Pharmacokinetics of Herbal Medicinal Products: Useful or not?

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Scientific approach

➢ to link results from pharmacological *in vitro* assays and clinical studies

- **Clinical studies**
- **Pharmacokinetics**
  - Bioavailability?
  - Metabolic pathways?
- **first step**
  - phytochemical analyses and pharmacological *in vitro* studies
Constituents relevant for activity

Otherwise, the performance of pharmacokinetic studies is useless!

➢ The role of alkamides as the active principle of Echinacea

  • significant anti-inflammatory and immunomodulatory properties [Woelkart et al. 2007]
  • inhibition of COX-2 activity with a significant decline of the PGE$_2$ levels [Hinz et al. 2007]
  • modulation of TNF-α gene expression and an ex vivo significant decrease in production of pro-inflammatory cytokines [Gertsch et al. 2004, Woelkart et al. 2006]

➢ Echinacea alkamides trigger most of their effects via CB-2-binding [Woelkart et al. 2005, Gertsch et al. 2004, Raduner et al. 2006]
Preparation of new galenic formulations or comparison of different formulations/1

**Echinaforce Junior tablets** with 95% (380 mg) *Echinacea purpureae* herba and 5% (20 mg) *Echinacea purpureae* radix, but **beta-cyclodextrin (betadex)** as excipient

*To what extent the Echinacea alkamides are bioavailable?*

- randomized, open crossover study with 8 volunteers
- Single oral dose of
  - 10 Echinaforce® Junior tablets (beta-Cyclodextrin; Betadex) or
  - 12 Echinaforce® tablets from *Echinacea purpurea*
    (Tetraene concentration: 141.3 µg or 143.2 µg/Dosis)

The study was approved by the “Ethics Committee of the University of Medicine Graz“, Austria (EK-No.: 17-112 ex 05/06) and by „AGES PharmMed“ Vienna, Austria. (EudraCT 2005-005853-23)
Pharmacokinetic results of the new galenic formulation (Betadex Echinaforce tablets)

Dodeca-$2E,4E,8Z,10E/Z$-tetraenoic acid isobutylamides (Tetraene)

<table>
<thead>
<tr>
<th></th>
<th>Echinaforce Junior tablets (Betadex)</th>
<th>Echinaforce® tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>0.1413 mg</td>
<td>0.1432 mg</td>
</tr>
<tr>
<td><strong>$C_{\text{max}}$ [ng/ml]</strong></td>
<td>0.22 ± 0.15</td>
<td>0.22 ± 0.07</td>
</tr>
<tr>
<td><strong>$T_{\text{max}}$ [h]</strong></td>
<td>1.13 ± 0.35 (~68 min)</td>
<td>0.47 ± 0.25 (~28 min)</td>
</tr>
<tr>
<td><strong>AUC [ng/ml*h]</strong></td>
<td>0.22 ± 0.09</td>
<td>0.23 ± 0.05</td>
</tr>
</tbody>
</table>
Pharmacokinetic/Pharmacodynamic modelling

Pharmacokinetic:
- randomized, open crossover study with 8 volunteers
  - Single oral dose of
    - 4 ml Echinaforce® tincture or
    - 12 Echinaforce® tablets from Echinacea purpurea
      (Tetraene concentration: 0.07 mg/Dose)

The study was also approved by the „Ethics Committee of the University of Medicine Graz“, Austria (EK-No.: 16-009 ex 04/05) and by „AGES PharmMed“ Vienna, Austria (EudraCT 2004-002632-26)

[K. Woelkart et al. R. Bauer; Int J Clin Pharmacol & Ther, 2006, 44 (9), 401 - 408]
Pharmacokinetic results of the two different formulations (Echinaforce® tincture and tablets) / A

Dodeca-2E,4E,8Z,10E/Z-tetraenoic acid isobutylamides (Tetraene)

<table>
<thead>
<tr>
<th></th>
<th>Echinaforce® tincture</th>
<th>Echinaforce® tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>0.07 mg</td>
<td>0.07 mg</td>
</tr>
<tr>
<td>$C_{\text{max}}$ [ng/ml]</td>
<td>$0.40 \pm 0.11$</td>
<td>$0.12 \pm 0.03$</td>
</tr>
<tr>
<td>$T_{\text{max}}$ [min]</td>
<td>$30.1 \pm 0.1$</td>
<td>$45.3 \pm 0.4$</td>
</tr>
<tr>
<td>AUC [ng*min/ml]</td>
<td>$27.55 \pm 8.94$</td>
<td>$11.36 \pm 2.74$</td>
</tr>
</tbody>
</table>
Ginkgo pharmacokinetic study (commercial Ginkgo tincture and Ginkgo tablets, new Ginkgo tablets)

- to demonstrate, that a new product is in the range of commercial available products
- randomized, open parallel study with 24 volunteers
  Single oral dose of a commercial available Ginkgo biloba tincture or commercial available Ginkgo biloba tablets or the new, not approved, Ginkgo biloba tablets

The study was also approved by the „Ethics Committee of the University of Medicine Graz“, Austria (EK-No.: 18-142 ex 06/07) and by „AGES PharmMed“ Vienna, Austria (EudraCT 2007-000539-25)
Pharmacokinetic results/comparison of $c_{\text{max}}$

**Bilobalide**
- Median
- 125%
- 80%

**Ginkgolide A**
- New not approved Ginkgo tablets
- Ginkgo tincture commercial available
- Ginkgo tablets commercial available

**Ginkgolide B**
- New not approved Ginkgo tablets
- Ginkgo tincture commercial available
- Ginkgo tablets commercial available

new not approved Ginkgo biloba tablets are highly comparable with commercial available preparations
Pharmacokinetic results/comparison of AUC_{tot}

Bilobalide

**Median**

- New not approved
- Ginkgo **tablets**
- Ginkgo **tincture** commercial available
- Ginkgo **tablets** commercial available

Ginkgolide A

- 125%
- 80%

Ginkgolide B

- New not approved
- Ginkgo **tablets** commercial available
- Ginkgo **tincture** commercial available
- Ginkgo **tablets** commercial available
PK/PD studies for designing rational dosage regimes

Pharmacological active constituents are known

Dosage

Pharmacokinetic

Effect
Pharmacokinetic interactions – for safety reasons

- a result of activity changes of drug-metabolizing and transporting proteins (CYP enzymes, P-gp)

**Pharmacokinetic herb-drug interaction studies are important for most of the common used HMPs**

**Problem:**
most of the performed studies used phytochemically uncharacterized HMPs

**Intention:**
Phytochemically define the test product to make statements:
- which group of compounds are responsible for any obtained effect
- for which preparation, species, plant part and extraction procedure care must be taken when coadministered with prescription medications
Summary and Conclusion

pharmacokinetic studies are only meaningful, if the pharmacological active constituents are known

Accordingly you can use pharmacokinetic studies to

- link results from pharmacological *in vitro* assays and clinical studies
- get information to what extent the active constituents are bioavailable from new galenic formulations, or to compare two different formulations
- demonstrate that a new formulation is in the range of commercial available products
- adjust the dosage to a more rational use of the HMPs
- perform pharmacokinetic herb-drug interaction studies for safety reasons

➢ much more work is needed to characterize the bioavailability and pharmacokinetics of HMPs in order to fully take advantage of their therapeutic potential
Acknowledgements

A. Vogel Bioforce AG for the financial support of the pharmacokinetic studies (Andy Suter and Roland Schoop)

All volunteers, who participated in the studies