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Interpretation of the toxicological findings in a **probably Energy drink intake-related** fatality

F. HAKIM^{1,2}, T. CHIANEA³, F. STURTZ³, F. PARAF⁴, J.M. GAULIER^{1,2,5*}

¹CHU Lille, Unité Fonctionnelle de Toxicologie, F-59000 Lille, France

²Univ. Lille, EA 4483 – IMPECS – IMPact de l'Environnement Chimique sur la Santé humaine, F-59000 Lille, France

³CHU Limoges, Biochemistry Laboratory, F-87047 Limoges, France

⁴CHU Limoges, Forensic Unit, F-87047 Limoges, France

⁵CHU Limoges, Laboratory of Toxicology, F-87047 Limoges, France

*Address correspondence to this author at:

Laboratory of Toxicology

Bd du Professeur Jules Leclercq

CS 70 001

59037 LILLE Cedex

France

Email: jean-michel.gaulier@chru-lille.fr

Fax : +33 320444960

Abstract

Nowadays, energy drinks (ED) are frequently used or abused in private, sporting or festive contexts. However, adverse health consequences of acute ED intake remain to be clarified on a forensic point of view. We report the **death** of a 36 year-old man with a recent acute pericarditis antecedent in order to illustrate this **challenging** situation. He was found dead after an overnight party. Witnesses reported consumptions of alcohol, cannabis and energy drinks (Red Bull™) during this party. Autopsy findings consisted in acute pulmonary edema together with adhesive pericarditis. Collected biological samples were sent to the laboratory for forensic toxicological analysis. General toxicological screenings for drugs and other toxics including caffeine and taurine were performed using gas chromatography - mass spectrometry (GC-MS), liquid chromatography-tandem mass spectrometry (LC-MS/MS) and LC with diode array detection. Toxicological findings are coherent with ethanol, cannabis, caffeine and taurine consumption in the few hours before death. Generally, adverse effects of acute ED intake can be related to either the toxicity of ingredients (especially, caffeine), the combination of those ingredients, or specific situations like **combination** of energy drinks with alcohol, or cardiologic pre-dispositions. In this case, the observed taurine concentration in peripheral blood (984 µmol/L) cannot be related to any toxic effect. As a consequence, the toxicological implication of the ED-Alcohol intakes could only be suggested, but not established in this fatality.

Key words

Energy drinks, fatality, GC-MS/MS, LC-MS/MS, alcohol, cannabis, **taurine**

Introduction

Energy drinks (ED) are popular and commonly used or abused beverages **mostly in young male**. They are used in sport or private contexts for their **taste especially in adolescents**¹, stimulating and energizing effects, as well as in festive context where they are often mixed with alcohol. ED contain usually taurine and always caffeine². There are regular reports on the risk of repeated intakes of ED, especially when associated with alcohol. **Those reports indicate serious cardiovascular events as side-effect of ED's abuse. The most likely ingredient responsible for those cardiovascular events (increased heart rate and blood pressure, arrhythmia) is reported to be caffeine**³ although some studies⁴ suggest that caffeine is not responsible for the QTc prolongation effect. Required ED consumption levels associated with those adverse effects (prolongation of the QTc interval, palpitations, severe nausea, shortness of breath, severe tremor, anxiety etc.) are reported to be elevated (about 1L) for healthy adults. Regarding children and adolescent, those consumption levels are still unknown. **Both the co-ingestion with alcohol causing cardiac arrhythmias and combination with intense physical activity which is reported to have additive effect on blood pressure, are common practices and requires further investigation in order to clarified dose-response relationships with ED consumption**⁵.

However, in forensic **situation**, their adverse health consequences remain to be clarified, and **related-cases to be analytically documented**. This manuscript aims to report a fatality case **probably** linked to **Energy drink** intake and the difficulties in the interpretation of the toxicological findings owing to this lack of data.

Case history

A 36-year-old man was in charge of the music (DJ) for an overnight party in a private house. Witnesses reported **that he consumed** alcohol (**moderately**), cannabis and energy drinks (Red Bull©). At the end of the night, he complained about thoracic and/or abdominal pain and went outside to "take a breath of fresh air". One hour later, he was found dead face down on the pavement outside the house.

