
The Schwarting Senior Symposium
Aqua Turf Club
Plantsville, CT
April 6, 2017

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Medication Safety Pharmacist
Saint Francis Hospital and Medical Center
Hartford, Ct.

At the conclusion of this knowledge-based activity, the participant will be able to:

• Review appropriate management strategies for the safe use of amiodarone in elderly patients and develop a monitoring schedule for detecting or preventing adverse drug effects.

• Define and discuss nonalcoholic fatty liver disease and its complication, steatohepatitis, and their effects on drug metabolizing enzymes with potential clinical implications.

• Describe the ocular disposition of beta-blocker eye drops and its clinical implication for adverse systemic effects and possible preventative strategies.

• Discuss the adverse effects detailed in recent reports related to the use of certain important medications in the elderly.
Dennis J Chapron reports no real or potential conflicts of interest relevant to this lecture.

Antibiotic-induced Delirium
Consequences of Delirium

- Increased length of hospital stay
- Increased risk for in-hospital complications
- Increased likelihood of discharge to LTC facility
- Increased likelihood of rehospitalization
- Subsequent protracted/permanent cognitive impairment.
- Increased 1 yr mortality

Antibiotic-associated encephalopathy

**ABSTRACT**

Delirium is a common and costly complication of hospitalization. Although medications are a known cause of delirium, antibiotics are an underrecognized class of medications associated with delirium. In this article, we comprehensively review the clinical, radiologic, and electrophysiologic features of antibiotic-associated encephalopathy (AAE). AAE can be divided into 3 unique clinical phenotypes: encephalopathy commonly accompanied by seizures or myoclonus arising within days after antibiotic administration (caused by cephalosporins and penicillin); encephalopathy characterized by psychosis arising within days of antibiotic administration (caused by quinolones, macrolides, and procaine penicillin); and encephalopathy accompanied by cerebellar signs and MRI abnormalities emerging weeks after initiation of antibiotics (caused by metronidazole). We correlate these 3 clinical phenotypes with underlying pathophysiologic mechanisms of antibiotic neurotoxicity. Familiarity with these types of antibiotic toxicity can improve timely diagnosis of AAE and prompt antibiotic discontinuation, reducing the time patients spend in the delirious state. Neurology® 2016;86:963-971.
Antibiotic-Associated Encephalopathy
3 Distinct Clinical Syndromes

• Type-1 AAE – Penicillins/Cephalosporins – onset within days of tx initiation, s/s include myoclonus, seizures, abn EEG, normal MRI, and resolve within day of dc. Use in setting of kidney injury increases risk of AAE.

• Type-2 AAE – Sulfonamides, quinolones, macrolides, procaine penicillin – onset within days of tx initiation, s/s include psychosis, rarely seizures, infrequent abn EEG, normal MRI and resolve within days of dc.

• Type-3 AAE – Metronidazole – onset with weeks of tx initiation, s/s include cerebellar dysfunction, rarely seizures or abn EEG, see characteristic reversible MRI abnormalities in cerebellar dentate nuclei, dorsal midbrain and corpus callosum splenium.

Neurology 86: 963;2016

Images in Clinical Medicine

Lindsey R. Baden, M.D., Editor

Metronidazole-Associated Encephalopathy

On metronidazole

Off metronidazole

N ENGL J MED 374:15  NEJM.ORG  APRIL 14, 2016
A 58-YEAR-OLD MAN WITH CRYPTOGENIC CIRRHOSIS WAS ADMITTED TO the intensive care unit with confusion after a fall at home. He had been taking a prolonged course of metronidazole (500 mg three times per day for >3 weeks) for Clostridium difficile infection. A few days before his hospitalization, dysarthria and gait instability had developed, which had contributed to the fall. A magnetic resonance imaging (MRI) scan of the brain showed a symmetric, enhanced fluid-attenuated inversion recovery (FLAIR) signal in the dentate nuclei of the cerebellum (Panel A, arrow), a finding that is consistent with encephalopathy associated with metronidazole use. On admission, the patient was intubated for airway protection and was sedated; central catheter–related bacteremia developed soon thereafter. Discontinuation of metronidazole resulted in resolution of the imaging findings 1 month later (Panel B). Neurologic assessment was difficult, and the patient never regained his baseline mental status. Encephalopathy associated with metronidazole use is an uncommon side effect of the medication. It typically manifests as dysarthria and gait instability. Risk factors include liver dysfunction and a prolonged course of metronidazole (typical cumulative dose, >20 g). MRI of the brain is usually diagnostic and typically reveals a symmetric, enhanced FLAIR signal in the dentate nuclei of the cerebellum. During the course of hospitalization, this patient died from complications due to central catheter–related bacteremia.
Antimicrobial Agent Drug-Drug Interactions

- **Antimicrobial Agent** | **Affected CYP or Transporter**
- Ciprofloxacin: CYP-1A2, CYP-3A4
- Clarithromycin: CYP3A4, PGP, OAT
- Co-trimoxazole: CYP-2C8, CYP-2C9
- Erythromycin: CYP-3A4, OAT
- Fluconazole: CYP-2C9, CYP-2C19, CYP-3A4
- Isoniazid: CYP-2C19, CYP-3A4
- Itraconazole/ketoconazole: CYP-3A4, PGP
- Metronidazole: CYP-2C9, 2A6
- Nafcillin/Dicloxacillin: Inducer - CYP-2C9 and CYP-3A4
- Posaconazole: CYP-3A4, PGP
- Rifampin: Inducer - CYPs 2C8,2C9,2C19,3A4,PGP
- Voriconazole: CYP-2C9, CYP-2C19, CYP-3A4

Antibiotic-induced Eosinophilia
Peripheral blood eosinophilia and hypersensitivity reactions among patients receiving outpatient parenteral antibiotics

Kimberly G. Blumenthal, MD, Ilan Youngster, MD, MMSc; Dustin J. Rabideau, ScM; Robert A. Parker, ScD; Karen S. Manning; Rochelle P. Walensky, MD, MPH; and Sandra B. Nelson, MD

Conclusions: Drug-induced eosinophilia is common with parenteral antibiotics. Although most patients with eosinophilia do not have an HSR, eosinophilia increases the hazard rate of having rash and renal injury. DRESS syndrome was more common than previously described.

HSR = Hypersensitivity reaction

J Allergy Clin Immunol 2015 Nov 136:1288
About 25% of patients on long-term intravenous antibiotics develop eosinophilia. Most of these patients can finish their antibiotic courses without adverse effects. About a third of patients with eosinophilia will develop hypersensitivity reactions; patients taking vancomycin are at highest risk. Patients who develop eosinophilia earlier in their antibiotic courses or who have higher eosinophil counts are more likely to experience hypersensitivity reactions; for these patients, especially those with eosinophil counts >1500 cells/mL, we should consider switching to another antibiotic even if asymptomatic.

