European Journal of Food Research & Review
2(4): 93-100, 2012

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Scientific Opinion on the Regulatory Status of 1,3-Dimethylamylamine (DMAA)

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Authors' contributions

This work was carried out in collaboration between all authors. Author BJV performed the literature study, data analysis and wrote the first draft of the manuscript. Author DK took the initiative to prepare a scientific opinion and performed a critical review of the first draft. All authors read and approved the final manuscript.

Research Article

Received 8th June 2012
Accepted 19th September 2012
Published 26th November 2012

SUMMARY

1,3-Dimethylamylamine (DMAA) is a pressor amine often found in food supplements for athletes at dosages of 25-65 mg. Historically, the compound has been used as a nasal decongestant but its oral application is largely unstudied leaving the regulatory status of such food supplements as unlicensed medicines undetermined. We therefore reviewed the literature on DMAA and similar amines in order to deduce an effective oral dosage. Based on our findings we conclude that oral preparations with >4 mg DMAA per dose unit should be considered as effective as a bronchodilator. Food supplements that exceed that limit are in fact subject to the Medicines Act and require licensing. Dosages higher than 100-200 mg are expected to cause serious adverse events.

Keywords: 1,3-Dimethylamylamine (DMAA); geranamine; regulatory status; food supplements; oral efficacy.

1. INTRODUCTION

DMAA is an aliphatic amine with vasoconstricting properties. It can easily be prepared synthetically [1,2] and was used between 1940-1970 as the active pharmaceutical ingredient in Forthane® nasal inhalers (Lilly) for relieving nasal congestion. Although DMAA is banned

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by the international anti-doping organisation (WADA) as a stimulant it is often listed on the label of food supplements for athletes. Laboratory analysis showed that products may contain 25-65 mg DMAA per dose unit (data not shown) [3,4]. Zhang et al. (2012) even found dosages of 285 mg [5].

According to EU law the marketing of pharmacologically active compounds for human consumption requires licensing as a medicine. To alleviate regulatory pressure on natural products this definition is applied to food supplements only when they are pharmacological effective. Since the oral efficacy of DMAA is poorly understood this left its regulatory status as an oral medicine undetermined [5].

To determine whether food supplements with DMAA should be considered as unlicensed medicines we reviewed international scientific and patent literature on the pharmacology of DMAA and similar compounds using Scopus, Pubmed and SureChem. Based on our findings we formulate a scientific opinion on the regulatory status of DMAA in food supplements.

2. NOMENCLATURE

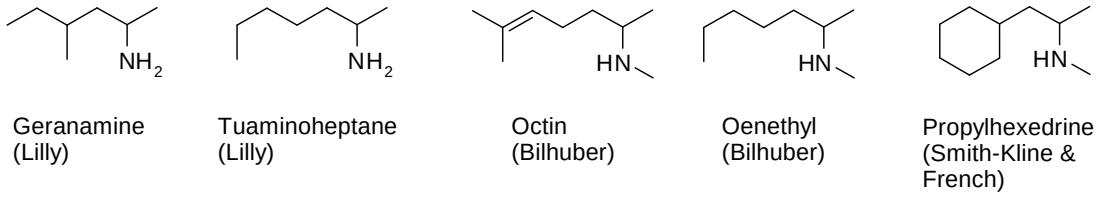
DMAA is one of the many trivial names for '4-methyl-hexane-2-amine' (Table 1). The trivial name 'Geranamine' refers to geranium oil being claimed as a natural source of DMAA [6]. However, elaborate studies could not confirm the presence of DMAA in geranium oil and even suggest that this claim may have been fabricated in order to justify its use in food supplements [7,8].

