Chronotherapeutics and Chronopharmaceuticals of asthma

Caribbean Association of Pharmacists & Pharmaceutical Society of Jamaica Joint convention, 24-31 July 2016 JAMAICA

“Pharmacists: Knowledgeable, Accessible, Promoting Health & Wellness”
LEARNING OBJECTIVES

By the end of this presentation, participants will be able to:
• Review the physiologic factors that impact drug action
• Describe the biologic clock known as circadian rhythm
• List the key body functions that obey circadian rhythm
• Explore the potential contribution of circadian rhythm to therapeutic outcome of a patient on specific management plans
• Utilize the knowledge of circadian rhythm to optimize the therapeutic choices for patients
Outline

- Factors controlling drug absorption, pharmacological effects and biodisposition
  - Review of biopharmaceutics, pharmacokinetics and pharmacodynamics principles
- Biological constants and rhythms
  - Chronobiology: Components of biological timings
  - Properties & effects of body clock in human
- Rhythms & Pharmacokinetics
  - Chronokinetics: concepts and therapeutic applications
Bioavailability: rate & extent

- Bioavailability deals with the transfer of drug from its site of administration into the body system and this is manifested by its appearance in general circulation.

- Because a transfer system is involved, bioavailability is characterized by the rate of transfer and the total amount transferred.
Factors Influencing the time course effect of a drug in plasma

- Age
- Disease state
- TC in plasma
  - Drug
  - Phy/chem Prop.
  - Dosage form
  - Composition & mtd. of mfr.
  - Dose size & Freq. of admin
  - Admin/Absoption site
- Genetic composition
- Co-admin. drug/food
Dynamic relationship between drug, drug product & pharmacologic effect

Administration
Drug release
Absorption
Drug in Systemic Circulation
Distribution
Drug in Tissues
Elimination
Metabolism & Excretion
Pharmacologic or Clinical Effect
Role of Bioavailability on Pharmacodynamics of drug

Cp = Plasma drug concentration; MTC = Minimum Toxic Concentration
MEC = Minimum Effective Concentration
PK/PD interface

PRESCRIBED DOSE
- medication errors
- patient compliance

ADMINISTERED DOSE
- rate and extent of absorption
- body size and composition
- distribution in body fluids
- binding in plasma and tissues
- rate of metabolism and excretion

CONCENTRATION AT SITE(S) OF ACTION
- physiological variables
- pathological factors
- genetic factors
- interaction with other drugs
- development of tolerance and desensitization

DRUG EFFECTS
- drug-receptor interaction
- functional state of targeted system
- selectivity of drug, propensity to produce unwanted effects
- placebo effects
- resistance (anti-microbial agents)
Course of Drug sojourn in the Body: Absorption-Distribution-Metabolism-Excretion (ADME)
Circadian Rhythms

PROPERTIES & EFFECTS OF BODY CLOCK IN HUMAN
Definition of Key Terms

**Chronobiology** - "the study of how plants and animals measure time and of how time of day and the seasons affect biological processes"
- Emphasis is placed on the biological clock

**Chronotherapeutics** - application of the principles of chronobiology to the treatment of diseases

**Chronopharmaceutics** - "a branch of pharmaceutics (science and technology of drug dosage forms) devoted to the design and evaluation of drug delivery systems that release a bioactive agent at a rhythm that ideally matches in real time the biological requirement for a given disease therapy or prevention."
Homeostasis

- Internal environ of body is maintained within narrow limits in spite of tendency for individual’s environment
- Thermoregulatory reflexes mechanism controlling other physiological & biochemical variations

BSA, respiration, circulation
#CONSTANCY & RHYTHM

Three mechanical rhythms -

1. **Circadian**
2. **Ultradian**
3. **Infradian**

<table>
<thead>
<tr>
<th>Body Rhythms</th>
<th>Duration</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Ultradian Rhythms</td>
<td>&lt;20 hours</td>
<td>90 Minute sleep cycle</td>
</tr>
<tr>
<td>Circadian Rhythms</td>
<td>24 hours</td>
<td>Sleep-wake cycle</td>
</tr>
<tr>
<td>Infradian Rhythms</td>
<td>&gt;24 hours</td>
<td>Menstrual cycle</td>
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</table>
Circadian Rhythm
The study of circadian rhythm is called chronobiology

- Physical, mental and behavioral changes that follow a roughly 24-hour cycle, responding primarily to light and darkness in an organism’s environment.

