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REVIEW

Clinical and Analytical Toxicology of Dietary Supplements: A Case Study and a Review of the Literature

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Abstract The use of dietary supplements has grown dramatically in the last decade. A large number of dietary and herbal supplements escape regulatory and quality control; components of these preparations are poisonous and may contain, among other toxins, heavy metals. Uncontrolled use of dietary and herbal supplements by special populations, such as the military, may therefore pose a health risk. Clinical symptoms are not always properly attributed to dietary supplements; patients often do not mention supplement use to their health care provider. Therefore, a health risk estimate is hard to make on either the individual or the population level. The literature on this issue was reviewed and discussed in the light of a representative clinical–chemical case study. This case study was performed on a host of preparations that were used by one single individual in the military. Both essential (chromium, copper, zinc, and iron) and poisonous (arsenic, lead, and nickel) trace elements were determined using inductively coupled plasma combined with optical emission spectrometry (ICP–OES) or with mass spectrometry (ICP–MS). Arsenic and lead were detected at exposure levels associated with health risks. These health risks were detected predominantly in hormone-containing supplements and the herbs and botanicals used for performance enhancement. To the extent that this is a representative sample, there is an underestimation of supplement use and supplement risk in

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the US military, if not in the general population. Since clinical symptoms may be attributed to other causes and, unless patients are specifically asked, health care providers may not be aware of their patients' use of dietary supplements, a strong support of laboratory diagnostics, such as a toxicological screening of blood or urine, is required. In addition, screening of the preparations themselves may be advised.

Keywords Dietary supplements · Herbal supplements · Adverse effects · Clinical toxicology · Laboratory diagnosis · Toxicology screening · Quality control · Essential metals · Poisonous metals · Arsenic · Lead

Introduction

Dietary supplements contain at least one substance originating from any of the following categories: vitamins, minerals, amino acids, fatty acids, proteins (enzymes), hormones, herbs, and/or other botanicals. Supplements may be prepared as concentrates, extracts, or metabolites of any of these categories and formulated as tablets, capsules, powders, gels, or liquids. To be considered a dietary supplement, the supplement must be taken orally. All dietary supplements may be grouped into two broad categories, vitamin and mineral containing preparations or herbal preparations [1, 2]. The underlying concept is to ingest these preparations to supplement, not replace, the normal diet and ensure adequate nutrient intake. In popular practice, however, ingestion of these supplements may serve a range of objectives such as the treatment and prevention of illness, the maintenance and improvement of health, and also the build-up and improvement of physical performance.

In the US and Europe, dietary supplements exist in a grey zone somewhere between nutrients and drugs. In the US, the Office of Nutritional Products, Labeling and Dietary Supplements at the Food and Drug Administration (FDA) is responsible for regulating dietary supplements [3]. The Office of Dietary Supplements [4] and the National Center for Complementary and Alternative Medicine [5] both at National Institutes of Health are advocates for solid scientific evidence, database building, and education in this field. In spite efforts by the FDA, the market is flooded with preparations that seem to escape regulatory and registration oversight. Frequently, they originate from sources labeled in the West as modalities for complementary and alternative medicine often related to traditional Eastern medical practices. The consumer is bombarded with legitimate and illegitimate health claims and expectations regarding the marketed preparations. However, the consumer is often not able to properly judge the veracity of the health claim or the safety of the preparation.

In spite of this, the use of dietary supplements has grown dramatically in the US in the last decade [6, 7]. A recent publication on a 2002 telephone survey [8] mentions that 73% (n=2,101) of a population of US English speaking adults aged 18 years or older used a dietary supplement of some kind in the previous 12 months. Moreover, 4% (n=87) of this population had experienced an adverse effect, apparently related to the supplement use.

Adverse Effects

Supplements may be described physico-chemically as mixtures. Contrary to other drug preparations, the active components are often beyond complete qualitative and quantitative control, especially for herbal supplements. This issue may be compounded for supplement preparations of foreign origin.

Adverse effects of dietary supplements are generally related to the following issues [9, 10].