Table 1. Systematic name and trivial names for DMAA

4-Methyl-hexane-2-amine (syst. name)	Forthan
Geranamine	Methylhexaneamine
1,3-Dimethylpentylamine	4-Methyl-2-hexylamine
Floradrene	4-Methyl-2-hexaneamine
Forthane*	Forthan

**The brand name 'Forthane' is currently attached to an anesthetic unrelated to DMAA.*

The molecular structure of DMAA contains two chiral centres (Fig. 1). For reasons of clarity this document only uses the name DMAA for all optical isomers and mixtures thereof, free base and all salt forms unless stated otherwise.



Geranamine (Lilly) | Tuaminoheptane (Lilly) | Octin (Bilhuber) | Oenethyl (Bilhuber) | Propylhexedrine (Smith-Kline & French)

Fig. 1. Molecular structures of aliphatic amines that were used in medicines.

3. PHARMACOLOGY

DMAA is an indirect sympathomimetic with vasoconstricting properties and cardiovascular effects [9]. These properties are common among many other aliphatic amines which therefore are generally referred to as 'pressor amines' [10-14]. Table 2 shows the pharmacological effects of DMAA observed in several species of animals.

Table 2. Pharmacological effects of DMAA in animal studies

System	Effects	Species
Cardiovascular	Increase in arterial blood pressure	Dog, cat, rat [9,12,15]
	Vasoconstriction	Rat, frog [16]
	Myocardial depression	Rat, guinea pig, rabbit, dog [16]
	Tachycardia	Dog [9]
Respiratory	Bronchodilation, increased nasal and lung volume	Dog [9]
CNS	Shortening of pentobarbital narcosis	Mouse [16]
Renal system	Diuresis	Dog [9]
Intestines	Depression of the peristaltic activity	Guinea pig, rat [16]
Reproductive organs	Antagonises acetylcholine induced contraction of the uterus	Rat [16]

Animal studies with DMAA have shown some similarities with the effects of ephedrine and amphetamine [9,11,12,17]. Literature shows that DMAA is largely equipotent to tuaminoheptane on most pharmacological aspects [16,17]. The hypertensive effect of DMAA was best described in literature. This suggested that the hypertensive effect of DMAA (iv) is 1-2x the effect for the same dose of tyramine [15]. In the dog, the hypertensive effect after oral dosing showed to be 4x weaker than ephedrine and 2x weaker than amphetamine [17]. Toxicological data are scarce. DMAA did not induce eye irritation in the rabit and the LD_{50} values (iv) were 39.0 and 72.5 mg/kg in mice and rats, respectively [16].

The therapeutic potential of aliphatic amines was extensively investigated by pharmaceutical industry in the first part of the 20th century [9,11-13,17]. At least 5 different aliphatic amines were eventually marketed as an active ingredient of a medicine: DMAA, tuaminoheptane, octin, oenethyl and propylhexedrine (Table 3) [11]. The therapeutic use of DMAA was limited to a nasal decongestant. Tuaminoheptane, octin en oenethyl were also used as medicines for their cardiovascular, bronchodilating, or anti-migraine properties. Propylhexedrine was also used as a weight-loss drug [23]. Detailed clinical studies were not found in scientific literature. DMAA and all structurally similar compounds are banned as stimulants by the World Anti-Doping Authority (WADA).

4. INTRANASAL APPLICATION

In 1944-1945 patents were granted to Lilly on the medical use of certain aliphatic amines, specifically for DMAA [1,2]. The patents describe the vasoconstricting action of DMAA and its usefulness as a nasal decongestant. DMAA was marketed as a nasal decongestant by Lilly under the name of 'Forthane®' until about 1970 [24]. Lilly advertisements for Forthane

state that intranasal use should normally not cause psychic disturbances, rise in blood pressure, cardiac irregularities or over-constriction [24].

