JOURNAL OF MEDICINAL FOOD
J Med Food 17 (11) 2014, 1–4

DOI: 10.1089/jmf.2014.0026

CASE STUDY

Long-Term (5 Years), High Daily Dosage of Dietary Agmatine—Evidence of Safety: A Case Report

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ABSTRACT There is presently a great interest in the therapeutic potential of agmatine, decarboxylated arginine, for various diseases. Recent clinical studies have already shown that oral agmatine sulfate given for up to 3 weeks provides a safe and, as compared with current therapeutics, more effective treatment for neuropathic pain. These studies have ushered in the use of dietary agmatine as a nutraceutical. However, in view of information paucity, assessment of long-term safety of oral agmatine treatment is now clearly required. The authors of this report undertook to assess their own health status during ongoing consumption of a high daily dosage of oral agmatine over a period of 4–5 years. A daily dose of 2.67 g agmatine sulfate was encapsulated in gelatin capsules; the regimen consists of six capsules daily, each containing 445 mg, three in the morning and three in the evening after meals. Clinical follow-up consists of periodic physical examinations and laboratory blood and urine analyses. All measurements thus far remain within normal values and good general health status is sustained throughout the study period, up to 5 years. This case study shows for the first time that the recommended high dosage of agmatine may be consumed for at least 5 years without evidence of any adverse effects. These initial findings are highly important as they provide significant evidence for the extended long-term safety of a high daily dosage of dietary agmatine—a cardinal advantage for its utility as a nutraceutical.

KEY WORDS: • *agmatine sulfate* • *dietary ingredients* • *neuropathies* • *nutraceuticals*

INTRODUCTION

AGMATINE, DECARBOXYLATED ARGININE [$(NH_2(CH_2)_4 NH_2C(NH=)NH$], is a ubiquitous, naturally occurring molecule that was discovered a century ago by Kossel (1910).[1] Substantial preclinical and initial clinical evidence recently reviewed by Piletz *et al.*[2] suggests the utility of agmatine in treating a spectrum of complex diseases with unmet therapeutic needs, including diabetes mellitus, neurotrauma (*e.g.*, stroke, brain and spinal cord injury, and glaucoma), neuropathies and neuropathic pain, opioid analgesia and addiction, neurodegenerative diseases (*e.g.*, Parkinson's disease), and mood (*e.g.*, anxiety and depression) and cognitive disorders.

Agmatine is capable of modulating, potentially synergistically, multiple molecular targets that are implied in its beneficial effects and hence we metaphorically refer to it as a ''molecular shotgun.'' These targets were recently summarized by Piletz *et al.*[2] and include (1) modulation of several neurotransmitter receptors and receptor ionophores, (2) blockade of key ionic channels, (3) inhibition of membrane transporters, (4) modulation of nitric oxide (NO) formation, (5) modulation of polyamine metabolism, (6) inhibition of protein ADP-ribosylation and thus interfering with cell signaling, (7) inhibition of matrix metalloproteases (MMPs) and enzymes implicated in nerve cell death neuropathic pain, and (8) inhibition of advanced glycation end (AGE)-product formation, a process involved in the pathology of diabetes and neurodegenerative diseases.

While agmatine is synthesized in the body, it is also acquired from the diet where it is found in low amounts in a wide variety of plant-, fish-, and animal-derived foodstuff.[3] Additionally, many gastrointestinal (GI) bacteria produce agmatine and the significant concentrations of agmatine found in the mammalian GI tract implicate microbial production as the main source of systemic agmatine.[3,4] Animal studies demonstrated that exogenous agmatine sulfate, the commonly used salt form of agmatine, is absorbed in the GI tract and then rapidly (within minutes) distributed throughout the body,[3] including the brain.[2] In humans, ingested agmatine is readily absorbed and eliminated unmetabolized by the kidneys with an apparent blood half-life of about 2 h.[5]

Agmatine is principally metabolized into urea and putrescine, the diamine precursor of polyamines, which are not only essential for cell proliferation, but also essential for viability of mature cells in general and specifically so for nerve cells.[6] Agmatine-derived putrescine may also serve as a minor precursor for the neurotransmitter GABA (γ-aminobutyric acid).[3] Additionally, agmatine can also be oxidized resulting in agmatine-aldehyde formation, which may be toxic and

Manuscript received 4 February 2014. Revision accepted 13 June 2014.

