further light on the potential mechanism of hepatotoxicity in these sisters. Although it cannot be established for certain if autoimmunity or a pharmaco-genetic preponderance is the driving force behind these events, the reactive hepatitis in the two sisters suggests a common mechanism. Dr. Manso et al. raise the possibility that green tea or aloe vera ingredients, previously reported to induce hepatotoxicity may also be the cause in the Spanish group of patients. However, these ingredients were not taken uniformly by all the reported patients from Israel and Switzerland, and therefore a detailed list of all the ingredients including the chemical composition is required as stated in the two original reports. In Spain as well as in Israel and Switzerland, it was not possible to establish the true incidence of hepatotoxicity among Herbalife™ users since the number of consumers and their demographic characteristics are only partially known. A rough calculation suggested an incidence of 25–30 cases per 100,000 Herbalife™ products among Israeli consumers. We agree with the colleagues from Spain that the true incidence may be higher since liver injury may remain occult and asymptomatic as is well known by practising hepatologists. Thus, it is important to draw the attention of the Journals readers to reports of similar cases.

References


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Herbalife nutritional products and liver injury revisited

To the Editor:

Recently, two reports of 12 and 10 cases of idio-pathic liver disease from Israel [1] and Switzerland [2], respectively, appeared in the same issue of this journal alleging in the articles and in an accompanying editorial that these cases were caused by the consumption of Herbalife products. In fact, the two papers [1,2] concluded unequivocally that causation was certain in some cases. Despite the authors’ strong assertion that a cause and effect relationship between Herbalife product use and liver injury exists, an objective review of the facts raises serious doubt whether such a conclusion can be drawn. In Israel [1], the observed liver abnormalities resolved in eleven of the twelve cases reported. The remaining patient succumbed to complications of liver transplantation and despite the fact that this patient also had evidence of hepatitis B infection, sole attribution of the liver injury to Herbalife products was made. Another patient had stage I primary biliary cirrhosis and other patients consumed a variety of substances or had other co-morbid diseases that could have caused or contributed to the liver disease observed. In Switzerland [2], a total of 10 evaluable case reports with similar characteristics were documented over seven years.

Taken at face value, these few cases represent an extremely low incidence of suspected liver injury among the millions of Herbalife consumers worldwide (5.5 million consumers in 2004 alone). In 2004 more than 40,000,000 servings from 29 different products were distributed to approximately 37,000 Israeli consumers. A similar number of servings from 26 different products were distributed to approximately 80,000 Swiss consumers. In the 5 combined cases where causation was assessed as “certain” due to a reported combination of positive dechallenge and rechallenge, the case details remain unclear. As an example, 4 of these patients described between 3 and 17 different and specific Herbalife products previously consumed prior to dechallenge, and in the remaining patient no specific Herbalife product in either the reported dechallenge or rechallenge could be identified. Equally concerning is the fact that there is no mention of which of the initially reported products were subsequently consumed by any of the patients that allegedly led to the recurrence of symptoms. Even if all 4 patients consumed the exact same 3–17
products, respectively, there was no purported toxic ingredient identified by the authors in the article that was common among all 4 of these patients. It is also interesting that in one of these 4 patients, rechallenge of unspecified Herbalife product was reported to result in recurrence of symptoms, yet the patient purportedly continues to use unspecified Herbalife product(s) and remains asymptomatic.

The generally accepted criteria for causality of liver diseases cited in the editorial, including dechallenge/rechallenge, were designed to consider drug-induced hepatotoxicity when a specific defined ingredient has been identified, and were not designed to consider the effects of multiple different foods, supplements, and distinct nutritional products in combination or totality. The comment made in the editorial [3] that "there can be little doubt that these products were the cause" is simply not supported by the facts. In acute hepatotoxicity, liver injury typically occurs with a substantial and predictable frequency, its severity is dose-dependent, and a responsible agent can be identified. In contrast, liver injury from an immune-mediated hypersensitivity reaction is sporadic, and clinical symptoms and abnormal liver biochemical tests occur in only a very small number of individuals who metabolically convert some constituent of the product consumed into a substance that stimulates an immune reaction [4]. While this is the generally accepted scenario among hepatologists, the exact cause, predisposing individualistic factors, and precise pathophysiology of this rare form of liver disease remain poorly understood.

