Clinical Pearls and Safety Precautions for Oral Pharmacotherapy

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Disclosure Statement
- Alcon
- Allergan
- Bausch & Lomb Pharmaceuticals
- Jobson Publishing
- United States Pharmacopeia
- Wolters Kluwer Health

Please silence all mobile devices.

Prescriptive Authority for Oral Medications in Optometry (2013)

Prescriptive Authority for Controlled Drugs in Optometry (2013)

THE HISTORY
- Gives clues to drug contraindications!
  - Medical
  - Medications
  - Family

MEDICAL HISTORY
- Renal or upper GI disease
  - Systemic steroids and NSAIDs
- Cardiovascular disease
  - Topical phenylephrine
  - Topical β blockers
    - Safe with pacemaker
  - Antihistamines
    - Avoid decongestants
MEDICAL HISTORY (cont’d)
- Respiratory disorders
  - β blockers
  - Opioids
- Graves’ disease
  - Topical phenylephrine
  - Systemic decongestants
- Diabetes
  - Systemic steroids
  - β blockers?

MEDICAL HISTORY (cont’d)
- Central nervous system disorders
  - Cyclopentolate
  - β blockers
  - Oral CAIs
  - α2 agonists

MEDICATION HISTORY

DRUG INTERACTIONS
- Change in effect of one drug (object drug) by prior or concurrent administration of another drug (precipitant drug)
- Result is increase, decrease, or loss of therapeutic effect
- Increased toxicity

EPIDEMIOLOGY
- Approximately 6.5% of ADRs are due to drug interactions
- About 25% of patients in an outpatient setting are taking two or more drugs
- Due to systemic absorption, ophthalmic drugs can interact significantly with systemic medications
**MECHANISMS OF INTERACTIONS**

- Alterations in gastrointestinal absorption
- Displaced protein binding
- Alterations in metabolism
- Altered renal excretion

**Decreased Gastrointestinal Absorption**

- Avoid milk, dairy, and antacids
- Formation of drug-drug complexes (Ca^{2+}, Mg^{2+})
  - Tetracyclines – milk, dairy, antacids

**Displaced Protein Binding**

- Protein-bound drugs are inactive pharmacologically
- Administration of more than one drug bound to the same plasma protein binding site can cause either drug to be displaced from its binding site
  - NSAID -- oral hypoglycemics

**Common Oral Sulfanylurea Hypoglycemics**

- Diabeta
- Amaryl
- Orinase
- Glucotrol
- Glucotrol XL

**Displaced Protein Binding**

**Alterations in Metabolism**

- Precipitant drug may increase or decrease metabolism or change first-pass metabolism of object drug
- Major hepatic enzyme system consists of cytochrome P450 (CYP) oxygenesis
Foods That Interfere With Hepatic Metabolism

- Naringenin, a bioflavonoid found in grapefruit juice, may inhibit CYP3A4, decreasing metabolism of cyclosporine and calcium channel blockers.

IDENTIFYING DRUGS WITH INTERACTION POTENTIAL

Epocrates Rx

DRUG INTERACTIONS

- Check for interactions among up to 30 drugs at one time
- Potential interactions are organized by clinical category

DRUG-DRUG INTERACTIONS

<table>
<thead>
<tr>
<th>Systemic Drug</th>
<th>Ocular Drug</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac glycosides</td>
<td>β Blockers</td>
<td>Cardiac depression</td>
</tr>
<tr>
<td>Quinidine</td>
<td>β Blockers</td>
<td>Cardiac depression</td>
</tr>
<tr>
<td>Xanthines</td>
<td>β Blockers</td>
<td>Bronchospasm</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Tetracyclines</td>
<td>Reversal of contraception</td>
</tr>
<tr>
<td>Oral hypoglycemias</td>
<td>Oral NSAIDs</td>
<td>Acute hypoglycemia</td>
</tr>
</tbody>
</table>

MEDICATION HISTORY (cont’d)

- Drug allergies
  - Penicillin
    - Avoid PCN and cephalosporins
  - Opioids
    - Avoid *all* narcotic analgesics
  - Sulfonamides
    - Avoid CAIs?
    - Avoid sulfacetamide and sulfamethoxazole/trimethoprim (Bactrim)
Antibiotic Combinations

Trimethoprim/Sulfamethoxazole – A Broad Spectrum Antibiotic

<table>
<thead>
<tr>
<th>Name/Language</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimethoprim/sulfamethoxazole (generic)</td>
<td>80 mg trim/400 mg sulf</td>
</tr>
<tr>
<td>Bactrim, Bactrim DS</td>
<td>Same as above</td>
</tr>
<tr>
<td>Cotrim, Cotrim DS</td>
<td>Same as above</td>
</tr>
<tr>
<td>Septra, Septra DS</td>
<td>Same as above</td>
</tr>
</tbody>
</table>