1. Variability in product content and composition within and between batches of preparations of dietary supplements; this is of particular concern for herbal supplements. The information on labels often does not agree with the actual contents.
2. Inherent toxicity of any of the substances used in the preparation. This may be true for specific phytochemicals in herbal supplements, but also may be a result of the addition of toxic substances, e.g., heavy metals, during the preparation procedure.
3. Conditions of use, including the dose level and exposure period. Because of the variability among preparations and the fact that use is often not monitored by a clinician, adverse affects are a predictable outcome.
4. Individual variability among people.

(a) Bioavailability due to dietary habits. Some common dietary factors may enhance uptake of active substances and subsequently increase toxicity.

(b) Susceptibility to and metabolic handling of substances in the supplement preparation due to genetics as well as life style factors such as alcohol use. This may include allergies but also variations in the metabolic conversion rate for specific substances.

(c) Metabolic handling of substances due to developmental stage (pregnant women, elderly people) and due to underlying diseases.

5. Interactions among—mainly—herbal supplements and other medications [11–15]. These interactions are reported for almost every group of prescription drugs (e.g., Garlic, Ginkgo, St John's Wort, and Panax Ginseng all interact with anticoagulants (warfarin); Ginkgo, St John's Wort, and Siberian Ginseng all interact with antiarrhythmics (digoxin); Ginkgo interacts with various antihypertensives). In fact, adverse interactions may be significantly underestimated as patients often do not discuss their use of supplements with their prescribing clinicians.

Diagnosis

Dietary supplements are seldom used by consumers as a single substance supplement (e.g., a single vitamin or a single mineral). In addition, adverse effects and toxicity are usually related to combinatorial and interactive effects. From Table 1, it can be seen that the vast majority of people use various supplements in combinations. Thirty-two percent of users combine multivitamin/minerals with a single vitamin/mineral preparation and an additional

Table 1 Dietary Supplement Use (Adapted from Timbo et al. [8])

Use of	All users (n=2,101) (%)	Users with adverse events (n=87) (%)
Multivitamins alone	15.9	10.1
Multivitamins/minerals plus single vitamin/mineral	32.0	31.1
Multivitamins plus herbs/botanical	5.2	4.7
Multivitamins/minerals plus single vitamin/mineral plus herb/botanical	31.8	41.9
Single vitamins or minerals	9.8	2.9
Single vitamins/mineral plus herb/botanical	2.9	1.1
Herb/botanical alone	1.9	0.0

In a population of 2,101 supplement users a number of 87 (4%) experienced adverse effects. The percentages in the table refer to the number of supplement users reporting the use of specific supplements

32% combine another herb or botanical with this. Not coincidentally, these are the groups that have the highest percentage of adverse events (31% and 42%, respectively).

From Table 2, we can see that clinical symptomatology does not provide a clear diagnosis of dietary supplement toxicity. The symptoms are often not specific to a particular supplement and if the patient is not asked the health care provider may not suspect dietary supplements as the culprit. Even when the use of dietary supplements is known, the clinician may have a hard time attributing any of these symptoms to the use of specific supplements or to a specific substance. Good toxicological knowledge exists on overdose and interactions of many of the separate components in a dietary supplement and is easily available. However, the label on the bottle may not supply sufficient information additionally, in many cases, the information is wrong anyway. When the contents and composition are obscure, any interpretation regarding dose and duration has no meaning. Therefore, in serious cases, laboratory diagnostics, such as a toxicological screening of blood or urine, is necessary for the clinician to establish actual exposure and internal body load of some substances. Moreover, these diagnostics may have to be expanded to include an analytical screening of the preparation itself and in rare cases a determination of prescription drug levels in blood is recommended. Only then may a course of treatment be based on the nature and extent of the causative agent. Otherwise, treatment remains preventive and symptomatic.

Use in the Military

Military populations present a unique opportunity for the study of dietary supplements. In this population, the use of dietary supplements is principally for build-up and improvement of performance rather than on overcoming health deficiencies. In this respect, the military may differ from the general population in that supplements are selected with a certain bias on pursuing ergogenic claims [16].

