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CHOOSE WISELY
Pharmacokinetics of Intracameral Antibiotics for Endophthalmitis Prophylaxis
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Disclosure
I have no financial conflicts of interest.

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Off-Label Use
• No drug has been approved by the FDA for prevention of endophthalmitis after cataract surgery
• THEREFORE,
• Every use of antibiotics for prevention of endophthalmitis is off label:
  • Topical
  • Subconjunctival
  • Intracameral

(FDA logo)
Postcataract Endophthalmitis

- Uncommon
- Rate: less than 1/10,000 up to 3.6% of cataract cases
- Severe:
  - Months of disability
  - Less than half of patients return to 20/40 acuity
  - 30% suffer severe, long-term visual loss, less than 20/200 acuity
  - Preventable

Risk factors for postcataract endophthalmitis

- Leaky incisions
- If aqueous gets out, bacteria can get in
- Posterior capsule tear/vitreous loss
- Even 5 bacteria in the vitreous can cause endophthalmitis
- Using Silicone IOL’s
- Bacteria adhere to silicone
- Failure to use Povidone/Iodine on the surface of the eye
- Failure to use intracameral antibiotics

The Kaiser Permanente Colorado Endophthalmitis Story
1998-2001: increase in postcataract endophthalmitis

- 1998-2001: increased postcataract endophthalmitis
- 13 cases/8382 cataracts, rate = 1.55/1000
- Similar to U.S. Medicare increase
- Prophylaxis was Betadine skin prep and postop antibiotics

What to do (in 2001)?

Mark Speaker, MD

- Povidone-iodine versus silver protein irrigation of ocular surface, added to skin prep
- Povidone-iodine: 2/3384 cases of postcataract endophthalmitis
- Silver protein: 8/3289 cases
- 4-fold reduction
- P=0.05

Ophthalmology 1991;98:1769-75
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Why put antibiotics into the eye?

• PHARMACOKINETICS!
  • Much higher drug concentration in the eye,
  • Example: Moxifloxacin
    • Drops: 2 ug/mL
    • Subconj injection: 4 ug/mL
    • Intracameral: 500 ug/mL

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Local intervention to reduce endophthalmitis (2001)

• Reviewed aseptic technique with OR staff
• Reviewed importance of meticulous wound closure with surgeons
• Switched to acrylic IOL's
• Monitored surgeon's cataract complications
• Mentored surgeons with high complication surgeons
• Moved multiply comorbid cases to high-volume, low-complication surgeons
• Added povidone/iodine irrigation of the ocular surface to the usual prep and drape
• Added vancomycin 20 mg/mL to the Balanced Salt Solution irrigation

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Results! HOWEVER...

[Graph showing results]
What to do in 2006?

• Switch to bolus injection of intracameral cefuroxime? Vancomycin?
• Our surgeons were reluctant to inject a bolus of intracameral antibiotics at the end of surgery
• Concentration errors
• Contamination
• Toxic Anterior Segment Syndrome

Chang D, JCRS 2007;33:1801

So what did we do at Kaiser Permanente Colorado in 2006?

• Comfortable with experience of vancomycin irrigation
• 12,400 cataracts: every patient got vancomycin irrigation
• 5 endophthalmitis cases in 4 years
• Rate 0.4/1000 (about equal to ESCRS Cefuroxime rate)
• Much lower than U.S. Medicare rate
• No Toxic Anterior Segment Syndrome
• No allergic reactions
• Risk of harm from TASS, contamination, mixing errors
• Reviewed the PHARMACOKINETICS of intravitreal injections
• Slightly modified intravitreal technique: “mini-intracameral”

Pharmacokinetics overview

Antibiotic sensitivity and resistance
• Minimum Inhibitory Concentration for 90% of common endophthalmitis bacterial strains (MIC90)
• Killing kinetics: depends on bugs and drugs
• Drug concentration in the anterior chamber: at the end of surgery
• Half-life
• Log plots
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Simple approach

