TIMING IS EVERYTHING! CHRONOTHERAPEUTICS AND CHRONIC DISEASE STATE MANAGEMENT: FOCUS ON RHEUMATOID ARTHRITIS

ACTIVITY DESCRIPTION
Chronobiology is the science concerned with the biological mechanism of the diseases according to a time structure. Chronopharmacology is the science that considers the variations in the pharmacological actions of various drugs over a period of time. Putting this all together, chronotherapeutics is the science of considering the timing of drug delivery according to inherent activities of a disease over a certain period of time. This presentation will provide practical examples of common biological rhythms, and will focus on the management of three common disease states and how the timing of medication administration can optimize therapeutic outcomes.

TARGET AUDIENCE
The target audience for this activity is pharmacists in hospital, community, and retail pharmacy settings.

LEARNING OBJECTIVES
After completing this activity, the pharmacist will be able to:

- Define the terms of biological rhythms, chronobiology, chronopharmacology, and chronotherapeutics
- Describe the biological rhythms of common conditions including hypertension, myocardial infarction, cerebrovascular accidents, bronchial asthma, peptic ulcer disease, arthritis and hypercholesterolemia
- Given an actual or simulated patient with rheumatoid arthritis describe implications for medication administration based on the chronobiology of the disease

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Universal Activity No. 0798-0000-13-234-L01-P
Credits: 1 contact hour (0.1 CEU)

Release Date: November 14, 2013
Expiration Date: November 14, 2016

ACTIVITY TYPE
Knowledge-Based Live Webinar
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Dr. McPherson serves on the Board of Directors of the Hospice Network of Maryland and is Chairman of the Board of the American Society of Pain Educators. She is a fellow in the American Society of Health-Systems Pharmacists and the American Pharmacists Association. Dr. McPherson has received the American Pharmacists Association Distinguished Achievement Award in Specialized Practice, the Maryland Pharmacists Association Innovative Practice Award, and the Maryland Society of Health-Systems Pharmacists W. Purdum Lifetime Achievement Award, among others. She has written four books, and many book chapters and peer-reviewed articles on pain management, palliative care, and other topics.

Mary Lynn McPherson, PharmD, BCPS, CDE
Professor, University of Maryland School of Pharmacy

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Learning Objectives

- At the conclusion of this educational session, the participant will be able to:
  - Define the terms biological rhythm, chronobiology, chronopharmacology, and chronotherapeutics.
  - Describe the biological rhythms of common conditions including hypertension, myocardial infarction, cerebrovascular accidents, bronchial asthma, peptic ulcer disease, arthritis, and hypercholesterolemia.
  - Given an actual or simulated patient with rheumatoid arthritis describe implications for medication administration based on the chronobiology of the disease.
Definitions

- Biologic rhythm / biorhythm
  - The rhythms of life
  - An innate, cyclical, biological process or functions
  - Ultradian rhythms – range in period from milliseconds to a few hours
  - Circadian rhythms – have a period of about 24 hours
  - Infradian rhythms – range in period from several days, months (e.g., menstrual cycle) to years
- Chronobiology
  - Study of biological rhythms in disease processes and morbid and mortal events

Circadian Rhythms

- Self-sustaining, endogenous oscillations that occur every 24 hours approximately
  - Synchronized to internal biologic clocks related to sleep-wake cycle
  - Night-shift workers have a shifted circadian cycle to match their sleep-wake cycle
- Hormones secreted in the morning
  - Cortisol, catecholamines, plasma renin, aldosterone, angiotensin
- Hormones secreted in the evening/during sleep
  - Gastric acid, growth hormone, prolactin, melatonin, follicle-stimulating hormone, luteinizing hormone, ACTH peak in evening or during sleep

