Geriatric Clinical Pharmacology: State of the Art in a Neglected Minority

Pharmacometric Approaches to Streamline Pharmacotherapy in Older Adults

ASCPT 2019 Annual Meeting
March 15, 2019 / Jan F. Schlender
Population Pharmacokinetics

Physiologically based Pharmacokinetics

Quantitative Systems Pharmacology
Physiology of aging

Cardiovascular System
Reduction of myocytes and capacity

Skeletal muscles
Decline of mass, function and strength

Liver
Altered metabolic capacity

Body composition
Shift of fat to muscle mass ratio and body water distribution

Brain
Altered blood-brain barrier permeation

Respiratory tract
Reduced functional capability

Kidney
Sclerotization of functional mass and filtration rate

Gastrointestinal tract
Reduced digestion and altered pH-regulation

Capacity/Functionality

Chronologic

Biologic
Physiologically based Pharmacokinetics (PBPK) approaches to describe an aging population

Adaptation of ADME processes

Re-parametrization of Minimal PBPK database

Re-parametrization of whole-body PBPK database

Informing ADME processes from descriptive observations
Navid et al. CPT Pharmacometrics Syst Pharmacol 2016

Incorporation of specific physiological changes
Chetty et al. Adv Drug Deliv Rev 2018

Consideration of whole-body physiological changes
Stader et al. Clin Pharmacokinet 2018
PBPK approaches to describe an aging population

Re-parametrization of Minimal PBPK physiological database

Heterogeneous physiological aging progress is not characterized and may lead to mispredictions of distribution.

Depending on the application, a more simple structure of a PBPK model might be sufficient.

Chetty et al. Adv Drug Deliv Rev 2018
PBPK approaches to describe an aging population

Re-parametrization of whole-body physiological database

// Complexity
// Distinguish between disease and age-related changes
// Supportive for mechanistic PD modeling

Schlender et al. Clin Pharmacokinet 2018
## Availability of Information in aging adults

**Knowledge gaps**

<table>
<thead>
<tr>
<th></th>
<th>Young Adults</th>
<th>Midlifers</th>
<th>Young Old</th>
<th>Oldest Old</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anatomy</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>❌</td>
</tr>
<tr>
<td>Physiology</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>❌</td>
</tr>
<tr>
<td>Blood flow rates</td>
<td>✔</td>
<td>✔</td>
<td>❌</td>
<td>❌</td>
</tr>
<tr>
<td>Protein abundance/activity</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>❌</td>
</tr>
<tr>
<td>GI-Tract</td>
<td>✔</td>
<td>❌</td>
<td>❌</td>
<td>❌</td>
</tr>
<tr>
<td>PK Data</td>
<td>✔</td>
<td>❌</td>
<td>✔</td>
<td>❌</td>
</tr>
</tbody>
</table>

- ✔: Data available (quantitative, human)
- ❌: Limited or conflicting data
Consideration of aging in Population Pharmacokinetics/Pharmacodynamics

M&S can be employed to “synthesize” the available evidence on PKPD, safety, and efficacy.

Model predictions can then be “confirmed” by conducting small observational or prospective (exploratory) bridging studies in the target patient population, if deemed appropriate.

Therefore, a decision tree is proposed that delineates a strategy for bridging the evidence gap for safe/effective use of medicines in elderly patients.
Consideration of aging in Population PK/PD

- Simvastatin has a well-characterized PKPD relationships
- Known PK-changes in the older adults population considered for simulation of pharmacodynamic alterations
- Exposure of simvastatin and simvastatin acid in each scenario are elevated causing an amplification of the PD effect
Consideration of aging in Population PK/PD

Disease Progression

- Beta regression model to describe the longitudinal progression of the 11 item Alzheimer’s disease assessment scale cognitive subscale (ADAS-cog) in Alzheimer’s disease patients in both natural history and randomized clinical trial settings.

- Disease progression was dependent on time, ApoE4 status, age, and gender.

**Table 5** Model predicted expected mean change in ADAS-cog score over one year in the absence of a placebo or drug effect, by baseline age.

