Sudden Cardiovascular Death Associated with Supplement Use in the Young


Department of Defense Cardiovascular Death Registry Group
San Antonio, TX and Washington, DC
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**Department of Defense Cardiovascular Death Registry Group, San Antonio Military Medical Center, San Antonio, TX**

## 13. Supplementary Notes

Introduction

- Sudden cardiac death in young adults is rare, but remains a highly litigious and emotionally charged topic.

- Evaluation is complicated by the presence of normal physiologic adaptations of cardiac anatomy at autopsy.

- In young adults, up to 35% of non-traumatic deaths do not have a clear etiology despite autopsy.

- Herbal supplements have been suggested as one possible mechanism of predisposition for arrhythmic sudden cardiac death.
Herbal Supplements

- Prominent in this field is *Ephedra sinica*
  - Ma huang
    - Used for treatment of asthma, the common cold, and as a stimulant.
  - Widespread use in the US initially in the 1920’s
    - Again, used as decongestants and CNS stimulants
  - In the last 20 years, Ephedra gained popularity again
    - Now for weight loss and as an energy supplement

- In 2001, 17.8 Billion dollars spent on supplements in the US
- In 2001, Ephedra containing products accounted for 64% of all adverse reactions to herbs in the US, while representing <1% of all herbal products sold.

AHRO Publication No. 02-E022. February 2003
Known Physiologic Effects

- Increases blood pressure, heart rate, cardiac output, peripheral vascular resistance
- Metabolife 356 was used by ~12 million Americans in 2002.
  - 15 healthy young volunteers using Metabolife 356
  - Increased systolic blood pressure and stroke index
  - QTc was prolonged a mean of 27 msec
  - For purposes of drug approval, the FDA considers an absolute QTc of 450, 480, and 500, or a relative increase of 30 and 60 msec to represent escalating risk.
- In animal models, ephedrine supplements in standard over the counter dosing increase ischemia dependent ventricular arrhythmias.

Risk : Benefit Ratio

- FDA regulation?
- FDA adverse event reports
  - 87 adverse events associated with ephedra
    - 10 deaths -- 47% secondary to cardiovascular cause
  - 926 cases of possible Ma Huang toxicity
    - 37 patients with stroke, myocardial infarction, or sudden cardiac death
- In Denmark, ephedrine/caffeine supplements are a prescription product
  - 250,000 patients
  - No increase in cardiovascular events

Can this *really* be healthy . . .?

Found in the bunk of a U.S. Army Soldier in Iraq with unexpected non-traumatic death . . .
Study Design

- We hypothesize that herbal supplementation, and specifically ephedra, are temporally related to idiopathic sudden cardiac death in the military population.

- Review of non-traumatic sudden death within the Department of Defense with an available clinical record or autopsy for adjudication as to the cause of death.

- Sponsored by the Air Force Medical Research Program (AF/SGRS).
Defining the Cohort

- 1,044 non-traumatic deaths suspected to be cardiac or idiopathic identified from 1998 to 2008.
  - 51 (5.1%) subjects excluded for lack of clinical history or autopsy
  - 130 (12.5%) subjects excluded for unavailability of records
  - 12 (1.2%) subjects excluded for clear non-cardiac etiology

- 902 subjects with available records and clinical history or autopsy form the basis of the cohort.
Results

- 48 subjects identified with toxicologic or reported use of substances of interest.
  - Mean age 34±10 years
  - Gender – male 44, 91.7%
  - Race
    - Caucasian (33, 68.8%)
    - African-American (11, 22.9%)
    - Asian (1, 2.1%)
Use of Supplements

- Thermogenic agents – 34 (70.1%)
  - Diet Fuel, Ripped Fuel, VigorPlex, Xtreme Lean, etc.
- Clinical or toxicologic ephedrine or phenylpropanolamine – 28 (58.3%)
- Negative toxicology findings – 23 (47.9%)
Activity at Time of Death

- **Exertional:** 56%
- **PFT:** 25%
- **Basketball:** 11%
- **Running:** 40%
- **Swimming:** 11%
- **Weight Lifting:** 11%

Reported Activity at Time of Death

- **Number of subjects**
  - Exertional: 35
  - PFT: 25
  - Basketball: 11
  - Running: 40
  - Swimming: 11
  - Weight Lifting: 11

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Antemortem Scenario

- Reported prodrome 16 (33.3%)
  - Chest pain (n=7)
  - Syncope or palpitations (n=4)
  - Dyspnea (n=3)
  - Seizure (n=1)

- Location of death
  - Out of hospital 15 (31.3%)
  - Emergency Department 27 (56.3%)
  - In hospital 3 (6.3%)
Coronary Disease
- Anomalous Coronaries, 10%
- Myocardial Bridge, 5%

Atherosclerosis, 85%

Cardiomyopathies
- HCM, 18%
- ARVD, 64%
- Idiopathic LVH, 18%

Idiopathic, 31.3%

Coronary Disease
- 43.8%

Valvular, 2.1%

Cardiomyopathy
- 22.9%

Cause of Death
Findings on Autopsy of those with Death due to Atherosclerosis

- Atherosclerosis, 85%
- Anomalous Coronaries, 10%
- Myocardial Bridge, 5%

<table>
<thead>
<tr>
<th>Finding</th>
<th>Number of Subjects with Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multivessel disease</td>
<td>66.7%</td>
</tr>
<tr>
<td>Plaque Rupture</td>
<td>16.7%</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>22.2%</td>
</tr>
</tbody>
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**Prevalence of idiopathic sudden cardiac death**

- Supplement use (n=48)
- No known supplement use (n=854)

**Age at time of death stratified by use of supplements**

- All cause mortality
- Death due to ASCAD

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**Notes:**
- $p=0.034$
- $p=0.006$
- $p=0.576$
Context of Findings

- Previous case reports of sudden death temporally associated with supplement use may be anecdotal.

- Case ascertainment bias limits the ability to identify high risk characteristics of ‘at risk’ individuals.

- Testing bias may not identify those older, senior personnel who may also be using supplements.
Conclusion

- Supplement use has an anecdotally skewed risk:benefit ratio
- The aforementioned limitations may limit generalizability.
- Health care providers must query about intake of supplements and assess for abuse across all ages and ranks.
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