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Editorial

Alternate Medical Therapies Complicating Severe Metabolic Derangements in Diabetes Mellitus

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Abstract

Self-directed subscriptions to alternative therapies are popular but costly. The cost to the patient is due to the high price of purchase plus the cost of treatment of the medical complications resulting from these substances. A case here is presented demonstrating extreme numbers and doses of ingestions of herbal and vitamin and hormonal therapies. The consequences to her metabolism, encephalopathy, and morbidity were prolonged acidosis, coma, and respiratory failure. A brief review of the toxicities of the more than twenty substances consumed by a single patient serves as a catalogue of possible disorders commonly available through vitamin shops, pharmacies, and wellness or anti-aging providers.

INTRODUCTION

Alternative therapies to traditional medical pharmacologic practice include vitamins, nutraceuticals, herbal medicines, and anti-aging hormones often described as “supplements” (DHS). Quite often that the public is more compliant with these products than prescribed medications. Toxicities and side effects of these consumptions are frequently reported in previously normal individuals. In the elderly and in patients with diseases, the risk intensifies as changes in organ physiology leads to less reserve to respond to complications from these substances. Diabetics would seem to be one of the highest risk groups for complications from these agents as they already are at risk for disordered metabolism, renal insufficiency, and interactions with traditional medications like metformin which could magnify their adverse reactions. A case is presented which illustrates these risks.

CASE PRESENTATION

A 77 year-old white female with a past medical history significant for type 2 diabetes, hypertension, and hyperlipidemia presented to the emergency department (ED) after being found altered by her husband who provided her history. Her husband reported that she had experienced headache and vomiting the day prior to admission. She was admitted to the intensive care unit (ICU) with a diagnosis of ketoacidosis as she had an anion gap of 27. Medication reconciliation revealed the patient was on the following medications as an outpatient: Hydrochlorothiazide, Metformin ER, Amlodipine, Metoprolol succinate (ER) tablets, Levothyroxine.

Over several months prior to admission she had been steadily losing weight. On exam she was found to be comatose and could not protect her airway. She was intubated and placed on mechanical ventilation. Initial laboratory results revealed a severe anion gap metabolic acidosis, ketonuria, ketonemia, and elevated lactate level. Later an elevated ammonia level was measured.

Over the next 4 days the ketone levels were eliminated with insulin therapy, the sugar was controlled but required high doses of insulin, but the patient had persistent coma, anion gap metabolic acidosis. Urine anion gap was done to be sure the metabolic acidosis was not due to bicarbonate losses. On day five the patient began to awaken. She was extubated on day 6. She resumed cognition except for slight disorientation to location. Her cognition was slow and her motor function revealed some generalized weakness likely due to deconditioning from the prolonged coma, bedridden status due to the need for mechanical ventilation.

Details of her visits to a provider of alternative medicines were identified by the 2nd hospital day and a list of self-administered supplements was provided by the family after they went through her home “medications.”

What was discovered was the list of supplements many of which contained multiple vitamins, herbal substances, and anti-aging hormones. Table (1) shows the list of these supplements. In addition the patient had received a subcutaneous depot administration of anti-aging hormones. Table (2) was the

Table 1: Supplements taken as an outpatient.
Bio TE Iodine Plus (12.5 mg)
Colustrum- LD
CO-Q Clear 100 mg Ubiquinone
Cortisol V
D3-5000
DHEA
Digestive enzyme ultra with betain HCL
DIM
GI-revive
Med caps
Mega sporebiotics
Milocore
Niatain
Pregnenelone
Progesterone
Red yeast rice

categorization of the various individual substances and their potential metabolic derangements. Table (3) is a list of calculations of the actual doses when the components were analyzed for total daily dose. The comparison to recommended daily allowances is also provided.

As can be seen these supplements when dissected for its components revealed components which could lead to hepatic toxicity, those which could cause hypoglycemia, those which interact with antihypertensives this patient required, those considered drug-drug interactions, those considered drug-disease interactions.

This report demonstrates how details of the magnitude of DHS consumption requires teasing out individual substances from combination products, painstakingly identifying total daily doses, and finally comparing these doses to recommended daily allowances or doses.

