Protocol Title: Evaluation of 5-Hour ENERGY® drink on the blood pressure and electrocardiographic parameters on young healthy volunteers: A randomized, double blind, crossover, placebo-controlled trial

Protocol #: FDG20110007H
Initial Approval Date: 22 Feb 2014
Date report Submitted: 29 Jan 2014

Date: 22 Feb 2014

Principal Investigator: Sachin Shah, Pharm D
Office Symbol: SGQP
Phone: 707-423-3277

1. Protocol Type
   [ ] Greater than Minimal Risk [x] Minimal Risk

2. Protocol Outcome Summary
   Were the protocol objectives met, and how will the outcome benefit the DOD/USAF?
   1) Please see poster for detailed results
   2) The data is relevant to the DOD and shows:
      a. When consumed appropriately, 5 Hour Energy does not prolong the QT interval
      b. Blood pressure is increased but is not elevated enough to cause an acute threat
      c. DOD personnel should not consume energy drinks outside the recommended doses
      d. DOD personnel with hypertension or those of older age should exercise caution when consuming energy drinks
      e. Current evidence does not warrant a cardiac threat enough to warrant placing restrictions on the appropriate use of energy drinks by DOD personnel

3. Protocol Status
   (Check one only)
   [ ] Inactive, protocol never initiated
   [ ] Inactive, protocol initiated but has not/will not be completed
   [x] All approved procedures/uses have been completed
INTRODUCTION: The impact of energy drinks on the cardiac rhythm remains unknown. QT/QTc interval prolongation has been known to induce life threatening arrhythmias. We sought to determine the impact of 5-Hour Energy shot on the QTc interval after acute and chronic consumption. METHODS: This was a randomized, placebo controlled, crossover study enrolling young healthy volunteers not on any medications. Subjects received the study drink (5 Hour Energy shot or placebo) twice daily separated by approximately 7 hours for the first 7 days. This was followed by a washout period of 6 days and the alternate study drink was consumed for the final 7 days. A 12-lead electrocardiogram (ECG) was performed at baseline, 1, 3 and 5 hours on days 1, 7, 15 and 21. The automated ECG measurements were used for per-treatment and ITT analysis and analyzed using the paired t-test. RESULTS: A total of 24 subjects (29±5.8 years) were included for analysis. QTc values after consumption of a single placebo-dose were 414±18, 413±15, 413±19 and 417±19 milliseconds at baseline, 1, 3 and 5 hours respectively. Post consumption of a single 5 hour Energy dose, QTc values were 415±17, 408±19, 410±20, and 413±17 milliseconds at baseline, 1, 3 and 5 hours, respectively (all time matched inter- group p-values > 0.292). QTc values after consumption of placebo for 7 days were 415±20, 413±18, 409±19, and 413±22 milliseconds at baseline, 1, 3 and 5 hours, respectively. Post consumption of 5 hour Energy for 7 days, resulted in QTc values of 415±22, 413±24, 415±24, and 415±21 milliseconds at baseline, 1, 3 and 5 hours, respectively (all time matched inter- group p-values >0.198 ). There was no difference between the PR interval, QRS duration, QT interval and heart rate between the two groups. CONCLUSION: 5-Hour Energy did not induce any significant changes in the QTc interval or other ECG parameters after single and multiple doses throughout a 7 day period. These results may vary between different energy drinks due to the varying ingredients within them.
<table>
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<tr>
<th>15. SUBJECT TERMS</th>
<th>16. SECURITY CLASSIFICATION OF:</th>
<th>17. LIMITATION OF ABSTRACT</th>
<th>18. NUMBER OF PAGES</th>
<th>19a. NAME OF RESPONSIBLE PERSON</th>
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<td>US Air Force, Medical Service, Medical Research, Graduate Medical Education</td>
<td>a. REPORT</td>
<td>unclassified</td>
<td>b. ABSTRACT</td>
<td>unclassified</td>
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4. **Number of Subjects Enrolled and Status of Subjects**
   Twenty-seven subjects were enrolled and began participation in the study. Twenty-five completed the study. Two subjects withdrew, 1 could not commit to the time and the other subject experienced adverse event of nausea and headache. Seven other subjects signed consent forms but never actually began the study. Three had time constraints at work that prevented them from participating and 4 had pre-existing conditions that prevented them from progressing further in the study.

