444-450

Example: Cisplatin Ototoxicity

in Adults with Testicular Cancer

- 20% clinical incidence with standard dose
- 50% or more, with dose greater than 400 mg/m^2
- Previous noise exposure may triple the risk

Bokemeyer et al. (1998) Br J Cancer 77: 1355-1362

Danielson TAA 2007

Cisplatin Ototoxicity

(Age-dependent) In Children

40% of kids <5yrs develop mod-severe SNHL, w/ dose >400 mg/m^2 (compared t 5% risk among ages 8-20) *Li et al. (2004) Eur J Cancer 40:2445-2551*

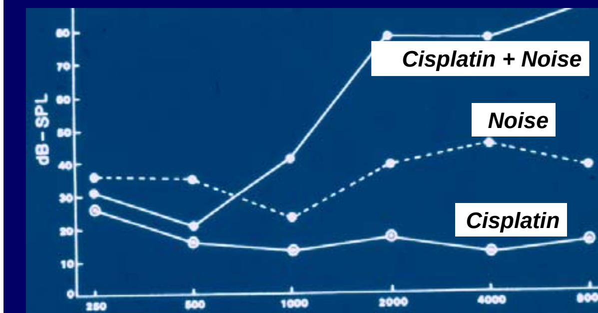
Cisplatin Ototoxicity in Children with Neuroblastoma

Every child < 5 years old had moderate to severe hearing loss *Kushner et al., (2006) Cancer 107:417 417- 422,*

Danielson TAA 2007

Issues of Ototoxic Pathophysiology:

Possible synergistic effects of ototoxic agents with noise exposure (Example: Cisplatin)



Danielson TAA 2007 *Boettcher, Henderson, Salvi, Gratton, Danielson, Byrne (1987) Ear and Hearing. 8:192-212*

The "LAUNDRY LIST"

AMINOGLYCOSIDES
amikacin
dihydrostreptomycin
gentamicin
kanamycin
neomycin
netilmicin
streptomycin
tobramycin

ANTISEPTIC/DISINFECTANT AGENTS
alcohol
chlorhexidine

ARSENICALS

CYTOTOXIC AGENTS
bleomycin
carboplatin
cisplatin
nitrogen mustard
vinca alkaloids

IRON-CHELATING AGENTS (Fe^{2+})
deferoxamine

LOOP DIURETICS
ethacrynic acid
furosemide

MACROLIDES
azithromycin
clarithromycin
erythromycin

NONSTEROIDAL ANTI-INFLAMATORY DRUGS (NSAIDs)

TOPICAL ANTIBIOTICS
all aminoglycosides
chloramphenicol
polymyxin

TRADITIONAL AGENTS
acetylsalicylic acid (ASA)
quinine

VANCOMYCIN
(in conjunction with aminoglycosides, primarily)

D

MEDICAL OPTIONS

If an ototoxic effect is suspected from medications, physician has options:

- ** Reduce amount of the dose*
- ** Change the timing of the dosage schedule*
- ** Temporary discontinuation of therapy so that the ear can "rest"*
- *Switch to a less ototoxic drug*

Danielson TAA 2007

MEDICAL RESPONSIBILITIES

- Apprise patients of potential for ototoxicity
- Vigilantly monitor patients for ototoxicity
- Weigh risk-to-benefit ratio, especially with prolonged treatment
  - In some cases, the physician will not be able to change the drug regimen because of the intensity or severity of the patient's illness

When ototoxicity occurs, refer for vestibular and/or aural rehabilitation

Danielson TAA 2007

AUDIOLOGIC RESPONSIBILITIES
MONITORING FOR OTOTOXICITY

- Early identification
  - Appreciate onset of tinnitus
- Develop protocols and criteria
  - Appreciate sensitivity and specificity, test-retest differences
  - Develop program goals (realistic?)
  - Consider target population

Danielson TAA 2007

DETECTION OF OTOTOXICTY WITH AUDIOMETRIC MONITORING

<u>ASHA Guidelines</u>

≥ 20dB threshold change at one frequency

≥ 10dB threshold change at 2 adjacent frequencies

Loss of response at 3 consecutive frequencies (where responses were previously obtained)

THRESHOLD CHANGE MUST BE CONFIRMED BY RETEST

ASHA (1994) Guidelines for Audiological Management of Individuals Treated with Cochleotoxic Drug Therapy