DISCUSSION AND REVIEW

This case represents the magnitude of types of alternative therapies which might be provided to a patient. Included were high doses of vitamins, herbal supplements, and anti-aging hormones. A recent review was published summarizing 472 articles examining DHS in hospitalized patients [1]. These authors identified that DHS use is common worldwide among inpatients from all socioeconomic backgrounds. Patients do not tend to disclose DHS use to primary care and hospital medical staff. We have found in comprehensive review of their medication lists, that they often are taking medications prescribed to their spounses, other family members, or even friends and neighbors [2]. DHS use is constantly rising. Risks were especially high in a malnourished diabetic hypertensive prone to metabolic derangements who were taking medications whose potentiation by these supplements could aggravate and sustain pathophysiology.

Older reports have summarized the most common herb-drug interactions [3]. *Ginkgo biloba* has been associated with bleeding, especially when combined with conventional antithrombotics or anticoagulants. *Ginseng* used for fatigue, immune function, and general health has a serious interaction with warfarin, decreasing the anticoagulant effect. *St. John's Wort* for depression or anxiety may reduce the efficacy of warfarin, simvastatin, and theophylline. Echinacea used for colds, cough, pharyngitis inhibits the activity of cytochrome P450 glycoprotein 1A2 and 2C9 which may result in toxic effects of drugs with narrow therapeutic indexes such as theophylline, warfarin and phenytoin. Digoxin toxicity has been associated with licorice-containing laxative and *Hawthorn leaf* which is used for mild heart failure. Finally *camomile tea* can influence levels of cyclosporin. A comprehensive list of herbal supplements can be found online and lists 80 different substances. They include: Alfalfa, Aloe Vera, Arnica, Ashwagandha, Astragalus, Barberry, Bilberry, Bitter Melon, Black Cohosh, Black Walnut, Blessed Thistle, Boswellia, Burdock Root, Calendula, Cascara Sagrada Bark, Catnip, Cat's Claw, Cayenne Pepper, Celery Seed, Chamomile, Chickweed, Comfrey, Cranberry, Damiana, Dandelion, Devil's Claw, Dong Quai (Angelica Sinensis), Echinacea, Elderberry, Eucalyptus, Evening Primrose Oil, Eyebright, Fenugreek, Feverfew, Garlic, Ginger, Ginkao Biloba, Ginseng, Goldenseal, Gotu Kola, Grape Seed Extract, Green Tea, Fuarana, Guggui (Commiphoramukul), Hawthorn Hops, Horse Chestnut, Horsetail, Juniper Berry, Kava Kava, Lavender, Lemon Balm, Licorice, Lobelia, Ma Huang (Ephedra), Maitake Mushroom, Milk Thistle, Motherwort, Mullein, Myrrh, Stringing Nettle, Noni (Morindacitrifolla), Olive Leaf Extract, Passion Flower, Pau D'arco, Peppermint, Psyllium, Red Clover, Reishi Mushroom (Ling Zhi), Rhodiolarosea, Rosemary, Saw Palmetto, Slippery Elm, Spirutlina, St. John's Wort, Tea Tree Oil, Valerian, Vitex (Shasteberry), Wild Yam, Wormwook, Yohimbe (Yohimbine).

Similarly, a comprehensive list of vitamins taken over-the-counter includes 19 items. They include: vitamin A (retinol and beta-carotene), vitamin B1 or thiamine, vitamin B2 or riboflavin, vitamin B3 or riboflavin, vitamin B5 or pantothenic acid, vitamin B6 or pyridoxine, vitamin B12 or methylcobalamin, biotin, bioflavonoids, vitamin C or ascorbic acid, choline, coenzyme Q10, vitamin D or ergocalciferol or cholecalciferol, vitamin E or tocopherol, inositol, vitamin K or phylloquinone, omega 3 or EPA or DHA, omega 6 or GLA. The most common of these which can cause side effects include: vitamin A – liver damage increased in cerebral and papilledema, bone pain and skin changes; vitamin D – hypercalcemia, nausea and vomiting, renal failure;vitamin C– gastrointestinal irritation, oxalate kidney stones; and niacin – flushing,, hepatotoxicity.