Hormones and their Circadian Rhythm

<table>
<thead>
<tr>
<th>Circadian Rhythmicity</th>
<th>Hormone/biological functions affected</th>
</tr>
</thead>
</table>
| Late at night or early during sleep | Gastric acid secretion  
|                            | White blood cell count  
|                            | Calcitonin gene-related protein  
|                            | Atrial natriuretic peptide |
| Peaks during sleep        | Growth hormone  
|                            | Thyroid stimulating hormone  
|                            | Melatonin, Prolactin  
|                            | Follicle stimulating hormone  
|                            | Adrenocorticotropic hormone |
| Peaks during the morning  | Cortisol, Renin, Angiotensin  
|                            | Vascular resistance  
|                            | Platelet aggregation  
|                            | Blood viscosity |
| Peaks at noon             | Hemoglobin, Insulin release  
| Peaks during the evening  | Triglycerides, Cholesterol  
|                            | Urinary diuretics |

Conditions That Show Circadian Pattern

- Hypertension
- Myocardial Infarction
- Cerebrovascular Accident
- Bronchial Asthma
- Peptic Ulcer Disease
- Hypercholesterolemia
- Glaucoma
- Cancer
- Arthritis
Cardiovascular/Cerebrovascular

- HR and BP increase in early morning hours
  - BP peak between 6 am and noon
  - BP declines from mid-afternoon and is at minimum at midnight
- Patients with hypertension experience “AM surge” in BP
- Between 6 am – 12 noon
  - Risk of MI 40% higher
  - Risk of cardiac death 29% higher
  - Risk of stroke 49% higher
  - Risk of aortic dissection also more common in the AM
- CVA more likely to occur between 10 am – 12N

MORE Definitions!

- Chronopharmacology
  - Biological rhythm influences on the effects of medications
- Chronotherapeutics
  - Purposeful alteration of drug levels to match biological rhythms in order to optimize therapeutic outcomes and minimize side effects
- Chronopharmaceuticals
  - Drug dosage formulations designed to match the needs of disease-related biorhythms

Chronopharmaceuticals

- Hypertensive management to reduce morning blood pressure surge
  - Cardizem LA (diltiazem)
  - Covera HS (verapamil)
  - InnoPran XL (propranolol)
  - Verelan PM (verapamil)
Asthma and Allergic Rhinitis
- Bronchial asthma
  - Lung function is worst around 4 am and best around 4 pm
  - Symptoms are 100 times more likely to occur in the few hours prior to awakening than during the day
  - Inhaled steroids late in the afternoon (5:30 pm) equivalent to QID inhaled steroids
  - Oral prednisone administered at 3 pm rather than 8 am
- Allergic rhinitis symptoms of sneezing, runny nose and stuffy nose – typically worse in early waking hours than later in day
  - Allergy medications before going to bed

GERD and Peptic Ulcer Disease
- Gastric secretion increases during the night
- Gastric and intestinal motility decreases
  - Gastric emptying rates for meals consumed at 8 pm are 50% slower than a meal consumed at 8 am
- GERD
  - 2.5 x longer exposure to acid exposure sufficient to cause esophageal injury after dinner vs. breakfast
  - 3 x more episodes of reflux after dinner vs. breakfast
- Peptic Ulcer Disease
  - 88% duodenal ulcer sufferers have night time pain
  - Treat H. pylori, acid suppression best administered before dinner (vs. bedtime or throughout day)

Hypercholesterolemia
- There is a circadian rhythm to cholesterol biosynthesis
  - Higher rates of cholesterol intake and hepatic cholesterogenesis occur during the evening hours, even in the fasted state
- For most 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors it is recommended they be administered between the evening meal and bedtime
  - Atorvastatin may be an exception to its long elimination half-life

Glaucoma and Cancer
- Open angle glaucoma is the second leading cause of blindness (caused by increased IOP).
  - Secretion of aqueous humor follows a circadian rhythm with a great quantity secreted during the day as compared to the night
- Cancer chemotherapy can be administered synchronously with circadian rhythm to reduce the cytotoxicity of some chemotherapeutic agents.
The Skeletal System

- Both osteoarthritis and rheumatoid arthritis follow a circadian rhythm
- Osteoarthritis
  - Have less pain in the morning when compared to the rest of the day
  - NSAIDs taken twice daily in a larger dose are more effective than four smaller doses, provided one is taken at night
- Rheumatoid Arthritis
  - More likely to have pain symptoms in the morning

Rheumatoid Arthritis (RA)

- A systemic, chronic, progressive inflammatory autoimmune disease in which the immune system destroys synovial joints and accessory structures, resulting in symmetric polyarthritis.