The military has recognized the health risks related to supplements use in the past few years and considers ascertaining the use of dietary supplements in the military an important safety issue [17]. They urge military health care providers to document adverse effects related to supplements in the patient's record and to notify the Army Pharmacy & Therapeutics Committee as well as the FDA. This information is needed to build a solid survey and evaluate possible medical contraindications, interactions with medications or foods, surgical risks, and education needs.

Table 2 Symptoms Related to Dietary Supplement Use (Adapted from Timbo et al. [8])

A number of 87 (4%) in a population of 2,101 supplement users experienced adverse effects (see Table 1). The percentages in the table refer to the number of supplement users, out of these 87, reporting specific symptoms. Symptoms were not specified on the list when they were reported by less than 2% of the users

Symptom	%
Heart problems/chest pain	12.5
Abdominal pain	8.4
Headache	7.7
Rashes	6.7
Allergy/reaction	6.0
Nausea	5.1
Blood pressure problems	4.7
Diarrhea	4.5
Cramping/muscle aches	4.4
Dizziness/fainting	3.1
Sleep problems	2.8
Less frequently reported symptoms	29.7

On the website for the Directorate of Health Promotion and Wellness, under the US Army Center for Health Promotion and Preventive Medicine, there is a considerable amount of information on dietary supplements directed at both the military consumers and military health care providers [16].

A Case Study

However, these educational and monitoring efforts do not seem to prevent the widespread and often ill-advised use of dietary and herbal supplements in the military. Recently, we were given the opportunity to perform an analytical chemical study on essential and poisonous trace metals from a host of preparations that were thought to have been used by an individual in the military for physical performance enhancement. This individual had died of cardiac arrest after completing his daily physical training. Subsequent investigation revealed that he had been taking a large variety of supplements (Fig. 1) as listed in Table 3. An examination of this list reveals that many are performance-enhancing preparations and are grouped under vitamins & minerals, hormones & proteins, herbs & botanicals, and prescription & over-the-counter (OTC) drugs.

Among this first category of vitamins and minerals in Table 3, the SSS Tonic is essentially a multivitamin supplement fortified with iron, and Focus Factor is essentially a multivitamin supplement with additional choline and some herbs. Under the category of hormones & proteins, he had been taking human growth factor (HGH) and insulin-like growth factor (IGF), both often used in body building. The list of prescription and over-the-counter drugs includes a number of pain killers, cold–cough remedies, and allergy drugs such as Creomulsion. It is interesting to note the number of herbs and botanicals made from or including Ginseng preparations with an advertised effect on sexual performance

Fig. 1 Supplements used. Overview of the supplements that were collected and processed for analysis. The specifications and analytical findings are presented in Table 3

Table 3 Trace Metal Content of Various Supplements

Supplement	Source	Lot#	As ppb =ng/g	Pb ppb =ng/g	Ni ppb =ng/g	Cr ppb =ng/g	Cu ppm =μg/g	Zn ppm =μg/g	Fe ppm =μg/g
Vitamins & minerals									
Vitamin A	Nature Made	MC10243	3	2	55	18	0.1	<DL	0.8
Vitamin C Supplement	Mason Vitamin Inc	1656U	<DL	11	12.6	23	<DL	<DL	1.6
SSS Tonic	SSC Company	23105	1	1	431.5	411	<DL	0.3	2,386.3
Focus Factor	Vital Basics Inc	858104	115	45	118	2953	90.5	2050.5	968.0
Hormones & proteins									
HGH-Pro Formula	Herbal Commerce LLC	unknown	82	40	295	425	0.5	1.6	8.1
IGF	Natural Enhancer LLC	28A104	1193	11267	291	298	3.8	4246	160.2
Pure Whey	Prolab Nutrition Inc	4258J40 09/04	<DL	11	<DL	165	3.8	11.7	26.9
Herbs & botanicals									
Panax Ginseng extract	China	unknown	33	<DL	<DL	7	<DL	<DL	6.8
Korean Ginseng Royal jelly	Dong-A Amer Corp.	5315	<DL	16	15	17	0.6	<DL	94.4
Korean Ginseng Royal jelly	Dong-A Amer Corp.	5315	1	26	146	<DL	0.1	<DL	1.00
Korean Ginseng Gingko	Dong-A Amer Corp.	4307	3	20	<DL	4	0.1	<DL	3.20
Ginseng	Naturex, NSL-distributed	unknown	35	169	135	211	0.2	2.4	45.5
Ginseng	Sundown	592647 02 05	265	2064	1645	753	2.9	25.1	369.5
Ginsa gold	General Nutrition Corp	62192	251	321	1420	371	<DL	18.8	102.4
Horny goat weed	General Nutrition Corp	1703EC0636	521	552	1176	868	0.6	13.6	38.2
Magna Rx+	Right Choice Lab	22659	72	452	<DL	161	2.8	580.1	58.3