*J Allergy Clin Immunol* 2015 Nov 136:1288

**Absolute eosinophil count (AEC)**

AEC = WBC x % as eosinophils

Mild (AEC 600-1500 cells/μL),
Moderate (AEC 1500-5000 cells/μL),
Severe (AEC >5000 cells/μL).

Target organ damage is unusual with mild eosinophilia, but its occurrence in association with moderate to severe eosinophilia does not appear to depend on the specific cause of eosinophilia.
DRESS
Drug rash with eosinophilia and systemic symptoms
The syndrome classically presents 2 to 6 weeks after starting the responsible drug with severe rash, internal organ involvement, eosinophilia, fever, and lymphadenopathy. A widespread maculopapular or erythematous rash is nearly always present. DRESS is relatively rare, with an estimated incidence between 1 in 1000 and 1 in 10 000 drug exposures.

Possible DRESS syndrome occurred in 7 (0.8%) of 824 patients; 4 (57%) were receiving vancomycin.

*J Allergy Clin Immunol* 2015 Nov 136:1288
Top 6 Medications April 2014 – March 2015

The top 10 medications by number of monthly prescriptions are:

- Synthroid (levothyroxine), 21.5 million.
- Crestor (rosuvastatin), 21.4 million.
- Ventolin HFA (albuterol), 18.2 million.
- Nexium (esomeprazole), 15.2 million.
- Advair Diskus (fluticasone), 13.7 million.
- Lantus Solostar (insulin glargine), 10.9 million.

More items...

The 10 Most-Prescribed and Top-Selling Medications - WebMD

Subclinical Hypothyroidism

Elevation in TSH concentrations with normal circulating levels of thyroid hormones.

Population-based reference range of normal TSH is 0.45–4.5 mIU/liter,
New analysis has shown that the TSH distribution curve and upper reference limit progressively shifts to higher values with advancing age.

FIG. 2. Shift in TSH distribution to higher concentrations with age. Data from NHANES III (NH3) and NHANES 1999–2002 (NH 99_02) populations. [Reprinted with permission, Surks MI and Hollowell JH (20).]

(J Clin Endocrinol Metab 95: 496–502, 2010)
The upper reference limit for older patients (70 yrs or more) without thyroid disease or thyroid antibodies is as high as 7.5 mIU/L compared to 3.5 mIU/L for people less than 50 yrs of age.

A majority of elderly individuals with [TSH] above 4.5 mIU/L, who are currently considered to have subclinical hypothyroidism, actually fall within their age-specific limits.

JCEM 94:4768, 2009
Extreme Longevity Is Associated with Increased Serum Thyrotropin

Gil Atzmon, Nir Barzilai, Joseph G. Hollowell, Martin I. Surks, and Ilan Gabriely

Division of Endocrinology, Departments of Medicine (G.A., N.B., M.I.S., I.G.), Genetics (G.A., N.B.), and Pathology (M.I.S.), Albert Einstein College of Medicine, Bronx, New York 10461; and Department of Pediatrics (J.G.H.), University of Kansas Medical Center, Kansas City, Kansas 66160

Conclusions: The TSH population shifts to higher concentrations with age appear to be a continuum that extends even to people with exceptional longevity. The inverse correlation between TSH and FT4 in our populations suggests that changes in negative feedback may contribute to exceptional longevity. (J Clin Endocrinol Metab 94: 1251–1254, 2009)
Issues with Overprescribing of Levothyroxine in Patient with Subclinical Hypothyroidism

• Cost
• Inconvenience
• Adverse effects

Levothyroxine dose and risk of fractures in older adults: nested case-control study

Marc R Turner, medical resident,¹ Ximena Camacho, analyst,² Hadas D Fischer, epidemiologist,² Peter C Austin, senior scientist,² Geoff M Anderson, professor,³ Paula A Rochon, senior scientist,³ Lorraine L Lipscombe, scientist³

Conclusion Among adults aged 70 or more, current levothyroxine treatment was associated with a significantly increased risk of fracture, with a strong dose-response relation. Ongoing monitoring of levothyroxine dose is important to avoid overtreatment in this population.

BMJ 2011;342:d2238
DPP-4 Inhibitors

- Saxagliptin
- Sitagliptin
- Linagliptin
- Alogliptin

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Active Ingredient(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Januvia</td>
<td>sitagliptin</td>
</tr>
<tr>
<td>Janumet</td>
<td>sitagliptin and metformin</td>
</tr>
<tr>
<td>Janumet XR</td>
<td>sitagliptin and metformin extended release</td>
</tr>
<tr>
<td>Onglyza</td>
<td>saxagliptin</td>
</tr>
<tr>
<td>Kombiglyze XR</td>
<td>saxagliptin and metformin extended release</td>
</tr>
<tr>
<td>Tradjenta</td>
<td>linagliptin</td>
</tr>
<tr>
<td>Glyxambi</td>
<td>linagliptin and empagliflozin</td>
</tr>
<tr>
<td>Jentadueto</td>
<td>linagliptin and metformin</td>
</tr>
<tr>
<td>Nesina</td>
<td>alogliptin</td>
</tr>
<tr>
<td>Kazano</td>
<td>alogliptin and metformin</td>
</tr>
<tr>
<td>Oseni</td>
<td>alogliptin and pioglitazone</td>
</tr>
</tbody>
</table>
Cases of severe, sometimes disabling, arthralgia (joint pain) have been reported with the use of dipeptidyl peptidase-4 (DPP-4) inhibitors. Patients are advised not to discontinue therapy but to contact their health care professional immediately if they experience severe and persistent joint pain while taking any of the DPP-4 inhibitors. These medications should be considered as a possible cause of joint pain and discontinued if appropriate. The FDA has identified 33 cases of severe arthralgia with the use of DPP-4 inhibitors, all of which resulted in substantial reduction of the patient’s prior level of activity and, in 10 cases, required hospitalization. In the reported cases, the onset of symptoms occurred from 1 day to several years after the start of therapy with a DPP-4 inhibitor. Symptoms resolved with discontinuation of therapy, usually in less than a month; however, some patients experienced a recurrence of joint pain when restarting the same drug or switching to another DPP-4 inhibitor. Twenty-one of the 33 patients were treated for arthritis with drug therapies that included corticosteroids, nonsteroidal anti-inflammatory drugs, methotrexate, and immune-modulating drugs.
Rx with DDP-Inhibitor

New onset joint pain

oral NSAID prescribed

PPI added as prophylaxis

Systolic BP increased
dose of antihypertensive med increased or new AH med added

Patient experiences a fall with trauma
Inflammatory mediator

DPP-4-mediated inactivation

Inflammatory arthritis

Amiodarone
**Clinical Significance**

- Amiodarone is the most commonly used antiarrhythmic drug to treat supraventricular and ventricular arrhythmias.
- Because of severe and potentially life-threatening adverse drug reactions, careful use is essential to derive optimal benefits from the drug with the least risk.