Epidemiology

- Affects ~1% of adult population
- Usually diagnosed between the 3rd and 5th decade
- Female to male ratio 3:1
  - Age 15-45 female to male ratio 6:1
- Can occur at any age
- Genetic factors (Certain HLA alleles)
- Environmental factors
  - Smoking
  - Infectious agents

Clinical Presentation of RA

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint pain/stiffness ≥ 6 weeks</td>
<td>Tenderness and warmth over affected joints</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Symmetric joint involvement</td>
</tr>
<tr>
<td>Weakness</td>
<td>Rheumatoid nodules</td>
</tr>
<tr>
<td>Low grade fever</td>
<td></td>
</tr>
<tr>
<td>Loss of appetite</td>
<td></td>
</tr>
</tbody>
</table>
**Rheumatoid vs. Osteoarthritis**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rheumatoid Arthritis</th>
<th>Osteoarthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Description</strong></td>
<td>Chronic inflammatory arthritis; synovium primarily affected</td>
<td>OA: wear and tear arthritis; caused by breakdown of cartilage</td>
</tr>
<tr>
<td><strong>Age of onset</strong></td>
<td>At any time in life</td>
<td>Usually later in life</td>
</tr>
<tr>
<td><strong>Speed of onset</strong></td>
<td>Relatively rapid, weeks-months</td>
<td>Slow, over years</td>
</tr>
<tr>
<td><strong>Cause</strong></td>
<td>Unknown trigger of abnormal autoimmune response</td>
<td>Cartilage breakdown; increased risk with joint injury, repetitive use, obesity, family history</td>
</tr>
<tr>
<td><strong>Joint symptoms</strong></td>
<td>Joints are painful, swollen and stiff</td>
<td>Joints ache and may be tender but have little or no swelling</td>
</tr>
<tr>
<td><strong>Pattern of joints affected</strong></td>
<td>Small and large joints on both sides of the body (symmetrical), such as both hands, wrists or elbows, on the b</td>
<td>Symptoms often begin on one side of the body, may spread to other side. Symptoms begin gradually and usually in one set of joints (eg., finger joints), large weight-bearing joints (hips, knees) or the spine</td>
</tr>
<tr>
<td><strong>Duration of AM stiffness</strong></td>
<td>More than an hour</td>
<td>Less than an hour; returns at the end of the day or after periods of activity</td>
</tr>
<tr>
<td><strong>Presence of systemic symptoms</strong></td>
<td>Frequent fatigue and general feeling of being ill</td>
<td>Whole body symptoms not present</td>
</tr>
</tbody>
</table>

**Classification Criteria for Rheumatoid Arthritis**

<table>
<thead>
<tr>
<th>Classification Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint involvement</td>
<td></td>
</tr>
<tr>
<td>1 large joint (shoulder, elbow, hip, knee, ankle)</td>
<td>0</td>
</tr>
<tr>
<td>2-10 large joints</td>
<td>1</td>
</tr>
<tr>
<td>1-3 small joints (MCP, PIP, thumb IP, MTP, wrists)</td>
<td>2</td>
</tr>
<tr>
<td>4-10 small joints</td>
<td>3</td>
</tr>
<tr>
<td>&gt;10 joints (at least 1 small joint)</td>
<td>5</td>
</tr>
<tr>
<td>Serology</td>
<td></td>
</tr>
<tr>
<td>Negative RF and negative anti-CCP antibodies</td>
<td>0</td>
</tr>
<tr>
<td>Low positive RF/anti-CCP antibodies (≤3 times ULN)</td>
<td>2</td>
</tr>
<tr>
<td>High positive RF/anti-CCP antibodies (≥3 times ULN)</td>
<td>3</td>
</tr>
<tr>
<td>Acute phase reactants</td>
<td></td>
</tr>
<tr>
<td>Normal CRP and normal ESR</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal CRP or abnormal ESR</td>
<td>1</td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td></td>
</tr>
<tr>
<td>&lt;6 weeks</td>
<td>0</td>
</tr>
<tr>
<td>≥6 weeks</td>
<td>1</td>
</tr>
</tbody>
</table>