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Table 1. Baseline Demographic Information and General Health Measures

Category	Participants	
	V.H.G.	*G.M.G.*
Demographics		
Age (years)	58	61
Gender	Female	Male
Ethnicity	White	White
Occupation	Scientist	Scientist
Smoking	No	No
Alcohol	No	3 wine glasses per week
Drugs	Levothyroxine	None
Health measures		
Weight (kg)	57.5	72.5
Height (cm)	169	185
BMI	20.1	21.2
Blood pressure (mmHg)	105/55	110/65
Heart rate (beats/min)	70	66

BMI values are calculated as kg/m^2 (weight in kg divided by the square of height in meters).

BMI, body mass index.

secreted by the kidneys.[7] This latter route is tissue specific, being significant in some tissues,[3] but minor in others,[8,9] and apparently negligible in the central nervous system.[3]

This evidence and the intense interest in agmatine's therapeutic potential[3] have clearly indicated the requirement for assessment of the longer-term effects of oral agmatine treatment. Recent observations in laboratory rats have provided evidence that subchronic (95 days) high-dosage oral agmatine sulfate regimen (829.85 and 568.51 mg/kg per day in female and male rats, respectively) is safe.[10] Importantly, human clinical trials by Keynan *et al.*[11] have shown that high doses of oral agmatine sulfate (1335–3560 mg/day) given for up to 3 weeks are safe and, as compared with current therapeutics, more effective treatment for lumbar-disc-associated radiculopathy (sciatica), with low incidence of mild diarrhea reported at the highest used dosage. These studies have ushered in the utility of dietary agmatine as a nutraceutical. However, while clearly required, longer-term (years) studies on the safety of agmatine treatment are still lacking. In view of this paucity, therefore, we have decided to follow up on our previous studies[3,11] and undertook to assess our own health-related measures during several years of continuous high-dosage oral agmatine sulfate consumption.

PARTICIPANT INFORMATION

Table 1 summarizes demographic information and general health measures of the two participants (the authors of this report) in the present study.

STUDY INTERVENTION

As illustrated in the timeline (Fig. 1), participants began taking oral agmatine sulfate, 2.670 g/day, on February 2009 (V.H.G.) or March 2010 (G.M.G.). Agmatine sulfate was supplied as the nutraceutical dietary supplement, AgmaSet® (Gilad&Gilad LLC, Reseda, CA, USA), in size-0 gelatin capsules containing 445 mg per capsule. AgmaSet is manufactured under cGMP (current good manufacturing practice) conditions in an accredited facility in the United States.

This is an ongoing study where both participants continue with the same high-dose agmatine sulfate regimen for the foreseeable future. The ongoing study regimen consists of six capsules daily, taken three in the morning and three in the evening after meals.

STUDY MEASURES AND FINDINGS

To ascertain safety, aside from self-assessment, participants underwent evaluations of physical examinations and laboratory blood and urine tests (Table 2) before commencing agmatine sulfate treatment (baseline) and at various follow-up times thereafter (Fig. 1). The physical examinations and laboratory tests were performed by medical doctors and clinical personnel unaware of the present ongoing surveillance, and the clinical records were supplied by the health insurers as part of their routine services.

As indicated in Table 2, baseline and last follow-up measures were within accepted normal values for both participants. At all intervening follow-up times (Fig. 1) values remain within the normal range and no trends were observed (results not shown). The following exceptions are noted: V.H.G. is on chronic levothyroxine sodium over the past 4 decades to compensate for thyroid deficiency due to Hashimoto's disease (Table 1). And slightly elevated cholesterol and triglyceride values, which have been noticed in GMG blood tests over the past 15 years, remained at their elevated levels throughout the study (Table 2).

No adverse effects or, otherwise, side effects were noticed throughout the study period. All study measures remained unchanged within the individual's normal range as compared with baseline values, and good general health status was sustained throughout the study.