*The American Journal of Medicine (2016) 129, 468-475*

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**Practical Management Guide for Clinicians Who Treat Patients with Amiodarone**

Andrew E. Epstein, MD,1 Brian Olshansky, MD,2 Gerald V. Naccarelli, MD,1 John I. Kennedy, Jr., MD,1,3,4
Elizabeth J. Murphy, MD, DPhil,3,5 Nora Goldschlag, MD,1,6
1Cardiovascular Division, Electrophysiology Section, Department of Medicine, University of Pennsylvania, Philadelphia; 2Mercy Hospital-North Issa, Mason City; 3Penn State Heart and Vascular Institute, Penn State University, Hershey, Pa; 4Division of Pulmonary, Allergy & Critical Care Medicine, Department of Medicine, University of Alabama at Birmingham; 5Department of Medicine, Birmingham VA Medical Center, Birmingham, Ala; 6Department of Medicine, University of California, San Francisco; 7Division of Endocrinology, Department of Medicine, San Francisco General Hospital, San Francisco, Calif; 8Division of Cardiology, Department of Medicine, San Francisco General Hospital, San Francisco, Calif.

Amiodarone, an iodinated benzofuran derivative with Class I, II, III, and IV antiarrhythmic properties, is the most commonly used antiarrhythmic drug used to treat supraventricular and ventricular arrhythmias. Appropriate use of this drug, with its severe and potentially life-threatening adverse effects, requires an essential understanding of its risk-benefit properties in order to ensure safety. The objective of this review is to afford clinicians who treat patients receiving amiodarone an appropriate management strategy for its safe use. The authors of this consensus management guide have thoroughly reviewed and evaluated the existing literature on amiodarone and apply this information, along with the collective experience of the authors, in its development. Provided are management guides on the intravenous and oral dosing of amiodarone, appropriate outpatient follow-up of patients taking the drug, its recognized adverse effects, and recommendations on when to consult specialists to help in patient management. All clinicians must be cognizant of the appropriate use, follow-up, and adverse reactions of amiodarone. The responsibility incurred by those treating such patients cannot be overemphasized.

*Published by Elsevier Inc. • The American Journal of Medicine (2016) 129, 468-475*
### Table 1. Adverse Reactions to Amiodarone

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Incidence, %</th>
<th>Diagnosis</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td>2</td>
<td>Cough or dyspnea (or both), especially with focal or diffuse opacities on high-resolution CT scan and decrease in DLCO from baseline</td>
<td>Usually discontinue drug; corticosteroids may be considered; occasionally, continue drug if levels high and abnormalities resolve; rarely, continue drug with corticosteroid if no other option</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>30</td>
<td>Nausea, anorexia and constipation</td>
<td>Symptoms may decrease with decrease in dose</td>
</tr>
<tr>
<td></td>
<td>15-30</td>
<td>AST or ALT level &gt;2× normal</td>
<td>If hepatitis considered, exclude other causes</td>
</tr>
<tr>
<td></td>
<td>&lt;3</td>
<td>Hepatitis and cirrhosis</td>
<td>Consider discontinuation, biopsy, or both to determine whether cirrhosis is present</td>
</tr>
<tr>
<td>Thyroid</td>
<td>4-22</td>
<td>Hypothyroidism</td>
<td>L-thyroxine</td>
</tr>
<tr>
<td></td>
<td>2-12</td>
<td>Hyperthyroidism</td>
<td>Corticosteroids, propylthiouracil or methimazole; may need to discontinue drug; may need thyroidectomy</td>
</tr>
<tr>
<td>Skin</td>
<td>&lt;10</td>
<td>Blue discoloration</td>
<td>Reassurance; decrease in dose</td>
</tr>
<tr>
<td></td>
<td>25-75</td>
<td>Photosensitivity</td>
<td>Avoidance of prolonged sun exposure; sunblock; decrease in dose</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>3-30</td>
<td>Ataxia, paresthesias, peripheral neuropathy, sleep disturbance, impaired memory and tremor</td>
<td>Often dose dependent, and may improve or resolve with dose adjustment</td>
</tr>
<tr>
<td>Ocular</td>
<td>&lt;5</td>
<td>Halo vision, especially at night</td>
<td>Common and does not require drug discontinuation</td>
</tr>
<tr>
<td></td>
<td>≤1</td>
<td>Optic neuropathy</td>
<td>Discontinue drug and consult an ophthalmologist</td>
</tr>
<tr>
<td></td>
<td>&gt;90</td>
<td>Photophobia, visual blurring, and microdeposits</td>
<td>Corneal deposits common, indicate that drug is being taken, and do not require discontinuation.</td>
</tr>
<tr>
<td>Heart</td>
<td>5</td>
<td>Bradycardia and AV block</td>
<td>May need permanent cardiac pacing</td>
</tr>
<tr>
<td></td>
<td>&lt;1</td>
<td>Ventricular pre-excitation</td>
<td>Usually discontinue drug</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>&lt;1</td>
<td>Epididymitis and erectile dysfunction</td>
<td>Pain may resolve spontaneously</td>
</tr>
</tbody>
</table>

*The American Journal of Medicine (2016) 129, 468-475*

### Table 3. Recommended Laboratory Testing in Patients Receiving Amiodarone

<table>
<thead>
<tr>
<th>Type of Test</th>
<th>Time When Test is Performed*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver function tests</td>
<td>Baseline and every 6 mo</td>
</tr>
<tr>
<td>Thyroid function tests</td>
<td>TSH, free T4, and total or free T3 at baseline with a follow-up TSH every 6 mo</td>
</tr>
<tr>
<td>Chest x-ray study</td>
<td>Baseline and then yearly</td>
</tr>
<tr>
<td>Ophthalmologic evaluation</td>
<td>Baseline if visual impairment or for symptoms</td>
</tr>
<tr>
<td>Pulmonary function tests (with DLCO)</td>
<td>Baseline and for unexplained cough or dyspnea, especially in patients with underlying lung disease, if there are suggestive x-ray film abnormalities, and if there is a clinical suspicion of pulmonary toxicity</td>
</tr>
<tr>
<td>High-resolution CT scan</td>
<td>If clinical suspicion of pulmonary toxicity</td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td>Baseline and when clinically relevant</td>
</tr>
</tbody>
</table>

DLCO = diffusion capacity of carbon monoxide; Free T4 = free thyroxine; TSH = thyroid stimulating hormone.

*If clinical circumstances warrant, more frequent follow-up will be necessary.