Medical antecedents included a recent (2 years **before**) acute pericarditis. The main autopsy findings **consisted** in cyanosis, acute pulmonary edema (APO) with blood in **the** trachea (probably due to the cardio-pulmonary resuscitation) and bronchus, left anterior descending artery (LAD) blood clot and macroscopic adhesive pericarditis. The conclusion of **the** autopsy **was** an asphyxia following APO. This APO is probably due to the LAD blood clot with a subsequently **paroxysmal** heart muscle anoxia. Biological *post-mortem* samples [peripheral blood (PB), urine, vitreous humor, gastric content...] were collected and **sent** to the laboratory for toxicological investigations.

Material and methods

A large screening of drugs and toxicants was performed in *post-mortem* blood, gastric content and urine using both gas chromatography-mass spectrometry (GC-MS) and liquid chromatography with tandem mass spectrometry detection methods^{6,7}. More selective analyses for several classes of therapeutic drugs and drugs of abuse were carried out with various methods using gas and liquid chromatography with various detection modes.

In particular, a liquid chromatography coupled with diode array detector (LC-DAD) was used for caffeine determination in blood. Taurine was analyzed in blood using LC-DAD based on the method of Trautwein EA et al.⁸. Briefly, this method includes 3 consecutive **deproteinization steps using trichloroacetic acid and sulfosalicylic acid**, addition of **norleucine** as internal standard, assay using an S433 amino acid automated LC analyzer (SYKAM, Germany) and UV detection at 570 nm with a retention time of 5.205 min. Results was given in $\mu\text{mol/L}$ with a calibration range of 20 to 2000 $\mu\text{mol/L}$. In addition, given **the lack of data on post mortem** taurine concentrations, we conducted a study in order to assess **taurine concentrations** in *post-mortem* blood: **therefore**, 10 *post-mortem* PB samples (from victims without any suspected ED intake, and **regardless of** age, sex or cause of death) were assayed using the same method.

Results and discussion

Positive results of toxicological investigations (Table 1) highlighted the presence of THC-COOH, 11-OH THC, ethylglucuronide and ethanol (in all biological samples), in coherence with cannabis and ethanol intakes a few hours before death. Caffeine and taurine, which are part of the composition of RedBull©, were also detected in PB. No other xenobiotics (e.g. cocaine or related metabolites) were detected.

A 250 mL RedBull© can contains 80 mg of caffeine and 1000 mg of taurine and several other ingredients.

Caffeine is a methylxanthine type of alkaloid with a half-life of approximately 4 h and a T_{max} following oral administration ranging from 15 to 45 min. Its pharmacodynamics consists in an antagonism of adenosine A₁ receptors and an inhibition of phosphodiesterases that produce the chronotropic and inotropic effects of adrenaline. The maximal recommended daily dosage is 400 mg corresponding to about 5 cans (250 mL) of RedBull©. Several toxic effects can occur in case of caffeine intoxication: nausea, vomiting, nervousness, anxiety, insomnia, tremors, tachycardia, supraventricular and ventricular tachyarrhythmia. There is a poor correlation between blood concentration and clinical effects. However, a study⁹ reported toxic events from 25 mg/L (whole blood) and death from 80 mg/L (whole blood); this value is more than 25 times the caffeine blood concentration of the deceased (0.51 mg/L). To place this in perspective, a single cup of standard brewed coffee results in blood caffeine levels of 1 to 2 mg/L¹⁰.