Case Report

- 35 year-old WF
- Internal hordeolum, right upper lid
- Severe allergy to penicillin
- “Mycin drugs” upset stomach
- “Can’t swallow pills”

Bactrim is a Sulfonamide!
Drug Use in Special Patient Populations

PREGNANCY/LACTATION

19 yowf Presents for Second Opinion

FDA Pregnancy Categories

<table>
<thead>
<tr>
<th>FDA Pregnancy Categories</th>
<th>Definition</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>No risk to fetus</td>
<td>Levothyroxine, vitamin B₆</td>
</tr>
<tr>
<td>B</td>
<td>No evidence of risk</td>
<td>Azithromycin, erythromycin, brimonidine</td>
</tr>
<tr>
<td>C</td>
<td>Risk cannot be ruled out</td>
<td>Clarithromycin, ciprofloxacin, steroids, phenylephrine, latanoprost</td>
</tr>
<tr>
<td>D</td>
<td>Risk to fetus</td>
<td>Tetracycline, doxycycline</td>
</tr>
<tr>
<td>X</td>
<td>Definite risk!</td>
<td>Misoprostol, isotretinoin</td>
</tr>
</tbody>
</table>

Drug Use During Pregnancy
Avoid Category X!

Caveats

- Some drugs have different categories according to pregnancy trimester
  - ACE inhibitors (C, D, D)
- Some drugs have precautions despite “B” labeling
  - Ibuprofen (risk premature closure of fetal ductus arteriosus if given in third trimester)
  - Brimonidine (CNS depression)
- FDA Pregnancy Labeling Task Force

Final Rule Effective June 30, 2015

- Replaces current letter categories: A, B, C, D, X
- Three new detailed subsections provide explanations about potential benefits and risks for mother, fetus, and breastfeeding child
  - Pregnancy
  - Lactation
  - Females and males of reproductive potential
- New requirements phased in gradually for existing products

The Pregnant Glaucoma Patient

- Alphagan P is the only contemporary glaucoma drug with a pregnancy category B rating

Pupillary Dilation During Pregnancy

- Avoid phenylephrine and other adrenergics – tropicamide is safe

PEDIATRIC PATIENTS
**Pediatric Dosage Calculation**

**Clark’s Rule**

Pediatric Dose = Adult Dose $\times \frac{\text{Weight (kg)}}{70}$

or

Adult Dose $\times \frac{\text{Weight (lb)}}{150}$

*5 ml = 1 tsp*

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**Pediatric Dosage Calculation By Age**

<table>
<thead>
<tr>
<th>Age</th>
<th>Percent of Adult Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;12</td>
<td>100%</td>
</tr>
<tr>
<td>6-12</td>
<td>50%</td>
</tr>
<tr>
<td>2.6</td>
<td>25%</td>
</tr>
</tbody>
</table>

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**Pediatric Zithromax**

- 8 year-old male
- Weighs 80 lb
- Recent URI
- Presents with red, swollen, painful LUL
- Dosage is 10mg/kg x 1d, then 5mg/kg x 4d

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**Pediatric Zithromax**

- Zithromax 200mg/5 ml
- Sig.: Two tsp PO on first day, then one tsp QD x 4 days for eye infection. Take 1 h ac or 2 h pc

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**Reread Your Prescription for Accuracy!**

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**GERIATRIC PATIENTS**
POLYPHARMACY
- Contraindicated drug combinations
- Redundant medications prescribed by several clinicians
- Erroneous duplications of drugs or categories of drugs
- Interactions from prescription and OTC medications
- Outdated drugs or dosage schedules

DOSAGE CONSIDERATIONS
- Systemic medication dosages are lower than the “normal adult dosage”
- Renal function
- Clinical judgment and common sense guide individualized drug therapy

PRACTICAL CONSIDERATIONS
- Use a single pharmacy
- Stress understanding and compliance
- Keep dosage directions clear, simple, and achievable
- Use handwritten dosing charts, large numerals, and color codes for drug identification
- Fit dosage schedule to patient’s lifestyle
- Educate family members or caregivers

PRACTICAL CONSIDERATIONS
- Refrigerate topical medications
- Use large print and large numerals
- Emphasize color coding
- Must be able to identify medications and dosing schedules
- Telephone access?

