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Toxic hepatitis in a group of 20 male body-builders taking dietary supplements

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ABSTRACT

Dietary supplements have been used for decades for enhancing muscle growth. The harm caused by some of these products is well documented. We investigated and reported toxic hepatitis in 20 male athletes following self-prescribing of a number of dietary supplements which are lesser known. The patients' ages ranged from 24 to 32 with a mean of 28 years. They had taken three kinds of supplements for 1 year including testosterone optimizer agent T Bomb II, a creatine supplement Phosphagen and an amino acid based supplement Cell-Tech. Based on the history, clinical examination, and laboratory findings the cases were diagnosed as toxic hepatitis. After discontinuation of taking the supplements, clinical recovery and improvement of liver function tests were achieved within 30 days. Causality assessment with the CIOMS (Council for International Organization Medical Sciences) scale showed a "possible" grade of causality (+5 points) for these supplements. It can be concluded that these newer anabolic supplements may induce toxic hepatitis. Since the health risks of them may be severe, the use of these kinds of dietary supplements should be discouraged.

1. Introduction

Athletes are affected in various ways by self-prescription of the over-the-counter medications and by the misuse of food supplements. Dietary supplements and their effects on the performance of the body builders should be a matter of concern to the athletes' health. Despite the fact that these supplements are sometimes associated with serious or deadly adverse effects, they are not generally under serious investigations for their efficacy and safety. Even safe supplements like vitamins, creatine, and protein powders can be toxic particularly if they are taken in high doses for a long time. For example, creatine supplementation may cause renal dysfunction and hepatotoxicity (Bizzarini and De Angelis, 2004). There are four different categories of supplements on the market according to their principal contents (i.e., creatine, prohormones, mental enhancers, and branched chain amino acids). There may be some harmful additives in dietary supplements not indicated on the label of their packages. These added substances may also be the reason of a positive doping test in an athlete during sport competitions (Foster and Tyler, 1999; King et al., 1999; Haller and Benowitz, 2000; Poortmans and Dellalieux, 2000; Kamber et al., 2001). This study was conducted in 2011 for the purpose of evaluating the possible side effects of some commonly used supplements on the human health.

2. Methods

In this study, we documented the cases of 20 male body-builders with no past medical history, who developed hepatitis secondary to chronic ingestion of Phosphagen, a creatine supplement (Fig. 1); T- Bomb II, an optimizer of testosterone production (Fig. 2) and Cell-Tech, an amino acid and creatine-based supplement (Fig. 3) for 1 year. They were separately referred to a physician with symptoms such as fever, chills, weakness and fatigue. Clinical examinations suggested them as the cases of suspicious toxic hepatitis with no past history of alcohol consumption. Therefore, the following laboratory tests were requested for confirmation of clinical diagnosis: complete blood count (CBC), blood aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin (T Bili), urea, creatinine (Creat), prothrombin time (PT), hepatitis B surface antigen (HBS Ag), anti hepatitis B core antibody (HBc Ab), anti hepatitis C virus antibody (HCV Ab), anti hepatitis E virus antibody (HEV Ab), and anti hepatitis A virus antibody (HAV Ab). Additional test included anti CMV-IgM, anti EBV-IgM, and anti HSV-IgM were performed.

Biochemical tests were performed via colorimetric methods using Technicon RA-1000 chemistry analyzer (Bayer Diagnostics, Ireland). To reject the presence of infectious hepatitis, relevant tests were conducted on the serum samples using commercially available human ELISA kits according to the manufacturer's protocols. All experiments were done in Abou-Reihan clinical laboratory (Mashhad, Iran).

3. Results

The ages of the patients ranged from 24 to 32 years. They had used all three supplements. Briefly, in clinical examinations, they

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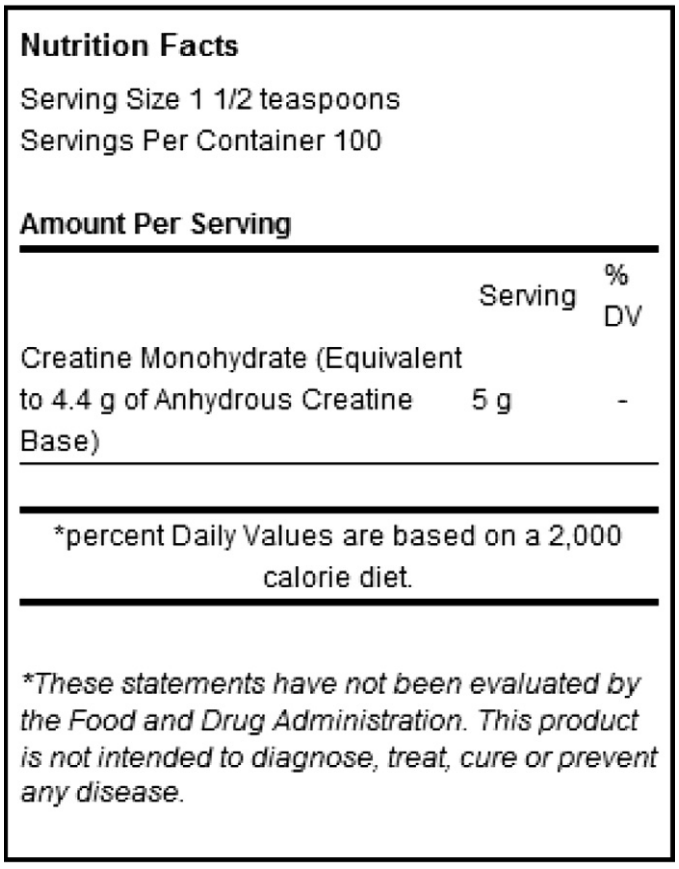

Nutrition Facts

Serving Size 1 1/2 teaspoons
Servings Per Container 100

Amount Per Serving

	Serving	% DV
Creatine Monohydrate (Equivalent to 4.4 g of Anhydrous Creatine Base)	5 g	-

*percent Daily Values are based on a 2,000 calorie diet.