Furthermore, the incidence of these cases appears to be very low compared to the risks associated with some over-the-counter and prescription drugs on the market. A population-based survey in Atlanta, Georgia, USA published in 2007 found that the incidence of acute liver failure in eight counties was 5.5 per million individuals, and the use or abuse of acetaminophen was associated with 41 percent of the cases, while a significant percentage of adults had liver failure of unknown etiology [5]. As indicated in the Swiss article, the rare incidence of these events having been ten cases collected over seven years, makes the overall incidence some 1.8 per million patients/year [2]. This low level of risk of liver disease is indistinguishable from the background incidence of idiopathic liver disease, where no cause can be found. In a study of 71,000 North Americans in 1992, the background rate of idiopathic or cryptogenic liver disease was 24 cases per 100,000 individuals compared to 14 per 100,000 attributed to cases of hepatitis B, 25 per 100,000 due to alcoholism, and 7 per 100,000 due to other viral illnesses [6]. While the spectrum of liver diseases has certainly changed since 1992 when this survey was done, the number of idiopathic liver diseases remains a significant percentage of all the cases.

Herbalife nutritional products are registered and notified as foods, meal replacements, and dietary supplements and not as herbal medicines. There are ingredients such as guarana, green tea, and caffeine, which are being used extensively in numerous food products and are not unique to Herbalife. Herbalife conducts testing, through independent laboratories, on product batches for heavy metals, pesticides, ochratoxin A, aflatoxins, comfrey retrosine (pyrrolizidine alkaloids; PAs), and kava kavalactones. Completed tests have consistently shown no detection of pesticides, kava or PAs, and traces of ochratoxins, aflatoxins, and heavy metals are below minimum threshold levels. Also, the company has a well-developed adverse event reporting system which monitors and evaluates adverse events globally and has sought the involvement of outside, independent experts to evaluate its adverse event experience.

The core products of Herbalife provide healthy solutions to the worldwide epidemic of obesity. The products are designed to deliver balanced nutrition and assist in the promotion of fitness and a healthy lifestyle. These products are primarily based in vegetable proteins, fish oils, vitamins, and minerals for which safe use is very well established. Some of the company's products also contain botanical ingredients that are well characterized and tested. These botanicals are included in Herbalife products at levels that are in a safe nutritional range where they have antioxidant properties and support normal function, and are labeled in accordance with all the applicable laws. The company does not promote or encourage the use of any of its products as medicines for the treatment of specific diseases.

There were no undefined or unlabeled herbs in these products as suggested in the articles and contrary to what has been portrayed, the company has cooperated fully with the ministries of health in their investigation of these cases. In fact, government officials and clinicians investigating these cases in both countries were given access to full product formulas and ingredients. These ingredient disclosures were documented in numerous communiqués and included full product dossiers and results of independent testing regarding product purity and integrity.

It is also unfortunate in our view that Herbalife's brand name was generically linked to liver injury rather than specific products or ingredients where such an association could not be established. This approach is unprecedented. Although Herbalife remains committed in the spirit of product stewardship to
To the Editor:

We read with interest the Herbalife™ response by Dr. Ignarro and co-authors to the two reports and Editorial printed in the Journal on association of Herbalife™ with hepatotoxicity. We wish to address a number of statements in their letter:

1. Incidence

We agree with the authors that the incidence of Herbalife™-associated hepatotoxicity is probably low, but not as low as they suggest. We disagree with their comment that 22 cases among 5.5 million consumers world-wide can be used as proof for a low incidence of the compound(s) associated hepatotoxicity. The cases reported by us, were identified through an ICD-9 search in all Israeli hospitals during a two year period, starting in 2004. This survey identified 12 cases which reported intake of Herbalife™ products among 33 patients diagnosed with cryptogenic liver dysfunction. The association between intake of Herbalife™ products and hepatic injury was classified as certain in 3, probable in 6 and possible in 3 patients using WHO criteria. A rough calculation of the incidence of Herbalife™ associated hepatotoxicity could recently be made, following information requested from Herbalife by the Israeli ministry of health and received in 2007. An estimated incidence of 25–30 cases per 100,000 consumers was made. This figure is only an approximation, since demographic data on the population of consumers was unavailable at time of analysis. We also disagree with the authors of the letter that the so called "low level of risk of liver disease is indistinguishable from the background incidence of idiopathic liver disease". In our survey in all Israeli hospitals, we identified initially 12/33 hospitalized patients with liver injury of so called undetermined etiology who reported intake of Herbalife™ products. This still leaves 21/33 patients with so called idiopathic liver disease reflecting an incidence of <6 cases/million of undetermined etiology of the liver injury (after exclusion of Herbalife™ consumers). Finally it is common knowledge among hepatologists that sub-clinical, asymptomatic ALT elevation may occur in patients with occult liver disease. Our survey included only hospitalized patients, identified retrospectively through hospital records. Therefore, the number of patients who may have developed occult hepatotoxicity in association with Herbalife™

Herbalife revisited: Reply

References


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