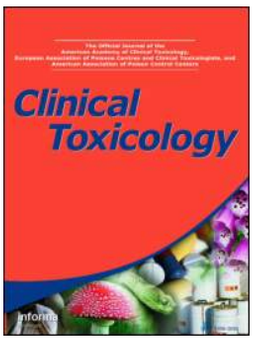

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RESEARCH ARTICLE

The stimulant higenamine in weight loss and sports supplements

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ABSTRACT

Background: Higenamine is a stimulant with cardiovascular properties recently prohibited in sport by the World Anti-Doping Agency (WADA). Higenamine is also a natural constituent of several traditional botanical remedies and is listed as an ingredient in weight loss and sports supplements sold over-the-counter in the United States.

Objectives: We analyzed dietary supplements available for sale in the United States prior to WADA's prohibition of higenamine in sport for the presence and quantity of higenamine.

Methods: All supplements labeled as containing higenamine or a synonym (i.e., norcoclaurine or demethylcoclaurine) available for sale in the United States were identified. For each brand, one sample was analyzed by NSF International (Ann Arbor, MI) and one sample by the Netherland's National Institute for Public Health and the Environment (RIVM). NSF International carried out qualitative and quantitative analyses using ultra high performance liquid chromatography (UHPLC) with tandem mass spectrometry. RIVM carried out qualitative analysis using UHPLC quadrupole time of flight mass spectrometry for an independent confirmation of identity.

Results: Twenty-four products were analyzed. The majority of supplements were marketed as either weight loss (11/24; 46%) or sports/energy supplements (11/24; 46%); two brands did not list a labeled indication. The quantity of higenamine (±95% CI) ranged from trace amounts to 62 ± 6.0 mg per serving. Consumers could be exposed to up to 110 ± 11 mg of higenamine per day when following recommended serving sizes provided on the label. Five products (5/24; 21%) listed an amount of higenamine, but none were accurately labeled; the quantity in these supplements ranged from <0.01% to 200% of the quantity listed on the label.

Conclusion: Dosages of up to 62 ± 6.0 mg per serving of the stimulant higenamine were found in dietary supplements sold in the United States.

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Cardiovascular; dietary supplements; sports supplements; weight loss supplements

Introduction

Dietary supplements lead to an estimated 23,000 emergency department visits each year in the United States (US), and weight loss and sports supplements contribute to a large proportion of these emergency department visits [1]. It is not known which ingredients in weight loss and sports supplements pose the greatest risk to consumers, but a series of recent studies have found experimental stimulants [2], pharmaceutical stimulants [3], anabolic steroids [4], and selective androgen receptor modulators [5] in these products. There is also the potential that high dosages of naturally occurring stimulants, such as caffeine or yohimbine, might also contribute to health risks [6,7].

Higenamine, a stimulant found in plants, has beta-agonist activity with chronotropic and inotropic properties (Figure 1) [8]. The stimulant has been studied in clinical trials in China [9–11] but has never been approved as a drug by the US Food and Drug Administration (FDA). Higenamine occurs naturally in a variety of traditional botanical remedies, such as *Aconitum carmichaelii* (Sichuan aconite) [12] and *Nandina domestica* (nandina fruit) [13], and is sold over the counter in the United States as an ingredient in dietary supplements.

The FDA has received reports of adverse effects from higenamine-containing supplements since 2014, but higenamine's health risks remain poorly understood [8]. The stimulant has recently been prohibited from sport by the World Anti-Doping Agency (WADA) in 2017 and now poses risks to competitive athletes' careers [14]. Several athletes have been sanctioned for its use, some claiming that they inadvertently consumed higenamine in dietary supplements [15,16].

In the current study, we investigated the presence and quantity of higenamine in sports and weight loss supplements listing higenamine as an ingredient and sold in the US prior to WADA's prohibition of higenamine in sport.

Materials and methods

Materials

All supplements listing higenamine or a synonym (i.e., norcoclaurine or demethylcoclaurine) as an ingredient were

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Supplemental data for this article can be accessed here.