*The American Journal of Medicine (2016) 129, 468-475*
Effectiveness of Pharmacist-Led Amiodarone Monitoring Services on Improving Adherence to Amiodarone Monitoring Recommendations: A Systematic Review

Dave L. Dixon,1,# Steven P. Dunn,2 Michael S. Kelly,3 Timothy R. McLarkey,4 and Roy E. Brown,5
1Department of Pharmacoapeutics & Outcomes Science, Virginia Commonwealth University School of Pharmacy, Richmond, Virginia; 2Heart & Vascular, Department of Pharmacy Services, University of Virginia Health System, Charlottesville, Virginia; 3PGY-2 Ambulatory Care – Family Medicine Pharmacy Resident, University of Colorado Skaggs School of Pharmacy & Pharmaceutical Sciences, Aurora, Colorado; 4Chippenham Hospital, Richmond, Virginia; 5Virginia Commonwealth University, Richmond, Virginia

Table 1. Monitoring Recommendations for Patients Receiving Amiodarone6

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Incidence (%)</th>
<th>Baseline</th>
<th>Follow-up Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated AST/ALT level</td>
<td>15–30</td>
<td>Liver function tests</td>
<td>Every 6 mo</td>
</tr>
<tr>
<td>Hepatitis and cirrhosis</td>
<td>&lt; 3</td>
<td>Chest x-ray</td>
<td>Every 12 mo</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>1–22</td>
<td>Thyroid function tests (TSH, free T4, and total T3)</td>
<td>Every 6 mo</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>2–12</td>
<td>Pulmonary function tests (with DLCO)</td>
<td>Patients who develop unexplained cough or dyspnea, or have preexisting lung disease, or if there is clinical suspicion of pulmonary toxicity</td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>2</td>
<td>High-resolution CT scan</td>
<td>Clinical suspicion of pulmonary toxicity</td>
</tr>
<tr>
<td>Corneal microdeposits</td>
<td>&gt; 90</td>
<td>Ophthalmologic evaluation (only in patients with significant visual changes)</td>
<td>Perform in any patient reporting visual abnormalities</td>
</tr>
<tr>
<td>Halo vision</td>
<td>&lt; 5</td>
<td>Electrocardiogram</td>
<td>As needed when clinically relevant</td>
</tr>
<tr>
<td>Cystic neuropathy</td>
<td>≤ 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradycardia, AV block</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>&lt; 1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AST = asparatate aminotransferase; ALT = alanine aminotransferase; TSH = thyroid-stimulating hormone; T4 = thyroxine; T3 = triiodothyronine; DLCO = diffusing capacity of the lungs for carbon monoxide; CT = computed tomography; AV = atrioventricular.

(Pharmacotherapy 2016;36(2):230–236)
Amiodarone and the Thyroid

Amiodarone = 75 mg of iodide per tablet

Amiodarone may induce 3 types of thyroid dysfunction

<table>
<thead>
<tr>
<th>Table 3. Features of Amiodarone-Induced Thyroid Dysfunction.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feature</td>
</tr>
<tr>
<td>Mechanism</td>
</tr>
<tr>
<td>Thyroid antibodies</td>
</tr>
<tr>
<td>Thyroid function</td>
</tr>
<tr>
<td>24-Hour $^{131}$I uptake*</td>
</tr>
<tr>
<td>Findings on color Doppler ultrasonography</td>
</tr>
<tr>
<td>Therapy</td>
</tr>
</tbody>
</table>

* $^{123}$I denotes iodine-123.
Substrates

Thyroid Gland

Substrates

Thyroid Hormone

Decreased Circulating thyroid hormone levels

Iodide

Iodide

Iodides + Preexisting Thyroid Disease

Thyroiditis (+ATA)
Prior RAI therapy
Subtotal thyroidectomy

HYPOTHYROIDISM
Iodides + Autonomous Thyroid Function

Hyperfunctioning thyroid adenoma
Multinodular goiter
Graves’ Disease

HYPERTHYROIDISM

HYPOTHYROIDISM

Presentation of excess iodide to a compromised thyroid gland

Reduced effectiveness of thyroxine replacement via inhibition of T-4 → T-3 conversion

AMIODARONE

HYPERTHYROIDISM

Increased thyroxine synthesis via iodide excess to an autonomous gland

Thyroid follicle disruption with release of T-4/T-3 into circulation
P450-Based Drug-Drug Interactions of Amiodarone and its Metabolites: Diversity of Inhibitory Mechanisms

Matthew G. McDonald, Nicholas T. Au, and Allan E. Rettie

Department of Medicinal Chemistry, University of Washington, Seattle, Washington (M.G.M., N.T.A., A.E.R.)

Received May 21, 2015; accepted August 20, 2015

In conclusion, this study implicates AMIO and two of its metabolites, MDEA and DDEA, as major contributors to in vivo drug interactions involving multiple drug-metabolizing P450 enzymes. Results from IC_{50} shift and TDI experiments, measuring the reversible and TDI of several specific P450 metabolic activities in HLM, predict that the minor metabolite, DDEA, is responsible for precipitating drug interactions that arise as a consequence of inhibition of either CYP1A2- or CYP2C9-mediated metabolism, while both AMIO and MDEA appear to be important in DDIs resulting from inhibition of CYP2D6. Although DDEA is the strongest reversible inhibitor of CYP3A4 activity, MDEA shows a moderate ability to inactivate this enzyme. Thus, it is possible that both of these AMIO metabolites contribute to in vivo DDIs resulting from CYP3A4 inhibition. However, the observation that clinical DDIs (measured for the interactions of AMIO with lidocaine, warfarin, metoprolol, and simvastatin) are in good agreement with predictions based solely on the reversible inhibition of CYP1A2, CYP2C9, CYP2D6, and CYP3A4 activities in HLM by parent drug and metabolites would seem to suggest that TDI of these enzymes may not play a critical role in vivo.

Drug Metab Dispos 43:1661-1669, November 2015
Major Drug-Drug Interactions with Amiodarone as the Perpetrator

- Digoxin
- Warfarin
- Simvastatin/lovastatin
- Phenytoin
- Dabigatran
- Colchicine
- Sofosbuvir