**Prognosis**

- 10% patients undergo spontaneous remission within 6 months of disease onset
- Over 50% patients unable to work 10 years after disease onset
- Mortality rate in RA 2x greater than general population
- Poor prognostic factors
  - Functional limitation
  - Extraarticular disease
  - Positive RF or anti-CCP antibodies
  - Bony erosions on radiograph

**Therapeutic Objectives**

- Slow progression of disease activity
- Disease remission
- Control joint pain
- Prevent joint damage
- Preserve or improve functional status
Non Pharmacologic Therapy

- Energy conservation
- Heat/cold therapy
- Exercise
- Occupational therapy
- Orthotics
- Adaptive equipment
- Surgical intervention

Pharmacologic Therapy

- Acute symptomatic treatment
  - NSAIDs
  - Corticosteroids
- Disease modifying antirheumatic drugs (DMARDs)
  - Non-biologic
  - Biologic

NSAIDs

- Equally efficacious
- Individualized patient response
- Agent related variables
  - Cost
  - Duration of action
- Adverse effects
  - Gastrointestinal
  - Cardiovascular risk
  - Bleeding risk
  - Fluid retention, hypertension, heart failure
  - Headache, nervousness, confusion

NSAID Gastropathy

- Addition of a gastroprotective agent
  - Misoprostol
  - H2 Receptor Antagonist
    - Standard dose vs. double dose
  - Proton Pump Inhibitor
- Adherence to combination therapy / pill burden
  - Diclofenac plus misoprostol (Arthrotec)
  - Naproxen plus esomeprazole (Vimovo)
  - Ibuprofen plus famotidine (Duexis)
Corticosteroids

Place in therapy
• Achieve rapid control of disease
• Management of acute flares
• Chronic low dose therapy for poorly responsive disease

<table>
<thead>
<tr>
<th>Corticosteroid</th>
<th>Equivalent potency (mg)</th>
<th>Mineralocorticoid activity</th>
<th>T ½ (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisone</td>
<td>25</td>
<td>2+</td>
<td>8-12</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>20</td>
<td>2+</td>
<td>8-12</td>
</tr>
<tr>
<td>Prednisone</td>
<td>5</td>
<td>1+</td>
<td>12-36</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>4</td>
<td>0</td>
<td>12-36</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>4</td>
<td>0</td>
<td>12-36</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.75</td>
<td>0</td>
<td>36-54</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>0.6</td>
<td>0</td>
<td>36-54</td>
</tr>
</tbody>
</table>

Disease Modifying Anti-Rheumatic Drugs (DMARDs)

Approach to treatment
• Start DMARD within 3 months of symptom onset
• Patient related variables
  • Disease duration (early vs. established)
  • Disease activity (low, moderate, high)
  • With or without poor prognostic features
• Frequently reassess

Non-Biologic DMARDs
• Hydroxychloroquine
• Sulfasalazine
• Methotrexate
• Leflunomide
• Gold salts
• D-penicillamine
• Azathioprine
• Cyclosporine
• Cyclophosphamide
• Minocycline
Biologic DMARDs

- Anti-TNFα agents
  - Etanercept (Enbrel)
  - Infliximab (Remicade)
  - Adalimumab (Humira)
- Abatacept (Orencia)
- Rituximab (Rituxan)
- Tocilizumab (Actemra)
- Anakinra (Kinareta)*

So What’s the Rhythm with RA?