MORE CLINICAL PEARLS AND SAFETY CONSIDERATIONS

Pill Boxes
MRSA UPDATE

Methicillin-Resistant *Staphylococcus Aureus*

Penicillins

- Gram-positive
  - Penicillins G and V
- Penicillin-resistant penicillins
  - Methicillin, nafcillin, cloxacillin, dicloxacillin
- Extended spectra
  - Ampicillin, amoxicillin
The acronym MRSA signifies that the isolates are resistant to all beta-lactam antibiotics, not just methicillin.

Evolving Prevalence of MRSA
- *S. aureus* resistance was first discovered in 1944
- MRSA prevalence is now 3%-53%
- In the US, approx 14% of *S. aureus* isolates (bacterial conjunctivitis) are methicillin-resistant
- Excluding endophthalmitis, nationally the prevalence of ocular MRSA is about 40%

Range of MRSA Eye Infections
- Blepharoconjunctivitis (78%)
- Keratitis (15%)
- Cellulitis (2.5%)
- Dacryocystitis (2.5%)
- Endophthalmitis (2%)

Best Therapeutic Options

Ocular TRUST
- A longitudinal nationwide antimicrobial susceptibility surveillance program specific to ocular isolates
  - *S. aureus*
  - Coagulase-negative staphylococci
  - *S. pneumoniae*
  - *H. influenzae*

Susceptibility Testing
- *In vitro* susceptibility testing to nine antimicrobials
  - Ciprofloxacin, levofloxacin, gatifloxacin, moxifloxacin
  - Azithromycin
  - Trimethoprim
  - Tobramycin
  - Polymyxin B
  - Penicillin


Ocular TRUST 2: *S. aureus* Susceptibility

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MIC Range</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt;</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>≤0.25 – 2</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>≤0.008 – 8</td>
<td>0.03</td>
<td>1</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>≤0.008 – 64</td>
<td>0.06</td>
<td>8</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>≤0.03 – 256</td>
<td>0.12</td>
<td>8</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>≤0.015 – 512</td>
<td>0.5</td>
<td>256</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>≤0.06 – 256</td>
<td>0.5</td>
<td>256</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>≤0.25 – 5512</td>
<td>128</td>
<td>&gt;512</td>
</tr>
</tbody>
</table>

- 50.0% of ocular *S. aureus* isolates were MRSA
- 39.9% of ocular *S. aureus* isolates were FQ resistant

**First and Only Ophthalmic Chlorofluoroquinolone**

- Fluorine at C6
- Chlorine at C8

**Antibiotic Resistance Monitoring in Ocular Microorganisms (ARMOR)**

- Ocular antimicrobial surveillance program across the US
- Profiles *in vitro* activity of ophthalmic agents against ocular isolates:
  - *Staphylococcus aureus*
  - Coagulase-negative staphylococci
  - *Streptococcus pneumoniae*
  - *Haemophilus influenzae*
- Tested concurrently for susceptibility to besifloxacin, moxifloxacin, gatifloxacin, ciprofloxacin, azithromycin, tobramycin, trimethoprim, vancomycin

**Besifloxacin (Besivance) Suspension**

- New chemical entity: An 8-chloro fluorooquinolone
- NOT used systemically – only available in U.S.
- No oral counterpart
- FDA-approved only for bacterial conjunctivitis
- FDA-approved dosage: TID for 7 days
- Pediatric approval: ages 1 and older
- Preserved with 0.01% BAK
- Durasite vehicle for long retention time on ocular surface

**Besifloxacin MIC<sub>90</sub> for All Staphylococcus aureus Isolates**

**Broad Spectrum Coverage**

- Gram-positive organisms
  - *Staphylococcus epidermidis*
  - *Staphylococcus aureus (methicillin resistant)*
  - *Staphylococcus haemolyticus*
  - *Staphylococcus lugdunensis*
  - *Staphylococcus intermedius*
  - *Staphylococcus schleiferi*
  - *Staphylococcus warneri*
  - *Staphylococcus epidermidis ami typing group 1*
  - *Staphylococcus epidermidis ami typing group 2*
  - *Staphylococcus cohnii*
- Gram-negative organisms
  - *Haemophilus influenzae*
  - *Escherichia coli*
  - *Pseudomonas aeruginosa*
  - *Klebsiella pneumoniae*
  - *Citrobacter freundii*
  - *Providencia stuartii*
  - *Proteus mirabilis*
  - *Proteus vulgaris*
Durasite Vehicle

- Mucoadhesive polymer matrix

Besifloxacin Tear Concentrations Relative to MIC\textsubscript{90} for Ciprofloxacin-Resistant MRSA and MRSE

- At 12 hours postinstillation, concentration of besifloxacin remains higher than the MIC\textsubscript{90} for MRSA-CR and MRSE-CR