Table 3. Aliphatic amines with properties similar to DMAA

Compound	Description
Tuaminoheptane (also: Tuamine)	Initially used as a nasal decongestant. An inhaler contained 325 mg tuaminoheptane adsorbed on a cotton plug [18]. The dosage of the spray was about 0.25 mg per spray [19].
Octin (also: Isometheptene)	Initially marketed as a nasal decongestant but still in use to control blood pressure during anesthesia, and for the treatment of migraine and muscle cramps [14,20].
Oenethyl	Initially marketed as a nasal decongestant and also used to control blood pressure during anesthesia [21,22]. ENREF_23
Propylhexedrine	Marketed as a nasal decongestant and also used as a weight-loss drug with a low potential for abuse [23].

Forthane® was a multiple use nasal inhaler containing DMAA carbonate adsorbed a cotton plug (equivalent to 250 mg DMAA as a free base). An effective dose is not reported for this drug delivery system. However, the Lilly patent also reports a different formulation; an effective nasal spray with a concentration of 0.6 mg/ml. Assuming the spray volume is not more than 1 ml, intranasal dosages of 0.6 mg and higher should be considered as therapeutically effective.

5. ORAL APPLICATION

Scientific literature was searched for articles mentioning the oral application of DMAA and similar amines. Only three articles were retrieved that described the oral use of DMAA. Several other articles were retrieved describing the effects of DMAA in laboratory animals and of similar amines in laboratory animals and humans.

Marsh et al. [25] described that a single oral dose of 3 mg/kg in a human (210 mg/70 kg) results in a moderate increase in the heart rhythm and blood pressure. In addition to a dry mouth, a runny nose and goose pimples, the subject also experienced serious side effects such as confusion and concentration problems. No signs of stimulation could be identified in the central nervous system. Lower doses were not investigated.

Perrenoud et al. [3] described the excretion of DMAA in urine following a single oral dose of 40 mg. They found that about 32 mg DMAA was found unchanged in the urine. The authors did not investigate the pharmacological effects.

Lisi et al. [7] described the excretion of DMAA in urine following a single oral dose of an undetermined quantity.

6. DISCUSSION

The pharmacology of DMAA is best known after intranasal application for relieving nasal congestion (Forthane®). Its medicinal use is based on the vasoconstricting effects in the nose after local application. Nevertheless, literature shows that systemic exposure may cause vasoconstriction of blood vessels of the lungs and the heart. The article by Perrenoud

et al. shows that DMAA is absorbed very well by the body when taken orally and that it is hardly metabolized [3]. DMAA is absorbed relatively slowly by the body (4-12 hours) and urinary excretion is very slow ($t_{0,5}$ = 24 hours). The slow urinary excretion of unchanged DMAA is also shown by Lisi et al. [7]. Therefore, there is a risk of a buildup of doses through daily use whereby the efficacy increases.

Because scientific literature on the oral use of DMAA is scarce its oral efficacy was deduced by assessing its intrinsic efficacy and oral efficacy relative to known values for similar amines (Table 4).

Table 4. Literature data on the pharmacological effect of DMAA and similar amines on the increase of blood pressure in dogs and humans

Blood pressure increase in dogs (iv dosing)		
Authors	**Compound**	**Normalization to epinephrine (rel. intrinsic efficacy)**
Swanson (1946)[12]	DMAA sulfate	4,7 mmol DMAA ≈ 3.55 µg epinephrine (1 : 0.76)
Marsh (1951) [25]	DMAA HCl	4,6 mmol DMAA ≈ 3.7 µg epinephrine (1: 0.80)
Swanson (1948) [17]	Propylpentadrine HCl*	1 mmol DMAA ≈ 0.97 µg epinephrine (1 : 0.97)
	Propylhexedrine HCl	1 mmol DMAA ≈ 0.26 µg epinephrine (1 : 0.26)
Blood pressure increase in dogs (po dosing)		
Author	**Compound**	**Rel. oral efficacy**
Swanson (1948) [17]	DMAA sulfate	0.93 – 1.88 mmol = 20% effect
	Propylpentadrine HCl	0.56 – 0.84 mmol = 100% effect
	Ephedrine sulfate	0.63 – 1.25 mmol = 90% effect
Blood pressure increase (17-23 mmHg) in humans (po dosing)		
Author	**Compound**	**Dose**
Marsh (1949) [26]	Ephedrine HCl	25 mg
	Propylhexedrine HCl	120 mg
Relative efficacy iv (intrinsic efficacy) versus po		
Compound	**Rel. intrinsic efficacy**	**Rel. oral efficacy**
DMAA	0.8	0.2
Propylpentadrine	0.97	1
Propylhexedrine	0.26	0.26#
Ephedrine	-	0.9