- NO EQUATIONS
- Pattern recognition
- 3 drugs
- 2 bugs
- Straight lines

Simple concept:
- Enough drug in the eye
- For a long enough time
- To kill the most common bugs

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PHARMACOKINETICS plot example

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Log concentration plot, straight line
Decay slope known from half-life measurements
Pattern recognition

• If the concentration line stays above the MIC90 “floor” for longer than the kill time:
  • Effective prophylaxis

• If the concentration line dips below the MIC90 “floor” before the kill time:
  • Potential prophylaxis failures
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**Bugs**

- Bacterial contamination of aqueous is common after cataract surgery
- ADSF: less than 20-60 Colony Forming Units (CFU)
- Killing 99% (2 Log units) of bacteria is sufficient for effective prophylaxis
- Endophthalmitis species are identical to patient's ocular flora
- Staphylococcus species are most common

2. Han DP. Am J Ophthalmol 1996;122:1

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**3 drugs**

- Cefuroxime
- Moxifloxacin
- Vancomycin

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**Cefuroxime**

- ESCR randomized trial: 5-fold reduction of endophthalmitis rate
- Inject 1 mg/0.1mL into the anterior chamber at the end of surgery
- Concentration: 2745 ug/mL
- Half-life: 0.5 hours
- Gram-positive and gram-negative coverage
- However, MIC90 for MRSA and MRSE is 256 ug/mL
- In Europe (but not U.S.) commercial intracameral cefuroxime for injection is available

1. ESCR Study Group. JCRS 2007;33:978
3. Woods GL. AAC 1987;31:1332
Resistant bugs: MRSE, MRSA and cefuroxime

- Multicenter study of eye cultures of 399 cataract surgery patients in the U.S.
- Most common: Staphylococcus epidermidis "coagulase negative"
- Of these, about half were methicillin-resistant (MRSE)
- Fewer Staph aureus
- Of these, 29.5% were methicillin-resistant (MRSA)
- MRSE and MRSA species are highly resistant to cefuroxime

MIC90: 256 ug/mL

1. Olson R. Clin Ophth 2010;4:1505
2. Woods GL. AAC 1987;31:1332

Cefuroxime kill kinetics versus sensitive Staphylococcus epidermidis

- 3 h for 1-log kill of sensitive staph species, probably 6 h for 2-log kill
- Concentration remains above MIC90 (1 ug/mL) for 6 hours
- Effective prophylaxis


Cefuroxime kill kinetics versus resistant Staphylococcus epidermidis

- Over 3 h for 1-log kill of sensitive staph species, probably over 6 h for 2-log kill
- Slower for resistant species: MRSA and MRSE
- Concentration drops below MIC90 (256 ug/mL) in less than 2 hours
- Prophylaxis failures are possible for MRSA and MRSE

Moxifloxacin

- Non-randomized trial showed a 3-fold reduction in the endophthalmitis rate
- Inject 0.2 mL of a 3:1 dilution of unpreserved moxifloxacin 0.5% drops into the anterior chamber, OR
- Flush 3–5 mL of a 10:1 dilution of unpreserved moxifloxacin 0.5% into the capsular bag and anterior chamber
  - Concentration is 400 ug/mL
  - Half-life is 1 hour
- MIC90 for staphylococcus epidermidis endophthalmitis isolates is 32 ug/mL

1. Matsuura K. JCRS 2013;39:1702

Resistant bugs: moxifloxacin

- Bascom Palmer study of 59 coagulase-negative endophthalmitis isolates in the U.S.
  - 52% of isolates were resistant to moxifloxacin
  - MIC90 was 32 ug/mL


Moxifloxacin kill kinetics versus fluoroquinolone-sensitive Staphylococcus epidermidis

- Less than 2 hours for 1000-fold kill of fluoroquinolone-sensitive staphylococcus isolates
- Concentration stays above MIC90 (1 ug/mL) for 8 hours
- Effective prophylaxis

Moxifloxacin kill kinetics versus RESISTANT Staphylococcus epidermidis

- Over 2.5 hours for 10-fold kill of fluoroquinolone-resistant staph epidermidis, probably 5 hours.
- Concentration drops below MIC90 (32 ug/mL) in 4 hours.
- Prophylaxis failures are possible for fluoroquinolone-resistant staphylococcus epidermidis.


