RENAL STONE RISK DURING SPACEFLIGHT: ASSESSMENT AND COUNTERMEASURE VALIDATION

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Risk

- Mission risk and Impacts:
  - Potential risk condition exists during the pre-, in- and postflight phases
  - Risk to crewmember for both acute and chronic health effects
  - Potential for significant impact to mission operational objectives
    - Early termination of mission
    - Significant impact to affected crewmember’s performance
    - Significant impact to other crewmembers for medical care and treatment of affected crewmember
As of 2008, 15 symptomatic urinary calculi have been experienced by 13 U.S. astronauts (Pietryzk, et al, 2006; Jones et al, 2008)

Multiple stone events among cosmonauts reported by Russian medical investigators

One in-flight episode nearly causing a mission termination but was resolved by spontaneous stone passage
NEPHROLITHIASIS – A MULTIFACTORIAL DISEASE

RENAL STONE FORMATION

Urine supersaturation of stone-forming salts

- Excess calcium excretion
  - Bone loss
- Low urine volume
  - Low fluid intake
- Low urinary pH
- Decreased urinary citrate
- Nutrition
  - High calcium intake
  - High sodium intake
- Renal stone history
- Underlying medical disease
  - High protein intake
SYMPTOMS/SIGNS

• Severe / agonizing pain in the flank (back just below the ribs spreading around to the front of the abdomen) often extending into the groin area.

• Usually nausea and often vomiting

• Fever chills and sepsis, if infection is present

• Gross or microscopic blood in the urine

• Progression if not treated, hydronephrosis, renal shutdown
<table>
<thead>
<tr>
<th>Stone Size</th>
<th>Chance of Spontaneous Passage</th>
<th>Time to Pass Stone</th>
<th>Require surgical intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 mm</td>
<td>&gt;85%</td>
<td>4.5-8 days</td>
<td>5%</td>
</tr>
<tr>
<td>&lt;5 mm</td>
<td>78-80</td>
<td>7 – 14.5 days</td>
<td>17%</td>
</tr>
<tr>
<td>5-7 mm</td>
<td>20-50%</td>
<td>5.5-22 days</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>(35% avg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;7 mm</td>
<td>&lt; 10%</td>
<td>53 days - never</td>
<td>&gt;80%</td>
</tr>
<tr>
<td></td>
<td>(8% avg)</td>
<td></td>
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</tbody>
</table>

Stones 3 mm in size can cause transient or complete obstruction.
Recurrence approx 5-10%/year up to 75% at 20 years.
STUDY OBJECTIVES

- Quantitate the pre-, in- and postflight risk of renal stone formation associated with space flight.

- Determine the efficacy of potassium citrate as a countermeasure in reducing the in-flight and postflight for renal stone formation.

- Evaluate dietary impact on the urinary biochemistry.
SUBJECTS

**Placebo Group: n = 18**
- NASA-Mir missions: 12 male subjects, mission duration 129 - 208 days
- ISS missions: 6 male subjects, mission duration 93 - 175 days

**KCIT Group: n = 12**
- ISS missions: 11 male/1 female subjects, mission duration 93 - 175 days
METHODS

- 24-hour urines collected pre-, in-, and post-flight
- Food, fluid, exercise, and medications monitored before and during the urine collection period
- Two potassium citrate (KCIT) pills, 10 mEq/pill, ingested daily (with the last meal of the day) from L-3 days to R+14 days
  - Double-blind study design except for last 3 ISS subjects
- Biochemical analysis of urine samples for urinary factors associated with stone formation
- Dietary analysis completed to assess environmental influences on the urinary biochemistry
INVESTIGATION RESULTS
The majority of oral citrate is metabolized in the liver to bicarbonate, each citrate ion producing three bicarbonate ions.

**Potassium Citrate**

KCIT dosage of 20 mEq/d selected based on:
- results from Shuttle and NASA-Mir missions
- minimize any potential for in-flight GI upset (wax matrix/slow release prep)
- minimize the potential to exaggerate the risk for CaP stones (higher pH 7.25-7.5)
- minimize impact to crew time

Effects on renal physiology
- 65-90% of filtered citrate is reabsorbed
- 10-35% of citrate is excreted into the urine

Effects of dosage used (20 mEq/d)
- expected urinary increase of 130-140 mg/d
- expected rise in urinary pH of 0.2 – 0.3 units
FLUID BALANCE

Similar fluid intake and total urine volumes between groups

Low urine volumes (< 2L/d)

↓ Fluid intake during flight
Effect of Potassium Citrate on Urinary pH

Urinary pH in KCIT crewmembers, but not too high.
Effect of Potassium Citrate on Uric Acid Supersaturation

Risk of uric acid stone formation in KCIT crewmembers

Uric Acid Stones
Image from Mission Pharmacal
**CALCIUM BALANCE**

- **Dietary Calcium (mg/d)**
  - Placebo
  - KCIT
  - Dietary Ca intake below recommended levels

- **Urinary Calcium (mg/d)**
  - Placebo
  - KCIT
  - Urinary Ca excretion in KCIT crewmembers
Comparison of in-flight risk to individual’s preflight risk

KCIT subjects maintained calcium oxalate risk at preflight levels
CASE STUDY

CREWMEMBER PARTICIPATED IN BOTH MIR AND ISS MISSIONS
MIR – No Treatment
ISS - KCIT

MIR IN-FLIGHT HYPERCALCIURIA

IN-FLIGHT CALCIUM EXCRETION DURING KCIT INGESTION
Low urine volume during both missions
CASE STUDY

Decreased urinary supersaturation during KCIT ingestion

Supersaturation values >2.0 indicate greater risk for stone formation
SIGNIFICANT FINDINGS

- KCIT treated subjects exhibited decreased urinary calcium excretion.

- KCIT subjects maintained the levels of calcium oxalate supersaturation risk at their preflight levels.

- Increased urinary pH levels in KCIT treated subjects reduced the risk of uric acid stones.

- Individual crewmember response may play a role in renal stone susceptibility and efficacy of countermeasures.
Risk Mitigation Strategies and Recommended Actions
Recommendations

- Encourage increased fluid intake to increase urine volume
Recommendations

- **Use of Potassium Citrate**
  - urinary inhibitor of calcium-containing stones, binds with calcium reducing the amount of calcium available to form CAOX.
  - inhibits crystal growth, aggregation and nucleation.
  - alkalinizes urine and decrease urinary calcium excretion.
  - supported by Space Medicine.
  - in Transition to Medical Practice process for operational use.

- **Assess dietary influences**
  - decrease protein, sodium and oxalate intake.
  - maintain calcium intake to recommended levels.

- **Perform urinary risk assessments**
  - identify crewmembers who are at any elevated risk.
  - provides an education program to help humans remain healthy during space exploration.
FUTURE POTENTIAL
Potential In-Flight Prediction of Stone Risk

Capability to measure urine volume provided with the installation of the UMS on Flight 20A and the addition of the in-line calcium sensor for real-time data collection.

Development of an oxalate sensor would be required to optimize real-time risk.
“I'd rather give birth to an elephant than go through this”.

“Like being hit with a two-by-four”.

“Like being shot with an arrow”.

“Pain came on suddenly and did not pass until doctors hopped me up on pain meds. I've had my gall bladder removed and nearly severed my thumb but I never in my life felt pain like this. Would wish it upon no one!!

“I have had my leg crushed by a car backing over it and that has nothing compared to the pain of a kidney stone” !!!!
ACKNOWLEDGEMENTS

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