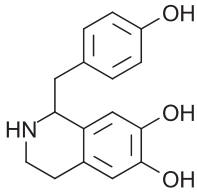

Figure 1. Chemical structure of higenamine.

identified using the following databases: The National Institute of Health's Dietary Supplement Label Database, the Natural Medicines Comprehensive Database, and the Google search engine. Two samples of each supplement were purchased online in March 2016. The label of the purchased supplement was inspected, if the label did not include higenamine or a synonym as an ingredient, the supplement was excluded from the study.

For each brand, one sample was analyzed by NSF International (Ann Arbor, MI) and one sample by the Netherland's National Institute for Public Health and the Environment (RIVM). NSF International carried out qualitative and quantitative analyses using ultra high performance liquid chromatography (UHPLC) with tandem mass spectrometry. RIVM carried out qualitative analysis using UHPLC quadrupole time of flight mass spectrometry for an independent confirmation of identity. NSF synthesized higenamine for use as a reference standard [17,18] (see Supplemental data for details) and RIVM obtained higenamine reference standards from Sigma-Aldrich (Zwijndrecht, NL).

Analytical methods

Two different methanol extraction methods were utilized. The extracts were analyzed using two liquid chromatography mass spectrometry methods (see Supplemental data for full details of the analytical methods and their validation).

Results

Thirty-two brands of supplements were identified using our search criteria. Twenty-seven brands (27/32; 84%) were available for purchase, but three of these did not list higenamine, norcoclaurine or demethylcoclaurine on the actual label. Twenty-four products met the inclusion criteria and were analyzed. The majority of supplements were marketed as either weight loss (11/24; 46%) or sports/energy supplements (11/24; 46%); two brands did not list a labeled indication.

The quantity of higenamine (±95% CI) ranged from trace amounts to 62 ± 6.0 mg per serving (Table 1). Consumers could be exposed to up to 110 ± 11 mg of higenamine per day when following recommended serving sizes provided on the label. Five products (5/24; 21%) listed a specific amount of higenamine on the label, and none were accurately labeled; the quantity in these supplements ranged from <0.01% to 200% of the quantity listed on the label.

Discussion

The presence of higenamine was confirmed in 24 dietary supplements sold in the United States from trace amounts to 62 ± 6.0 mg higenamine per serving. To our knowledge, only two prior studies have quantified higenamine in supplements: 25 mg per capsule in one US brand (OxyELITE^{TM} Pro, USPLabs) [19] and trace amounts (6 ng/mL and 19 ng/mg) in two supplements available in Europe [20].

Higenamine has been studied as an investigational drug in China for use as a pharmacological agent for cardiac stress tests as well as for treatment of a number of cardiac conditions including bradyarrhythmias [9–11,21–34]. Clinical trials of higenamine from China are summarized in Table 2. The trials reporting hemodynamic measurements were relatively small (ranging from 10 to 120 subjects) and higenamine was administered intravenously, most commonly using gradual infusions of 2.5 or 5 mg [9–11,21–28]. Higenamine consistently increased heart rate but had variable effects on blood pressure (Table 2). Subjects who received higenamine in these trials reported dyspnea, palpitations, dizziness, headaches, chest tightness as well as other adverse effects [28,30]. One small study described higenamine's effect on cardiac output: 2.5 mg of higenamine infused over 30 min led to an increased ejection fraction from 46% ±9% to 60% ±15% ($p < .005$) in 15 patients with heart disease [9].

While the effects of 2.5 and 5 mg of higenamine administered intravenously have begun to be understood, no trial provides data to permit calculating intravenous to oral dose conversions. Although it is known that higenamine can be absorbed orally [35], the effect of the dosages found in supplements remain uncertain. Trimetoquinol, an analogue of higenamine, is used in Japan as a bronchodilator and is available in oral dosages of 2–4 mg [36].