Magna Rx+	Right Choice Lab	22659	79	448	<DL	238	1.8	754.8	65.0
Man of iron	Natureplex	1963	11	260	<DL	141	0.9	6.9	43.7
VRX2	Herbal Commerce LLC	16J103	1852	667	1583	960	10.1	63.6	136.1
Prescription & OTC drugs									
Aspirin	unknown	unknown	<DL	2	<DL	120	<DL	<DL	1.6
Flonase	unknown	unknown	<DL	<DL	<DL	4	<DL	<DL	3.2
Clarytine	unknown	04C0208	153	1	<DL	47	0.4	92.7	243.6
Pyridium	Pfizer	406137A	7	54	79	60	0.6	<DL	24.4
Creomulsion	Summit Industries Inc	03E	<DL	1.3	<DL	<DL	0.2	0.4	<DL
Alka-Seltzer	Bayer Corp	A3K101	<DL	<DL	<DL	21	<DL	<DL	<DL
Antiflu-DES	Productos Faraceuticos	ZDD301	43	<DL	<DL	271	1.4	0.2	15.8
Sildenafil	NA	NA	17	9	<DL	341	0.3	39.6	38.1
Equate cold relief	Perrigo	4JE0473	<DL	19	<DL	57	0.2	0.4	<DL
Pseudophedrine	LNK International Inc	134287	47	27	<DL	417	0.5	163.4	114.2

Total element levels were established for all analytes and no chemical speciation was performed

As, Pb, Ni, and Cr were analyzed using ICP–MS while Cu, Zn, and Fe were analyzed using ICP–OES

The analytical results were expressed as ppb (=ng/g) or ppm (=μg/g)

The estimated average intake per preparation was 1 g/day

The detection limits were 0.05, 0.05, 0.5, and 0.5 ppb for As, Pb, Ni, and Cr, respectively; and 20, 20, and 20 ppb for Cu, Zn, and Fe, respectively

DL detection limit

enhancement. In addition, the botanicals 'Horny goat weed' and Magna Rx contains Epimedium, while "Men of Iron" also contains Epimedium, Yohimbe, and Got Kola—all thought to enhance sexual performance. Finally, VRX2 is claimed to be the natural counterpart of the prescription drug sildenafil (Viagra).

Procedures

Either 0.2–1 g of solid material (tablet, powder) or 0.5 ml liquid drug was collected for each preparation and digested in concentrated nitric acid (HNO_3) with lead (^{206}Pb), yttrium (Y), and selenium (^{74}Se) as internal standards in a microwave system (Mars Express, CEM Corporation, NC, USA). Two samples per preparation were analyzed for all trace elements. All analyses were performed in duplicate.

Copper (Cu), zinc (Zn), and iron (Fe) were analyzed with inductively coupled plasma combined with optical emission (ICP–OES, Optima 300, Perkin Elmer, MS, USA). The method was previously developed as a standard operating procedure in our laboratory and validated. One milliliter digested sample was diluted with double distilled water while gallium (Ga) and antimony (Sb) were added as internal standards. Calibration was performed using standards containing 0.05, 0.2, 1, 2, and 5 ppm Zn, Cu, Fe and 2 ppm Ga and 5 ppm Sb as internal standards. Cu, Zn, and Fe were respectively detected at a wavelength of 324.8 nm, 213.9 nm and 238.2 nm. Plasma parameters were set at—all elements, 15 l/min plasma gas and 0.5 l/min auxiliary gas. Sample flow rate was set at 0.6 ml/min. Detection limits were 20, 20, and 20 ppb for Cu, Zn, and Fe, respectively. The analytical results for these elements are presented as ppm (=μg/g).

