GROWTH, FEEDING, TREATMENT OF RENAL FANCONI SYNDROME. Does early treatment with substrate depletion therapy prevent late complications?

PD. Dr. Katharina Hohenfellner
Kinderklinik Traunstein
10/2010 - Interdisciplinary Cystinosis Clinic
Cooperation with the German Patient Organization

children and adults

3 times /year – in addition to regular medical care
3 hours as outpatient

Prof. Harms
Nephrology (pediatrics, adult)
Orthopedics
Cardiology
Pulmonology
Ophthalmology
Gastroenterology
Endocrinology
Neurology
Internal Medicine
Dermatology
Dietician
Logopedics
Physiotherapist
Social worker
Prof. Marquardt
Interdisciplinary Cystinosis Clinic Traunstein

10/2010 – 10/2014

n = 92 patients / 7 clinics
56 individual patients
Contact with 77 patients

n = 35 < 18 y
n = 32 > 18 y
What is the optimal Cysteamine dose?
Treatment

Cumulative dose-response curve for orally administered cysteamine and peripheral leukocyte nonprotein cystine content at progressively increasing dose levels

At dose over 80mg/kg/day: leukocyte nonprotein cystine level was in the range of asymptomatic heterozygotes

### Optimal dose of cysteamine

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Kleta R. et al</th>
<th>1 – 7 years:</th>
<th>70-90 mg/kg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>J Pediatr</td>
<td>7 – 8 years:</td>
<td>70 mg/kg/day</td>
</tr>
<tr>
<td></td>
<td>(2004); 145 :555-560</td>
<td>&gt; 8 years:</td>
<td>60 mg/kg/day</td>
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<tr>
<td></td>
<td></td>
<td>&gt; 10 years :</td>
<td>40 mg/kg/day</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Emma F. et al</th>
<th>≤ 12 years :</th>
<th>1,30g/m²/day</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Nephrol Dial Transplant</td>
<td>&gt; 12 years, &gt; 50 kg:</td>
<td>2,00 gr/day</td>
</tr>
<tr>
<td></td>
<td>(2014); 29: iv87-iv94</td>
<td></td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Bouazza N. et al</th>
<th>10-17 kg:</th>
<th>80 mg/ kg /day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Orphanet Journal of Rare Disease</td>
<td>17- 25 kg:</td>
<td>70 mg/ kg /day</td>
</tr>
<tr>
<td></td>
<td>(2011); 6:86</td>
<td>25- 40 kg:</td>
<td>60 mg/ kg /day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40-70 kg:</td>
<td>50 mg /kg /day</td>
</tr>
</tbody>
</table>
Pharmacokinetics and pharmacodynamic study

n= 69 nephropathic cystinosis patients
age: 0.4 – 36 years
bodyweight: 7.6-83 kg
(mean cysteamine dose: 35.5 mg/kg/day)

Determination of cysteamine plasma concentration/
PMN cells cystine levels

Model linking cysteamine concentrations to
WBC cystine levels

Dosing scheme - not exceeding max.
recommended dose of
1.95 g/m²/day

Bouazza N. et al, Orphanet Journal of Rare Disease 2011,6:86
Optimal dose of cysteamine

Initiation of treatment as early as possible to preserve renal function:

Kleta R. et al*: sibling 10 week of age
J Pediatr (2004); 145 :555-560

Harms E. et al*: as soon as possible
Angeborene Stoffwechselerkrankungen
bei Erwachsenen
2014; 167-175

*Initial therapy 10 mg/kg/day increasing weekly until (60)-90 mg/kg/day
or 1300 g/m²
Diagnosis at 5 days (11.08.2005)

Treatment with Cystagon:
14.11.05 80 mg/kg/day
08.10.09 85 mg/kg/day 0.53 nmol cystine/mg protein
16.10.12 82 mg/kg/day 0.46 nmol cystine/mg protein
21.10.13 78 mg/kg/day

06.10.2014:
Creatinine 0.35 mg/dl, Cystatin C 0.87 mg/dl,
Cystatin-C-GFR 128 ml/min/1.7m2

Urine:
Albumin 19.6 mg/l < 20mg/dl
Imunglobulin G 8.2 mg/l
α1-Mikroglobulin 50.6 mg/l
Α2-Makroglobulin< 2.3 mg/l
Optimal dose of cysteamin

- cystine levels < 1nmol half-cystine/mg protein
- maximum recommended Dose: 1.95 g/m²/day

At what age should treatment be started (siblings)?

Prenatal diagnostic- postpartal cystine levels- postpartal genetics?

Which dose regime should be used?

Maximal dose in adults?

Timing of PML cells cystine measurement after intake of medication?
Feeding Problems

Common problems in patients with nephropathic cystinosis

at diagnosis
during course of disease

### Feeding Problems

45 patients (3.5 y - 33 y)

<table>
<thead>
<tr>
<th>Age at Diagnosis</th>
<th>Number of Patients</th>
<th>PEG/Button</th>
</tr>
</thead>
<tbody>
<tr>
<td>postpartal</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>0-6 months</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>6-12 months</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>12-24 months</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>&gt;24 months</td>
<td>12</td>
<td>5</td>
</tr>
</tbody>
</table>

45 patients, 22 PEG/Button

Mean time of PEG/Button: 6.6 years

10 patients with swallowing difficulties – 3 patients > 25 years with additional severe diarrhea
Feeding Problems

Therapy to improve clinical course

- large volume of fluid
- polypharmacy for metabolic control
  - (high dose) bicarbonate / citrate
  - (large volume of) electrolyte supplements
    - (\(K^+\), \(Na^+\), phosphate, Ca)
- Treatment with cysteamine
- several times a day

feeling unwell
GI discomfort
poor appetite
vomiting
nausea
distension
pain
Questions

• Small volumes of electrolyte supplements – more often /day
  Use of Amilorid?

