assay inaccuracies, the subsequent reanalysis, and results of the reanalysis were imperative to communicate to the medical community.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jhep.2008.05.009.

Reference


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Spanish reports of hepatotoxicity associated with Herbalife® products

To the Editor:

We have read with interest the articles recently published in this journal by Elinav et al. [1] and Schoepfer et al. [2], as well as the editorial by Stickel [3], reporting and discussing two series of cases from Israel and Switzerland of hepatotoxicity associated with the consumption of Herbalife® slimming products. Stickel [3] raises the question of why products which are distributed in at least 60 countries only seem to induce hepatotoxicity in two.

In Spain, as perhaps in other countries, Herbalife® distributes its products through door-to-door salesmen and the internet. Some products are registered as dietetic supplements, but others are not registered at all. In 2005, three cases of hepatotoxicity (two hepatitis and one of increased liver enzymes) were reported to the Pharmacovigilance Centre of Asturias, an area in the north of Spain. Another case of increased liver enzymes was reported in 2006. All the four cases occurred in women between 47 and 57 years old, and all came from the same hospital. Three of these were published last February in a Spanish medical journal [4].

In the two cases of hepatitis the patients were sisters. One of whom developed severe liver damage. After taking Herbalife® products for 1 year and losing 20 kg in weight, she was referred to hospital suffering from widespread pruritus, jaundice, fatigue and abdominal strain. Biochemical tests showed liver transaminases over 1000 U/l and 12 mg/dl of total bilirubin. Test antibodies to hepatitis were negative. Abdominal ultrasound showed a cholelithiasis that was surgically removed. Although she was recommended to cease taking Herbalife® products, she continued to do so for another 2 years and developed chronic liver disease with recurrent exacerbations. Liver biopsy showed acute hepatitis grade 4 on chronic liver disease stage 3. She was diagnosed as having idiopathic or toxic autoimmune hepatitis, and is currently being treated with corticosteroids. Her sister took Herbalife® products for six months and developed diarrhea, hyperbilirubinemia, jaundice and pruritus. Biochemical tests showed transaminases over 1000 U/l and 26.7 mg/dl of total bilirubin. Viral antibodies were negative. Subacute cholestatic hepatitis was diagnosed and the withdrawal of Herbalife® products was recommended. Some months later, the patient had totally recovered. The two sisters took the following Herbalife® products: formulas 1, 2, 3 and 4, RoseOx, Herbalifeline, Guarana, Classic Aromatized Tea and Herbal Aloe.

The patients in the other two cases of reported hepatotoxicity were also taking Herbalife® products over a period of 1 month in one case and 3 years in the other, and developed increased transaminases which were detected on routine analysis. After the withdrawal of Herbalife® products, the enzyme levels returned to normal.

To explain the mechanism involved in the hepatotoxicity induced by Herbalife® products, Elinav et al. [1] have suggested genetic susceptibility to develop an immune-mediated liver toxicity associated with one or more constituents. The family ties between the two cases of hepatitis reported in Spain and the diagnosis of autoimmune hepatitis in one case support this observation. We agree with Stickel [3] when he explains that it is extremely difficult to identify the crucial compounds when consumers of Herbalife® are taking several products.

Although toxic or bacteriological contamination of some batches cannot be dismissed, we believe that some components of Herbalife® products could be the hepatotoxicity inducers. Firstly, as Schoepfer et al. [2] have suggested, the green tea contained in the Classic Aromatized Tea and also in other Herbalife® products. In the last 5 years, evidence on the ability of green tea to induce
liver damage has increased [5,6]. In April 2003, the Spanish Agency of Medicine and Health Products withdrew the over the counter medicine Exolise® from the market. This contained an ethanolic extract of green tea, and was the cause of four cases of hepatotoxicity in Spain [7] and nine in France [8]. In none of the Herbalife® products containing green tea is the type of extract or the amount of active substances specified. On the other hand, several authors [9–11] have reported cases of acute hepatitis associated with the consumption of Aloe vera tablets or capsules. Aloe vera is the main component of the drink Herbal Aloe sold by Herbalife®.

We do not believe that the hepatotoxicity of the Herbalife® products is confined to three countries alone. The lower use in some areas, the underreporting of adverse reactions, and the lower ability to detect or report information in the international scientific media could be the reasons for explaining this lack of information from other countries. For some time, Latin American and Spanish health professionals have been discussing the safety of Herbalife® products and similar compounds on internet forums.

