Disturbances of the Potassium and Phosphorus Metabolism in Periparturient Dairy Cows

Walter Grünberg

Similarities between Potassium and Phosphorus

- Predominantly intracellular electrolytes
- Balance strongly dependent on oral intake
- Important losses through the mammary gland
- Both associated with muscle function
- Disturbances of the electrolyte balance are common in periparturient dairy cows
- ...
**Dissimilarities**

- **No storage form of potassium available in the body**
  - Large reserves of phosphorus in bone

- **Tight regulation of extracellular potassium concentration**
  - Plasma [Pi] not tightly regulated

- **Regulation of potassium homeostasis reasonably well understood**
  - Poor understanding of mechanisms regulating the P homeostasis

- **Symptoms of acute disturbances of the (extracellular) potassium homeostasis well defined**
  - Relevance of hypophosphatemia controversially debated

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**Potassium and Phosphate in Blood**

**Periparturient Period – Healthy Cow**

[Graphs showing plasma potassium and phosphate levels over time relative to calving.]

*Grünberg et al. 2011*
Potassium and Phosphate in Blood

Periparturient Period – Sick Cow

Left displaced abomasum

<table>
<thead>
<tr>
<th></th>
<th>normal</th>
<th>57 %</th>
<th>decreased</th>
<th>35 %</th>
<th>increased</th>
<th>8 %</th>
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<tbody>
<tr>
<td>Plasma [Pi]</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>normal</th>
<th>45 %</th>
<th>decreased</th>
<th>55 %</th>
<th>increased</th>
<th>&lt;1 %</th>
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<tbody>
<tr>
<td>Plasma [K]</td>
<td></td>
<td></td>
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</table>

Grünberg et al. 2006

Constable et al. 2013

Potassium and Phosphate in Blood

Periparturient Period – Sick Cow

Constable et al. 2013

Grünberg et al. 2006
Relevance of a Disturbed Electrolyte Balance in Periparturient Cows

• Hypokalemia
  – Membrane potential disturbances of excitable cells
    • Altered function of striated and smooth muscles
    • Altered cardiac function
  – Extracellular [K] sustained at expense of intracellular K?

• Hypophosphatemia
  – Relevance uncertain
  – Intracellular P balance is presumably more relevant
    • Intracellular P sustained at expense of extracellular P?

Potassium Homeorrhesis in Early Lactation

• Feed intake at it’s nadir around parturition
• Sudden onset of K losses through milk after parturition
Regulation of the Extracellular Potassium Balance

• Counterregulation to hyperkalemia
  – Compartmental shift of K into the cell
  – Renal excretion
  – Intestinal excretion

• Counterregulation to hypokalemia
  – Shift of K from intracellular to extracellular space
    • Less efficient with less muscle mass
  – Renal retention of K
    • Requires water and Na excretion
  – Reduced [K] in milk

Hypokalemia in Sick Cows

• Etiology not entirely understood
  – Decreased feed intake
  – Delayed gastrointestinal transit time
  – Alkalosis
  – Dehydration (Aldosterone)?
  – Iatrogenic (glucose, rehydration, glucocorticoids...)
  – ...

Hypokalemia in Sick Cows

• Etiology not entirely understood
  – Decreased feed intake
  – Delayed gastrointestinal transit time
  – Alkalosis
  – Dehydration (Aldosterone)?
  – Iatrogenic (glucose, rehydration, glucocorticoids...)
  – ...
Iatrogenic Exacerbation of Hypokalemia

- Parenteral Dextrose Infusion
- Parenteral Hypertonic NaCl
  - Expect decline > 0.8 mmol/L with standard treatment
- Administration of NaHCO₃
- Large volumes of fluid
- Corticoids
  - ....

Clinical Implications of Hypokalemia
Hypokalemic Recumbency

- Clinical presentation differs from milk fever
- Resembling botulism
  - Decreased tone of tongue- and head / neck muscles
  - “Rubber neck” / head on the ground
- Pronounced hypokalemia
  \[ [K] < 2.0 \text{ mmol/L} \]
- Frequently associated with cardiac arrhythmia
  - Atrial fibrillation

Subclinical Implications of Hypokalemia

Hypokalemia and Abomasal Motility

Turck & Leonhard-Marek 2010
Potential Clinical Implications of Hypokalemia

Decreased Resting-Membrane Potential of Excitable Cells

Potassium as Ca-Antagonist with Hypercalcemia
Potassium as Ca-Antagonist with Hypercalcemia

Increased risk of complications after IV calcium in hypokalemic cows??