- Animals, plants and microbes experience these self-sustaining changes.

- Change affects sleep-wake cycles, hormone release, body temperature and other important bodily functions.
Observed rhythms

Body temperature, cortisol hormone and blood pressure, mental, physical & GI activity

Day

Night

Melatonin, growth, testosterone and prolactin hormones, adrenaline & cortisol

Day

Night

Adapted from http://team.genetics.utah.edu/content/genes/dna/clockgenes/
Exogenous/Endogenous Components

- **Exogenous**: Individual’s life style & environment
  - Result from behavioral changes associated with sleep-wake cycle (Night-day cycles)
  - Not completely explained rhythm
    - Jet lag
    - Shift workers
  - Body cannot adjust sleep-activity cycle immediately

- **Endogenous component** – “The Body Clock” =>
  - Endogenous: clock-driven components (free running)
Origin of Body Clock: Suprachiasmatic Nucleus

The Suprachiasmatic nuclei (SCN) region is located in the hypothalamus of the brain.

The SCN sends signals throughout the body in response to light and dark.

http://khan.genetics.utah.edu/content/_begin/dna/lockgenes/
Clock Inputs

- The reticulohypothalamic tract (RHT)
- Geniculohypothalamic tract (GHT)
- The Raphe-hypothalamic tract (RaHT)
- Converging photic & non-photonic signals
IGH – intrageniculate leaflet of the hypothalamus
Zitgeber: envin agent or event provide stimulus, setting/resetting bio. clock - Light as zeitgeber – information passes directly from the retina to the suprachiasmatic nuclei (SNC) of the hypothalamic tract. Origin of input – subgroup of receptors in retina whose visual pigment is based on vitamin B2 rather than conventional A1-based opsin

**Melatonin:** ingestion adjusts the phase of the body clock. Depending on time of ingestion, melatonin can phase-delay, phase advance or have no effect on body clock. Shift are inverse to those produced by light: ingestion in afternoon & early evening advances the body clock; Ingestion in the night & early morning delays it Light inhibits melatonin secretion, amount depends on intensity of light => Making phase-shifting effect of the 2 zeitgebers reinforcing each other.
Rhythms & Pharmacokinetics
- EFFECTS ON LADMEP
Chronokinetics in human

- Until about 10 – 20 years, time dependent (biological rhythms) in PK were being assumed to be due to:
  - *External factors such as posture*
  - *Presence or absence of food in the stomach*
  - *Disease states*

- Working of human body was assumed to be constant over the 24 h period (feedback mech. was maintaining the internal environ constant over time)

- This hypothesis no longer holds
Hepatic blood flow greater during the day, lower at night
Excretion is lower in resting period
Rhythm in Drug Absorption
Rhythms, phy-chem properties & formulation

• **Temporal variations in PK xtcs are independent of**
  – DF (solid, liquid, etc.)
  – High (e.g. propranolol)/low (e.g. diazepam) hepatic 1st pass effect

• **Physicochemical properties are important:**
  – Lipid soluble (BCS Classes 2 & 4) more likely to show variation than water-soluble (BCS Classes 2 & 4) drugs
Chronokinetic studies in human

- Single oral doses of medication given at 4 or > different times within 24 h show statistically significant differences in:

- $C_{\text{max}}$, $t_{\text{max}}$, $t_{1/2}$ and AUC of drugs

- Summary of important studies (next slide)
Chronokinetic studies in human (cont’d)

• Indomethacin (100mg) in 9 healthy University students (Clench et al, 1981):
  – Cmax @ 7.00 & 11.00 was double that at other times
  – T_{max} reached in half the time after morning dose c/f evening dose; no change in AUC

• Sulphamethoxazole (SMT), 1g in healthy, diurnally active male volunteers:
  – Cmax was 32% higher at 6.00 and noon than @ midnight (p<0.050)
  – Ka, T_{max}, Cmax & t1/2 indicate more rapid absorption during activity period
Rhythm in Drug Distribution
LADMEP
Rhythms in Drug Distribution

- Vd
- LogP
- Solubility
- MW
- Protein binding
Rhythm in Drug Metabolism

LADMEP
Rhythms in Hepatic Metabolism

- Phase 1
- Phase II
Rhythms in Excretion

LADMEP
Rhythms in Drug Excretion

- Cardiac output – renal perfusion
- Tubular secretion
- Tubular reabsorption
- Degree of molecular ionization
- Protein binding
- Intestinal/biliary excretion
Rhythms in Pharmacodynamics