Schoepfer et al. [2] and Stickel [3] consider that the hepatotoxicity associated with Herbalife® products does not seem to be a threat to public health and have suggested an incidence lower than that of the non-steroidal anti-inflammatory drugs. In our opinion, the evaluation of this safety problem is impossible because we have no precise consumption data nor isolated active substances of established efficacy. Perhaps the hepatotoxicity we are speaking about is of low incidence and affects patients with genetic susceptibility or other risk factors. However, the growing consumption of products promoted as “natural”, without defined composition, quality control and demonstrated activity and safety is a real health problem that should be kept under control. Today we are speaking only about the products of the Herbalife® brand, but tomorrow we may be speaking about other products or other brands.

References


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More reports of potential hepatotoxicity of Herbalife products: Reply

To the Editor:
The Letter to the Editor by Manso and colleagues from Spain [1] reiterates the deep concern recently raised [2–4] regarding the potential hepatotoxicity of one or more Herbalife™ products. This report adds 4 more patients to the already described 22 patients from two countries, who developed a variable degree of liver injury in association with the intake of Herbalife™ products.

Two of the Spanish patients developed quite severe hepatitis with jaundice and 3/4 recovered after stopping intake of the products. Although the information provided is not complete, causality may be established in at least two cases as probable and in the remaining two cases as possible, based on the same criteria as reported in Ref. [2–4]. The development of hepatitis in two sisters, one of whom has or progressed to chronic hepatitis, is an important observation which may shed
Herbalife nutritional products and liver injury revisited

To the Editor:

Recently, two reports of 12 and 10 cases of idiopathic 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. 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

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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 retroside (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, active 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 product 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 market 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
cooperate openly and fully in the evaluation of any adverse event potentially associated with a Herbalife product, we believe that objective review of these cases does not support a cause and effect relationship between any specific Herbalife product or ingredient and liver injury.

References


Herbalife revisited: Reply

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 worldwide 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™
products intake may be even higher than the estimated incidence figure described above.

2. Causality

Both the Israeli and the Swiss groups used cited, internationally-accepted criteria for determining causality. The fact that we were unable to identify yet a single agent as a potential hepatotoxic agent does not exclude causality between ingestion of the product(s) and the described liver injury. Moreover, among three Israeli patients, the cause and effect was clearly established in consumers who developed hepatic injury who discontinued treatment followed by normalization of liver function tests and then, by their own initiative restarted intake of Herbalife™ product(s) after initial resolution of the disease, resulting in a second bout of liver injury. Thus, these cases were classified as “certain.” While the described hepatotoxicity may have been the result of an idiosyncratic reaction, there are other potential explanations for the described phenomenon. These include among others, direct hepatotoxicity, immune-mediated hepatotoxicity (some patients were ANA+), interaction between several Herbalife™ ingredients, a pharmacogenetic susceptibility to one or more Herbalife™ products or contamination of one or more Herbalife™ batches by an unidentified etiologic agent or toxin. We also disagree with the statement that liver injury occurs with substantial and predictable frequency and severity in a dose-dependant fashion in such patients with suspected acute hepatotoxicity. The fact that the mechanism of Herbalife™-associated hepatotoxicity is not understood at present, does not exclude causality as often observed in DILI.

Indeed, Herbalife™ submitted to the Israeli MOH a large binder with information on extensive quality control tests performed by the company and a designated lab regarding some toxic ingredients and heavy metals. However, information on specific batch numbers and analysis of products used by the patients in Israel in 2004 has not been provided so far. Therefore, it is not possible at present to link the observed cases of liver injury to specific batches or ingredients in Herbalife™ products.

3. Additional comments

We also wish to draw the readers’ attention to a misquotation in the discussed letter. In our original report, we did not state that the severe liver injury in the HBsAg positive patient was the “sole” result of Herbalife™ hepatotoxicity. This patient developed massive hepatocellular necrosis with liver failure which required liver transplantation. Immuno-histochemical tests of the liver explant were negative for HBsAg and HbcAg in this patient, who consumed excessive amounts of Herbalife™ products. This observation suggests, in our opinion, possible superimposed injury in an HBV patient. Similarly, the patient with primary biliary cirrhosis (PBC) also developed an exacerbation of her liver dysfunction in association with intake of Herbalife™ products which was mainly hepatocellular, not typical for PBC.

In conclusion, we support the statement in the Editorial accompanying these two papers from Israel and Switzerland that there is little doubt that one (or more) Herbalife™ products was involved directly or indirectly in the described hepatotoxicity. Although the mechanism of the presumed Herbalife™ associated hepatotoxicity has not been established yet, we have recommended and still recommend an increased awareness by the medical community and the public regarding this association until further information is available.

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