Plasma Phosphate (Pi) in Healthy Periparturient Dairy Cows

Plasma Calcium

Grünberg et al. 2011
Mechanisms Presumed behind Periparturient Hypophosphatemia

- Loss of P through udder
- Decreased feed intake
- Decreased GI motility
- Hormonal adaptation
  - PTH
  - Cortisol
- Lag time of counter regulation
- ...

Plasma Calcium and Phosphate at the Onset of Lactation

Goff et al. 2002
Incidence of Periparturient Hypophosphatemia

Metabolic Profiling of Clinically Healthy Dairy Cows

• 54% on the day of calving
  Staufenbiel 2002
• Over 15% in the first 10 days of lactation
• 10% between 10 and 20 days of lactation
  Macrae et al. 2006
  Macrae et al. 2012
## Incidence of Hypophosphatemia in Recumbent Periparturient Dairy Cows

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>[Ca] ↓ [Pi] ↓</td>
<td>60,2%</td>
<td>67,5%</td>
<td>64,4%</td>
<td>62,4</td>
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<tr>
<td>[Ca] ↓ [Pi] →</td>
<td>10,8%</td>
<td>12,1%</td>
<td>1,0%</td>
<td>4,1%</td>
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<tr>
<td>[Ca] → [Pi] ↓</td>
<td>18,2%</td>
<td>13,7%</td>
<td>28,7%</td>
<td>18,4%</td>
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<tr>
<td>[Ca] → [Pi] →</td>
<td>10,8%</td>
<td>6,7%</td>
<td>5,9%</td>
<td>15,1%</td>
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</table>

**Incidence of Hypophosphatemia in Recumbent Periparturient Dairy Cows**

> 80% of recumbent periparturient cows are hypophosphatemic...
Hypophosphatemia and Periparturient Recumbency

Table 1
Median values of the variables [age, calcium (Ca), phosphorus (P), magnesium (Mg), potassium (K)] compared between the positive response (PR) and negative response (NR/ADC) groups in the study.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Age (years)</th>
<th>Ca (mmol/L)</th>
<th>P (mmol/L)</th>
<th>Mg (mmol/L)</th>
<th>K (mmol/L)</th>
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</thead>
<tbody>
<tr>
<td>Response</td>
<td>PR ADC PR ADC</td>
<td>PR ADC</td>
<td>PR ADC</td>
<td>PR ADC</td>
<td>PR ADC</td>
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<tr>
<td>Median</td>
<td>8.0 8.1 1.41 1.40</td>
<td>86(^a) .50(^a)</td>
<td>1.11 1.03 4.20 4.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cows (n)</td>
<td>50 36 50 36</td>
<td>50 36 50 36</td>
<td>50 36 50 36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>0.387</td>
<td>0.378</td>
<td>0.019</td>
<td>0.260</td>
<td>0.326</td>
</tr>
</tbody>
</table>

* Median values with superscripts are significantly different at the 0.05 level (Wilcoxon Rank-Sum Test)

PR= Positive responders
ADC= Alert Downer Cows

Ménard and Thompson 2007

What Happens if Dairy Cows are Transiently P-Deprived?

Some experimental results of the past years....
What Happens if Dairy Cows are Transiently P-Deprived?

Make the difference between transient (acute) and chronic phosphate deficiency

Chronic Dietary P-Deprivation

Average feed intake for cows fed different dietary P concentrations

Average body weight of cows fed different dietary P concentrations

Call et al. 1987
Chronic Dietary P-Deprivation

Recommendation Standards for Dietary P in the Industrialized World

**Lactation**

<table>
<thead>
<tr>
<th>Milk (kg/d)</th>
<th>DMI (kg/d)</th>
<th>UK</th>
<th>D</th>
<th>USA</th>
<th>NL</th>
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</thead>
<tbody>
<tr>
<td>15</td>
<td>17</td>
<td>56</td>
<td>0.33</td>
<td>46</td>
<td>0.27</td>
</tr>
<tr>
<td>25</td>
<td>20.3</td>
<td>77</td>
<td>0.38</td>
<td>65</td>
<td>0.32</td>
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<tr>
<td>35</td>
<td>23.6</td>
<td>99</td>
<td>0.42</td>
<td>84</td>
<td>0.36</td>
</tr>
<tr>
<td>45</td>
<td>26.9</td>
<td>121</td>
<td>0.45</td>
<td>103</td>
<td>0.38</td>
</tr>
<tr>
<td>55</td>
<td>30</td>
<td>142</td>
<td>0.47</td>
<td>121</td>
<td>0.40</td>
</tr>
</tbody>
</table>

Modified from Pfeffer et al. 2005
Phosphorus-Recommendation Standards for Dairy Cattle

* P-Digestibility = 70 %

Concerns with Transient P-Deficiency in Periparturient Cows

- Postparturient Hemoglobinuria
- Downer Cow Syndrome
- Disturbed liver function
Dietary P-Depletion of non-periparturient Dairy Cows

Pilot-Study on 10 past-peak Dairy Cows

• Fed a P-deficient diet for 5 weeks
  – Ration with 0.18 % P in DM

• Then supplemented with P for 2 weeks
  – Ration with 0.47 % P/in DM

Grünberg et al. 2015
Clinical Signs

- No altered demeanor
- No clinical disease
- No noticeable drop in feed intake or milk production
  - DMI: 20.4 ± 2.5 kg DM/day
  - Milk: 23.6 ± 3.7 kg Milk/day
- No signs of muscle weakness
- No signs of anemia or hemolysis

Counterregulatory Mechanisms

Bone Mobilization

Grünberg et al. 2015
Phosphorus in Muscle Tissue

![Graph showing Phosphorus levels in muscle tissue](Grönberg et al. 2015)

Electromyography

- No apparent signs of muscle weakness
- **EMG-results did not suggest energy deficiency** (ATP or creatine phosphate-depletion)
- Increased occurrence of pathologic spontaneous activity (PSA) in muscle fibers
  - Suggestive membrane instability or neuromyopathy

Grönberg et al. 2015
Dietary P-Deprivation in Transition Dairy Cows

- Two groups
  - Group C
  - Group LP (low-phosphate)

- Study period from 6 weeks ante- to 6 weeks post-partum
  - P-deficient diet for LP cows from 4 weeks a.p. to 4 weeks p.p.
    - 0.15% P in DM antepartum
    - 0.20% P in DM postpartum

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Dietary P-Deprivation in Transition Dairy Cows

**Graph** showing plasma Pi (mmol/L) over time from -60 to 60 days relative to calving. The graph displays three phases: acclimation, depletion, and repletion, with data points for both control and LP groups. The graph is labeled with 'Grüngberg et al. 2018.'
Clinical Findings

• No abnormal demeanor until parturition
  – No disease occurrence
  – No feed intake depression
  – No signs of muscle weakness

• Periparturient period
  – Control: 4 /18 Cows with clinical hypocalcemia (stage I and II)
  – Group LP: Uneventful parturition, no clinical hypocalcemia, no recumbencies

Periparturient Calcium Balance in P-deprived Dairy Cows

Cohrs et al. 2018
Mechanisms of periparturient Ca-Mobilisation

Bone Mobilization Despite of Blunted Increases in PTH

“Crosslaps”

Muscle Tissue Composition and Function

- No clinical signs of muscle function disturbance
- P-deprivation does not alter muscle tissue P, Pi, ATP, ADP, AMP or creatine phosphate content
- No biochemical indication of muscle cell damage
- Increased occurrence of pathological spontaneous activity (PSA) in muscle fibers
Feed Intake and Milk Production

Feed Intake

Milk Production

Negative Energy Balance

Plasma [NEFA]

Liver Triacylglycerol (TAG)
Postparturient Hemoglobinuria

- 5/18 P depleted cows
- Always in 2. week of lactation
- Duration 3 – 5 days

Preliminary Conclusions

- Hemolysis occurred in narrow time window relative to calving

- Predisposition?
  - P-Deprivation seems to play a role
  - Other factors?

- Destruction of specific erythrocytes?
  - Cannot be controlled
  - After lysis of specific erythrocytes, normal regenerative activity even during sustained P-deprivation
Disturbances of the Potassium and Phosphorus Metabolism in Periparturient Dairy Cows

Synopsis

• Homeostasis of phosphorus and potassium are both challenged in periparturient cows
  – Even more so in cows with feed intake depression

• Homeostatic disturbances may well be consequence rather than cause of a primary problem

• Clinical and subclinical effect of balance disorders for these electrolytes are poorly defined
Synopsis

• For both electrolytes increasing the supply in late gestation to prevent deficiencies in early lactation IS NOT an option

• Supplying these minerals (case by base basis) in cows off feed should be considered as supportive care treatment

Treatment Options

• For both minerals parenteral treatment is unsuitable for the field situation
  – Phosphorus
    • No products containing PO$_4$ commercially available
    • Bolus IV-infusion of PO$_4$-solutions short lived effect (and off label)
  – Potassium
    • Bolus IV-infusion not an option
    • Drip infusion requires constant monitoring of plasma [K]

• Oral supplementation of both minerals is
  – safe
  – effective
  – (relatively) inexpensive
Solubility of Various Phosphate Salts

<table>
<thead>
<tr>
<th>Phosphate salt</th>
<th>Solubility in g/100 g H₂O at 25 °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaH₂PO₄</td>
<td>Monosodium phosphate</td>
</tr>
<tr>
<td>Na₂HPO₄</td>
<td>Disodium phosphate</td>
</tr>
<tr>
<td>CaHPO₄</td>
<td>Dicalcium phosphate</td>
</tr>
<tr>
<td>Ca(H₂PO₄)₂</td>
<td>Monocalcium phosphate</td>
</tr>
<tr>
<td>KH₂PO₄</td>
<td>Monopotassium phosphate</td>
</tr>
<tr>
<td>K₂HPO₄</td>
<td>Dipotassium phosphate</td>
</tr>
<tr>
<td>MgHPO₄</td>
<td>Magnesium phosphate</td>
</tr>
</tbody>
</table>

Oral Treatment of Hypophosphatemia

Idink and Grünberg 2014
Oral Treatment of Hypophosphatemia

Monocalciumphosphate (Ca(H$_2$PO$_4$)$_2$) vs. Dicalciumphosphate (CaH$_2$PO$_4$)

Cohrs and Grünberg 2018

Oral Treatment of Hypophosphatemia

NaH$_2$PO$_4$, Na$_2$HPO$_4$, MgHPO$_4$, and Control

Cohrs and Grünberg 2018
Oral Treatment of Hypophosphatemia

Treatment recommendation: 50-60 g P orally every 12-24h in the form of:

- NaH$_2$PO$_4$ $\rightarrow$ 250-300 g (First choice)
- Na$_2$HPO$_4$ $\rightarrow$ 280-340 g
- KH$_2$PO$_4$ $\rightarrow$ 200-250 g (with concomitant hypokalemia)
- Ca(H$_2$PO$_4$)$_2$ $\rightarrow$ 200-240 g (less effective, but may provide Ca)
- CaHPO$_4$ $\rightarrow$ 300-330 g (unsuitable for rapid correction of hypophosphatemia)
- MgHPO$_4$ $\rightarrow$ 300-330 g (unsuitable for rapid correction of hypophosphatemia)

Oral Administration of Potassium

KCl as Bolus- or Drench

- Rapid onset (ruminal absorption)
- Safe to dose
- Duration of effect? Treatment interval?
- Avoid massive over dosage
  - Hyperkalemia
  - Osmotic diarrhea
  - Mucosal irritation?
**Oral KCl**

**Recommended Dosage**

- Recommendations are mostly empirical!
- **Mild / moderate Hypokalemia:** 60-90 g/600 kg/ KCl
- **Moderate / severe hypokalemia:** 90-150 g KCl / 600 kg
- **Avoid single doses > 250 g KCl / 600 kg**
- **Treatment interval:** 8-12h?

**Oral KCl**

**Pay Attention to Difference between K and KCl**

- Approx. 50% of the mass of KCl is K!
  \[ x \text{ g KCl} \approx \frac{x}{2} \text{ g K} \]
- Content of K on the label often given as amount K (NOT as KCl)
- To treat even mild hypokalemia a drench powder needs to contain at least 30 g K (or 60 g KCl) / dose
Oral Treatment with KCl

200 g of KCl as Drench

Plasma Potassium Concentration

Time relative to treatment (h)

Plasma [K] (mmol/L)

Feeding

Treatment

Feeding

Grünberg unpublished

Walter.gruenberg@tiho-hannover.de
Recommendation Standards for Dietary P

Dry Cow

• 2.5 - 3.0 g/kg (0.25-0.30%) DM (US)
• 2.5 - 2.8 g/kg (0.25-0.28%) DM (D)
• 2.0 - 2.5 g/kg (0.20-0.25%) DM (NL)
• Ca:P ratio considered obsolete in bovine
• Avoid excess of P (> 4.2 g/kg DM in close-up)

P below 2.0 g kg/DM is probably deficient in the dry-cow ration

Dietary P-Deprivation in Transition Dairy Cows

Dietary P-content

• Acclimation (dry cow)
  – 2.8 g P/kg DM both groups
• Dry cow-period (4-5 weeks)
  – Group LP: 1.5g P/kg DM
  – Group C: 2.8g P/kg DM
• Early lactation (4-5 weeks)
  – Group LP: 2.0g P/kg DM
  – Group C: 4.2g P/kg DM
• Repletion (2 weeks)
  – 4.2g P/kg DM both groups