Arsenic (As), lead (Pb), nickel (Ni), and chromium (Cr) were analyzed using inductively coupled plasma with mass spectrometry (ICP–MS, Element 2, Thermo Scientific, MA, USA). The method was also previously developed as a standard operating procedure in our laboratory and validated. For this method, 1 ml digested sample was diluted with acetic acid (CH_3COOH) and double distilled water to a final volume of 2 ml containing 5 ppb ^{205}Pb, 5 ppb Y, and 25 ppb ^{74}Se as internal standards. Calibration was performed using a mixed element (ME1, 26 elements) standard containing 10, 50, 100, 200, 500 and 1,000 ppt ME1 and 5 ppb ^{206}Pb, 5 ppb Y, and 25 ppb ^{74}Se. The system was optimized for low resolution mode, followed by optimization for high resolution mode. Detection limits were 0.05, 0.05, 0.50, and 0.50 ppb for As, Pb, Ni, and Cr, respectively. The analytical results for these elements are presented as ppb (=ng/g).

Results

The results of the analysis are summarized in Table 3. Results are given as total element concentration. No chemical speciation was performed, although it is important to emphasize that toxicity is often dependent on speciation and inorganic compounds may differ in their nutritional and toxic values from organic compounds, e.g., organic lead is more neurotoxic than inorganic lead at the same exposure.

An examination of Table 3 reveals a general trend: In the category Prescription and OTC drugs, there are generally lower concentrations of metals tested for. On the other hand, element concentrations are generally higher in the three other categories (vitamins & minerals, hormones & proteins, and herbs & botanicals). Also, within-batch and between-batch variability of element concentrations of similar preparations is lower in the Prescription and OTC drugs category. In fact, the highest variability is found in the group herbs & botanicals.

For further comparison and because no accurate clinical data on the amounts ingested by this individual were available, we are forced to resort to a reasonable guess in terms of risk assessment. We assume that an average pill weighs 0.5 g, and that a conservative estimate would be that one pill is taken twice a day. From these assumptions, we have estimated the average dietary load for each of the preparations.

Essential Elements

For all the elements tested, care should be taken by the consumer not to exceed the tolerable upper intake level. With iron, for example, the upper intake level is 45 mg/day and, when responsibly used, 8 mg/day is an adequate dietary intake [14]. Among the supplements tested, SSS Tonic makes the claim on its label to be fortified with iron and we were able to confirm the fortification of SSS Tonic with iron (nearly 2,400 ppm). On the other hand, Focus Factor does not have anything in its labeling with regards to its iron content yet it has a relatively high level of iron (almost 1,000 ppm). This is an example of insufficient consumer information.

The same may be said of zinc; none of the preparations contains enough zinc to exceed a tolerable intake level (40 mg/day, while an adequate intake level is 11 mg/day [18] if consumed responsibly. A note of caution: the IGF preparation under hormones & proteins contains more than 4,000 ppm zinc and thus the consumer should be aware of the potential for excessive consumption of zinc with this supplement. Again, in the case of Focus Factor, the zinc content we detected was more than 2,000 ppm and yet there is no mention of this high level on its label. Another supplement, Magna Rx, has high zinc content (>500 ppm). Because it is advertised for sexual performance enhancement, clinicians should be aware of the potential for excessive consumption.

In all supplements, the copper levels are rather low (<100 ppm). An adequate intake level for copper is about 1 mg/day and a tolerable upper intake level is 10 mg [18]. Considering these values against the background of our risk assessment, none of the preparations contains a risk at responsible use.