Two studies [37,38], both funded by a supplement manufacturer, purport to demonstrate the safety of orally administered higenamine, but neither provides clinically relevant information. In one study, 16 subjects were randomized to either a placebo or a supplement containing an unknown quantity of higenamine combined with caffeine and yohimbe bark [37]. Heart rate and blood pressure increased in subjects randomized to the higenamine-containing supplement, but no information regarding the quantity of higenamine in the supplement was provided nor can the effect of the higenamine in the supplement be distinguished from the other ingredients. In another study, 48 men were assigned to ingest either a placebo, higenamine (at a variable dose adjusted by each participant based on individual subjective experience with the supplement), caffeine or a combination of higenamine, caffeine and yohimbe bark extract [38]. At weeks 4 and 8 participants' physiologic parameters were measured after a minimum 10-hour fast (subjects were instructed not to consume any supplements during the fast). Given higenamine's very short half-life (i.e., intravenous half-life of 8 min [range 6–10 min]), the physiologic effects of higenamine would not be expected to be detectable 10 h after ingestion, even assuming a longer half-life following oral administration. Therefore, neither study provides useful

Table 1. Quantity of higenamine found in dietary supplements analyzed.

Supplement name (manufacturer)	Labelled indication	Ingredient listed on label that met inclusion criteria [amount]	Recommended serving size (grams)	Maximum daily intake (grams)	Higenamine in milligrams per serving (±95% CI)[a,b]	Higenamine in milligrams per maximum recommended daily intake (±95% CI)[a,b]
Adrenal Pump (Total Body Nutrition)	Preworkout	Norcoclaurine HCl (higenamine HCl)	2 capsules	None specified	[c]	[c]
Apidren (NutriPharm)	None specified	Higenamine	2 capsules	2 capsules	57 ± 5.5	57 ± 5.5
Beta-Stim (Ronnie Coleman Signature Series)	Weight loss	Higenamine	1 capsule	3 capsules	23 ± 2.2	69 ± 6.7
Burn-HC (VMI Sports)	Energy and focus	Higenamine (norcoclaurine) [20 mg]	1 capsule	1 capsule	29 ± 2.8	29 ± 2.8
Defcon1 Second Strike (Platinum Labs)	Preworkout	Higenamine [50 mg]	1 scoop (7.5)	1 scoop (7.5)	[c]	[c]
Diablo (ANS Performance)	Weight loss	Higenamine HCl	1 scoop (2.5)	3 scoops (7.5)	15 ± 1.4	44 ± 4.3
DyNO (RSP Nutrition)	Preworkout	Higenamine hydrochloride	1 scoop (8.1)	1 scoop (8.1)	27 ± 2.7	27 ± 2.7
Gnar Pump (Brosupps)	Preworkout	Higenamine	1 scoop (6)	2 scoops (12)	[c]	[c]
Higenamine (Powder City)	None specified	Higenamine HCl [20 mg]	1 scoop (0.02)	None specified	7.4 ± 0.72	Not applicable
High Definition (MBI Performance)	Weight loss	Higenamine HCl	1 capsule	4 capsules	29 ± 2.8	110 ± 11
HyperMax (PerforMax Labs)	Preworkout	Higenamine HCl	1 scoop (5.1)	2 scoops (10.2)	[c]	[c]
iBurn2 (M4 Nutrition)	Weight loss	Higenamine	2 capsules	2 capsules	6.8 ± 0.66	6.8 ± 0.66
Liporidex Max (Nuretix Research)	Weight loss	Norcoclaurine HCl (higenamine)	1 capsule	3 capsules	2.0 ± 0.20	6.1 ± 0.60
Liporidex PLUS (Nuretix Research)	Weight loss	Norcoclaurine HCl (higenamine)	2 capsules	4 capsules	2.9 ± 0.28	5.9 ± 0.57
LipoRUSH DS2 (NDS Nutrition)	Weight loss	Higenamine HCl	1 capsule	1 capsule	41 ± 4.0	41 ± 4.0
N.O. Vate (Applied Nutriceuticals)	Preworkout	Norcoclaurine HCl	1-3 tablets	5 tablets	15 ± 1.4	25 ± 2.4
OxyShred (EHP Labs)	Weight loss	Higenamine HCl	1 scoop (5.1)	2 scoops (10.2)	35 ± 3.4	70 ± 6.8
Prostun-Advanced Thermogenic (HD Labs)	Weight loss	Higenamine HCl [10 mg]	1 capsule	2 capsules	20 ± 1.9	39 ± 3.8
Pyroxamine (Myokem)	Weight loss	*Nelumbo nucifera* (std. to higenamine)	1 capsule	3 capsules	30 ± 2.9	89 ± 8.7
Razor8 (AllMax Nutrition)	Preworkout	Higenamine HCl (norcoclaurine) [45 mg]	1 scoop (9.5)	1 scoop (9.5)	62 ± 6.0	62 ± 6.0
Ritual (ANS Performance)	Preworkout	Higenamine HCl (norcoclaurine)	1 scoop (9)	2 scoops (18)	7.1 ± 0.69	14 ± 1.4
Stim Shot (LeCheek Nutrition)	Energy and focus	Higenamine HCl	1 scoop (0.625)	2 scoops (1.25)	44 ± 4.3	88 ± 8.6
ThermoVate (Applied Nutriceuticals)	Weight loss	Norcoclaurine	2 tablets	4 tablets	9.1 ± 0.88	18 ± 1.8
Uplift (NLA for Her)	Preworkout	Norcoclaurine	1 scoop (5.25)	2 scoops (10.5)	1.5 ± 0.15	3.0 ± 0.29

