bijwerkingen centrumlareb

Liver toxicity of the multi-herbal medicine Iberogast®

Introduction

Iberogast® is a multi-herbal medicine available as an Over The Counter (OTC) product in pharmacies and drugstores only. The product is registered as a medicine through the Dutch Medicines Evaluation Board. It is indicated *for the symptomatic treatment of dyspepsia in adults, especially the complaints of stomach pain, heartburn, bloating, stomach / intestinal cramps and nausea* (1).

Toxic liver disease may be accompanied by liver necrosis, hepatitis or cholestasis or a combination of these. Severe liver damage can lead to liver failure (2). The clinical presentation and severity can be highly variable, ranging from mild hepatitis to acute hepatic failure requiring transplantation (3). Herb induced liver injury (HILI) and drug induced liver injury (DILI) share the common characteristic of chemical compounds as their causative agents. Both natural and synthetic chemicals are foreign products to the body and need metabolic degradation to be eliminated. During this process, hepatotoxic metabolites may be generated, causing liver injury in susceptible patients. There is uncertainty whether a HILI case has an intrinsic background (to the drug related) or idiosyncratic background (interaction between the drug and patient factors). The idiosyncratic HILI develops among a few individuals under the treatment with drugs (herbs) used at recommended doses and is caused by unpredictable events due to immunologic or metabolic drug reactions. HILI can develop to acute liver failure requiring liver transplantation in single cases (4, 5).

Product information

Table 1. The ingredients of Iberogast® (1)

Extract of	Extraction agent	DER*	Quantity /100 ml
Iberis amara L., planta tota	Ethanol 50% (v/v)	1 : 1,5 – 2,5	15,0 ml
Angelica archangelica L., radix	Ethanol 30% (v/v)	1 : 2,5 – 3,5	10,0 ml
Melissa officinalis L., folium	Ethanol 30% (v/v)	1 : 2,5 – 3,5	10,0 ml
Carum carvi L., fructus	Ethanol 30% (v/v)	1 : 2,5 – 3,5	10,0 ml
Chelidonum majus L., herba	Ethanol 30% (v/v)	1 : 2,5 – 3,5	10,0 ml
Glycyrrhiza glabra L. and/or *Glycyrrhiza inflata Bat* and/or *Glycyrrhiza uralensa Fisch,* radix	Ethanol 30% (v/v)	1 : 2,5 – 3,5	10,0 ml
Matricaria recutita L. (Chamomilla recutita (L.) Rauschert), flos	Ethanol 30% (v/v)	1 : 2 – 4	20,0 ml
Mentha x piperita L., folium	Ethanol 30% (v/v)	1 : 2,5 – 3,5	5,0 ml
Silybum marianum L. Gaertner, fructus	Ethanol 30% (v/v)	1 : 2,5 – 3,5	10,0 ml

*Drug Extract Ratio

Reports

The Netherlands Pharmacovigilance Centre Lareb received one report of acute hepatic failure associated with use of Iberogast® oral liquid in February 2021.

Case NL-LRB-00436525, reported by a specialist doctor, concerns a 50-60 years-old man who took 15 drops of Iberogast® 2-3 times during the day against his dyspeptic complaints. Ten days later he was admitted to the hospital with jaundice, nausea and heartburn. His liver enzymes were elevated:

aspartate transaminase (ASAT) 561 U / L (ref. <35), alanine aminotransferase (ALAT) 663 U / L (ref. <45), alkaline phosphatase (AP) 230 U / L (ref. <115), gamma GT result is not reported due to interference from icterus. The condition progressed in the next ten days to liver failure with hepatic encephalopathy and impaired coagulation. The liver biopsy revealed acute hepatitis with local necrosis, bilirubin stasis and ductular proliferation. No significant fibrosis or steatosis was seen. Based on this results a toxic drug damage was the most likely cause of the liver failure. Autoimmune hepatitis was less likely but could not be ruled out completely. The patient was regarded as being eligible for liver transplantation. Beside the Iberogast®, the patient also used salbutamol and occasionally ibuprofen as needed. He consumed 1-2 glasses of alcoholic beverages daily.
Additional information from the follow-up
Two months later the patient's condition is improving: stools and urine color is normal, there is no pruritus, ascites or edema. The patient drinks 2.5 liters fluid per day and his food intake is good, only his taste has decreased. His weight is still decreasing. The liver enzymes are still not normalized and show fluctuations. The latest lab results revealed ALAT 110 U/L, ASAT 225U/L and AP 219 U/L.

Determination of the liver injury pattern and causality assessment
The liver injury pattern can be determined by assessing the ratio R, to be calculated through the multiple of the upper limit of normal (ULN) of serum ALAT divided by the multiple of the ULN of serum AP. Two types of liver injury are to be considered: a hepatocellular injury with R > 5, and a cholestatic/mixed liver injury with R ≤ 5. Based on the reported laboratory results the liver injury pattern could be determined as hepatocellular (R=663/45:230/115=7).
To establish HILI as the cause of liver damage, RUCAM (Roussel Uclaf Causality Assessment Method) is a useful tool (4). RUCAM is a validated, liver-specific, structured, and quantitative causality assessment method (CAM) with a clear scoring system of well-defined key elements that provide a transparent final causality grading after summing up of the individual element scores. For each injury type, a specific RUCAM subscale is available. For our case a RUCAM causality assessment is unreliable because of missing detailed information for 3 key elements (course of ALAT after cessation, search for alternative causes and response to re-exposure).