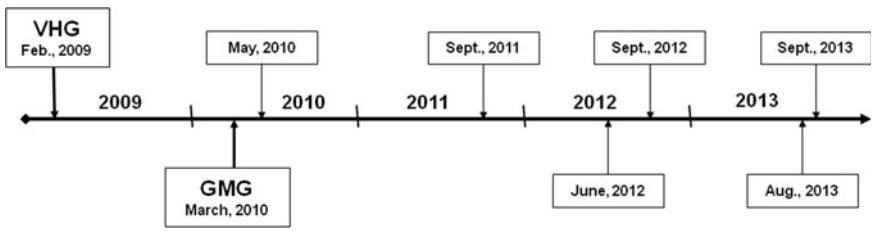

FIG. 1. Timeline (*horizontal arrow* with yearly intervals marked by *vertical lines*) indicating the year and month of agmatine sulfate treatment onset (*heavy vertical arrows* from framed initials) by V.H.G. (*above* timeline) and G.M.G. (*below* timeline) and the clinical follow-up times (*vertical arrows* from framed dates).

Table 2. Laboratory Tests Indicating Normal Female and Male Range Values, and Baseline and Last Follow-Up Values of Hematology, Blood Chemistry, and Urinalysis Measures

		V.H.G.			*G.M.G.*		
Parameter	*Units*	*Female normal range*	*Baseline values (Feb., 2009)*	*Last follow-up values (Sept., 2013)*	*Male normal range*	*Baseline values (Mar., 2010)*	*Last follow-up values (Aug., 2013)*
Hematology							
Red blood cell (RBC) counts	10^3CMM	4.2–5.4	3.98	3.95	4.6–6.1	4.80	4.82
Platelet count	10^3CMM	150–450	212	205	150–450	224	209
Hematocrit	%	37–47	36.8	36.7	42–52	44.1	45.9
Hemoglobin	GM/DL	12–16	11.9	12	14–18	15.5	16.1
Mean cell volume (MCV)	U^3	81–99	92.5	91.4	80–96	91.8	95.0
White blood cell (WBC) count	10^3CMM	4.0–10.8	4.1	4.3	4.0–10.8	7.0	5.8
Neutrophil absolute	10^9/L	2.4–7.6	3.5	3.1	2.4–7.6	3.5	3.5
Lymphocyte absolute	10^9/L	0.96–4.3	1.4	1.7	0.96–4.3	2.7	2.2
Monocyte absolute	10^9/L	0–0.86	0.4	0.1	0–0.86	0.63	0.63
Eosinophil absolute	10^9/L	0–0.5	0.1	0.2	0–0.5	0.14	0.10
Basophil absolute	10^9/L	0–0.11	0	0	0–0.11	0.05	0.02
Coagulation							
Prothrombin time (PT)	Seconds	11.2–15.3	12.2	12.9	11.2–15.3	12.7	12.0
Partial thromboplastin time	Seconds	29–37	32	33	29–37	34	31
Blood chemistry							
Chloride	MMOL/L	96–108	101	100	96–108	104	105
Potassium	MMOL/L	3.3–5.1	4.05	3.68	3.3–5.1	4.08	3.90
Sodium	MMOL/L	133–145	141	142	133–145	144	146
Calcium	MG/DL	8.6–10.2	8.90	9.23	8.6–10.2	9.57	9.30
Phosphorus	MG/DL	2.7–4.5	4.18	4.16	2.7–4.5	4.45	4.26
Creatinine	MG/DL	0.3–1.1	1.05	0.82	0.3–1.4	1.02	0.90
Urea	MG/DL	10–50	15.0	14.5	10–50	14.7	19.0
Glucose	MG/DL	70–105	102.0	99.1	70–105	92.8	91.0
Alanine aminotransferase (SGPT)	IU/L	10–31	10	16	10–41	20	28
Aspartate aminotransferase (SGOT)	IU/L	10–32	16	16	15–38	23	28
Alkaline phosphatase	IU/L	39–117	39	45	39–117	69	80
Albumin	G/DL	3.4–4.8	4.5	4.0	3.4–4.8	4.5	4.6
Total protein	G/DL	6.6–8.7	7.1	7.5	6.6–8.7	7.2	7.1
Total bilirubin	MG/DL	0.3–1.0	0.73	0.65	0.3–1.0	1.0	0.94
Total cholesterol	MG/DL	120–200	165	172	120–200	**213**	**226**
HDL cholesterol	MG/DL	35–85	51	51	35–85	56	67
LDL cholesterol	MG/DL	60–130	100	109	60–130	**135**	**165**
Triglycerides	MG/DL	35–170	71	58	35–170	**170**	**175**
C-reactive protein (CRP)	MG/L	0–10	2.9	3.4	0–10	4.0	3.1
Gamma-glutamyl transpeptidase (GGT)	IU/L	7.4–32	12	14	11–49	30	28
Uric acid	MG/DL	2.4–5.7	4.7	5.1	3.4–7.0	5.1	4.5
Globulin	G/DL	2.5–5.0	2.8	3.1	2.5–5.0	2.7	2.4
Urinalysis							
RBC	/HPF	Negative	Negative	Negative	Negative	Negative	Negative
WBC	/HPF	Negative	Negative	Negative	Negative	Negative	Negative
Epithelial cells	/LPF	Few	Few	Few	Few	Few	None
Crystals	/HPF	Negative	Negative	Negative	Negative	Negative	Negative
Yeasts	/HPF	Negative	Negative	Negative	Negative	Negative	Negative
Leukocytes	$/MM^3$	Negative	Negative	Negative	Negative	Negative	Negative
pH		5.0–7.5	5.0	5.5	5.0–7.5	6.5	6.5
Specific gravity		1.005–1.030	1.02	1.01	1.005–1.030	1.02	1.02
Protein	MG/DL	Negative	Negative	Negative	Negative	Negative	Negative
Glucose	MG/DL	Normal (0–15)	Normal	Normal	Normal (0–15)	Normal	Normal
Ketone	MG/DL	Negative	Negative	Negative	Negative	Negative	Negative
Blood (urine RBC)	$/MM^3$	0–5	0.5	1	0–5	0	0
Total bilirubin	MG/DL	Negative	Negative	Negative	Negative	Negative	Negative
Nitrite		Negative	Negative	Negative	Negative	Negative	Negative