Danielson TAA 2007

ULTRA-HIGH FREQUENCY AUDIOMETRY

Previously limited by our instrumentation, but better now

- Test-retest variability within +/- 10dB
  - As high as 94% for frequencies between 9 - 14 kHz
- Earphone options
  - Sennhauser HAD 200
  - ER-2 inserts
  - Koss HV/1A
  - Modified KOSS Pro /4X Plus

Danielson TAA 2007

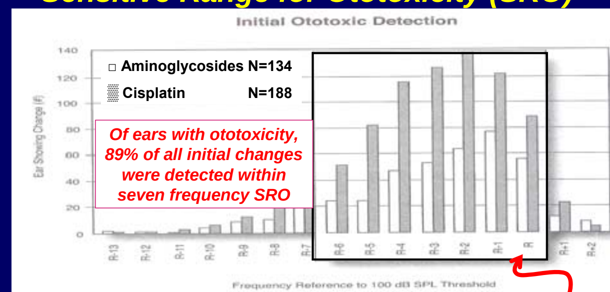
OPTION: SENSITIVE RANGE FOR OTOTOXICITY (SRO)

- **Full-frequency monitoring may be impractical for tired, ill, confined patients**
- **SRO (Fausti) abbreviated audiometry to test limited frequency range**
  - **Tests freqs are normalizes to each S's highest audible frequency with threshold at or below 100 dB SPL followed by next six lower adjacent frequencies in 1/6 octave steps, or the one octave range nearest the highest audible frequency**
  - **ASHA 1994 criteria still applied**

Fausti et al (2003), JAA 14:444-450

Danielson TAA 2007

Sensitive Range for Ototoxicity (SRO)



Fausti et al (2003), JAA 14:444-450

R = 12500 Hz
R-1 = 11200 Hz
R-2 = 10000 Hz
R-3 = 9000 Hz
R-4 = 8000 Hz
R-5 = 7130 Hz
R-6 =6350 Hz

Danielson TAA 2007

Other Measures of Ototoxicity

No accepted protocols or criteria for ototoxic changes

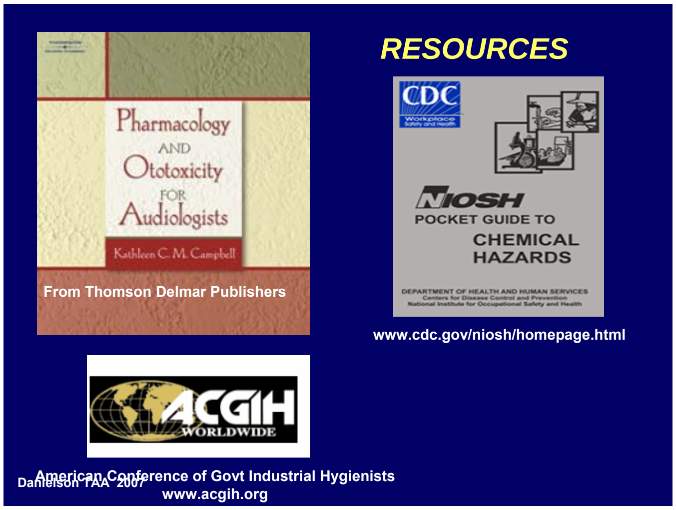
- **ABR** - ultra-high freq tone bursts more sensitive than clicks, but ABR time-intensive, subject to interpretation
- **DPOAEs** - Limited by frequency range of instrumentation, presence of middle ear disorders, poor hearing sensitivity

Danielson TAA 2007

Assessing Ototoxicity from Exposures? Consider:

- **Names of medications or chemicals**
- **Duration and frequency of administration/exposure**
- **Instrumentation & Protocols (baselines, periodics, post-treatment evals)**
- **Reporting**
  - **To referring physicians**
  - **To PATIENTS**
- **Tracking**

Danielson TAA 2007


RESOURCES
Pharmacology AND Ototoxicity FOR Audiologists
Kathleen C. M. Campbell
From Thomson Delmar Publishers
CDC
NIOSH
POCKET GUIDE TO
CHEMICAL
HAZARDS
www.cdc.gov/niosh/homepage.html
ACGIH
WORLDWIDE
American Conference of Govt Industrial Hygienists
www.acgih.org
Danielson TAA 2007