For chromium, an adequate intake may be 35 μg/day [18] and a tolerable upper intake level may be even up to 1 mg/day. Most preparations contain levels below 1 ppm. However, Focus Factor contains almost 3 ppm. Also, quite a number of the botanical supplements, especially those used for sexual performance enhancement, show relatively high levels of chromium, i.e., Ginseng manufactured by Sundown (753 ppb), Horny goat weed (868 ppb), and VRX2 (960 ppb). Health effects however may differ depending on the chromium speciation (i.e., trivalent or hexavalent chromium compounds). It might be argued that with responsible use even these supplements would not lead to toxic intake levels, and thus do not pose a health risk. The lack of specific knowledge as to the species of chromium in these preparations has led the authors to be cautious in making any conclusions with regards to toxic potential.

Toxic Elements

A serious consideration in nickel intake is its sensitizing potential, often related to long-term low dose exposure that could lead to dermatitis and allergies. A tolerable upper intake level for nickel is set at 1 mg/day [18]. From Table 3, it can be seen that for most preparations the nickel level is very low (<0.5 ppm). However, in the botanical supplements, Ginseng, Ginsa Gold, Horny goat weed, and VRX2 levels of approximately 1.5 ppm are found. This pattern resembles the one seen for chromium. Here too, health

risks are associated with the type of nickel compounds and therefore the expected intake level may not lead to any health risk but the lack of knowledge as to the nickel compound actually present may not support this conclusion.

Inorganic lead is a serious hematotoxin and neurotoxin [19]. As mentioned above, organic lead compounds are even more neurotoxic than the inorganic lead. The lead level in most samples is below 500 ppb. A number of botanical supplements are comparatively high in lead, with one of the Ginseng supplements containing as much as 2 ppm. It is known that herbal medicines of Asian origin are often adulterated during preparation with toxic inorganic lead or arsenic compounds [20]. Therefore, any excessive use of these preparations will increase exposure. Consumers and clinicians should be made aware of these possible health risks. Another, striking, observation is that the IGF sample (hormones & proteins category) contains up to 11 ppm. This implies that with regular and frequent use of this IGF preparation a significant exposure to lead will occur, and that deleterious health effects are possible.

Arsenic levels are generally below 500 ppb in most of the supplements. Again, one of the botanicals, VRX2, contains almost 2 ppm arsenic. In the category of hormones & proteins, the IGF sample contains more than 1 ppm. Arsenic as an organic compound may not be toxic at all but as an inorganic compound it may have the highest toxic potential of any of the elements tested [21]. It is known that herbal medicines of Asian origin are often adulterated during preparation not only with lead (as discussed above) but also with toxic inorganic arsenic compounds [20]. Therefore, especially for arsenic, frequent and regular use of these preparations may lead to significant exposure and possible deleterious health effects.

Concluding Remarks

Exposure by ingestion is not always an accurate measure of intestinal absorption and internal exposure. A more realistic risk assessment is made by regular biological monitoring of these elements in blood or urine. However, to relate any of our findings to a health effect something about the actual usage by the consumer of these supplements must be known. When there is no control over the daily dosage and the continuity of the exposure, then there is certainly a risk of negative health effects. Therefore, we hope that our observations will contribute to an increased awareness by both consumers and health care providers of the possible health risks.

The effects of quality control both in the raw materials and contamination control are clearly visible in the herbs & botanicals. This is especially obvious in the group of botanicals used for sexual performance enhancement. Highly significant contamination is seen in the group hormones & protein (i.e., IGF), especially from the contribution of lead and arsenic. Ingestion of these elements represents a potential health risk and should be carefully monitored.

It is unclear how representative this one individual is of the general use of supplements in the military or the population at large. If this is representative use for even a subpopulation of the military, there is reason for concern. As we mentioned earlier, in serious cases, the health care provider should suspect metal toxicity and resort immediately to laboratory diagnostics. Biological material such as blood or urine should be run through a toxicological screening to establish exposure and internal body load of these substances. Consumption of supplements needs to be brought more into the spotlight of public health and perhaps requires further regulatory oversight. In addition, health care providers need to

be aware of the potential risks and alert for excessive consumption of these and other supplements by their patients [22, 23].

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