- Is there a circadian rhythm with RA, why is this relevant for the clinical practice of rheumatology?
- How can the circadian rhythm influence the symptoms of my patient?
- Can I use this knowledge to my advantage to relieve my RA patients symptoms?

Circadian Rhythms of Serum Cytokine and Hormone Production

- Pro-inflammatory cytokines - Important in symptoms such as stiffness, joint swelling pain and mood
  - Tumor necrosis factor (TNF-α)
  - Interleukin (IL)-6

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Healthy Individuals</th>
<th>RA Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak IL-6 value</td>
<td>6 am</td>
<td>7 am</td>
</tr>
<tr>
<td>IL-6 levels decrease</td>
<td>9 am</td>
<td>11 am</td>
</tr>
<tr>
<td>IL-6 serum levels</td>
<td>2-4 pg/ml</td>
<td>20-40 pg/ml</td>
</tr>
</tbody>
</table>

What is driving the circadian oscillation of serum levels of cytokines?

Circadian Rhythm of Cortisol

- Cortisol
  - Endogenous steroid with anti-inflammatory action
  - Maximum at 8 am, nadir at midnight
  - Lag time between the cortisol risk vs. the increase of cytokine of approximately 60-120 minutes
- Cortisol rhythm in health subjects vs. RA patients with low-moderate disease activity same
  - Pertains to the period, amplitude, and time point of the minimum and peak of the cycle
  - Hormone curve is flattened when RA disease activity is high
Circadian Rhythm of Cortisol

- Levels of cytokine ten times higher than normal SHOULD drive a stronger cortisol response...
  - Serum levels of cortisol are similar in healthy patients vs. RA patients
- This phenomenon is called “inadequate secretion of cortisol in relation to inflammation.”
- Secreted cortisol is unable to dampen the proinflammatory response, therefore cytokine levels stay high.
- The cortisol nadir at midnight, and parallel increase of proinflammatory hormones (such as prolactin and melatonin) drive the increase in nightly TNF-α and IL-6. Cortisol finally dampens cytokine surge.

The Effect of Cytokines on Disease Expression and Mood

- Stiffness
- Swelling of joints
- Pain
- Bad mood

So who cares?

- Guidelines specify treatment of RA should be aimed at slowing/halting disease progression
- Treatment targeted at relief of morning stiffness, pain, and impaired morning function is not specified.
  - Should impaired morning function be treated?
  - What management approaches are currently used for this?
  - Do patients follow the management advice provided?
  - Are morning symptoms considered an inevitable consequence of the disease?
  - Do current management approaches help?
  - If morning function being optimally managed?
  - How can we improve impaired morning functioning?

To treat or not to treat...

- Should impaired morning function be treated?
  - 24% have morning stiffness lasting > an hour
  - 16% have morning stiffness lasting 30-60 minutes
  - 32% report no morning stiffness
  - Mean duration 55 minutes; mean duration 11.2 years
  - Does this impact morning functioning?
- Approaches used to treat morning symptoms?
  - 95% of rheumatologists agreed patients raise this issue
  - Recommendations most commonly included:
    - Simple or short exercises, application of heat or hot shower/bath
    - Referral to physical therapy, delay activities until later
  - Less than half of RA patients said their MD gave Rx
    - NSAIDs (78%), CCS (68%), DMARDs (42%), Biologics (37%)
To treat or not to treat...

- Do patients follow the management plan prescribed?
  - Adherence to medications in RA is 30-78%
  - Adherence to DMARDs is 60-68%
  - The majority of respondents use recommended non-pharmacologic approaches to reduce morning stiffness

- Are morning symptoms an inevitable consequence?
  - Most rheumatologists say yes
    - 2/5 rheumatologists (38%) state RA patients should accept this
    - 25% of rheumatologists tell patients this is a symptom of RA
  - Of the 251/750 RA patients with morning stiffness, almost half stated it was because morning stiffness is just part of RA; 15% thought something could be done about it

To treat or not to treat...