Digoxin case
<table>
<thead>
<tr>
<th></th>
<th>2nd admission</th>
<th>ED visit for n/v</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>One Day Columns</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30 Sep 13</td>
<td>29 Sep 13</td>
</tr>
<tr>
<td>Weight (kg) Actual</td>
<td>80.800</td>
<td>73</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>32.57</td>
<td>29.43</td>
</tr>
<tr>
<td>Amiodarone PO TABLET +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin IV/IVP AMPLUML +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin IV/IVP AMPLUML</td>
<td></td>
<td></td>
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<tr>
<td>Digoxin PO TABLET</td>
<td></td>
<td></td>
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<tr>
<td>Digoxin immune fab IVPB VIAL EA +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood Urea Nitrogen</td>
<td>24 H</td>
<td>22 H</td>
</tr>
<tr>
<td>Creatinine</td>
<td>4.7 H</td>
<td>4.7 H</td>
</tr>
<tr>
<td>Digoxin</td>
<td>3.2 C @ &gt;4.0 C @</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>1st admission</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>One Day Columns</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13 Sep 13</td>
<td>12 Sep 13</td>
</tr>
<tr>
<td>Weight (kg) Actual</td>
<td>78.000</td>
<td>79.200</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>31.77</td>
<td>31.93</td>
</tr>
<tr>
<td>Amiodarone PO TABLET +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin IV/IVP AMPLUML</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin IV/IVP AMPLUML +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin PO TABLET</td>
<td>125 MG</td>
<td>125 MG</td>
</tr>
<tr>
<td>Digoxin immune fab IVPB VIAL EA +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood Urea Nitrogen</td>
<td>31 H</td>
<td>30 H</td>
</tr>
<tr>
<td>Creatinine</td>
<td>3.9 H</td>
<td>3.8 H</td>
</tr>
<tr>
<td></td>
<td>1.7</td>
<td></td>
</tr>
</tbody>
</table>

Hepatobiliary

Digoxin

Kidney
Biliary Excretion

GI tract ↔ [serum Digoxin]

Renal Excretion

PGP mediated

Amiodarone is a PGP inhibitor

Amiodarone is a PGP inhibitor

PGP mediated
Lesson

• Amiodarone is potent inhibitor of digoxin elimination. When initiated as co-use therapy, aggressive monitoring and the use of lower maintenance doses of digoxin is required.
• Coexisting renal dysfunction exaggerates the amiodarone-digoxin interaction.

CASE

Exaggerated Response to Warfarin due to Drug Interaction with Amiodarone

Warfarin CYP-2C9 substrate and Amiodarone a CYP-2C9 inhibitor
**Lexi-Comp Online™ Interaction Monograph**

**Title**: Vitamin K Antagonists / Amiodarone

**Risk Rating**: D. Consider therapy modification

**Summary**: Amiodarone may enhance the anticoagulant effect of Vitamin K Antagonists.

**Severity** Major Onset Delayed Reliability Rating Excellent

**Patient Management**: Monitor for increased therapeutic effects of coumarin derivatives if amiodarone is initiated/dose increased, or decreased effects if amiodarone is discontinued/dose decreased. An empirical warfarin dosage reduction of 30% to 50% at the initiation of amiodarone might be considered.

**Vitamin K Antagonists Interacting Members**: Acenocoumarol, Warfarin*

* Denotes agent(s) specifically implicated in clinical data. Unmarked agents are listed because they have properties similar to marked agents, and may respond so within the context of the stated interaction.

**Discussion**: Several reports describe an increase in the hypoprothrombinemic effects of warfarin (and other coumarin derivatives, including acenocoumarol) following the addition of amiodarone. A doubling of the prothrombin time has been reported. The effects typically take at least one week to begin to show, and may increase over the course of the next several weeks. Likewise, the reversal of the effects following discontinuation of the amiodarone may take several weeks. The primary mechanism of these interactions is likely related to the ability of amiodarone to inhibit the CYP isoenzymes responsible for warfarin and acenocoumarol metabolism. The iodine content of amiodarone may, following chronic dosing, cause hyperthyroidism which may in turn cause an increase in the body's sensitivity to warfarin.
Warfarin – Amiodarone Interaction

**Discussion** Several reports describe an increase in the hypoprothrombinemic effects of warfarin (and other coumarin derivatives, including acenocoumarol) following the addition of amiodarone. A doubling of the prothrombin time has been reported. The effects typically take at least one week to begin to show, and may increase over the course of the next several weeks. Likewise, the reversal of the effects following discontinuation of the amiodarone may take several weeks. The primary mechanism of these interactions is likely related to the ability of amiodarone to inhibit the CYP isoenzymes responsible for warfarin and acenocoumarol metabolism. The iodine content of amiodarone may, following chronic dosing, cause hyperthyroidism which may in turn cause an increase in the body’s sensitivity to warfarin.

---

**Lesson**

- Amiodarone is potent inhibitor of warfarin metabolism and when initiated as co-use therapy requires aggressive monitoring and the use of lower loading and maintenance doses of warfarin.
- Alternative oral anticoagulants should be considered.
Falls and Medications

<table>
<thead>
<tr>
<th>Class</th>
<th>Specific Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>Chlordiazepoxide, diazepam, alprazolam</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Amitriptyline, nortriptyline, fluoxetine</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Fluphenazine, chlorpromazine, haloperidol, risperidone</td>
</tr>
<tr>
<td>Antiepileptics</td>
<td>Phenytoin, phenobarbital</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>Diphenhydramine, hyoscyamine, tolterodine, oxybutynin</td>
</tr>
<tr>
<td>Sedative hypnotics</td>
<td>All barbiturates, zolpidem, zaleplon</td>
</tr>
<tr>
<td>Muscle relaxants</td>
<td>Cyclobenzaprine, metaxalone, methocarbamol</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Diuretics, doxazosin, terazosin, clonidine, digoxin</td>
</tr>
</tbody>
</table>

American Journal of Medicine (2007) 120, 493-497
76 y.o. man admitted for:

Near syncope

<table>
<thead>
<tr>
<th>Medication</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>losartan (Coza) 50 mg</td>
<td>twice daily by mouth</td>
</tr>
<tr>
<td>simvastatin (Zocor) 80 mg</td>
<td>once daily by mouth</td>
</tr>
<tr>
<td>furosemide (Lasix) 40 mg</td>
<td>twice daily by mouth</td>
</tr>
<tr>
<td>metoprolol (Lopressor) 95 mg</td>
<td>once daily by mouth</td>
</tr>
<tr>
<td>lisinopril (Prinzide) 20 mg</td>
<td>once daily by mouth</td>
</tr>
<tr>
<td>enalapril (Vasotec) 2.5 mg</td>
<td>once daily by mouth</td>
</tr>
<tr>
<td>trazadone (Zolpidem) 150 mg</td>
<td>once daily by mouth</td>
</tr>
<tr>
<td>valium (Valium) 5 mg</td>
<td>as needed by mouth</td>
</tr>
</tbody>
</table>

MRN: 03389657
Fall noted 10/11

Tizanidine (first dose) given at 22:20 with terazosin, tramadol and metoprolol

Pulse low 90 minutes post med admin falling episode on 10/11 at 5:10 am
Profound Symptomatic Bradycardia Requiring Transvenous Pacing After a Single Dose of Tizanidine

Jennifer Cortes, PharmD, BCPP
Brad Hall, PharmD
Davellie Redden, MD
Lakeland Regional Medical Center, Lakeland, Florida

Hypotension and bradycardia associated with concomitant tizanidine and lisinopril therapy

Susan W. Publow and Donald L. Branam

Conclusion

The addition of tizanidine in a patient receiving long-term treatment with lisinopril was associated with severe hypotension and bradycardia.