Treatment Options for Initial Empirical Therapy of MRSA

- **Topical**
  - Vancomycin
  - Besifloxacin
  - Trimethoprim/polymyxin B

- **Oral**
  - Trimethoprim/sulfamethoxazole
  - Clindamycin
  - Doxycycline
  - Tedizolid (Sivextro)


Treatment Options for Initial Empirical Therapy of MRSA

- **Intravenous (monotherapy)**
  - Vancomycin
  - Daptomycin
  - Linezolid
  - Telavancin
  - Ceftaroline
  - Tigecycline


What’s Your Diagnosis?
Acne Rosacea

Clinical Features
- Macules
- Papules
- Pustules
- Affects skin of cheeks, nose, forehead
- Teleangiectasia
- Women 30-50 most often affected

ACNE ROSacea AND/OR MEIBOMIAN GLAND DYSFUNCTION (MGD)
(aka Ocular Surface Disease)
Tetracyclines

- **Doxycycline capsules 40 mg**
  - 30 mg immediate release
  - 10 mg delayed release beads
- Indicated for treatment of inflammatory lesions (papules and pustules) of rosacea in adult patients
- Dosage is one capsule once daily in AM, 1 hr before or 2 hr after breakfast

**Oracea™**

- **Doxycycline capsules 40 mg**
  - 30 mg immediate release
  - 10 mg delayed release beads
- Indicated for treatment of inflammatory lesions (papules and pustules) of rosacea in adult patients
- Dosage is one capsule once daily in AM, 1 hr before or 2 hr after breakfast

**Case Report**

**Antilipase Activity**
Low-dose Doxycycline

- Periostat
- 20 mg doxycycline hyclate

Prescription for Doxycycline

<table>
<thead>
<tr>
<th>Name</th>
<th>Age</th>
<th>Sex</th>
</tr>
</thead>
</table>

Doxycycline 50 mg
# 60
Sig.: Take one PO BID for ocular rosacea

Side Effects of Tetracyclines

- Nausea, vomiting, diarrhea, pseudomembranous colitis
  - For N&V, administer with food
- Tooth discoloration, bone deformity
- Liver toxicity
- Kidney toxicity
- Photosensitization
- Esophagitis (do not take within 1 hr of bedtime)
- Vestibular reactions
  - Dizziness, vertigo with doxy dosages above 100 mg

Topical Therapies

- Metronidazole (MetroGel, MetroCream)
- Azelaic acid gel (Finacea)
- Brimonidine gel (Mirvaso)

Azelaic Acid Gel 15% (Finacea®)

- 0.33% topical dermatologic gel for persistent facial erythema of rosacea
- FDA approved on August 23, 2013
- Applied once daily
- Effective for up to 12 hr
- Sustained effect for at least 12 months

Brimonidine Gel (Mirvaso)
Side Effects of Antibacterials

- Hypersensitivity reactions
- Irritant effects
- Nausea, vomiting, diarrhea
- Pseudomembranous colitis
- Vaginal candidiasis

Vaginal Candidiasis

- Treat with oral fluconazole (Diflucan)
  - 150 mg PO x 1 (single oral dose)
- 1-2 yogurts/day

MANAGEMENT OF OCULAR PAIN

Pain in Optometry
Clinical Uses of APAP
- When NSAID therapy is contraindicated
- Allergy to ASA or other NSAID
- Upper GI disease
- Bleeding disorders or following cataract extraction
- Children and adolescence
- Pregnancy and lactation (category B)
- Can be used with low-dose aspirin

Adult Dosage
- 325-650 mg q 4-6 h
- 1000 mg tid or qid
- Do not exceed 4 grams daily *from all sources*

APAP Formulations

Side Effects
- Liver damage in chronic alcoholics with pre-existing liver damage
- Liver toxicity in overdose (10-15 grams)
Contraindications

- Chronic alcoholism
- Severe liver impairment
- Use of any other products that contain APAP

Narcotic (Opioid) Analgesics

- Codeine
- Oxycodone
- Hydrocodone
- [Propoxyphene]
Recommended Hydrocodone/APAP Combos

- 5/300
- 5/325
- 7.5/300
- 7.5/325
- 10/300
- 10/325
- 7.5/325/15 ml
- 10/325/15 ml

Prescribe “Norco”

Available as 5/325, 7.5/325, 10/325

RESCHEDULING OF HYDROCODONE COMBINATION DRUGS

Ramifications for the Profession of Optometry

A Rapidly Depleting Pain Management Toolbox

Dosing and Administration of Tramadol (Ultram)

- Indicated for management of moderate to moderately severe pain
- Recommended dosage
  - 50-100 mg q 4-6 h
  - Do not exceed 400 mg/day
- Now available with APAP (Ultracet)
  - 37.5/325 mg (2 tabs PO q 4-6 h)