[a]Higenamine amounts were rounded after performing calculations.
[b]The 95% CI is the 95% confidence interval calculated from the single laboratory method validation and equivalent to the expanded method uncertainty.
[c]Less than 0.005 milligrams.

clinical evidence of either the efficacy or safety of higenamine as an oral drug.

One case report [39] purports to provide evidence of risks of higenamine but does not provide adequate information to be clinically useful: a 22-year-old male ingested "a supplement containing higenamine" then completed an intensive exercise routine after which he developed rhabdomyolysis. However, the supplement was not analyzed, therefore, no information is provided regarding the quantity of higenamine (or other ingredients) consumed, nor is there convincing evidence that the supplement, rather than the exercise routine or other factors, led to rhabdomyolysis.

Although the safety of oral dosages of higenamine as high as 62 mg remains unknown, higenamine-containing supplements can now pose immediate risks to competitive athletes' careers. On 1 January 2017, WADA prohibited higenamine in sports and, in the first 4 months of 2018, three US competitive weightlifters have accepted sanctions ranging from 1 to 4 years for the use of higenamine alone or in combination with other banned substances [15,40,41].

Despite the prohibition of higenamine in sport, the stimulant, when present as a constituent of botanicals, is permitted in US supplements because traditional botanical remedies are "grandfathered in" under the Dietary Supplement Health and Education Act of 1994 (DSHEA) [42]. However, neither synthetic versions of constituents of botanicals nor dosages of natural stimulants above traditional levels are permitted as "grandfathered" ingredients according to the FDA's 2016 draft guidance on new dietary ingredients [43]. The guidance, however, remains in draft form and has not been finalized. If these key points are preserved in the final guidance then the FDA could limit consumers' exposure

Table 2. Clinical studies of higenamine. Human studies of higenamine were not included (a) if subjects did not receive a specific dose of higenamine [37,38], or (b) if the investigators did not report hemodynamic measurements [29–35].