5. **Number of Amendment(s) to Protocol:** 9

   **Date(s) of Amendments:** Amendment 1. 24 May 11; Amendment 2. 19 Aug 11; Amendment 3. 01 Nov 11; Amendment 4. 12 Jul 12; Amendment 5. 21 Sept 12; Amendment 6. 17 Oct 2012; Amendment 7. 25 October 12; Amendment 8. 28 Feb 2013; Amendment 9. 06 May 2013

6. **Funding**
   Source of Funding: Surgeon General Office
   Funding allocated since start of study $5430.00  Funds remaining $0.00

7. **Protocol Personnel Changes**
   Have there been any Principal or Associate Investigator Personnel changes since approval, last review protocol, or annual review?  
   □ Yes  □ No

<table>
<thead>
<tr>
<th>Name</th>
<th>Rank</th>
<th>Study Role</th>
<th>Date of Investigator Training</th>
<th>Staff/Resident/Fellow/Civilian</th>
<th>Dept/Office Symbol</th>
<th>Addition or Deletion</th>
<th>Date of Change</th>
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<tr>
<td>Michael Lee</td>
<td>Lt</td>
<td>PI</td>
<td>10/16/10</td>
<td>Staff</td>
<td>SGQP</td>
<td>Changed from PI to AI</td>
<td>12 Jul 12</td>
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<tr>
<td>Sachin Shah</td>
<td>CTR</td>
<td>AI</td>
<td>10/31/13</td>
<td>STAFF</td>
<td>SGQP</td>
<td>Changed from AI to PI</td>
<td>12 Jul 12</td>
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<tr>
<td>Nicholas Milazzo</td>
<td>Lt</td>
<td>Col</td>
<td>10/12/11</td>
<td>Staff</td>
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<td>Add as AI</td>
<td>12 Jul 12</td>
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<td>10/16/10</td>
<td>Staff</td>
<td>SGBH (WHASC)</td>
<td>Deleted as AI</td>
<td>6 May 13</td>
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8. **Adverse Events and Unanticipated Events**
   Identify any problems or adverse events that have affected study progress.
   a. Had unexpected events been reported to the IRB?  □ Yes □ No □ N/A
      If yes, please describe

Revised as of 16 Mar 2012
Protocol Title: Evaluation of 5-Hour Emergency Drink...

9. **Manpower**
   List manpower expended on this study

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<tr>
<th>Rank</th>
<th>AFSC</th>
<th># hours duty time</th>
<th># hours off-duty time</th>
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<tr>
<td>LtCol Michael Lee</td>
<td>43P</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Capt Anthony Dargush</td>
<td>43PX</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>LtCol Nicholas Milazzo</td>
<td>43PX</td>
<td>5</td>
<td>0</td>
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<tr>
<td>Maj Carolyn Lacey</td>
<td>44M3B</td>
<td>20</td>
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<tr>
<td>Vicki Potts Contractor</td>
<td></td>
<td>750</td>
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<tr>
<td>Sachin A Shah Contractor</td>
<td></td>
<td>200</td>
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10. If this was an EMERGENCY protocol, attach a copy of the narrative summary.
   N/A

11. **Publications**
   Were there any publications as a result of this research?
   American Heart Association, Scientific Sessions, November, 2013. POSTER (attached)

   Sachin A Shah  
   (PI / AI Signature)  
   1/29/14  
   (Date)
ADVERSE EVENTS FOR THE 5 HOUR ENERGY DRINK STUDY.

FDG 20110007H

As reported to the IRB at the last continuing review January 2013, the adverse events that subjects reported during the course of the study are as follows:

7 patients experienced palpitations or increased heart rate.
6 patients reported being shaky/jittery or nervous
6 patients reported upset or nausea
4 patients reported headache
5 patients reported sleeplessness
3 patients reported being lightheaded or dizzy
3 reported facial flushing
1 reported vomiting
1 reported diarrhea
1 report of being “hyper”
1 report of appetite suppression
1 report of being edgy (not Jittery)

All adverse events were resolved by the time each patient had completed their portion of the study. No residual effects. None of these were deemed serious or unexpected.
Impact of Acute and Chronic 5-Hour Energy Consumption on Electrocardiographic and Blood Pressure Parameters

Sechin A Shah, PharmD,1,3 Carolyn S Lacy, MD,1 Vicki Ratz, BPh,1 Christopher M Logan,1 Ian C Riddick,1 MD, Michael Leo, PharmD,2 Nicholas Hillazo, PharmD,2 Anthony F Dargush, PharmD2

1. University of the Pacific, School of Pharmacy and Health Sciences, Stockton, CA; 2. David Grant USAF Medical Center, Travis Air Force Base, CA

ABSTRACT

INTRODUCTION: The impact of energy drinks on the cardiac system remains unknown. QT/QTc internal prolongation has been known to induce lethal arrhythmias. We sought to determine the impact of 5-Hour Energy shot and the QT interval after acute and chronic consumption.

