

## **Bilateral Vestibular Loss Napa Valley Course, 2006**

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## **Case: LB**

48 YO Airline stewardess developed an ingrown toe-nail infection. She underwent a course of gentamicin and vancomycin. 12 days after starting therapy she developed imbalance. 21 days after starting, she was “staggering like a drunk person”. Meclizine was prescribed. Gentamicin was stopped on day 29. One year later, the patient had persistent imbalance, visual symptoms, and had not returned to work. Hearing is normal. She presently does volunteer work and runs “wobblers anonymous”.

## **Causes of Bilateral Vestibular Loss**

- Aminoglycosides
- Bilateral forms of unilateral disease (e.g. vestibular neuritis)
  - Genetic
  - Syphilis

## **Diagnosis of Bilateral Loss is usually easy**

- History
  - recent course of IV antibiotic
  - Vestibular neuritis ?
- Eyes closed tandem Romberg is failed
- Dynamic illegible ‘E’ test (DIE) failed
- Ophthalmoscope test failed
- ENG and Rotatory chair confirm diagnosis

## **Bedside exam**

- Tandem Romberg
- DIE test
- Ophthalmoscope test
- Head shaking and head thrust (rapid dolls)
- Too good suppression
- Exclude other things

## **Romberg Testing: a gradient of difficulty.**

- Eyes Closed Tandem Romberg (6 seconds)
- Eyes Open Tandem Romberg
- Eyes Closed Regular Romberg
- Eyes Open Regular Romberg

Bilateral loss patients will all fail ECTR.

<b>Dynamic Illegible 'E' test (DIE)</b>	
<ul style="list-style-type: none"> <li>Distance vision with head still</li> <li>Distance vision with head moving (horizontal or vertical, 1-2 hz)</li> <li>Normal: 0-2 lines change.</li> <li>Abnormal: 4-7 lines drop with movement</li> </ul>	

<b>OPHTHALMOSCOPE TEST</b>	
<ul style="list-style-type: none"> <li>Gently oscillate head side to side at greater than 1 hz while viewing the optic disk</li> <li>Optic disk may appear stable (normal) or move (abnormal)</li> <li>Acutely, all patients with bilateral vestibular loss will fail this test</li> <li>Chronically, some patients will pass (because high-frequency VOR recovers)</li> </ul>	
Patient should wear habitual spectacles	

<b>Head shaking and rapid dolls</b>	
<ul style="list-style-type: none"> <li>Watch eyes DURING head-shaking, not afterwards.</li> <li>Rapid Dolls -- alternative method</li> </ul>	

<b>"Too good" suppression</b>	
<ul style="list-style-type: none"> <li>Patients can suppress "VOR" better than normal subjects</li> <li>They don't have a VOR to suppress</li> </ul>	

<b>COR test</b>	
<ul style="list-style-type: none"> <li>Rotate patient on swivel chair, with head still</li> <li>Look for eye movement synced to chair</li> <li>Not very useful.</li> </ul>	

<b>Malingering in Bilateral Patients</b>	
<ul style="list-style-type: none"> <li>Inconsistency in gait or vision <ul style="list-style-type: none"> <li>Lack of proper scaling between symptoms and signs.</li> <li>Positive DIE test, negative ophthalmoscope test</li> </ul> </li> <li>Difficult exam (i.e. blinking, exaggeration)</li> <li>Unreasonable clinical status – wheel chair or walker after 1-2 years.</li> </ul>	

	<b>Causes of Bilateral Vestibular Loss</b>
	<ul style="list-style-type: none"> <li>■ Aminoglycosides</li> <li>■ Bilateral forms of unilateral disease (e.g. vestibular neuritis)</li> <li>■ Genetic</li> <li>■ Syphilis</li> </ul>

	<b>Aminoglycosides</b>
	<ul style="list-style-type: none"> <li>■ General Structure – amino sugar bound by glycosidic linkage to a central hexose nucleus</li> </ul>
	<p style="text-align: center;">GENTAMICIN... <math>\cdot H_2SO_4</math></p> <p style="text-align: center;"><math>C_1: C_{21}H_{43}N_5O_7</math></p>

	<b>Things you need to know</b>
	<p>About 3% of hospital admissions involve aminoglycoside antibiotics.</p> <ul style="list-style-type: none"> <li>■ The aminoglycosides are all ototoxic and nephrotoxic</li> <li>■ They build up in the ear over long periods of time.</li> <li>■ Some people are genetically predisposed to get aminoglycoside toxicity.</li> <li>■ Aminoglycoside ototoxicity is potentiated by several other commonly used medications</li> </ul>