Am J Health-Syst Pharm—Vol 67 Oct 1, 2010
Comments

- Pt with history of hypertension on background tx with beta blocker and alpha blocker was given 4 mg of the muscle relaxant tizanidine, a clonidine derivative known to cause bradycardia and hypotension. Reaction was temporally related to tizanidine administration.

- Not sure why this muscle relaxant with CV ADEs was chosen for a pt with background antihypertensive medications and admitting dx of “near syncope”. Terazosin should be replaced by tamsulosin (Flomax®).
Another fall case

85 y.o. woman admitted to the CV service from the ED for syncope with falls. Discovered to be in AV block with bradycardia and hypotension.
### Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Start Date</th>
<th>End Date</th>
<th>Taking?</th>
<th>Authorizing Provider</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodipine (Norvasc) 10 mg</td>
<td>8/2/16</td>
<td></td>
<td>Yes</td>
<td>John Wenceslao, MD</td>
</tr>
<tr>
<td>Atenolol (Tenormin) 50 mg</td>
<td>8/3/16</td>
<td></td>
<td>Yes</td>
<td>John Wenceslao, MD</td>
</tr>
<tr>
<td>Atorvastatin (Lipitor) 40 mg</td>
<td>8/3/16</td>
<td></td>
<td>Yes</td>
<td>John Wenceslao, MD</td>
</tr>
<tr>
<td>Betimol 0.5% ophthalmic solution</td>
<td>4/13/16</td>
<td></td>
<td>Yes</td>
<td>Historical Provider, MD</td>
</tr>
<tr>
<td>Calcium-vitamin D (Oscar 900/200 D-3) 600-200 mg tablet</td>
<td>10/18/07</td>
<td></td>
<td>Yes</td>
<td>Historical Provider, MD</td>
</tr>
<tr>
<td>Combigan 0.2-0.5% ophthalmic solution</td>
<td>9/26/15</td>
<td></td>
<td>Yes</td>
<td>Historical Provider, MD</td>
</tr>
<tr>
<td>Folic acid (Folvite) 1 mg</td>
<td>3/3/16</td>
<td></td>
<td>Yes</td>
<td>Historical Provider, MD</td>
</tr>
<tr>
<td>Gabapentin (Neurontin) 300 mg capsule</td>
<td>3/3/16</td>
<td></td>
<td>Yes</td>
<td>John Wenceslao, MD</td>
</tr>
<tr>
<td>Glimepiride (Amaryl) 4 mg</td>
<td>3/3/16</td>
<td></td>
<td>Yes</td>
<td>John Wenceslao, MD</td>
</tr>
<tr>
<td>Insulin aspart (Novolog Flexpen) 100 units/mL</td>
<td>1/8/16</td>
<td></td>
<td>Yes</td>
<td>Joan F Schwartz, APRN</td>
</tr>
<tr>
<td>Levemir FlexTouch 100 unit/mL injection</td>
<td>2/19/16</td>
<td></td>
<td>Yes</td>
<td>John Wenceslao, MD</td>
</tr>
<tr>
<td>Lisinopril (Prinivil/Zestril) 20 mg</td>
<td>8/3/16</td>
<td></td>
<td>Yes</td>
<td>John Wenceslao, MD</td>
</tr>
<tr>
<td>Pantoprazole (Protonix) 40 mg tablet</td>
<td>6/8/16</td>
<td></td>
<td>Yes</td>
<td>John Wenceslao, MD</td>
</tr>
<tr>
<td>Rabagol (UL Tram) 50 mg tablet</td>
<td>9/10/16</td>
<td></td>
<td>Yes</td>
<td>John Wenceslao, MD</td>
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<tr>
<td>Zetia 10 mg tablet</td>
<td>8/3/16</td>
<td></td>
<td>Yes</td>
<td>John Wenceslao, MD</td>
</tr>
<tr>
<td>Duloxetine (Cymbalta) 60 mg</td>
<td>9/5/16</td>
<td></td>
<td>Yes</td>
<td>John Wenceslao, MD</td>
</tr>
</tbody>
</table>

**Combigan** = Brimonidine and Timolol

**Betimol** = Timolol
Comment

• Very elderly woman with long history of syncope and falls at home.
• Patient orthostatic with symptoms in the ED.
• Home medications indicate excessive beta blockers, two as eye medications (timolol) and one oral (atenolol). Excessive beta blockage can produce AV block.

Beta Blockers Eye drops and Systemic Effects
Acute non-selective beta-blocker eye drop exposure significantly affects lung function and increases asthma morbidity. These agents are still frequently prescribed to people with asthma and ocular hypertension despite safer drugs (betaxolol) being available.

BJCP 2016;82:814-822

Beta Adrenergic Blockers - Topical Agents

- Nonselective: timolol, carteolol (ISA active), levobunolol, metipranolol; Selective: betaxolol,
- Provides reductions of 20 - 30% in IOP and is additive with other agents. Less effective if patient is already receiving oral BB.
- Systemic absorption well documented with numerous possible complications in susceptible patients. Gel and suspension formulations may reduce rate and extent of systemic absorption.
RESPIRATORY EFFECTS OF TIMOLOL

To the Editor: The 34th most commonly prescribed medication in the United States in 1983 was an eye drop used in the management of glaucoma, timolol (Timoptic, Merck Sharp and Dohme). Beta-blocking agents given for the topical ophthalmic effects are contraindicated in patients with bronchial asthma, bronchospasm, or severe chronic obstructive pulmonary disease. The National Registry of Drug-Induced Ocular Side Effects, at the Department of Ophthalmology, Oregon Health Sciences University, has now received over 200 reports of possible major timolol-induced respiratory effects.

Although the manufacturer's package insert has included asthma as a contraindication to timolol administration since 1983, physicians and patients have not generally appreciated the fact that this agent may have serious respiratory effects. Topical ocular timolol is absorbed through ocular and nasal mucosa, and therapeutic blood levels that affect the lung may be achieved before the drug reaches the liver to be detoxified.

NEJM November 29, 1984

In fact, acute bronchial asthmatic attacks have accounted for progressively increasing proportions of the systemic adverse effects secondary to topical ocular timolol that have been reported to the registry over the past five years (23 per cent of systemic effects for 1983-1984). Sixteen fatal cases of status asthmaticus following ocular application of timolol in patients with a prior history of bronchial asthma or other chronic pulmonary diseases have been reported to the registry. Aggravation or precipitation of pulmonary disorders, presumably related to effects of systemic beta-blockade, have been noted in patients with asthma as well as in patients with chronic obstructive lung disease.1-3 Patients with reactive airway disease have been shown to have a decrease in airflow, measured by forced expiratory volume, when topical ocular timolol has been administered.4 We emphasize the need to take a careful cardiopulmonary history before prescribing timolol and to question patients experiencing shortness of breath, coughing, or wheezing about the use of topical ophthalmic beta-adrenergic blocking agents.