Reference	Country (Language)	No. of subjects	Subjects: volunteers or patients	Objective	Intervention	HR	SBP	DBP	Cardiac output
Shanghai Med J 1979 [21]	China (Mandarin)	14	Patients with heart disease	To determine effect on bradyarrhythmia	Higenamine 5 mg IV slow infusion	⬆	⬆⬇	⬆⬇	n/a
Chin J Cardiol 1980 [26]	China (Mandarin)	68	Patients with heart block	To determine effect on patients with heart block	Higenamine 2.5 mg IV slow infusion	⬆	⬆⬇	⬆⬇	n/a
Beijing Med J 1981 [22]	China (Mandarin)	18	Patients with heart disease	To determine effect on bradyarrhythmia	Higenamine 2.5 mg IV slow infusion	⬆	n/a	n/a	n/a
Chin J Integrated Trad West Med 1981 [24]	China (Mandarin)	19	Patients with heart disease	To determine effect on the function of left ventricle	Higenamine 2.5 mg IV slow infusion	⬆	⬆	⬇	⬆
Chin Med J 1982 [11]	China (English)	14	Patients with heart block	To determine effect on patients with heart block	Higenamine 5 mg IV slow infusion	⬆	⬆⬇	⬆⬇	n/a
Eur J Nucl Med 1983 [9]	China (English)	15	Patients with heart disease	Tolerability study	Higenamine 2.5 mg IV slow infusion	⬆	n/a	n/a	⬆
Chin J Integrated Trad West Med 1984 [23]	China (Mandarin)	22	Patients with sick sinus syndrome	To determine effect on sick sinus syndrome	Higenamine 2.5 mg IV slow infusion	⬆	n/a	n/a	n/a
Chin J Clin Pharmacol 2007 [27]	China (Mandarin)	32	Healthy volunteers	Tolerability study	Higenamine IV infusions escalating between 0.5 and 4 μg/kg/min	⬆	–	⬇	n/a
Acta Pharm Sinica 2012 [10]	China (English)	10	Healthy volunteers	Pharmacokinetic and pharmacodynamics study	Higenamine IV infusions escalating between 0.5 and 4 μg/kg/min for 3 min	⬆	–	⬇	n/a
Chin Hosp Pharm J 2012 [25]	China (Mandarin)	71	Patients with suspected heart disease	To determine suitability as pharmacological stress agent	Higenamine IV infusions escalating between 0.5 and 4 μg/kg/min	⬆	–	⬇	n/a
Chin J Nucl Med Mol Imaging 2014 [28]	China (Mandarin)	120	Patients with confirmed or suspected heart disease	To determine suitability as pharmacological stress agent	Higenamine IV infusions escalating between 0.5 and 4 μg/kg/min	⬆	–	⬇	n/a

An additional series of clinical studies have compared higenamine to other agents for cardiac stress testing, if these studies did not provide hemodynamic measurements [29,30,32–34], they were not included in the table.
IV: intravenous; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; n/a: not assessed; min: minute(s); – no change, ⬆ increased, ⬇ decreased, ⬆⬇ variable effects.

to large dosages of higenamine and similar stimulants when consuming US supplements.

Our study has several limitations. We purchased supplements at only one time point prior to WADA prohibiting higenamine in sport, and it is possible that the quantity of higenamine may vary over time [44] as manufacturers have unlimited flexibility to reformulate products. However, the number of supplements listing higenamine as an ingredient has not decreased since WADA's 2017 prohibition of higenamine in sport, as of June, 2018 the National Institute of Health's Dietary Supplement Label Database lists more than 30 brands of supplements labeled as containing higenamine [45]. Furthermore, we did not analyze the supplements for additional ingredients, and these ingredients, such as caffeine and yohimbine, might have important synergistic physiological effects [8]; therefore, the current study does not address the safety of any individual supplement product, but rather focuses on the presence and quantity of higenamine. Finally, we did not analyze supplements that did not list higenamine or a synonym on the label. As higenamine is a constituent of several botanicals, a variety of botanical supplements might contain higenamine without the stimulant being listed as an ingredient on the label.