	<b>Aminoglycoside Toxicity: Specific agents</b>
	<p>High Vestibulotoxicity <span style="float: right;">High Cochleotoxicity</span></p> <div style="display: flex; align-items: center; justify-content: space-around;"> <div style="text-align: center;"> </div> <div style="text-align: center;"> <ul style="list-style-type: none"> <li>■ Streptomycin</li> <li>■ Gentamicin</li> <li>■ Tobramycin</li> <li>■ Neomycin</li> <li>■ Kanamycin</li> <li>■ Amikacin</li> </ul> </div> <div style="text-align: center;"> </div> </div>

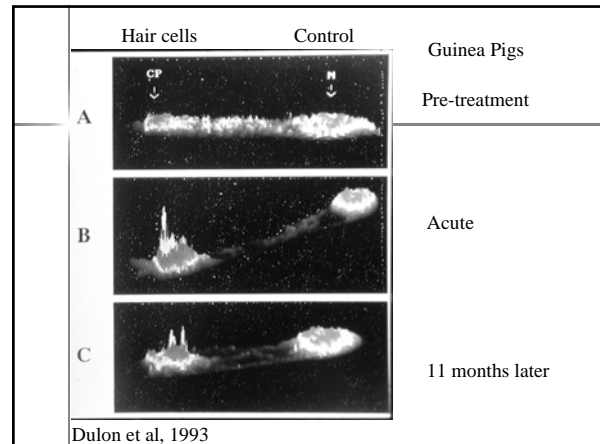
	Aminoglycoside ototoxicity
	<p><b>Cochleotoxicity</b></p> <p>Related to number of free amino (-NH<sub>2</sub>) groups Neomycin, kanamycin</p> <p><b>Vestibulotoxicity</b></p> <p>Related to number of free methylamine groups (-NHCH<sub>3</sub>) Streptomycin, gentamicin</p>

	<b>Aminoglycoside pathology</b>
	<ul style="list-style-type: none"> <li>■ Vestibular damage occurs first in the crista of the semicircular canals and then extends to the saccule and utricle.</li> <li>■ Pathologically there is hair cell loss.</li> </ul>

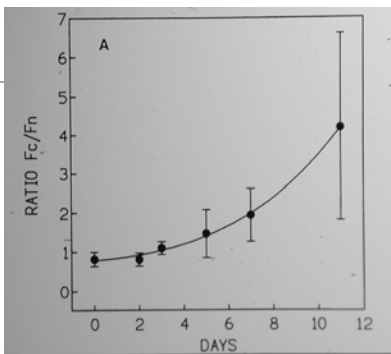
## Aminoglycosides: Pharmacokinetics are different in the ear than blood

- All aminoglycosides have roughly a 2 hour serum half-life in persons with normal renal function<sup>1</sup>
- IV gentamicin in humans rapidly transfers from serum to inner ear (5 minutes)<sup>2</sup>
- Inner ear levels build up over days and persist for months<sup>2</sup>

1. Edson et al, 1991
2. Becvarovski et al, 2002
3. Dulon et al, 1993

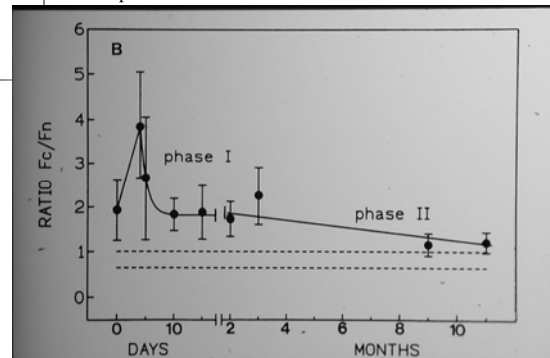


Gentamicin builds up in the inner ear (Guinea pigs)



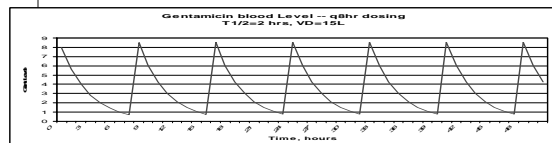
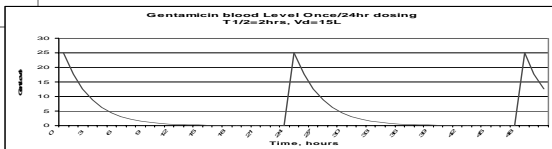
Dulon et al, 1993

Gentamicin persists in the inner ear for months



Dulon et al, 1993

## Different peaks, same toxicity



## Aminoglycoside pharmacokinetics Implications

• High serum "peak" levels are not necessarily correlated with ototoxicity because drug bound to the inner ear gradually builds up over weeks and is eliminated very slowly. Contemporary regimens use single doses every day or other day (with very high peak levels).