Taurine is a sulfonic acid with an amino group with no direct role in protein synthesis. However, taurine is implicated in a wide array of physiological phenomena including: membrane stabilization, modulation of intracellular calcium homeostasis, contribution to bile salt formation, prevention of epileptic seizures (GABA(A) agonist), antioxidant properties and protection against toxicity of various substances (such as lead and cadmium)¹¹⁻¹⁵... Daily nutritional input is between 40 to 400 mg and there is a minor synthesis in the liver from methionine and cysteine (B6 Vitamin as co-factor)^{16,17}. The maximal recommended daily dosage is 3000 mg corresponding to 3 cans (250 mL) of RedBull©. One study¹⁸ indicates basal serum taurine concentrations in the range of 870 µmol/L +/- 220 (min: 500 ; max: 1200; n=28). When taken orally, T_{max} is reached in 90 min and maximal blood concentration after 180 to 270 min¹⁹. There is no defined toxic taurine blood concentration and rare negative effects are found in particular clinical or pathological contexts with no genotoxic, carcinogenic, teratogenic capacity²⁰. A reduced excretion of lithium can, in theory, be expected. In rats, a unique dose of taurine can lead to a drop of arterial pressure (beneficial) but if the supplementation is continued, an increase in arterial pressure can occur (probably owing to the fact it is almost an amino acid!)²¹. Our study (conducted in order to assess usual taurine concentration in *post-mortem* blood) showed a *post-mortem* blood taurine concentration ranging from 400 µmol/L to 2500 µmol/L with a mean of 1140 µmol/L (Figure 1), higher than the taurine blood concentration of the victim (984 µmol/L). This high mean can be explained by cell lysis occurring immediately after death and *post-mortem* redistribution. As a consequence, the taurine blood concentration observed in the presented case is unable to confirm the taurine consumption stated in the anamnesis.

All in all, the true question in the presented case consists in the liability of ED intake in the occurrence of the death of a victim with cardiac predispositions: in a sudden cardiac death hypothesis, (i) given the various other ingredients of RedBull© [glucuronolactone 600 mg, saccharine 21.5 g, glucose 5.25 g, inositol 50 mg, niacin 20 mg, vitamin B6 5 mg, pantothenic acid 5 mg, vitamin B12 0.005 mg, adjuvants and additives (citric acid (E 330), natural and artificial aroma, dyes (caramel et riboflavin)], combined with an alcohol level sufficient to potentially induce cardiotoxicity (arrhythmia or tachycardia)²² together with cannabinoids findings reflecting a recent cannabis use that is suggested to potentially increase heart rate and blood pressure²³, a cardiac cocktail toxic effect can be suggested, and (ii) in a victim with cardiac electrical instability susceptibility (suggested by macroscopic adhesive pericarditis together with old fibrous infarction scar) medical backgrounds' liability can be also suggested. The answer is uncertain. Some studies²⁴⁻

²⁶ seems to indicate protector effects, others indicate non-significant (ns) effect²⁵ or only a slight effect (increase of cardiac frequencies: ns)²⁷ in case of a unique ED intake. In case of regular ED intakes, an elevation of the QT (ns) and the cardiac frequency (s) is reported²⁸. In addition, recent reports suggest that ED, like an **exercise** test, can unmask an underlying primary pathogenic disorder, such as long QT^{29,30}, Brugada syndrome³¹ or Takotsubo cardiomyopathy³²⁻³⁴. To sum up, some studies reported non-significant increases of cardiac frequency and arterial pressure in healthy patients but in case of cardiac diseases, these effects can be significant³⁵.

Conclusion

In this case, adverse effects of ED intakes are not (solely) liable for the death. A **cardiac event** promoted by the combination of the RedBull© intake with alcohol (and cannabis) and cardiovascular predispositions can be suggested. In such situation, interpretation of taurine concentration measured in the victim's blood **remains restricted**. At least, additional data about **the post-mortem** blood level of taurine in documented Redbull drinking case-related death are needed to clarify such tricky forensic situations.

Conflict of interest

There are no financial, or other, relations that could lead to a conflict of interest.

Ethical approval

This article does not contain any studies with living human participants or animals that were performed by any of the authors.

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Table legends

Table 1: positive results of the toxicological investigations (nd: not detected; nt: not tested).

Figure 1: **comparison** between taurine blood concentration observed in *post-mortem* cases not **related** to ED intakes (n=10) and taurine blood concentration of the victim [F: female; M: male; (age)]

Table 1

Sample	Caffeine (mg/L)	Taurine (μ mol/L)	Ethanol (g/L)	Ethylglucuronide (mg/L)	Cannabinoids (μ g/L)		
					THC	THC-COOH	11-OH THC
Peripheral blood	0.51	984	0.79	nt	< 1	4.1	< 1
Urine	nt	nt	0.77	194	nd	>100	nd
Vitreous humor	nt	nt	0.65	nt	nt	nt	nt
Gastric content	nt	nt	0.65	nt	nt	nt	nt

Figure 1