NEJM November 29, 1984
### Summary of 32 Deaths Associated with Ophthalmic Timolol Use

<table>
<thead>
<tr>
<th>Cause</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>13*</td>
</tr>
<tr>
<td>Respiratory</td>
<td>12*</td>
</tr>
<tr>
<td>Unknown</td>
<td>7</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>68</td>
</tr>
</tbody>
</table>

**Duration of Timolol Use**
- 44% within Prior to Death
- 85% with preexisting CV / Respiratory disease

---

**Am J Ophthalmol 1986;102:606**

---

**Diagram:**
- **Eye drop applied** → **Mixing with lacrimal fluids** → **Corneal penetration**
  - **Nasal lacimal duct drainage** → **Nasal passages** → **Absorption via GI Tract** → **Liver**
  - **Conjunctival sac residence** → **Systemic circulation**
Value of Nasal Lacrimal Occlusion

- Reduces systemic effects of ocular medications. Punctal (NLO) occlusion and eyelid closure may decrease systemic absorption by up to 65%.
- Improves response
- May allow for longer dosing frequencies
- May allow for use of lower concentration of medication.

Effect of eyelid closure and nasolacrimal occlusion on systemic absorption of ophthalmic timolol
Bradycardia Induced by Interaction Between Quinidine and Ophthalmic Timolol

Abstract

Topical administration of timolol, a beta-blocking agent, is currently the treatment of choice in open-angle glaucoma (1). This route of administration delivers the drug directly to the systemic circulation, whereas oral doses are subject to presystemic hepatic metabolism (2). Systemic complications, such as severe bradycardia, have been associated with ophthalmic timolol (3). No adverse interaction has been reported, to our knowledge, with the coadministration of ocular timolol and oral quinidine. We report a case of sinus bradycardia related to an interaction between ophthalmic timolol and oral quinidine, substantiated by the negative rechallenge with timolol alone and by positive rechallenge with
Potent Inhibitors of CYP-2D6

- Abiraterone (Zytiga®)
- Amiodarone (Cordarone®)
- Bupropion (Wellbutrin®)
- Celecoxib (Celebrex®)
- Chloroquine (Aralen®)
- Chlorpheniramine
- Chlorpromazine (Thorazine®)
- Cinacalcet (Sensipar®)
- Cobicistat (Stribild®)
- Darifenacin (Enablex®)
- Diphenhydramine (Benadryl®)

Potent Inhibitors of CYP-2D6

- Dronedarone (Multaq®)
- Flecainide (Tambocor®)
- Fluoxetine (Prozac®)
- Hydroxychloroquine
- Paroxetine (Paxil®)
- Perphenazine (Trilafon®)
- Promethazine (Phenergan®)
- Propafenone (Rythmol®)
Potent Inhibitors of CYP-2D6

- Propoxyphene (Darvon®)
- Quinacrine
- Quinidine
- Quinine
- Ritonavir (Norvir®)
- Terbinafine (Lamisil®)
- Thioridazine (Mellaril®)

Even moderate CYP-2D6 inhibitors can potentiate the systemic effects of timolol eye drops

Examples in include
- Cimetidine
- Duloxetine
Drug Interaction between Cimetidine and Timolol Ophthalmic Solution: Effect on Heart Rate and Intraocular Pressure in Healthy Japanese Volunteers

Yoko Ishii, MD, PhD, Koichi Nakamura, MD, PhD, Kimiko Tsutsumi, PhD, Tsutomu Kotegawa, MD, PhD, Shigeyuki Nakano, MD, PhD, FCP, and Kazuo Nakatsuka, MD, PhD

In conclusion, administration of cimetidine with topical ocular timolol increased the degree of beta-blockade, resulting in a reduction of resting heart rate, intraocular pressure, and exercise tolerance. Attention should be paid in special patient populations because the interaction could be substantial.


![Graph showing IOP at rest (%change) over time (hr) for T + P and T + C conditions.](image)
Nonalcoholic Fatty Liver and Steatohepatitis
67 yo obese man with an exaggerated response to 5 mg of oxycodone, requiring 0.4 mg naloxone rescue
Evidence of ongoing liver injury

<table>
<thead>
<tr>
<th>Component</th>
<th>Lowest Ref Range</th>
<th>5/6/2018</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea</td>
<td>15 - 45 mg/dL</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>BUN</td>
<td>7 - 20 mg/dL</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.7 - 1.3 mg/dL</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>eGFR  Non-African American</td>
<td>90 - 120 mL/min/1.73 m²</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>eGFR African American</td>
<td>90 - 120 mL/min/1.73 m²</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>Bar / Creatinine Ratio</td>
<td>8 - 22 (obs)</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>135 - 146 mEq/L</td>
<td>137</td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td>3.5 - 5.0 mEq/L</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>Chloride</td>
<td>84 - 112 mEq/L</td>
<td>105</td>
<td></td>
</tr>
<tr>
<td>CO₂</td>
<td>13 - 26 mmHg</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td>8.5 - 10.5 mg/dL</td>
<td>9.5</td>
<td></td>
</tr>
<tr>
<td>Protein, Total</td>
<td>6.1 - 8.1 g/dL</td>
<td>6.3</td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>3.5 - 5.5 g/dL</td>
<td>4.0</td>
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</tr>
<tr>
<td>Glucose</td>
<td>90 - 110 mg/dL</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>Albumin/Albumin Ratio</td>
<td>1.0 - 2.5 (obs)</td>
<td>1.7</td>
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</tr>
<tr>
<td>Bilirubin, Total</td>
<td>0.2 - 1.2 mg/dL</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>40 - 115 U/L</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Aspartate Aminotransferase (AST)</td>
<td>10 - 26 U/L</td>
<td>25 (D)</td>
<td></td>
</tr>
<tr>
<td>Alkaline Phosphatase (ALP)</td>
<td>12 - 45 U/L</td>
<td>46 (D)</td>
<td></td>
</tr>
<tr>
<td>White Blood Cell Count</td>
<td>5.6 - 10.2 Thousands/µL</td>
<td>4.8</td>
<td></td>
</tr>
<tr>
<td>Red Blood Cell Count</td>
<td>4.35 - 5.80 Million/µL</td>
<td>4.89</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>13.5 - 17.5 g/dL</td>
<td>14.5</td>
<td></td>
</tr>
<tr>
<td>Hematocrit</td>
<td>38.5 - 50.0</td>
<td>44.9</td>
<td></td>
</tr>
<tr>
<td>MCV</td>
<td>80.0 - 100.0 fL</td>
<td>99.0</td>
<td></td>
</tr>
<tr>
<td>MCH</td>
<td>27.0 - 35.0 pg</td>
<td>33.0</td>
<td></td>
</tr>
<tr>
<td>MCHC</td>
<td>32.0 - 34.0 g/dL</td>
<td>32.5</td>
<td></td>
</tr>
<tr>
<td>HGB</td>
<td>11.0 - 15.0 g/dL</td>
<td>12.3</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin F</td>
<td>8.0 - 15.5</td>
<td>10.7</td>
<td></td>
</tr>
<tr>
<td>LD methods</td>
<td>2 - 3</td>
<td>1.5 (D)</td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td>23.0 - 38.0</td>
<td>26.0</td>
<td></td>
</tr>
<tr>
<td>Creatine, AM</td>
<td>11.0 - 15.0 SEC</td>
<td>12.0</td>
<td></td>
</tr>
</tbody>
</table>
Liver Disease and ALT/AST ratio