<table>
<thead>
<tr>
<th>Age</th>
<th>Median</th>
<th>5% LB</th>
<th>95% UB</th>
</tr>
</thead>
<tbody>
<tr>
<td>69</td>
<td>4.92</td>
<td>3.71</td>
<td>6.13</td>
</tr>
<tr>
<td>75</td>
<td>4.39</td>
<td>3.51</td>
<td>5.39</td>
</tr>
<tr>
<td>80</td>
<td>4.00</td>
<td>2.97</td>
<td>5.17</td>
</tr>
</tbody>
</table>
Quantitative Systems Pharmacology

Alzheimer disease (AD) – Discover Treatment Options

- QSP model for AD with a particular focus on investigating the relevance of dysregulation of cholesterol and sphingolipids
- Model captures the modulation of several biomarkers in subjects with AD and age, as well as the response to pharmacological interventions
- Targeting the sphingosine-1-phosphate 5 receptor (S1PR5) as a potential novel treatment option

Clausznitzer et al. CPT Pharmacometrics Syst Pharmacol. 2018

Clausznitzer et al. CPT Pharmacometrics Syst Pharmacol. 2018
Endometriosis – Understanding target response

Model-based guidance for GnRH-modulating clinical programs intended for endometriosis management

Targeting estradiol between 20 and 40 pg/ml was predicted to provide efficacious endometrial pain response while minimizing BMD effects

- Bone-specific alkaline phosphatase (BSAP)
- Urine N-telopeptide of type I bone collagen (NTx)
- Plasma calcium
- Transforming growth factor-β
- Parathyroid hormone

Model-based guidance for GnRH-modulating clinical programs intended for endometriosis management

Targeting estradiol between 20 and 40 pg/ml was predicted to provide efficacious endometrial pain response while minimizing BMD effects

Guide study design:
- Treatment duration
- Biomarker selection
- Target response

Efficacy: patient-level data
- Biomarker: estradiol (E2)
- Response: endometriosis symptom severity score (ESSS)

Side effect: literature metadata
- Biomarkers: E2 → bone markers
- Response: bone mineral density (BMD)

Time course and magnitude of responses

Logistic model

Multiscale model

Plasma calcium
Transforming growth factor-β
Parathyroid hormone

Bone-specific alkaline phosphatase (BSAP)
Urine N-telopeptide of type I bone collagen (NTx)
Pharmacometric Approaches to Streamline ASCPT 2019

**Clinical impact/decision points**

**PopPK/PD**

**Preclinical**
- Mechanistic understanding of drug behavior and physiologic pathways involved

**PBPK/PD model (preliminary)**
- Applying biological age
- Drug-drug interactions
- Comorbidity knowledge

**Phase I/IIa**
- Considerations for further processing
  - Adults vs. older adults with similar:
    - Disease progression and pathophysiology
    - Exposure-response
    - Treatment outcome

**PBPK/PD predictions**
- Applying biological age
- Drug-drug interactions
- Comorbidity knowledge

**Final PK/PD model (adults & elderly)**
- Guidance on dosing and study design
- Study population size
- Sampling times
- Treatment duration

**Geriatric PK/PD model**
- Guides study design
- Study population size
- Sampling times
- Treatment duration

**PBPK/PD predictions**
- Age-related physiological changes
- Disease pathophysiology
- Extrapolation of clinical response
- Informs dosing and study design

**Approval/Label**
- Young adults vs. elderly
  - Dose
  - Pharmacokinetics
  - Pharmacodynamics
  - Clinical outcomes

**Schlender et al. Eur J Pharm Sci. 2018.**
Quantitative approaches to describe an aging population

Proliferation

Study- and Therapy-optimization

Disease understanding

Pharmacokinetics/Pharmacodynamics

Conclusion

Challenges

// Complex dosing regimes
// Narrow therapeutic index drugs
// Poly-medication
// Multimorbidity
// Lack of information
// Utilization of postapproval data

Opportunities

// Confidence in Dose Selection
// Understanding physiologic linkages
// Conversion of theoretical into quantitative predictions
// Development of deep expertise and system knowledge
// Efficient trial and therapy designs
// Halting/accelerating programs

Table 1. Proportion of 2013 and 2014 Approvals Without Explicit Dosing Recommendations at the Initial Approval

<table>
<thead>
<tr>
<th>Section</th>
<th>Population</th>
<th>2013 (n = 27)</th>
<th>2014 (n = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.1</td>
<td>Pregnancy</td>
<td>70%</td>
<td>100%</td>
</tr>
<tr>
<td>8.2</td>
<td>Labor and delivery</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>8.3</td>
<td>Nursing mothers</td>
<td>92.5%</td>
<td>100%</td>
</tr>
<tr>
<td>8.4</td>
<td>Pediatrics</td>
<td>88.8%</td>
<td>97%</td>
</tr>
<tr>
<td>8.5</td>
<td>Geriatrics</td>
<td>22.2%</td>
<td>25%</td>
</tr>
<tr>
<td>Not explicitly defined but appears several times in labeling guidance</td>
<td>Female and male reproductive potential</td>
<td>63%</td>
<td>84%</td>
</tr>
</tbody>
</table>

Thank you!

Bye-Bye