Why should we study the pharmacokinetics of administered nutrients?
The example of amino acids

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The example of amino acids

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Learning objectives

• The behaviour of administered AAs cannot be extrapolated from biochemistry textbooks

• AAs, even when metabolically close, behave differently

• Association of AAs modifies their behaviour unpredictably. So any new combination must be tested in patients
Three cases

1. An AA largely metabolized in the splanchnic area: glutamine

2. An AA $\approx$ not metabolized in the splanchnic area: citrulline

3. An AA that may have altered pharmacokinetics depending on other co-administered nutrients: arginine, ornithine $\alpha$-ketoglutarate
• Glutamine given by the parenteral route is found to decrease morbidity and mortality in various subgroups of patients

• Initial studies cast doubt on efficacy when given enterally

True or not?
Why?
## Glutamine: enteral vs. parenteral
*(clinical and bioclinical studies in ICU)*

<table>
<thead>
<tr>
<th>Parenteral</th>
<th>Enteral</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>10 studies:</strong></td>
<td><strong>9 studies:</strong></td>
</tr>
<tr>
<td>3 post-operative, 4 ICU</td>
<td>5 ICU</td>
</tr>
<tr>
<td>2 bone marrow transplant</td>
<td>2 bone marrow transplant</td>
</tr>
<tr>
<td>1 burn injury</td>
<td>2 burn injury</td>
</tr>
<tr>
<td><strong>0.18 to 0.57 g GLN/kg</strong></td>
<td><strong>0.20 to 0.45 g GLN/kg</strong></td>
</tr>
<tr>
<td>Bio+clin</td>
<td>9</td>
</tr>
<tr>
<td>Clin</td>
<td>5</td>
</tr>
</tbody>
</table>

Confirmed by Novak et al.'s meta-analysis *(Crit. Care Med. 2002;30:2022-9)*
Pharmacokinetics of nutrients AA ESPEN2011 11-105

30% → 55% → 100% → [1³C₂] - glutamine

1³CO₂

58%
Do not expect any action when bioavailability is poor.

Transport in enterocytes → X

Metabolism in enterocytes → X

Blood → X

Muscle → X

action
# GLUTAMINE IN ENTERAL NUTRITION

<table>
<thead>
<tr>
<th></th>
<th>Glutamine</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>n =</td>
<td>35</td>
<td>37</td>
</tr>
<tr>
<td>Age (years)</td>
<td>35.1 ± 11.8</td>
<td>34.5 ± 13.4</td>
</tr>
<tr>
<td>ISS</td>
<td>32.4 ± 11.3</td>
<td>31.8 ± 10.6</td>
</tr>
<tr>
<td>APACHE II</td>
<td>16.3 ± 5.9</td>
<td>15.6 ± 4.5</td>
</tr>
<tr>
<td>GLN</td>
<td>33 g</td>
<td>-</td>
</tr>
<tr>
<td>ALA, ASP, GLY, PRO, SER</td>
<td>-</td>
<td>isoN</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>17%*</td>
<td>43%</td>
</tr>
<tr>
<td>Bacteraemia</td>
<td>9%+</td>
<td>38%</td>
</tr>
<tr>
<td>Sepsis</td>
<td>3%*</td>
<td>22%</td>
</tr>
</tbody>
</table>

* *p < 0.02, + *p < 0.05 (in intention to treat)

from Houdijk APJ et al. Lancet 1998;352:772-776
Three cases

1. An AA largely metabolized in the splanchnic area: glutamine

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Citrulline: a grey area to maintain ARG homeostasis

⇒ allows adequate nitrogen disposal and \( \diamond \)NO production
Replaces L-arginine (sickle cell disease)

$C_{\text{max}}$

CIT –

ORN –

ARG –

Plasmatic CIT concentration (umol/L)