**These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.*

Fig. 1. Information sheet of Phosphagen.

had the symptoms such as fever, chills, weakness, fatigue, itching, jaundice, and elevated blood pressure in common (Table 1). Hemoglobin content, Hct%, WBC and differentiation counts did not show any significant pathological findings (Table 2). Transaminases and total bilirubin were highly elevated as described in Table 3. Creatinine was mildly elevated. Relevant tests for hepatitis A, B, C and E were negative. Tests for anti CMV-IgM, anti EBV-IgM, anti HSV-IgM were negative. In the present study the ratios of ALT:its upper limit of normal range (R_1) and ALP:its upper limit of normal range (R_2) were determined. Then, the ratio (R) of R_1:R_2 was calculated. Since the R was more than 5 in all patients, therefore, they had a clear hepatocellular type of liver toxicity rather than a cholestatic or cholestatic-hepatocellular injury (Teschke et al., 2008, 2009). The patients were improved clinically (symptoms free) and their biochemical data returned to near normal values one month after cessation of the supplements at different time intervals (Table 3).

In this study we also used a main-test of a structured causality assessment method suitable for the diagnosis of DDS (drugs and dietary supplements) hepatotoxicity (Teschke et al., 2008, 2009). This main-test represents the quantitative causality assessment and is based on the CIOMS (Council for International Organization of Medical Sciences) scale (Benichou et al., 1993; Danan and Benichou, 1993).

4. Discussion

With the main-test for hepatocellular damage all three supplements were evaluated quantitatively, and the answers were scored from −3 to +3. The total number of the score was +5 points. Therefore, the grade of causality for probable hepatocellular injury caused by these supplements was "possible" (Table 4).

In the last decades, dietary supplements like creatine, prohormones and amino acids have been widely taken by athletes who thought that these products would elevate their physical abilities (Ekblom, 1996; Engelhardt et al., 1998; Appelgate, 1999; Di Luigi et al., 1999; Terjung, 2000; Ziegenfuss et al., 2002; Sundgot-Borgen et al., 2003). T Bomb II is a brand name for a product made by Maximum Human Performance, Inc. (MHP). This product is widely commercially available and marketed on line. It is an optimizer of testosterone production. It has been suggested that oral intake of this product increase circulating testosterone levels and induce muscle gain. Contrary to these claims however, some studies have showed that these compounds are neutral at increasing athletic performance (Brown et al., 2006). According to the manufacturers, T Bomb II is scientifically formulated to help optimize the production and balance of key hormones for male performance. It helps boost the natural production of testosterone, lowers estrogen levels by inhibiting the conversion of testosterone to estrogen, increases free testosterone by lowering SHBG (Sex Hormone Binding Globulin), and inhibits the production of DHT (Dihydrotestosterone). Anabolic steroids such as testosterone have been associated with abnormal liver function tests (Dickerman et al., 1999; Kicman, 2008). There are several different types of herbal medicines in this supplement as hormone optimizing blend. Herbal preparations are widely used as nonprescription medications and thought to be safe because they are "natural". They are classified as dietary supplements and also cannot be sold as a treatment or cure for a particular disease or condition. For this reason they do not require prior approval by the Food and Drug Administration (Stedman, 2002; Willet et al., 2004).

The search for natural products with side effects has provided a clue that some herbal medicines of T Bomb II are hepatotoxic. Saw palmetto extract can reduce the symptoms of enlarged prostate, including frequent urination, painful urination, sudden urge to urinate, and inability to urinate. There are some concerns that saw palmetto extract might cause liver or pancreas problems in some people. There are two reports linking saw palmetto products to hepatotoxicity (Web/MD). Red clover and Puereria root extracts contain "isoflavones" which are changed in the body to "phytoestrogens" that are similar to the hormone estrogen (Web/MD). Isoflavones are a common class of phytoestrogens. They are plant-derived compounds capable of estrogenic or anti estrogenic effects. Isoflavones are structural mimics of endogenous 17 beta-estradiol (Seielstad et al., 1995). Phytoestrogens are hypothesized to induce hepatotoxicity through mechanisms similar to hormonal estrogens (Melgarejo and Cupp, 2000). Thus, Saw palmetto berry, Red clover and Puereria root extracts might cause hepatotoxicity. We didn't find any clear hepatotoxicity report in different medical databases or literature reviews for the remaining herbal medicines of T Bomb II. Nevertheless, hepatotoxicity or drug induced liver injury (DILI) is unpredictable and herbal remedies can cause DILI (Tarantino et al., 2009a,b). On the other hand, hepatotoxicity due to taking natural preparations has become widespread in countries. For example, an internet search revealed that use of these products has continuously increased in the United States over the past decade and that about thirty percent of patients attending a liver center use herbal preparations (Stedman, 2002). However, we collected the side effects of herbal substances used in T Bomb II (Table 5) based on available information on the internet medical databases (Web/MD,[1] Emedicinehealth[2] and RX list[3]).

Creatine is an organic compound which is synthesized in the liver and kidneys. It is found in most protein rich foods such as meat (Metzl et al., 2001). Using creatine as a component of athletes'

[1] Web/MD. [http://webmd.com].
[2] Emedicinehealth. [http://emedicinehealth.com].
[3] Rxlist. [http://rxlist.com].