Conclusions

Higenamine, a constituent of several botanical remedies, has cardiovascular effects and has been evaluated for use in cardiac stress testing and treatment of several cardiac conditions [9–11]. We analyzed supplements to verify the presence of higenamine and to determine the quantity that would be consumed in a recommended serving size. In 24 dietary supplements listing higenamine (or a synonym) on the label, we found that quantities of the stimulant ranged from trace amounts to 62 ± 6.0 mg per serving. Consumers could be exposed to up to 110 ± 11 mg of higenamine per day when following recommended serving sizes provided on the label. All products listed as containing a specific quantity of higenamine were inaccurately labeled. The safety of these dosages remains unknown. Since WADA's prohibition in

2017, however, consumption of higenamine poses immediate risks to competitive athlete's sporting careers. Nevertheless, stimulants such as higenamine that are natural constituents of botanical remedies will likely remain in unpredictable dosages in US dietary supplements. The FDA may be able to reduce consumers' exposure to higenamine by finalizing their draft guidance on new dietary ingredients. Physicians, in the meantime, should be aware that supplements listing higenamine as an ingredient may contain a stimulant with important cardiovascular properties.

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Disclosure statement

Drs. Cohen, Keizers, and Venhuis have no conflicts of interest. Mr. Travis and Mr. Boyer are employees of NSF International. Some of NSF International's clients are dietary supplement manufacturers.

References

[1] Geller AI, Shehab N, Weidle NJ, et al. Emergency department visits for adverse events related to dietary supplements. N Engl J Med. 2015;373:1531–1540.

[2] Cohen PA, Travis JC, Keizers PHJ, et al. Four experimental stimulants found in sports and weight loss supplements: 2-amino-6-methylheptane (octodrine), 1,4-dimethylamylamine (1,4-DMAA), 1,3-dimethylamylamine (1,3-DMAA) and 1,3-dimethylbutylamine (1,3-DMBA). Clin Toxicol. 2018;56:421–426.

[3] Cohen PA, Avula B, Venhuis B, et al. Pharmaceutical doses of the banned stimulant oxilofrine found in dietary supplements sold in the USA. Drug Test Anal. 2017;9:135–142.

[4] Cohen PA, Maller G, DeSouza R, et al. Presence of banned drugs in dietary supplements following FDA recalls. JAMA. 2014;312:1691–1693.

[5] Van Wagoner RM, Eichner A, Bhasin S, et al. Chemical composition and labeling of substances marketed as selective androgen receptor modulators and sold via the internet. JAMA. 2017;318:2004–2010.

[6] Cohen PA, Attipoe S, Travis J, et al. Caffeine content of dietary supplements consumed on military bases. JAMA Intern Med. 2013;173:592–594.

[7] Cohen PA, Wang Y-H, Maller G, et al. Pharmaceutical quantities of yohimbine found in dietary supplements in the USA. Drug Test Anal. 2016;8:357–369.

[8] Calvert R, Vohra S, Ferguson M, et al. A beating heart cell model to predict cardiotoxicity: effects of the dietary supplement ingredients higenamine, phenylethylamine, ephedrine and caffeine. Food Chem Toxicol. 2015;78:207–213.

[9] Liu XJ, Wagner HN, Tao S. Measurement of effects of the Chinese herbal medicine higenamine on left ventricular function using a cardiac probe. Eur J Nucl Med. 1983;8:233–236.

[10] Feng S, Jiang J, Hu P, et al. A phase I study on pharmacokinetics and pharmacodynamics of higenamine in healthy Chinese subjects. Acta Pharmacol Sin. 2012;33:1353–1358.

[11] Bao Y, Yu G, Xu J, et al. Effect of acute higenamine administration on bradyarrhythmias and His bundle. A clinical study of 14 cases and an animal experiment on dogs. Chin Med J. 1982;95:781–784.

[12] Bai G, Yang Y, Shi Q, et al. Identification of higenamine in Radix *Aconiti Lateralis Preparata* as a beta$_2$-adrenergic receptor agonist. Acta Pharmacol Sin. 2008;29:1187–1194.