METHODS: This was a randomized, placebo-controlled, crossover study enrolling young healthy volunteers not on any medications. Subjects received the study drink (5-Hour Energy shot or placebo) twice daily separated by approximately 7 hours for the first 7 days. This was followed by a washout period of 6 days and the same study drink was consumed for the next 7 days. A 12-lead electrocardiogram (EGC) was performed at baseline, 1, 3 and 5 hours on days 1, 7, 15 and 21. The automated ECG measurements were used for per treatment and ITT analysis and analysis using the paired t-test.

RESULTS: A total of 24 subjects (9-5-8 years) were included for analysis. QTc values after consumption of a single placebo dose were 414-415, 413-415, 417-419 milliseconds at baseline, 1, 3 and 5 hours respectively. Post consumption of a single 5-Hour Energy dose, QTc values were 413-415, 410-419, 410-419, and 414-415 milliseconds at baseline, 1, 3 and 5 hours, respectively (all site matched edge group p-value = 0.322). QTc values after consumption of placebo for 7 days were 415, 410, 410, and 413-415 milliseconds at baseline, 1, 3 and 5 hours respectively. Post consumption of 5-Hour Energy for 7 days, resulted in QTc values of 410-412, 413-415, 413-415 and 414-415 milliseconds at baseline, 1, 3 and 5 hours, respectively (all site matched edge group p-value < 0.05). There was no difference between the PR interval, QRS duration, QT interval and heart rate between the two groups.

CONCLUSION: 5-Hour Energy did not induce any significant changes in the QTc interval or other ECG parameters after single and multiple doses throughout a 7 day period. These results may vary between different energy drinks due to the varying ingredients within them.

INTRODUCTION

- From 2006 to 2012, the market for energy drinks increased by 50%, reaching $20 billion in 2012.
- The number of emergency department visits involving energy drinks has been steadily rising from 10,269 in 2007 to 38,138 in 2011. Of those visits, 56% involved only energy drinks while the remaining 42% involved energy drinks in combination with other substances.
- There have been reports of an altered state, tachycardia, and sudden cardiac death in healthy individuals after energy drink consumption.
- The FDA does not regulate transactions as rigorously as new drug entities and the safety of energy drink consumption needs further exploration.
- The goal of this study is to assess the acute and chronic effects of 5-Hour Energy consumption on electrocardiographic and hemodynamic parameters in healthy humans.

METHODS

- This was a randomized, double blind, placebo controlled, crossover study.
- The study planned to enroll 45 subjects.
- Inclusion Criteria: Healthy individuals between 18 and 40 years of age.
- Exclusion Criteria: Abnormal baseline cardiac rhythm, history of atrial or ventricular arrhythmia, baseline corrected QT (QTc) interval greater than 450 milliseconds (ms), concurrent use of drugs potentially interacting with either 5-Hour Energy drink or affecting electrocardiographic or hemodynamic parameters, or having consumed any type of energy drink prior to randomization.
- Informed: 2 doses separated by 7 hours of either 5-Hour Energy or matching placebo daily for 7 days.
- 12-Lead ECG and office blood pressure were measured at baseline and at 1, 3 and 5 hours post consumption on days 1, 7, 15 and 21.
- Intergroup comparisons were performed using a paired student’s t-test.

RESULTS

- Twenty-four subjects were included for analysis.
- Age 24 ± 4.5 years
- Weight 79 ± 11.5 kg
- Height 1.63 ± 0.05 m
- Blood pressure 120/80 mm Hg

CONCLUSIONS

- Differences in PR interval, QT duration and heart rate between the two groups were not significant.
- 5-Hour Energy did not significantly prolong the QTc interval or any other ECG parameters after a single shot or post 7 days of consumption.
- A single dose of 5-Hour Energy significantly increased SBP and DBP but the effects appear to dissipate with chronic consumption.
- Future studies are needed to further assess the cardiac effects of energy drinks using differing products, doses, populations and durations of consumption.

The views expressed in this material are those of the authors and do not reflect the official policy or position of the U.S. Government.