Underlined values in bold indicate results outside the normal range.

DISCUSSION

Results of the present self case study suggest for the first time that a high-dosage agmatine sulfate regimen (2.670 g/day) can be safely consumed continuously for up to 5 years.

As case reports go, observations from *n* of one, or in this case *n* of 2, are limited in scope. Also, this is a self-reported case and as such may be prone to bias, especially when considering the authors' own interests in promoting agmatine use. In support of the present results, however, is the absence of any record of adverse events associated with the high-dose agmatine sulfate regimen since it has been introduced to market in 2010. Moreover, no adverse events were reported in a postmarketing surveillance of 1015 individuals (46% women and 54% men) who took the high-dose agmatine sulfate regimen between February 2010 and March 2013, for periods ranging from 3 weeks to 3 years. This surveillance is ongoing with no adverse events reported thus far (Gilad and Gilad, unpublished observations).

A comment is in order regarding the marketing of agmatine sulfate for the bodybuilding consumers, which is available from many companies online by Internet commerce. Beginning in 2007 and based on unsubstantiated claims, agmatine sulfate has been introduced to commerce for body builders at recommended dosage of up to 1.0 g/day and later, starting in 2012, at up to 2.0 g/day. Although there are no data on actual dosage or on the length of use, there have been no reports of adverse events so far, thus further supporting the safety of dietary agmatine.

Agmatine has been known as a natural product for over 100 years,[1] but only recently the demonstration of its biosynthesis in mammals revived research, indicating its exceptional modulatory action at multiple molecular targets. By acting as a molecular shotgun, agmatine interacts with its targets, notably several neurotransmitter systems, nitric oxide (NO) synthesis, and polyamine metabolism, which play important roles in cellular physiology and repair mechanisms, and thus provides basis for broad therapeutic applications.[2] Indeed, there is intense interest in agmatine's therapeutic potential and substantial preclinical and initial clinical evidence indicates that agmatine treatment can exert beneficial effects in a host of complex clinical disorders, such as diabetes, neurotrauma and neurodegenerative disorders, opioid addiction, mood disorders, cognitive disorders, and cancer.[2]

In sum, when taken together with available evidence, the main takeaway message of this case report is that it provides support for the extended long-term safety of the recommended high daily dosage of dietary agmatine. The evidence thus significantly supports the utility of agmatine as a nutraceutical dietary ingredient.

AUTHOR DISCLOSURE STATEMENT

Gad M. Gilad and Varda H. Gilad hold stocks in Gilad&Gilad LLC and are co-owners of intellectual property and patents related to agmatine usage. The medical doctors and clinical personnel who performed the test were unaware of the study and were not compensated in any way.

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