[13] Tsukiyama M, Ueki T, Yasuda Y, et al. ß$_2$-adrenoceptor-mediated tracheal relaxation induced by higenamine from *Nandina domestica* Thunberg. Planta Med. 2009;75:1393–1399.

[14] Grucza K, Kwiatkowska D, Kowalczyk K, et al. Analysis for higenamine in urine by means of ultra-high-performance liquid chromatography-tandem mass spectrometry: interpretation of results. Drug Test Anal 2018;10:1017–1024.

[15] U.S. Anti-Doping Agency. U.S. weightlifting athlete Kaitlyn Jarrett accepts sanction for anti-doping rule violation; 2018 Mar 23 [cited 2018 May 18]. Available from: https://www.usada.org/kaitlyn-jarrett-accepts-doping-sanction/

[16] U.S. Anti-Doping Agency. U.S. weightlifting athlete, Carlee Acevedo-Fuller, accepts sanction for anti-doping rule violation; 2017 Aug 16 [cited 2018 May 18]. Available from: https://www.usada.org/carlee-acevedo-fuller-accepts-doping-sanction/

[17] Chang KC, Yun-Choi HS, Lim JK, et al. Synthesis of higenamine, a cardiotonic principle of aconite root. Arch Pharm Res. 1984;7:133–136.

[18] Shen L, Yang X, Yang B, et al. Novel hybrids from lamellarin D and combretastatin A 4 as cytotoxic agents. Eur J Med Chem. 2010;45:11–18.

[19] Miousse IR, Skinner CM, Lin H, et al. Safety assessment of the dietary supplement OxyELITE^{TM} Pro (New Formula) in inbred and outbred mouse strains. Food Chem Toxicol. 2017;109:194–209.

[20] Stajić A, Anđelković M, Dikić N, et al. Determination of higenamine in dietary supplements by UHPLC/MS/MS method. J Pharm Biomed Anal. 2017;146:48–52.

[21] Bao X, Xu J, Xu Y, et al. [Clinical efficacy of higenamine (Fuzi One) on bradyarrhythmia and study of its mechanism of action on cardiac conduction system with His bundle electrocardiogram]. Shanghai Med J. 1979;2:770–773. Mandarin.

[22] Guo S, Chen K, Qian Z, et al. [Clinical efficacy study of intravenous infusion therapy of higenamine combined with Shengmai injection on bradyarrhythmia in 18 cases]. Beijing Med J. 1981;3:46–47. Mandarin.

[23] Chen FH, Jiang W, Zeng G. [Clinical electrophysiology study of the effects of higenamine (Fuzi One) on sick sinus syndrome]. Chin J Integr Trad West Med. 1984;4:30–31. Mandarin.

[24] Jiang W, Liu X, Tao S, et al. [Clinical study of higenamine (Fuzi One)]. Chin J Integr Trad West Med 1981;1:6–8. Mandarin.

[25] Cao Y, Wang Z, Wang F, et al. [Influence of higenamine hydrochloride myocardial stress test on heart rate, blood pressure, myocardial oxygen consumption]. Chin Hosp Pharm J 2012;32:1353–1355. Mandarin.

[26] Jiang W, Tao S, Li J, et al. [Effects of acute administration of higenamine on bradyarrhythmias: a preliminary clinical study]. Chin J Cardio. 1980;8:95–98. Mandarin.

[27] Du Y, Li F, Xu R, et al. [Tolerability of higenamine hydrochloride in healthy volunteers]. Chin J Clin Pharmacol. 2007;23:258–260. Mandarin.

[28] Du Y, Li F, Wang Q, et al. [Efficacy and safety of a novel pharmacological stress test agent – higenamine in radionuclide myocardial perfusion imaging: phase II clinical trial]. Chin J Nucl Med Mol Imaging. 2014;34:34–38. Mandarin.