LADMEP
Rhythms in Pharmacodynamics

LADMEP
### Examples of Chronotherapeutics in Specific Disease States

<table>
<thead>
<tr>
<th>Disease State</th>
<th>Target of Chronotherapeutics</th>
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<tbody>
<tr>
<td>Asthma</td>
<td>After midnight or early morning hours minimization of provoking attacks.</td>
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<tr>
<td>Arthritis</td>
<td>Early morning and day time pain</td>
</tr>
<tr>
<td>Attention Deficit Disorder</td>
<td>Afternoon increase in DOPA level</td>
</tr>
<tr>
<td>Cardiovascular Disease</td>
<td>During sleep cycle blood pressure LOWERS</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>After meals increase blood sugar levels</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>During night INCREASED cholesterol synthesis</td>
</tr>
<tr>
<td>Peptic Ulcer</td>
<td>At night, acid secretion INCREASES</td>
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</tbody>
</table>
Times when common medical conditions are likely to worsen and when morbid and mortal events are likely to occur with reference to the diurnal activity-nocturnal sleep routine of patients.

3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitors
Application of chronotherapeutics in Asthma Mgt.

**Controllers**
- Inhaled corticosteroids
- Inhaled Cort. & LA β2-agonists
- Systemic corticosteroids
- Leucotriene modifiers
- Anti-IgE

**Releivers**
- Short acting β2-agonists
- SA anticholinergics
<table>
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<tr>
<td><strong>Inhaled corticosteroids (ICS)</strong> e.g. beclometasone, ciclesonide, fluticasone, propionate, fluticasone furoate, memetazone, triamcinolone</td>
</tr>
<tr>
<td><strong>Inhaled corticosteroids and long-acting beta2-agonist bronchodilator combinations (ICS/LABA)</strong> e.g. beclometasone/formoterol, budesonide/formoterol, fluticasone furoate/vilanterol, fluticasone propionate/formoterol, fluticasone propionate/salmeterol, and mometasone/formoterol</td>
</tr>
<tr>
<td><strong>Leukotriene modifiers (tablets)</strong> e.g. montelukast, pranlukast, zafirlukast, zileuton</td>
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<tr>
<th>Medications</th>
<th>Action and use</th>
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<td><strong>Controller Medications</strong></td>
<td></td>
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<tr>
<td>Cromones e.g. sodium cromoglicate and nedocromil sodium</td>
<td>Very limited role in long-term treatment of asthma. Weak anti-inflammatory effect, less effective than low-dose inhaled corticosteroids. Require meticulous inhaler maintenance.</td>
</tr>
<tr>
<td>Anti-IgE e.g. omalizumab</td>
<td>A treatment option for patients with severe persistent allergic asthma uncontrolled on high dose ICS-LABA.</td>
</tr>
<tr>
<td>Systemic corticosteroids (tablets, suspension or intramuscular [IM] or intravenous [IV] injection) e.g. prednisolone, prednisolone, methylprednisolone, hydrocortisone</td>
<td>Oral corticosteroid (OCS) therapy is preferred for short-term treatment (5 to 7 days in adults) of severe acute exacerbations. OCS is as effective as IM or IV therapy in preventing relapse.</td>
</tr>
<tr>
<td><strong>Reliever Medications</strong></td>
<td></td>
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<tr>
<td>Short-acting beta₂-agonist bronchodilators (SABA) e.g. salbutamol, terbutaline</td>
<td>For quick relief of asthma symptoms and bronchoconstriction including acute exacerbations, and for pre-treatment of exercise-induced bronchoconstriction.</td>
</tr>
<tr>
<td>Short-acting anticholinergics e.g. ipratropium bromide, oxitropium bromide</td>
<td>For acute asthma, the combination of inhaled ipratropium and SABA reduces the risk of hospital admission.</td>
</tr>
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Summary and Conclusions

- Pharmacokinetics factors have time-dependent circadian components
- Part of the biological clock, modifiable by zeitgebers (light & melatonin)
- Chronokinetics defined by time-dependent variations in LADMEP processes
- Significant impacts on therapeutic outcomes, requires more attention in therapeutic care
References