• Ototoxicity can occur with normal levels (prolonged doses)

- Yee GC, Evans WE, 1981, Nicolau et al. 1995, Barza M, Lauerma M. 1978

## Genetic Susceptibility

- Mutation of 12S rRNA makes the region homologous to that which is involved in aminoglycoside binding in bacterial rRNA
- Three Chinese and two Japanese pedigrees with aminoglycoside otosensitivity had A to G mutations.
- 17% of persons with hearing loss after systemic aminoglycoside exposure had this mutation.

Fischel-Ghodsian et al, 1997

## MEDICATIONS WHICH POTENTIATE AMINOGLYCOSIDE OTOTOXICITY

- VANCOMYCIN
- LOOP DIURETICS
- CIS-PLATINUM
- METRONIDAZOLE

## Prognosis of vestibulotoxicity

- Hair cells don't regrow (in humans)
- Vestibular damage may progress for months after drug is stopped (because drug is bound to inner ear for months)
- Rule of thumb – 6 months damage is complete
- High-frequency VOR nearly always eventually recover (which reduces oscillopsia)

## Aminoglycoside Vestibulotoxicity

- Streptomycin
- Gentamicin
- Tobramycin
- Kanamycin
- Amikacin
- Neomycin



Begg EJ, Barclay ML. Aminoglycosides—50 years on. Br. J. Clin Pharm 39, 597-603, 1995

## Streptomycin vestibulotoxicity

- Streptomycin is mainly vestibulotoxic
- 15% of patients treated with 1g of Streptomycin daily for tuberculosis developed vestibulotoxicity (Bignall et al, 1951).
- Hearing disturbance is an uncommon complication of systemic streptomycin

## Gentamicin vestibulotoxicity

- Gentamicin is a mainly a vestibulotoxin.
  - About 2-10% of IV courses of Gentamicin result in ototoxicity (usually mild cochleotoxicity). Nobody knows the exact incidence of vestibulotoxicity (probably higher)
  - Gentamicin solution is used to purposefully ablate vestibular function in Meniere's disease.

	<b>vestibulotoxicity (Cortisporin, Coly-mycin S)</b>
	<b>Amikacin</b> <ul style="list-style-type: none"> <li>■ Vestibulotoxicity of Neomycin is thought to be minor, as is Amikacin</li> <li>■ Cochleotoxicity is substantial (more discussion later)</li> </ul>

	<b>Tobramycin vestibulotoxicity</b>
	<ul style="list-style-type: none"> <li>■ Tobramycin is only mildly ototoxic systemically. It is significantly less vestibulotoxic than gentamicin (Prazma et al, 1981; Israel et al, 1976)</li> </ul>

	<b>Gentamicin systemically is not very cochleotoxic.</b>
	<ul style="list-style-type: none"> <li>■ No cochleotoxicity was found in healthy volunteers (Forey et al, 1978). Minimal is found patients on ordinary doses (Chueng et al, 1990)</li> <li>■ Frequently patients are encountered with profound vestibulotoxicity but no cochleotoxicity (up to 8000 hz)</li> <li>■ Occasional cases are reported of systemic cochleotoxicity after massive doses (e.g. Backus et al, 1987)</li> </ul>

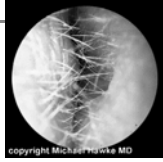
	<b>Case of complete vestibular loss in dialysis patient (FM)</b>
	<div style="display: flex; justify-content: space-around;"> <div style="text-align: center;"> <p>Pre-gent (1995)</p> </div> <div style="text-align: center;"> <p>Post-gent (1996)</p> </div> </div>

	<b>Gentamicin is surprisingly cochleotoxic when used for Menieres</b>
	<ul style="list-style-type: none"> <li>■ About 25% incidence of reduced hearing</li> <li>■ Is it the route ?</li> <li>■ Is it the levels ?</li> <li>■ Is the Meniere's ear more vulnerable ?</li> </ul>

	<b>Otological Ototoxicity</b>
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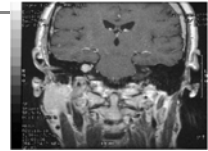
### Case: GB -- external otitis

GB, A 73 year old retired industrial engineer, deaf on the right side from an acoustic neuroma, presents with external otitis on the left. He also has diabetes, sinusitis, and fluctuating hearing on the left side. Previous examinations had documented a small healed perforation in that ear, a "monolayer"



### Case: GB (2) -- litigious patient

GB has a long history of adverse contacts with physicians. On the right side, at the onset of his hearing problem, a hearing aid was prescribed. The patient attributed a 4 year decline in his hearing to the aid, not realizing that an acoustic neuroma was the cause.