Finally, a complete list of anti-aging hormones includes 5items. They include: DHEA, melatonin, estrogen, testosterone, and human growth hormone. Their corresponding side-effects include: DHEA -acne, hair loss, high blood pressure, changes in menstrual cycle, facial hair in women, deepening voice in women, and fatigue; melatonin– headache, daytime sleepiness, depression, dizziness, abdominal cramps,, and irritability; , estrogen – bloating, breast tenderness, blood clots, stroke; testosterone -headache, male-pattern baldness, high red blood cell counts, blood clots, stroke, liver injury; human growth hormone– carpal tunnel syndrome, edema, joint and muscle pain, gynecomastia, heart enlargement, increased insulin resistance.

Table 2: Catalogue of potential toxicities and adverse actions or interactions.
Supplements that can lead to hepatic toxicity
Chromium
Niacin
Colustrum
Red yeast rice
Supplements that increase the risk of hypoglycemia
Vitamin E
Chromium
Niacin
Tumeric
Supplements with interactions with antihypertensives
CoQ-10
Vitamin E
Supplements with drug-drug interactions
Vitamin E + niacin = increased niacin side effects
Niacin + Red yeast rice = increased risk of myopathy
Supplements with drug-disease interactions
Chromium + levothyroxine = chromium may bind thyroxine to reduce absorption
Niacin + levothyroxine = each may interfere with actions of each other
Biotin + Iodine Plus = unreliable side effects of either
Androgens + estrogens + levothyroxine = each may cancel or offset the actions of the others

Table 3: Calculated doses versus recommended daily doses.
Daily doses
Vitamin E > 333%
Vitamin A - 433%
Vitamin D - 1625%
Zinc – 787%
Magnesium > 87%
Chromium – 976%
Niacin – 2594%
CALCULATIONS
Vitamin E – multivitamin (100IU), AstaF x ingredients: d-alpha tocopheryl acetate, Mitrocore mixed tocopherols (50 mg) = 333%
Vitamin A – multivitamin (5000IU x 100%), Mitocore 3000 mcg = 333%
Vitamin D – multivitamin (1000IU x 250%, vitamin D supplement (5000 IU x 1250%), Mitrocore vitamin D (1000IU x 125%) = 1625%
Zinc – GI Revive (75 mg of zinc carnosine), Mitrocore (5 mg x 45%), Advanced D (10 mg zinc x 67 %) = 787%

CONCLUSIONS AND RECOMMENDATIONS

We conclude that this patient's alternative therapies lengthened the pharmacodynamics half-life of metformin, had neurologic toxicities, sustained her metabolic acidosis longer than the usual course of diabetic-ketoacidosis or metformin-induced lactic acidosis, prolonged her coma, prolonged her acute respiratory failure, prolonged her intensive care unit (ICU) stay, prolonged her hospital stay, led to subacute cognitive deficits, caused physical deconditioning due to prolonged bed ridden requirement, and magnified the cost of her hospitalization.

These vitamins, herbals, and anti-aging hormonal therapies are all often euphemistically lumped together under the umbrella of "supplements" which the public seeks through clinics, in vitamin shops, and through internet advertisements. These can be partially administered through anti-aging clinics, but are often self-administered. The possible interactions are therefore not being monitored. The toxicities can be magnified through interactions which may affect elimination of one substance by others. Levels can become higher and more sustained. Total doses of any of these substances cannot be assured since there is no supervision of manufacturing accuracy of the products.

Finally, we recommend without fail to ask the question of the

patient and the family about over-the-counter medications in every case of patients admitted to the Intensive Care Unit, ask the patient AND the family whether they are taking any of their spouse's or friends' medications. In addition it is important to also ask a second question about vitamins, and finally we recommend separately asking about herbal or other "supplements." These last several question pertain to the fact that patients may not recognize these substances as adding to their pathophysiology, interfering with drug actions, potentiating drug levels, or having their own adverse effects.

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