- Do current management approaches improve morning function?
  - Little information on effectiveness of non-pharmacologic interventions for impaired morning function
  - The effect of pharmacologic treatment on morning pain or functional ability is rarely, if ever, reported
  - 4 studies with DMARDs – baseline duration of morning stiffness of 1-2 hours; 50-74% reduction after treatment with MTX for 24-52 weeks
  - 3 studies with biological therapies – baseline duration of morning stiffness of 2.5-5 hours; 40-80% reduction after treatment for 8-24 weeks

To treat or not to treat...

- Is morning function being optimally managed with current treatments?
  - Data is not robust in capturing this information
  - 44% of patients considered to be in remission (per DAS28) still experience morning stiffness to some extent.
  - A survey of 599 patients taking medications for impaired morning function – only 14% reported it was completely effective.
  - Likely the majority of patients with RA continue to experience morning stiffness, suggesting that current treatments are suboptimal.

To treat or not to treat...

- How can treatment of impaired morning function be improved?
  - New developments consider chronotherapy (e.g., timing of treatments)
  - NSAIDs
    - If using short half-life NSAID, patients need to wake up early to take; 21% of patients use this technique (53% lose 30 minutes or more of sleep)
    - Long-acting formulation of NSAID may be preferred
  - Glucocorticoids
    - Prednisone is short-acting and usually administered in the AM
    - 2 am administration shown to reduce serum IL-6 levels and morning stiffness more than same dose given at 7:30 am
    - Delayed release prednisone tablet has been developed
Modified-Release Prednisone

- Evaluating a modified-release (MR) prednisone tablet
  - Tablet ingested at 10 pm; prednisone released at 2 am
  - IL-6 showed measurable circadian variation
  - MR prednisone 5 mg abolished IL-6 peak
  - Boosted endogenous cortisol production in early morning
  - Correlated with morning stiffness
- 12-week trial, 288 patients with active RA
  - Randomized to AM IR prednisone or 10 pm MR prednisone
  - After 12 weeks, duration of AM stiffness fell by 23% in MR prednisone arm


Modified-Release Prednisone

- 86% of patients continued in open-label phase
  - MR prednisone dose was 2-10 mg/day
  - 9 month open label extension
  - Assessed several variables:
    - Duration of morning stiffness of joints
    - Disease activity scores (DAS28)
    - Amer College of Rheumatology ACR20 response
    - Plasma levels of IL-6
    - Safety (adverse effects)
  - After 12 months, morning stiffness had halved (55% ↓); mean reduction by 83 minutes from baseline of 156 minutes
  - Switching from IR to MR prednisone – 45% reduction in morning stiffness (mean reduction of 88 minutes from 182 minutes)
  - 17% of those who switched had complete resolution
  - AEs indicative of aggravated HPA axis suppression not observed


Delayed-Release Prednisone

- US formulation – Rayos (delayed-release tablets)
  - 1 mg, 2 mg, 5 mg
- Indications
  - Rheumatoid arthritis, polymyalgia rheumatica, psoriatic arthritis, ankylosing spondylitis, asthma, COPD.
- Pharmacokinetic Profile
  - 4 hour lag time from that of IR prednisone
  - Inactive outer shell acts as a barrier between the product’s active core and a patient’s GI fluids
  - After 4 hours, water from GI tract diffuses through the shell, causing active core to expand, weakening and breaking the shell


Conclusion

- Many diseases exhibit a circadian rhythm.
- Drug therapies can be targeted to take advantage of this circadian rhythm, resulting in enhanced patient outcomes.
- Patients with rheumatoid arthritis display morning stiffness and impaired functional status in a circadian rhythm.
- Drug therapies in modified delivery systems can target the increase in inflammatory cytokines and supplement cortisol levels, reducing morning stiffness and quality of life.
Notes

Notes