** Propylpentadrine = 2-Methylamino-1-cyclopentyl-propane*
 # Assumption by the authors based on structural similarity with Propylpentadrine.

6.1 Effect on the Heart

Propylhexedrine (Benzedrex®, B.F Ascher) is a DMAA analogue that is used as an inhaler in the United States to treat nasal congestion. Old and modern inhalers give off 0.4-0.5 mg propylhexedrine per 800 ml of inhaled air [27,28]. Propylhexedrine has a therapeutic effect on, for example, bradycardia [29] both after inhalation (dose not reported) as well as after

oral application (50 mg). The intrinsic efficacy of DMAA measured against the effect of blood pressure is about 3 fold higher than that of propylhexedrine, but this is compensated by a 4 fold poorer oral absorption [3,17]. Therefore, effects on the heart similar to an oral dose of 50 mg benzedrex may be expected after a oral dose of about 50-75 mg DMAA.

6.2 Effect on the Blood Pressure

The effect of orally-dosed DMAA on the blood pressure of dogs is 4.5 times lower than that of orally-dosed ephedrine [17]. After intravenous application, the relative effect of DMAA is actually 4 times higher. This confirms a comparable intrinsic working and that a slow oral absorption of DMAA leads to a lower peak dose ($C_{max.}$). With ephedrine, the blood pressure increasing effects have been seen in humans after a single oral dose of 25-60 mg. [30,31]. The slow oral absorption of DMAA means a blood pressure increasing effect is expected after a single dose of up to about 100 mg.

An oral dose of 97 mg (free base) of propylhexedrine in humans results in an increase in blood pressure of 17-23 mmHg. [26]. It is expected that the greater intrinsic efficacy of DMAA on the blood pressure will be compensated by a slower oral absorption [3,17]. Based on this comparison an increase in blood pressure can also be expected after a single dose of DMAA of about 100 mg.

6.3 Effect on the Lungs and the Nose

Ephedrine was applied orally to alleviate nasal congestion and as a bronchodilator in doses of 15-60 mg. [31]. It does not seem to work as a bronchodilator at lower doses. As the free base DMAA is 19 times as potent as ephedrine in alleviating nasal congestion [32]. However, the oral efficacy of DMAA is 4.5 times less than that of ephedrine. Therefore, a single oral dose of 4-15 mg DMAA can be expected to be equivalent to a single oral dose of 15-60 mg ephedrine.

7. CONCLUSION

According to literature DMAA is a pharmacologically active compound of synthetic origin. The single known reason for using DMAA in humans is pharmacological. The body absorbs DMAA adequately, but relatively slowly, when taken orally. Pharmacological effects after oral intake can be expected on the lungs (bronchodilation) and the nasal mucosa following a singe oral dose of about 4-15 mg. Pharmacological effects on the heart can be expected following a single oral dose of about 50-75 mg. Pharmacological effects on the blood pressure can be expected after a single oral dose of about 100 mg. Because of the long half-life, there is a risk that repeated doses within 24-36 hours could lead to steadily stronger pharmacological effects (build up). Ba sed on our findings we conclude that oral preparations with >4 mg DMAA should be considered as effective as a bronchodilator. Therefore, food supplements containing >4 mg DMAA should be treated as subject to the Medicines Act and require licensing as a medicine. Dosages higher than 100-200 mg are expected to cause serious adverse events.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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