Vancomycin

- Non-randomized trials show very low endophthalmitis rates.
- Inject 1 mg/0.1 mL into anterior chamber as the last step of surgery.
- Concentration is 5458 ug/mL after surgery.
- Irrigate 10 mg/500 mL balanced salt solution (20 ug/mL) during surgery.
- The half-life is 1.9 hours for the first 2 hours, then 3.2 hours for the next 20 hours.
- MIC90 for staphylococcus endophthalmitis isolates is 3 ug/mL.

2. Gimbel HV. CRS Today 2005;73
3. Arshinoff SA. JCRS 2011;37:2105

Resistant bugs: vancomycin

- Vancomycin has little to no activity against gram-negative bacteria.
- Isolated cases of vancomycin-resistant enterococci endophthalmitis.
- In Japan, 20% of endophthalmitis isolates are enterococci, 2% in the United States.
- In large U.S. series of gram-positive endophthalmitis cultures, 99-100% of isolates were sensitive to vancomycin.

1. Matsuura K. JCRS 2013;39:1702
2. Han DP. Am J Ophthalmol 1996;122:1
Vancomycin kill kinetics versus Staphylococcus epidermidis: injection

- 4.6 hours to kill 99% of Staphylococcus epidermidis
- Vancomycin dislodges resistant, slime-forming bacteria from silicone IOL's in 1 hour
- Concentration remains well above MIC90 of 3 ug/mL throughout the kill time
- Effective prophylaxis

2. Kodjikian L. JCRS 2005;31:1050

Hang on. We’re almost there!

Howard Gimbel, MD

- “The actual concentration of intracameral vancomycin is much lower, because the drug is diluted by BSS added to repressurize the eye after the injection.”

Vancomycin kill kinetics versus Staphylococcus epidermidis: Irrigation, with BSS hydration and pressurization

- Initial concentration 20 ug/mL
- Repressurizing eyes and hydrating incisions with plain BSS washes some vancomycin out of the eye
- Concentration drops below MIC90 (3 ug/mL) in less than the 4.6 h killing time
- Potential prophylaxis failures (as we experienced)

Log concentration (ug/mL) vs time (h)

James Gills, MD

- Repressurize the eye using the “anterior chamber mixture,” (not plain balanced salt solution)
- Antibiotics, steroids, NSAID’s
- JCRS 2004;30:1616-7

Vancomycin kill kinetics versus Staphylococcus epidermidis: Irrigation, pressurization and hydration with vancomycin solution

- Initial concentration 20 ug/mL
- Remains 20 ug/mL when the eye is repressurized with the irrigating solution
- Concentration remains above the MIC90 (3 ug/mL) for longer than the killing time
- Effective prophylaxis
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2006-2015 KP Colorado endophthalmitis intervention

- Intervention: Irrigate, repressurize eyes, and hydrate incisions with vancomycin 20 μg/mL
- 17 surgeries, 6 venues, 10 years
- Outcome: Reduced endophthalmitis to one case after 52,603 cataracts
- Versus 2002-2005: Relative Risk: 21.2, p < 0.0001
- Yes, mere mortals can attain endophthalmitis rates equal to Dr. Gills' rate!

- Schelonka LP. Clin Ophth 2015;9:1337

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RESULTS!

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We chose wisely!

- But why did it work?