Other sources of information

SmPC
The Dutch SmPC of Iberogast® doesn't mention liver toxicity or other hepatic adverse drug reactions in Section 4.8 (Adverse drug reactions) or in section 4.4 (Special warnings and precautions for use). Only hypersensitivity reactions such as rash, pruritus and dyspnea are mentioned in section 4.8 (1).

Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)
The German authority responsible for the authorization of medicines, the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), indicated in 2008 that Bayer should inform consumers about the possible adverse drug reactions of one of the ingredients in Iberogast®, namely the *Chelidonium*. Bayer refused that at the time. Recently, sufficient indications were found that *Chelidonium majus* can cause liver problems (6, 7).

Based on the German reports of liver damage of Iberogast® Manufacturing Authorisation Holder (MAH) Bayer proposed changes in the Dutch package leaflet for doctor and pharmacist (SmPC). In section 4.4, a warning for developing hepatic impairment or symptoms of these (e.g. jaundice, dark urine or colorless stools) was proposed, and for the Section 4.8, the addition of liver disorders as a possible adverse drug reaction (ADR). The proposal was discussed in the 944th meeting of the Dutch Medicines Evaluation Board In January 2020 (8).

From October 2020, Bayer Germany expanded its Iberogast® range with the "Advance" variant. Iberogast® Advance is celandine, angelica root and milk thistle-free (9).

Literature

Iberogast® contains Chelidonium majus as part of a blend of nine extracts. Among those herbal extracts only Chelidonium majus (Greater celandine) has been associated with liver toxicity. No indication was found of a (potential) liver toxicity of the other plants extracts (3). Chelidonium majus contains at least 20 different alkaloids, such as berberine, coptisine, chelerythrine and chelidonine. Over a dozen publications, largely from Europe, have described clinically apparent acute liver injury attributable to greater celandine (Chelidonium majus). Liver injury typically arises after 1 to 6 months, with jaundice and moderate to marked elevations in serum aminotransferase levels. The pattern of injury is usually hepatocellular and the clinical presentation and liver histology resemble acute viral hepatitis. Immunoallergic features are uncommon, but autoantibodies may be present in low to moderate levels in many cases. The clinical syndrome, however, rarely resembles autoimmune hepatitis and usually resolves rapidly once the botanical is discontinued and without need of corticosteroid therapy (5, 10-17).

Mechanism

The rare cases of liver injury due to celandine have had idiosyncratic features (10). Crijns et al. described a case of hepatotoxicity and argued why in that case it was likely due to an idiosyncratic reaction to Cheladonium majus (11).
Idiosyncratic liver damage usually manifests itself in the form of acute hepatocellular hepatitis. The chance of it occurring is not related to the dosage of the drug and the latency time to onset of the acute form can be strong vary (5-90 days). The symptoms and course are very similar to an acute viral hepatitis where ALT is increased (18).

Prescription data

Because Iberogast® is an OTC drug there are no prescription data available through the GIP or SFK database.

Databases

The WHO database (VigiBase) contains 70 cases of hepatobiliary disorders (SOC) associated with Iberogast®. The most frequently reported ADR are assembled in the *Table 2*.

Table 2. Reports of Hepatobiliary disorders associated with the use of Iberogast® WHO database (19)

Drug	ADR	Number of reports	ROR (95% CI)
Iberogast	Drug-induced liver injury	16	61.95 [37.6—102.0]
Iberogast	Jaundice	14	16.52 [9.7-28.1]
Iberogast	Acute hepatic failure	11	86.15 [47.4-156.7]
Iberogast	Liver injury	9	33.65 [17.4-65.1]
Iberogast	Hepatitis	9	8.99 [4.7 -17.4]
Iberogast	Ocular icterus	8	128.42 [63.8-258.5]
Iberogast	Liver disorder	5	11.18 [4.6-27.0]
Iberogast	Hepatitis acute	4	36.55 [13.7-97.8]

Discussion and conclusion

in January 2020, the Dutch Medicines Evaluation Board discussed the addition of liver toxicity to the SmPC of Iberogast®. It was concluded that there was too little evidence for inclusion of this potentially adverse drug reaction in the SmPC (8). In this context Lareb wants to inform the MEB about the

recently received case report of liver toxicity associated with the use of multi-herbal medicine Iberogast® describing a male person who developed acute hepatic failure after use of Iberogast® drops. Liver biopsy showed signs of toxic drug damage. The severity of his condition made him eligible for liver transplantation. However, according to the latest information, this patient is recovering but his liver enzymes have not yet returned to normal. Unfortunately, no undisputed causality could be determined between Iberogast® and acute hepatic failure. In addition, the patient used ibuprofen occasionally and this compound has also been associated with hepatotoxicity in the literature. Ibuprofen-associated DILI presents commonly as hepatocellular damage. However, there is a low absolute risk of ibuprofen-induced liver complications (20). Also the SmPC of ibuprofen mentions that hepatitis, jaundice and abnormal liver function are uncommon ADRs, liver toxic reactions as part of generalized hypersensitivity rarely and hepatic failure very rarely (21).
Cases in the literature describe hepatic injury to preparations in which *Chelidonium majus* was present, as a mechanism idiosyncratic reactions are most often mentioned (10).
Despite the fact that Bayer Germany has now launched a new variant of Iberogast®, without *Chelidonium majus*, currently only the original Iberogast® is available on the Dutch market. Therefore, attention is still warranted for the association between hepatic adverse reactions and Iberogast®.

References

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This signal has been raised on May 11, 2021. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl