Omeprazole and Alterations of Calcium Levels in Equines

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Objectives

- Describe digestion and gastric ulcers in equines
- Define mechanism of action of GastroGard® (omeprazole)
- Describe role of calcium in equine physiology
- Discuss omeprazole and calcium retrospective analysis of NCSU CVM horses
- Discuss clinical implications of proton pump inhibitor use
Despite their large size, horses have very sensitive digestive tracts.
How the Factory Runs

- **Mouth**
  - 3 salivary glands
  - Contain bicarbonate and amylase

- **Esophagus**
  - Little to no reflux ability

- **Stomach**
  - Only holds 8-16 quarts with 3 primary components
    - Saccus caecus
    - Fundic region
    - Pyloric region
How the Factory Runs

- Small Intestine
  - Enzymatic digestion
  - Primary absorption of Ca²⁺
- Large Intestine
  - 5 compartments (cecum, large colon, small colon, rectum, anus)
  - Cecum has many specific microbes that create fermentation for remainder of undigested products
Equines and Ulcers

Upset to this delicate system has several causes:

- Stress
- Exercise
- NSAIDs
- Improper feeding

Result:

- Non-glandular and glandular ulcers
Equines and Ulcers

- Stress
- Illness
- Stabling
- Trailering
- Showing
- Weaning

Mechanism of action not definitive

Inflammation or $\Delta$ in mucosal $Q_H$

Murray, 2002.
StockHorse, 2009. stockhorseshowhorse.com
iNetGiant, 2011. arkansas.inetgiant.co
NationwideHorseTransportation, 2011.
Equines and Ulcers

Exercise

- Dressage, endurance, eventing, polo, reining, racing
- Movement increases acid exposure to the squamous mucosa area by raising the level of liquid gastric contents
Equines and Ulcers

NSAIDs are non-steroidal anti-inflammatory drugs that inhibit cyclooxygenase which allows them to act as
- Analgesics
- Antipyretics
- Anti-inflammatories

Examples
- Phenylbutazone
- Flunixin meglumine
- Ketoprofen
Mechanism of Action: NSAID
Mechanism of Action: NSAID

- NSAIDs block COX-1 and COX-2
  - COX-1 inhibition
    - “Housekeeping” enzyme
    - Decrease mucous layer and bicarb
    - Inhibit renal blood flow
    - Impair mucosal lining repair
  - COX-2 inhibition
    - Constitutively expressed enzyme
    - Block pain
    - Block inflammation
Equines and Ulcers

Improper Feeding

- Large meal once daily
  - Equine stomach is designed to work best when \( \frac{3}{4} \) full and have small meals often
- No pasture turnout
  - Nature intended grazing to select most digestible grasses
  - Continuous flow of saliva buffers stomach acid
- Primarily concentrates
  - Gut is designed for roughage intake
  - Carbohydrates ferment creating volatile fatty acids (VFA)
Equines and Ulcers

End Result
- Non-glandular and glandular ulcers
- Performance, appetite, and behavior affected
- Strong acids attack unprotected squamous cells of saccus caecus non-glandular region
Equines and Ulcers

Numbers to note
- 25% to 50% of non-competing horses have ulcers
- 93% of Thoroughbred racehorses have ulcers
- 75% to 90% develop glandular ulcers on an NSAID
Equines and Ulcers

Ulcers cause the following symptoms...
- Weight loss
- Irritability
- Chronic colic
- Lethargy
- Anorexia
- Poor coat condition
Gastric Ulcers

Treatment

- **Histamine-2 antagonist (H2 Blocker)**
  - Ranitidine, famotidine, cimetidine
  - Only block existing acid
  - Short acting, needs frequent dosing (TID)
  - Drug interactions

- **Gastric Mucosal Protectant**
  - Sucralfate (sucrose octasulfate + aluminum hydroxide)
  - Forms complex with positively charged proteins creating viscous adhesive paste protecting gastric lining against peptic acid, pepsin, and bile salts
  - Drug interactions
  - Short acting, needs frequent dosing (TID)

- **Proton Pump Inhibitor (PPI)**
  - Omeprazole, lansoprazole, pantoprazole
  - Blocks and prevents acid from forming in ~3 days
  - Helps heal ulcers and prevent future ones
  - Irreversible, longer acting (SID)
  - Drug Interactions
Omeprazole

Drug Class
- Proton Pump Inhibitor (PPI)
- Substituted benzimidazole

Mechanism of Action
- Irreversibly/specifically inhibits parietal cell hydrogen-potassium adenosine triphosphatase enzyme system
- Proton pump of gastric mucosa is $H^+, K^+-\text{ATPase}$
- Suppresses gastric basal and stimulated HCl secretion
Omeprazole
Treatment with Omeprazole

Efficacy

- Maintains gastric pH ≥4
  - Must give 30 minutes PRIOR to morning meal
- Established in many clinical trials
  - 77% of omeprazole treated horses remained ulcer free while in race training

Cost

- PPI > H₂ Blocker > Sucralfate

Safety

- Side effects are minimal
- Long term use?
  - Studies in human population of ↓ calcium
  - Newer studies examining risk for fractures
Effect of gastric acid secretion on intestinal phosphate and calcium absorption in normal subjects

Nephrology Dialysis Transplantation, 1995

Non-randomized, placebo-controlled, cross-over clinical trial

Objectives: To determine if gastric pH truly affects calcium absorption

Methods: Normal subjects 24-h urinary calcium phosphate and postprandial blood calcium measured

Study: Following exclusion criteria, 8 subjects received 60mg omeprazole or placebo and 1 gram of calcium with each meal for 3 doses and then the washout period occurred and same procedure repeated

Results: Inhibition of gastric acid secretion by omeprazole significantly (p<0.05) reduces calcium in normal subjects
PPI use in Humans

Effects of proton pump inhibitors on calcium carbonate absorption in women

The American Journal of Medicine, 2005

- Randomized, double-blind, placebo-controlled, cross-over clinical trial
- Objective: To determine the role of PPI’s on pH in Calcium absorption
- Methods: Volunteers ingest omeprazole 20mg or placebo q am x 7 days along with a Ca-labeled calcium carbonate capsule such that calcium concentrations can be measured by atomic absorption spectrophotometry with blood levels drawn at baseline and 5 hours post ingestion
- Study: Following exclusion criteria, 18 subjects completed the trial to include 1 week treatment with 3 week wash out before using the other treatment for 1 week (drug vs. placebo)
- Results: 1 week course of omeprazole 20mg daily significantly (p<0.05) decreased fractional calcium absorption under fasting conditions.
PPI use in Humans

PPI’s and Risk of Fracture: A Systematic Review and Meta-Analysis of Observational Studies

American Journal of Gastroenterology 2011

Systematic review of and meta-analysis of controlled observational studies to evaluate the risks of PPI use on fracture outcome

Objectives: Studies suggest gastric suppression could result in decreased intestinal calcium absorption and subsequent bone fractures. Evaluating these risks via review and meta-analysis in hope of a conclusion.

Methods: All controlled observation studies that compared fracture outcome in patients with PPI therapy with a control group were included. Pooled odds ratios (ORs) were calculated with 95% confidence interval via random-effects model.

Results: 1,668 studies used and 10 (4 cohort and 6 case controlled) found 223,210 fractures included in analysis. There was significant statistical and clinical heterogeneity among studies and found a modest association between PPI use and increase risk of hip and vertebral fractures.
PPIs and Human Safety

- Gastric acid suppression associated with an ↑ risk of
  - Community-acquired pneumonia
  - *Clostridium difficile* infection
- Risk of a fracture ↑ with duration of treatment of PPI
  - High doses for > 1 year - hip fracture
  - Standard doses < 3 years - spine, forearm, wrist fractures
- Decrease in stomach acid ↓ ionized calcium in stomach
  - Interfere with absorption in SI
- Omeprazole may interfere with osteoclasts
  - Bone matrix density ↑ but bone remains brittle inside

Katz. 2010
Gray S. 2010
PPIs and Human Safety

➢ The FDA is revising Rx and OTC labels for PPIs
  ➢ Possible ↑risk of fractures (hip, wrist, spine)
  ➢ Based upon FDA review of long-term studies

➢ Osteoporotic fracture associated with increased
  ➢ Cost
  ➢ Morbidity
  ➢ Mortality

➢ Other contributing factors
  ➢ Diabetes
  ➢ Obesity
  ➢ Osteoporosis
  ➢ Fracture history
  ➢ Smoking

Katz. 2010
Gray S. 2010
FDA Drug Safety Communication: Possible increased risk of fractures of the hip, wrist, and spine with the use of proton pump inhibitors

Update: 3/23/2011

Safety Announcement

[05-25-2010] The U.S. Food and Drug Administration (FDA) is revising the prescription and over-the-counter (OTC) labels for a class of drugs called proton pump inhibitors to include new safety information about a possible increased risk of fractures of the hip, wrist, and spine with the use of these medications.

The new safety information is based on FDA's review of several epidemiological studies that reported an increased risk of fractures of the hip, wrist, and spine with proton pump inhibitor use. Some studies found that those at greatest risk for these fractures received high doses of proton pump inhibitors or used them for one year or more. The majority of the studies evaluated individuals 50 years of age or older and the increased risk of fracture primarily was observed in this age group.

Healthcare professionals and users of proton pump inhibitors: OTC PPIs are marketed at low doses are only intended for a 14 day course of treatment up to 3 times per year. Healthcare professionals should be aware of the risk for fracture if they are recommending use of OTC PPIs at higher doses or for longer periods of time than in the OTC PPI label.
99% of calcium is in the bone
- Remaining 1% in extracellular fluid
  - 40% Protein bound
  - 50% Ionized as Ca$^{2+}$
  - 10% Complexed with anions
    - Bicarbonate, citrate, lactate, phosphate

Adult horses need 40mg/kg/day
Growing horses need 50-75g/day
### Guaranteed Analysis

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Min.</th>
<th>Max.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude Protein</td>
<td>12.00%</td>
<td></td>
</tr>
<tr>
<td>Lysine (min.)</td>
<td>0.60%</td>
<td></td>
</tr>
<tr>
<td>Methionine (min.)</td>
<td>0.20%</td>
<td></td>
</tr>
<tr>
<td>Threonine (min.)</td>
<td>0.40%</td>
<td></td>
</tr>
<tr>
<td>Crude Fat (min.)</td>
<td>12.00%</td>
<td></td>
</tr>
<tr>
<td>Crude Fiber (max.)</td>
<td>15.00%</td>
<td></td>
</tr>
<tr>
<td>Calcium (min.)</td>
<td>0.75%</td>
<td></td>
</tr>
<tr>
<td>Calcium (max.)</td>
<td>1.25%</td>
<td></td>
</tr>
<tr>
<td>Phosphorus (min.)</td>
<td>0.45%</td>
<td></td>
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<tr>
<td>Magnesium (min.)</td>
<td>0.40%</td>
<td></td>
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<tr>
<td>Iron (min.)</td>
<td>250 ppm</td>
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<tr>
<td>Potassium (min.)</td>
<td>0.90%</td>
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<tr>
<td>Selenium (min.)</td>
<td>0.50 ppm</td>
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<tr>
<td>Zinc (min.)</td>
<td>160 ppm</td>
<td></td>
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<tr>
<td>Manganese (min.)</td>
<td>100 ppm</td>
<td></td>
</tr>
<tr>
<td>Copper (min.)</td>
<td>50 ppm</td>
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</tr>
<tr>
<td>Vitamin A (min.)</td>
<td>5,500 IU/lb</td>
<td></td>
</tr>
<tr>
<td>Vitamin D (min.)</td>
<td>750 IU/lb</td>
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</tr>
<tr>
<td>Vitamin E (min.)</td>
<td>150 IU/lb</td>
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</tr>
<tr>
<td>Ascorbic Acid (min.)</td>
<td>40 mg/lb</td>
<td></td>
</tr>
<tr>
<td>Biotin</td>
<td>0.25 mg/lb</td>
<td></td>
</tr>
<tr>
<td>Lactobacillus Acidophilus</td>
<td>1.4 million CFU/gm</td>
<td></td>
</tr>
<tr>
<td>Fermentation Product (min.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saccharomyces Cerevisiae</td>
<td>2.80 million CFU/gm</td>
<td></td>
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<tr>
<td>Yeast Culture (min.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellulase (Trichoderma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Longibrachiatum Fermentation Extract (min.)</td>
<td>125 CMC-ase Units/lb</td>
<td></td>
</tr>
<tr>
<td>Protease (Bacillus Subtilis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fermentation Extract (min.)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Ingredients

Calcium Absorption

- Insoluble and Soluble
  - Calcium Carbonate-insoluble
    - Most common
    - Low pH required for proper absorption in the intestine
    - Calcium carbonate is 40% elemental calcium
      - 1000 mg will provide 400 mg of calcium
  - Calcium Citrate-soluble
    - Uncommon in horse feeds
    - Choice for individuals taking H2Blockers or PPIs
    - More easily digested and absorbed than calcium carbonate
    - Calcium citrate is about 21% elemental calcium
      - 1000 mg will provide 210 mg of calcium
Calcium Absorption

- Stomach pH~2
  - Calcium absorbed in ionized form via acidic medium (HCl) releasing calcium from salt or food complex
- Omeprazole blocks acid
  - Calcium not becoming ionized therefore questionable ability to be absorbed in small intestine
- GastroGard© correlation
  - Calcium homeostasis
    - Low levels equal impaired bone deposition
    - Low levels stimulate PTH ↑bone resorption
Surveyed admitted CVM horses from 2009-2011
- Groups were: ≤6 months, 7 months to 24 months, >2 years to 14 years old, ≥15 years old
- Treatment naïve total serum calcium baselines to compare to PPI treatment groups

Exclusions
- Taking omeprazole or H₂ blocker
- Given calcium gluconate
- Bottle fed
- Pregnant
- Gastrointestinal disease: colic, diarrhea
- Abnormal albumin levels
- Death
27 met criteria in the ≤6 month old group
- 93% had total calcium level WNL (11.3-13.4mg/dl)
- Fractures, eye injuries, lethargy, born at hospital
- Mean calcium of 12 mg/dl
5 met criteria in the 7 month to 24 month old group

100% had total calcium WNL (11.3-13.4 mg/dl)

Lameness, cryptorchid, eye injuries

Mean calcium of 12.3 mg/dl
70 met criteria in the >2 years old to 14 year old group
92% had total calcium level WNL (11.3-13.4 mg/dl)
Lacerations, eye injuries, lameness, castration
Mean calcium of 12.1 mg/dl
37 met criteria in the ≥15 years old group
- 87% had total calcium level WNL (11.3-13.4 mg/dl)
  - Ophthalmology issues, lesions, lameness, choke, wounds
- Mean calcium of 12.4 mg/dl
# Treatment-Naïve Calcium Data

<table>
<thead>
<tr>
<th>Age</th>
<th>Mean Calcium</th>
<th>1º Breed Reported</th>
<th>Age Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 6 months</td>
<td>12 mg/dl</td>
<td>Quarter Horse</td>
<td>Most ≤ 3 months</td>
</tr>
<tr>
<td>7 months to 24 months</td>
<td>12.3 mg/dl</td>
<td>Quarter Horse</td>
<td>Most ~2 years old</td>
</tr>
<tr>
<td>&gt;2 years old to 14 years old</td>
<td>12.1 mg/dl</td>
<td>Arabian and Quarter Horse</td>
<td>NA</td>
</tr>
<tr>
<td>≥ 15 years old</td>
<td>12.4 mg/dl</td>
<td>Thoroughbred and Quarter Horse</td>
<td>Most &gt;20 years</td>
</tr>
</tbody>
</table>
NCSU CVM admitted horses from 2009-2011 analyzed

Exclusions
- Total serum calcium levels before and after PPI not measured
- Gastrointestinal diseases: colic, diarrhea
- Given calcium gluconate
- Bottle fed
- Pregnant
- Abnormal serum albumin levels

Inclusions
- All breeds
- All ages
- Taking treatment dose of omeprazole

Total of 30 met criteria
- Analyzed ↓ total serum calcium levels after omeprazole treatment
- 20 horses experienced a decrease
Omeprazole-Exposed Calcium Demographics

- Total population that experienced ↓ calcium
  - 67%
    - Analyzed via ANOVA and Δ in Ca^{2+} found to be statistically significant (p<0.0125)

- Subpopulation with decrease
  - 45% were 2 years old or younger
    - Age group where calcium availability is critical
# Omeprazole Subgroup Demographics

<table>
<thead>
<tr>
<th>Population</th>
<th>Quarter Horse</th>
<th>Thoroughbred</th>
<th>Appaloosa</th>
<th>Paint</th>
<th>Saddlebred</th>
<th>Arabian</th>
<th>Walking Horse</th>
<th>Standardbred</th>
<th>Total (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;6 months</td>
<td>3</td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Age 7months-24months</td>
<td>1</td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Age &gt; 2years to 14 years</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>Age ≥15 years</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>
# Omeprazole Subgroup Data Analysis

<table>
<thead>
<tr>
<th>Age</th>
<th>Population</th>
<th>Mean Duration of Treatment</th>
<th>Mean Ca(^{2+}) before PPI</th>
<th>Mean Ca(^{2+}) after PPI</th>
<th>Statistically Significant (p&lt;0.05)</th>
<th>Clinically Significant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foals (≤6 months)</td>
<td>n=5</td>
<td>7 days</td>
<td>12.8</td>
<td>10.8</td>
<td>0.002</td>
<td>Likely</td>
</tr>
<tr>
<td>Weanlings/Yearlings (7 months-24 months)</td>
<td>n=4</td>
<td>15 days</td>
<td>12.8</td>
<td>11.3</td>
<td>0.098</td>
<td>Perhaps</td>
</tr>
<tr>
<td>Adolescents/Adults (&gt;2-14 years)</td>
<td>n=9</td>
<td>13 days</td>
<td>12.4</td>
<td>11.7</td>
<td>0.007</td>
<td>Not likely</td>
</tr>
<tr>
<td>Seniors/Geriatrics (≥15 years)</td>
<td>n=2</td>
<td>17 days</td>
<td>12.9</td>
<td>11.5</td>
<td>0.257</td>
<td>Not likely</td>
</tr>
</tbody>
</table>
# Omeprazole Subgroup Data Analysis

<table>
<thead>
<tr>
<th>Age</th>
<th>Population</th>
<th>Mean Duration of Treatment</th>
<th>Mean Ca(^{2+}) before PPI</th>
<th>Mean Ca(^{2+}) after PPI</th>
<th>Statistically Significant (p&lt;0.05)</th>
<th>Clinically Significant</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-24 months</td>
<td>n=9</td>
<td>10 days</td>
<td>12.8</td>
<td>11</td>
<td>0.0078</td>
<td>Likely</td>
</tr>
<tr>
<td>&gt;24 months</td>
<td>n=11</td>
<td>11 days</td>
<td>12.5</td>
<td>11.6</td>
<td>0.0016</td>
<td>Not likely</td>
</tr>
<tr>
<td>0 months through 30 years</td>
<td>n=20</td>
<td>12.5 days</td>
<td>12.6</td>
<td>11.3</td>
<td>0.0001</td>
<td>Perhaps</td>
</tr>
</tbody>
</table>

*YourHorse. 2009. Yourhorse.co.uk*
Lesser of 2 evils
- Painful gastric ulcers
  - Delay career
  - Decrease quality of life
- Chance for fracture or developmental orthopedic disease (DOD)
  - Delay career
  - Decrease quality of life

Treatment
- Risks vs. Benefits
- Seriousness of disease vs. Seriousness of adverse effects
Clinical Implications

- 8 week old foal needs gastric ulcer treatment so you...
  - Treat with omeprazole 4mg/kg
  - Treat with omeprazole 2mg/kg
  - Treat with omeprazole 4mg/kg and sucralfate
  - Treat with ranitidine and sucralfate
  - Don’t treat and let nature run its course
Future Investigation

- Prospective, treatment randomized, placebo controlled trial with oral omeprazole to observe affects on blood calcium levels
  - Methods: Omeprazole 4mg/kg dose or placebo administered once daily for up to 3 weeks duration in healthy young horses
  - Populations: ≤12 months and 13 months-24 months
    - Control and treatment groups for each
    - Power calculations for group size undetermined
  - Inclusion criteria: Appropriate age, UTD on vaccines, no weight, gender or breed restrictions
  - Exclusion criteria: Previous PPI /H₂ treatment, history of colic, bottle fed, abnormal albumin or phosphate levels
  - Study: Obtain baseline and treatment serum calcium levels at 1 week, 2 weeks, and 3 weeks for each age group
  - Results: Determine if gathered values are statistically and (or) clinically relevant in each age group

Katz M. 2010
References


Thank You

- Gigi Davidson
- Dr. Wayne Weart
- Dr. Alison Reif
- Patti Andrews
Questions