### Case: GB (3) -- Topical agent was used in the ear

GB saw an otologist who cleaned out the ear and put him on Garamycin (gentamicin) ophthalmic drops. On the second day, there was a "strange sound" in the L ear, and that he suddenly lost hearing. Three days later, audiometry documented modest worsening of the low tone hearing on the left, and the patient is considering a lawsuit

### Case: GB (4) -- Patient is preparing a lawsuit claiming loss of hearing from topical agent.

Does he have a case ?

### Otic topical agents commonly used are often ototoxic

- Cortisporin (neomycin 0.3% and polymyxin B with hydrocortisone 1%). 94.5% use.
- Colymycin-S (neomycin with hydrocortisone 1% and colistin (Polymyxin E 0.3%)) 59.1% use
- Floxin-Otic (ofloxacin solution). New agent
- Cipro-HC Otic (ciprofloxacin and 1% hydrocortisone)
- Gentamicin ophthalmic solution (usage unclear)
- Tobramycin ophthalmic (usage unclear)

Source: Lundy and Graham, Am. J. Otolary 1:2, 1993

### Numerous case reports suggest ototoxicity of otic aminoglycosides

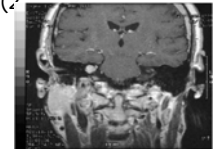
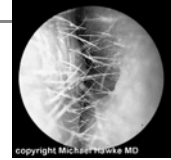
- Hui (1997) prolonged use of gentamicin, COS in 2 patients.
- Linder et al (1995), 12/134 patients given drops possible, 2/134 confirmed.
- Wong and Rutka (1997). 5 cases, 2 weeks or more. No controls.
- At least 7 others (see Linder, 1995)

## Vestibular ablation can be accomplished with topical gentamicin

- Kaplan et al (2002).
- 20 patients had gentamicin eardrops instilled TID for 1 month through PE tube.
- 15 had significant reduction in caloric test responses, 10 of which were complete loss.

## Answer to Case GB

- GB does not have a reasonable legal case because:
  - No perforation
  - Too short administration (? days)
  - Hearing loss is rare with gentamicin



## Bilateral Vestibular Neuritis

- Case: CTA worker developed vertigo 10 years ago, recovered.
- A second bout of vertigo 10 years later, followed by oscillopsia and persistent ataxia
- ENG – no response
- VEMP – good responses

## Pathophysiology

- 5% of persons with vestibular neuritis get it again
- Those individuals may develop recurrent vertigo (if same ear), or bilateral (if opposite ear).
- Because VN spares IVN, VEMP's usually are normal.

## Laboratory Testing for Bilateral Vestibular Loss

- ENG
- R-chair
- VEMP

## ENG testing should show

- Reduced total response to water (< 20), often 0
- No response to ice water
- Tests only low-frequency VOR

(of course, ENG does not test vertical canals or otoliths)

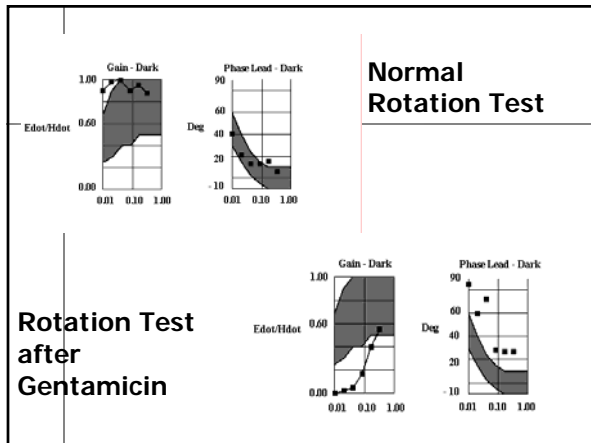


## Caloric testing is insensitive to Bilateral Paresis

- Criterion for BVL is total response < 20
- Normal total response is 100
- **Must lose 80% of caloric response**
- Rotatory chair testing easily detects unilateral vestibular loss (50% loss).
- Problem is anatomic variability in caloric responses. False positives also a problem.

## Rotation testing is the gold standard for vestibulotoxicity

- Tests both ears
- Tests high and low frequencies
- Probably more sensitive than calorics
- Does not test vertical canals or otoliths

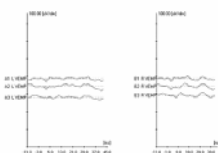
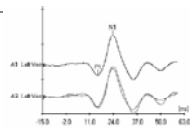


## Rotational testing

- Remember to look for “too good suppression” on r-chair too.
- Malingering patients may be tripped up by this because they try to “fail” the test.

## VEMP testing

- VEMP's are generally lost in bilateral vestibular weakness due to aminoglycoside toxicity.



Murofushi, 2002; Hain et al, 2006

## Summary

- Bilateral vestibular loss is easily diagnosed
- Many bedside maneuvers
- Laboratory testing shows abnormal ENG, R-chair and VEMP.