• Metabolic acidosis: exchange bicarbonate to citrate
  chemical compounds: Potassium- citrate or chloride
  instead of carbonate
  Magnesium organic compounds instead of
  anorganic compounds (Magnesiumoxid)
  Hydrochlorothiazide?
Feeding Problems

- Indication for Indomethacin – duration of treatment – dosage?
  Indomethacin: effective reducing levels of:
  urinary sodium, potassium, phosphate, urate, glucose, bicarbonate secretion *
  but: renal functional deterioration, ulcerogenic potential

- Early logopedic treatment for chewing and swallowing difficulties

- Muscle status: early physiotherapy

- Nutritional problems improve with age - training programs – for children/adolescent
  similar to other patient groups with chronic illnesses as diabetes

*Haycock GB et al, Arch Dis Child 1982 57:934-939
Cysteamine – Treatment

- slows progression of renal insufficiency
- protects extrarenal organs
- accelerates growth


Percentage of normal growth at different age intervals in Cysteamine-treated patients (solid bars) and Controls (hatched bars)

- First year: 73.5%±3.4 of normal growth velocity
- Untreated: 59±3.7
- Every succeeding year: 76.4 and 97.9% of normal growth velocity

93 patients treated with cysteamine
55 historical controls

Improved renal function in children with cystinosis treated with cysteamine.
Growth retardation in patients with cystinosis is multifactorial

- renal Fanconi Syndrome
- metabolic acidosis
- loss of sodium / potassium
- calcium/phosphate imbalance
- poor metabolic status
- impaired axis GH-IGF-1
- decreased renal function
- hypothyroidisms
- extrarenal complications
- primary hypogonadisms (males)
- diabetes
- bone disease
- rickets
- cystine accumulation in bones

Cysteamine therapy does not lead to catch-up growth*

Fanconi-Syndrome

- Elevated urinary excretion of PTH, GH, and IgF-1*
- Rickets
- Metabolic acidosis
- Elevated excretion of Vitamin D binding protein**

Adequate therapy:
- 625µgr/day ergocalciferol: No elevation of 1,25 Dihydroxycholecalciferol serum level
- Substitution with 1,25 Dihydroxycholecalciferol
- Supplement of calcium phosphate cave: nephrocalcinosis

Linear growth

** Wilmer MJ, Am J Kidney Dis (2008);51:893-903
Determination of Osteopenia

Osteopenia:
- deposition of crystals
- hypothyroidism
- diabetes mellitus
- primary hypogonadism
- urinary phosphate wasting
- chronic renal failure

11 transplanted children
- 5 male / 4 female
- 3/5 males primary testicular failure
- 7/9 patients – normal BMD

Correlation of BMD with growth parameters
- comparing to height, weight, pubertal stage growth

Correlation of areal BMD

BMD measurement by DEXA:
- predictive value for bone fragility is poor in patients with nephropathic cystinosis
- cannot be used to assess fracture risk

Endocrine Functions

positive influence of cysteamine treatment *:
• on thyroid function – without treatment: thyroid atrophy
  Hypothyroidism: adequately treated: 56% vs. 87%
• on Diabetes mellitus: adequately 4% vs.50%

no influence of cysteamine treatment:
• primary hypogonadisms (males) due to testis fibrosis and atrophy***(low testosterone, LH↑, FSH↑,)
• delayed puberty

Cysteamine-Treatment

Animal models: Effect of cysteamine on GH-IGF1 axis

**Rats**: GH  
- cysteamine is causing depletion of somatostatin  
- increase ghrelin plasma levels*

**carpe fish**: increase of GH, thyroxin, T3 and growth**

**chicken**: enhanced growth and body weight***

**Humans**: positive effect on GH  
- cystine depleting effect in bone particular in epiphysis**

Growth hormone secretion in cystinosis patients:

- **4/9 nocturnal GH measurements:**
  - normal mean GH level >3 ng/ml
  - normal number of peaks during 7 h of measurement
  - no difference to case control

- **4/9 glucagon test**
  - Glucagon-Test: 3/4 normal peak levels
  - 1/4 GH deficiency
  - 2/4 patients with abnormal peak timing

Before rhGH treatment exclusion of GH-deficiency with IGF-1

*Besouw et al, Pediatr Nephrol (2012) 27:2123-2127*
Growth

„Long-term treatment with growth hormone in short children with nephroathic cystinosis“

Safety of growth hormone treatment
74 children (3-18 years) men period 3.1 years

52 patients conservative (mean age 7.1y)
7 Patients on dialysis (12.5 y)
15 renal transplant (14.8 y)

1. SD -4.0±1.2 4.3±1.6 cm/y
2. SD -4.4±1.2 2.5±2.1 cm/y
3. SD -4.9±1.1 3.7±2.4 cm/y

no faster deterioration in renal function
no major side effects
Insulin fasting levels elevated – no significant change in glucose levels

Wühl, E et al, J Pediatrics, 138, 6, 2001, 880-887
Growth

Early oral cysteamine therapy
Growth

Optimal growth

- Management of rickets
- Vitamin D and 1,25 dihydrocholecalciferol treatment
- Supplement of phosphate and Calcium
- Parameters to start enteral feeding
- Hormonal treatment with rhGH
  - Exclusion of GH deficiency IGF1 measurements
  - IgF1 low – glucagon test
- Hormonal treatment with thyroxin
  - normal values – healthy children?
- Hormonal treatment of primary hypogonadisms in males
- Bone structure