Time after load (h)
Plasma citrulline

Plasma arginine

From Jourdan et al.
Citrulline transport systems in enterocytes

Three cases

1. An AA largely metabolized in the splanchnic area: glutamine

2. An AA $\approx$ not metabolized in the splanchnic area: citrulline

3. An AA that may have altered pharmacokinetics depending on other co-administered nutrients: arginine, ornithine $\alpha$-ketoglutarate
Plasma arginine availability controls nitric oxide synthesis by channelling of arginine pathways
Influence of associated salt
Ornithine $\alpha$-ketoglutarate

- 6 healthy males
- 10 g OKG
- 6.4 g ORN (as hydrochloride)
- 3.6 g $\alpha$KG (as calcium)

Fig. 12. Influence of OKG administration on metabolism of ornithine and $\alpha$-ketoglutarate.
But not so clear and not so simple:

- The influence of the route of administration: ALA-GLN, enteral *versus* parenteral
- Disease-specific behaviour: the case of endotoxemia
Fig. 3. Time course of disappearance of Ala-Gln from plasma (A) and liberation and subsequent elimination of free glutamine and free alanine (B) after bolus injection of Ala-Gln in 10 healthy subjects (mean ± SD). Adapted from Reference 35 with permission.
Plasma glutamine response

Plasma citrulline response

At this point everything seems clear and simple

But not so clear and not so simple:

- The influence of the route of administration: ALA-GLN, enteral *versus* parenteral

- Disease-specific behaviour: the case of endotoxemia
Acclimatization  

**E. coli LPS**

D–7  ↓  D 0  6 H  12 H  22 H 

Starvation  

Blood collection  (9 samples)

Amino acid administration  

Control group  

LPS group  

Control CIT (n = 6)  
Control ARG (n = 6)  
Control GLN (n = 6)  
LPS CIT (n = 6)  
LPS ARG (n = 6)  
LPS GLN (n = 6)
Pharmacokinetic parameters of *citrulline* in plasma after oral citrulline, arginine or glutamine supplementation in control and endotoxemic rats

<table>
<thead>
<tr>
<th>Amino acid administered</th>
<th>Citrulline</th>
<th>Arginine</th>
<th>Glutamine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AUC (µmol.min/ml)</strong></td>
<td><strong>Control</strong></td>
<td>761 ± 67</td>
<td>101 ± 16</td>
</tr>
<tr>
<td></td>
<td><em>LPS</em></td>
<td>508 ± 72*</td>
<td>43 ± 23</td>
</tr>
<tr>
<td><strong>Cmax (µmol/l)</strong></td>
<td><strong>Control</strong></td>
<td>3252 ± 459</td>
<td>388 ± 53</td>
</tr>
<tr>
<td></td>
<td><em>LPS</em></td>
<td>1453 ± 368*</td>
<td>216 ±84</td>
</tr>
</tbody>
</table>

Data are given as mean ± SEM

*Significantly different (p < 0.05) from control*

Pharmacokinetic parameters of *arginine* in plasma after oral supplementation of citrulline, glutamine or arginine in control and endotoxemic rats

<table>
<thead>
<tr>
<th>Amino acid administered</th>
<th>Citrulline</th>
<th>Arginine</th>
<th>Glutamine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AUC (µmol.min/ml)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>138 ± 12</td>
<td>101 ± 16</td>
<td>−18 ± 6</td>
</tr>
<tr>
<td>LPS</td>
<td>92 ± 9 *</td>
<td>43 ± 23</td>
<td>6 ± 4*</td>
</tr>
<tr>
<td><strong>Cmax (µmol/l)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>307 ± 23</td>
<td>388 ± 53</td>
<td>14 ± 10</td>
</tr>
<tr>
<td>LPS</td>
<td>256 ± 57</td>
<td>216 ± 84</td>
<td>33 ± 7</td>
</tr>
</tbody>
</table>

Data are given as mean ± SEM
* Significantly different (*p* < 0.05) from control
# *p* = 0.08 *versus* arginine
We must study pharmacokinetics of administered AAs because:

- In the context they act like drugs, not simply nutrients
- Specificity according to route of administration
- Major inter-organ exchanges
- Nutrient/nutrient interactions
- Disease-specific alterations
- Utility of *in silico* studies
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