[29] Cao Y, Wang Z, Wang F, et al. [Detection of coronary heart disease with ^{99m}Tc-MIBI myocardial perfusion imaging stressed by intravenous infusion of higenamine hydrochloride]. Chin J Nucl Med Mol Imaging. 2012;32:203–205. Mandarin.

[30] Zhou W, Wang F, Zhang L, et al. [Myocardial perfusion imaging with higenamine hydrochloride stress studies in diagnosis of coronary artery disease]. Chin J Nucl Med Mol Imaging. 2012;32:408–412. Mandarin.

[31] Feng S, Hu P, Jiang J. Determination of higenamine in human plasma and urine using liquid chromatography coupled to positive electrospray ionization tandem mass spectrometry. J Chromatogr B. 2011;879:763–768.

[32] Tian R, Wang Q, Mi Hz, et al. [Efficacy and safety of higenamine hydrochloride injection used in pharmacological stress myocardial perfusion imaging]. Chin J Clin Pharmacol. 2012;28:88–90. Mandarin.

[33] Sun Y, Hou P. [Hydrochloric acid higenamine load ^{99m}Tc-MIBI myocardial perfusion imaging in the diagnosis of coronary artery disease]. Chin Health Stad Management. 2015;6:67–68. Mandarin.

[34] Mi H, Wang Q, Tian R, et al. [The clinical availability of hydrochloric acid higenamine as a stress medicine in radionuclide myocardial perfusion imaging to diagnose coronary artery disease]. J Cardiovasc Pulm Dis. 2015;34:486–488. Mandarin.

[35] Okano M, Sato M, Kageyama S. Determination of higenamine and coclaurine levels in human urine after the administration of a throat lozenge containing *Nandina domestica* fruit. Drug Test Anal. 2017;9:1788–1793.

[36] Towa Pharmaceutical Company. Medication guides: Tosmerian Tablets; 2009 July [cited 2018 June 4]. Available from: http://www.rad-ar.or.jp/siori/english/kekka.cgi?n=36115

[37] Lee SR, Schriefer JM, Gunnels TA, et al. Acute oral intake of a higenamine-based dietary supplement increases circulating free fatty acids and energy expenditure in human subjects. Lipids Health Dis. 2013;12:148.

[38] Bloomer RJ, Schriefer JM, Gunnels TA. Clinical safety assessment of oral higenamine supplementation in healthy, young men. Hum Exp Toxicol. 2015;34:935–945.

[39] Jeter J, DeZee KJ, Kennedy L. A case of paraspinal muscle rhabdomyolysis in a 22-year-old male after ingesting a supplement containing higenamine. Mil Med. 2015;180:e847.

[40] U.S. Anti-Doping Agency. U.S. weightlifting athlete Lazaro Roman accepts sanction for anti-doping rule violation; 2018 Mar 9 [cited 2018 May 18]. Available from: https://www.usada.org/lazaro-roman-accepts-doping-sanction/

[41] U.S. Anti-Doping Agency. U.S. weightlifting athlete Teresa Britt accepts sanction for anti-doping rule violation; 2018 Apr 9 [cited 2018 May 18]. Available from: https://www.usada.org/teresa-britt-accepts-doping-sanction/

[42] Dietary Supplement Health and Education Act of 1994. Pub L No. 103-417, 1994. 103rd Congress, 2nd sess., S784.

[43] U.S. Food and Drug Administration. Dietary supplements: new dietary ingredient notifications and related issues: guidance for industry, 2016 Aug. Available from: https://www.fda.gov/food/guidanceregulation/guidancedocumentsregulatoryinformation/dietarysupplements/ucm257563.htm

[44] Attipoe S, Cohen PA, Eichner A, et al. Variability of stimulant levels in nine sports supplements over a 9-month period. Int J Sport Nutr Exerc Metab. 2016;26:413–420.

[45] National Institute of Health. Dietary Supplement Label Database. Version 7.0.2. 2018 Jun [cited 2018 June 27]; Rev 2557. Available from: https://www.dsld.nlm.nih.gov/dsld/index.jsp