- PHARMACOKINETICS
Pharmacokinetics change with broken capsules
• The vitreous is contaminated
• As few as 5 bacteria in the vitreous can cause endophthalmitis
• Antibiotics are distributed into a larger volume (5 mL vitreous)
• Injected or flushed moxifloxacin 500 ug/mL does not reach MIC90 of 32 ug/mL in the vitreous
• Switching to irrigation may be helpful
• Cefuroxime may not reach the MIC90 of 256 ug/mL
• Vancomycin irrigation gives 20 ug/mL in the vitreous, exceeding the MIC90


Summary of Pharmacokinetics
• Cefuroxime
• Effective prophylaxis for methicillin-sensitive staphylococci
• Potential prophylaxis failures for methicillin-resistant staphylococci; intact and torn lens capsules
Summary of Pharmacokinetics

• **Moxifloxacin**
  - Effective prophylaxis for fluoroquinolone-sensitive staphylococci
  - Potential prophylaxis failures for fluoroquinolone-resistant staphylococci
  - Intact and torn lens capsules

Summary of Pharmacokinetics

• **Vancomycin**
  - Effective prophylaxis for essentially all staphylococci, intact and torn lens capsules
  - Incision hydration and eye pressurization with plain BSS may cause prophylaxis failures with vancomycin irrigation
  - Surgeons who irrigate with vancomycin should strongly consider pressurizing eyes and hydrating incisions with the vancomycin irrigating solution

Safety of intracameral antibiotics

• Cefuroxime, moxifloxacin, and vancomycin have been used safely in hundreds of thousands of cataract operations
Safety of intracameral antibiotics - cefturoxime

- Mixing/concentration errors with cefturoxime have caused Toxic Anterior Segment Syndrome (TASS), macular edema and corneal edema.
- Using cefturoxime axetil (versus cefturoxime) has also caused TASS.
- Anaphylaxis has been reported with intracameral cefturoxime in penicillin allergic patients.

Safety of intracameral antibiotics - moxifloxacin

- No compounding required.
- Injecting extended-release moxifloxacin 0.5% drops, with sorbitol and tyloxapol, has been associated with severe Toxic Anterior Segment Syndrome.

Safety of intracameral antibiotics - vancomycin

- Vancomycin irrigation.
- Compounded vancomycin 10 mg/mL, diluted 500:1 in balanced salt solution.
- Dilutes and buffers contaminants, toxins, mixing, osmolarity, and pH errors.
- TASS is unlikely.
- Postoperative cystoid macular edema with vancomycin irrigation was noted in a teaching hospital (extended case times).
- No CME in recent series.
- Recent reports have associated devastating postoperative Hemorrhagic Disciform Retinal Vasculitis with intracameral vancomycin.
- We have not experienced a case after 14 years and 65,003 cataract operations with vancomycin irrigation.

1. Axer-Siegel R. Ophthalmology 1999;106:1660
2. Ball JL. JCRS 2006;32:789
Summary: CHOOSE WISELY in 2016

- Endophthalmitis is preventable
- Strict asepsis
- Monitor and mentor surgeons with high complication rates
- Use acrylic lenses
- Irrigate the eye with povidone-iodine before surgery

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Summary: CHOOSE WISELY in 2016

- Choose intracameral antibiotics
  - "Know your bugs to pick your drugs"

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Summary: CHOOSE WISELY in 2016

- Europe: cefuroxime
  - Commercially available single-dose injection
  - Lower rate of MRSA and MRSE than U.S.
  - Watch for beta-lactam allergies
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**Summary: CHOOSE WISELY in 2016**

- Japan:
  - Moxifloxacin may be best
  - Available in preservative-free eye drops
  - High rate of Enterococcal endophthalmitis, vancomycin resistance
  - Do not use extended release formulation (TASS)

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**Summary: CHOOSE WISELY in 2016**

- United States:
  - All work well, vancomycin may protect best
  - Injection: effective
  - Surgeons who irrigate with vancomycin should pressurize runs and hydrate incisions with the vancomycin mixture
  - Watch for postop retinal vasculitis
  - Exceedingly rare: less than 1/65,000 in our series
  - Devastating
  - Consider other agents for sequential bilateral surgery

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Thank You!