**ALT/AST ratio ≥ 1.0**
- Drug-induced liver injury
- Occupational toxin-induced liver injury
- Nonalcoholic fatty liver disease – steatohepatitis
- Congestive hepatopathy
- Genetic diseases – Wilson’s disease, hemochromatosis, alpha-1 antitrypsin def
- Tumor infiltration of liver

**ALT/AST ratio ≤ 1.0**
- Alcoholic hepatitis
- Cirrhosis due to viral hepatitis

Nonalcoholic Fatty Liver and Steatohepatitis

My diagnosis – never considered by patient’s provider
Nonalcoholic fatty liver disease (NAFLD) is defined by excessive hepatic fat content (HFC; >5% of liver weight, mainly in the form of triglycerides) in the absence of excessive alcohol consumption and other competing etiologies for hepatic steatosis.

Liver International 2016

The most common cause of NAFLD in developed countries is an increased caloric intake exceeding the rates of caloric expenditure, with consequent spillover of extra-energy in the form of lipid precursors (i.e. nonesterified fatty acids, NEFA) from adipose tissue into ectopic depots: liver, visceral fat (VF), skeletal muscle and pancreas.

Liver International 2016
Nonalcoholic steatohepatitis (NASH), an extreme form of nonalcholic fatty liver disease (NAFLD), is defined as the presence of hepatic steatosis with inflammation and hepatocyte injury. NASH can eventually lead to advanced fibrosis, liver cirrhosis and liver failure. During the past 20 years the incidence of NAFLD has more than doubled, and it is now the most common liver disorder in Western countries. The major risk factors are obesity, type 2 diabetes mellitus (T2DM), dyslipidaemia and metabolic syndrome. In the United States, the prevalence of NAFLD is estimated as between 10% and 46% of the population; approximately 10–30% of NAFLD patients progress to NASH. In the United States, NASH-associated cirrhosis is currently the third most frequent reason for liver transplantation and is predicted to become the leading cause by 2020.”

Nature Drug Review 2016
Altered Morphine Glucuronide and Bile Acid Disposition in Patients With Nonalcoholic Steatohepatitis

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The functional impact of altered drug transport protein expression on the systemic pharmacokinetics of morphine, heptatically derived morphine glucuronide (morphine-3- and morphine-6-glucuronide), and fasting bile acids was evaluated in patients with biopsy-confirmed nonalcoholic steatohepatitis (NASH) compared to healthy subjects. The maximum concentration (Cmax) and area under the concentration-time curve (AUC0-τ) of morphine glucuronide in serum were increased in NASH patients (343 vs. 225 nM and 58.8 vs. 37.2 μM*min, respectively; P < 0.005); morphine pharmacokinetics did not differ between groups. Linear regression analyses detected an association of NASH severity with increased morphine glucuronide Cmax and AUC0-τ (P < 0.001). Feeding serum glycocholate, taurocholate, and total bile acid concentrations were associated with NASH severity (P < 0.006). Increased hepatic basolateral efflux of morphine glucuronide and bile acids is consistent with altered hepatic transport protein expression in patients with NASH and may partially explain differences in efficacy and/or toxicity of some highly transported anionic drugs/metabolites in this patient population.
The effects of inflammation and associated cytokines on hepatic drug metabolism gene expression are a probable mechanism for reduced CYP3A4 activity in NAFLD (Abdel-Razzak et al., 1993; Muntané-Relat et al., 1995; Pascussi et al., 2000; Jover et al., 2002). Indeed, inflammatory infiltration occurs in SS and NASH together with increased hepatic expression of inflammatory cytokines (Gadd et al., 2014). Inflammatory cytokines, acting through nuclear factor κ-light-chain-enhancer of activated B cells, causes transrepression of the pregnane X receptor, a central transcription factor regulating CYP3A4 expression (Gu et al., 2006; Zhou et al., 2006). Moreover, the pregnane X receptor is downregulated by inflammatory cytokines (Pascussi et al., 2000) and its expression is reduced in human NASH (Bitter et al., 2014). Other mechanisms may be involved in the downregulation of CYP3A4 in NAFLD.
4β-hydroxycholesterol
Endogenous Biomarker of CYP-3A4

CYP-3A4

Cholesterol → 4β-hydroxycholesterol

[Box plot diagram showing comparison of Midazolam levels across different groups]
Multiple Choice Questions:

1. What is the threshold of the absolute eosinophil count that would require closer monitoring and possibly an antibiotic change during chronic antibiotic treatment?
   a. >200
   b. >400
   c. >1000
   d. >1500
   e. >5000

2. In an obese diabetic patient without a history of liver disease, what serum chemistry test if elevated would provide evidence that a patient may be experiencing nonalcoholic steatohepatitis?
   a. Triglycerides
   b. LDL cholesterol
   c. Albumin
   d. Hemoglobin A1C
   e. ALT
3. Which class of CYP-p450 inhibitors can augment the systemic effects of timolol eyedrops?

a. CYP-2D6 inhibitors  
b. CYP-3A4 inhibitors  
c. CYP-2C9 inhibitors  
d. CYP-2C19 inhibitors  
e. CYP-1A2 inhibitors

4. What serum laboratory values are consistent with subclinical hypothyroidism?

a. Normal serum TSH and depressed serum thyroid hormone concentrations.  
b. Depressed serum TSH and elevated serum thyroid hormone concentrations.  
c. Elevated serum TSH and normal serum thyroid hormone concentrations.  
d. Normal serum TSH and elevated serum thyroid hormone concentrations.  
e. Depressed serum TSH and depressed serum thyroid hormone concentrations.

5. Which medications require dose reduction and therapeutic monitoring when co-administered with amiodarone?

a. Gabapentin and amantadine  
b. Digoxin and warfarin  
c. Colchicine and simvastatin  
d. Cetirizine and lisinopril  
e. b and e

Answer Key

1. d  
2. e  
3. a  
4. c  
5. e
END