World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
wjg@wjgnet.com
doi:10.3748/wjg.v19.i32.5381

World J Gastroenterol 2013 August 28; 19(32): 5381-5384
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

CASE REPORT

Hepatotoxicity associated with glucosamine and chondroitin sulfate in patients with chronic liver disease

Cristian Cerda, Miguel Bruguera, Albert Parés

Cristian Cerda, Miguel Bruguera, Albert Parés, Liver Unit, Institute of Digestive and Metabolic Diseases, Hospital Clínic, 08036 Barcelona, Spain
Cristian Cerda, Miguel Bruguera, Albert Parés, Department of Medicine, University of Barcelona, 08036 Barcelona, Spain
Author contributions: Bruguera M designed the study and wrote de report; Cerda C and Parés A contributed to data gathering and writing the report.
Correspondence to: Miguel Bruguera, Professor, Liver Unit, Institute of Digestive and Metabolic Diseases, Hospital Clínic, Villarroel 270, 08036 Barcelona, Spain. bruguera@clinic.ub.es
Telephone: +34-93-2275753 Fax: +34-93-2271779
Received: February 26, 2013 Revised: April 30, 2013
Accepted: June 5, 2013
Published online: August 28, 2013

Abstract

Glucosamine and chondroitin sulfate are molecules involved in the formation of articular cartilage and are frequently used for symptom relief in patients with arthrosis. These molecules are well tolerated with scarce secondary effects. Very few cases of possible hepatotoxicity due to these substances have been described. The aim of this paper is to report the frequency of presumed glucosamine hepatotoxicity in patients with liver disease. A questionnaire was given to 151 consecutive patients with chronic liver disease of different etiology (mean age 59 years, 56.9% women) attended in an outpatient clinic with the aim of evaluating the frequency of consumption of these drugs and determine whether their use coincided with a worsening in liver function test results. Twenty-three patients (15.2%) recognized having taken products containing glucosamine or chondroitin sulfate previously or at the time of the questionnaire. Review of the clinical records and liver function tests identified 2 patients presenting an elevation in aminotransferase values temporarily associated with glucosamine treatment; one of the cases simultaneously presented a skin rash attributed to the drug. Review of these two patients and the cases described in the literature suggest toxicity of glucosamine and chondroitin sulfate. The clinical spectrum is variable, and the mechanism of toxicity is not clear but may involve reactions of hypersensitivity. The consumption of products containing glucosamine and/or chondroitin sulfate is frequent among patients with chronic liver diseases and should be taken into account on the appearance of alterations in liver function tests not explained by the underlying disease.

Key words: Toxic hepatitis; Hepatotoxicity; Glucosamine; Chondroitin sulphate; Osteoarthritis

Core tip: A questionnaire was given to 151 consecutive patients with chronic liver disease of different etiology (mean age 59 years, 56.9% women) attended in an outpatient clinic with the aim of evaluating the frequency of consumption of these drugs and determine whether their use coincided with a worsening in liver function test results. Twenty-three patients (15.2%) recognized having taken products containing glucosamine or chondroitin sulfate previously or at the time of the questionnaire.

Cerda C, Bruguera M, Parés A. Hepatotoxicity associated with glucosamine and chondroitin sulfate in patients with chronic liver disease. *World J Gastroenterol* 2013; 19(32): 5381-5384 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i32/5381.htm DOI: http://dx.doi.org/10.3748/wjg.v19.i32.5381

INTRODUCTION

Glucosamine and chondroitin sulfate are precursor molecules involved in the synthesis of glycosaminoglycans

which make up the connective tissue. Their integrity is important to maintain the strength and elasticity of articular cartilage which confers resistance to mechanical stress[1]. In addition to its role as a substrate in the synthesis of cartilage and connective tissue, anti-inflammatory properties through the inhibition of the synthesis of nitric oxide have been attributed to glucosamine[2]. In relation to these functions, glucosamine and chondroitin sulfate have been used in the treatment of articular hyaline cartilage degeneration with the aim of stimulating the production of cartilaginous matrix[3].

Adverse effects from the exogenous administration of glucosamine and/or chondroitin sulfate are observed in less than 5% of the patients, with the most frequent being: gastrointestinal disturbances (discomfort/epigastric pain, pyrosis, diarrhea, nausea, and dyspepsia), somnolence, cutaneous reactions and headache. Two patients receiving glucosamine who were attended in our unit presented an unexplained elevation in transaminase values with no associated symptoms which reverted on discontinuation of the medication and was interpreted as a possible toxic hepatitis by this drug. We therefore decided to prospectively investigate the frequency of use of glucosamine and the incidence of elevations in aminotransferase which might be related to this drug. We studied patients with chronic liver disease since we considered that these patients may have limitations for the use of non steroidal anti-inflammatory drugs due to the risk of gastrointestinal bleeding or renal failure and may, thus, be a group in which the use of glucosamine or chondroitin sulfate is frequent.

CASE REPORT

From May 2011 to July 2011, 151 consecutive patients attended in an outpatient clinic for liver diseases by one of the authors were evaluated. All were asked about previous or current intake of drug products composed of glucosamine or chondroitin sulfate using a questionnaire including the name of all the commercial products containing these compounds on sale in Spain as well as those which can be obtained by Internet. None of the patients refused to answer the questionnaire. Patients who replied affirmatively with respect to the use of these products were asked about the date of treatment initiation and the duration of drug use. The clinical charts were thereafter reviewed to determine if there were hepatic biochemical alterations coinciding with the use of the drug.

During the period mentioned, 151 patients, ranging from 19 to 85 years of age (mean 59.2 years), were interviewed; 56.9% being women. The liver diseases were chronic hepatitis/hepatic cirrhosis due to hepatitis C virus (38.2%), autoimmune hepatitis (12%), chronic hepatitis/cirrhosis by hepatitis B virus (7.1%), alcoholic cirrhosis (4.9%) and Wilson disease and primary biliary cirrhosis (3.5%).

Twenty-three patients (15.2% of the total) acknowledged having consumed products containing glucosamine (6 patients), chondroitin sulfate (16 patients) or both (1 patient). Ten were receiving the drug at the time of the interview. In 21 out of the 23 patients it could not be established whether the liver had sustained drug-induced damage since no elevation in aminotransferase above the usual values was observed in association with the administration of glucosamine or chondroitin sulfate. A relationship between an elevation in transaminases and product consumption was detected in 2 cases, both of which had taken glucosamine. The first was a 71-year-old woman with chronic hepatitis C who had taken glucosamine sulfate during one year and presented an elevation in aminotransferases of 5 to 7-fold greater than the normal values during this treatment. The clinical records did not mention the use of other drugs. Viral infection due to hepatitis A, hepatitis B, and cytomegalovirus was excluded by serological tests. Serum transaminases returned to the usual values after treatment discontinuation. The second case was a 77-year-old woman with chronic hepatitis C who had taken glucosamine for 3 mo in 1977 and had presented an allergic cutaneous reaction attributed to the drug. She had not been treated with any other drug. At that time the transaminase values rose 4-fold above normal. In the follow-up liver tests taken in June 2011, a minimum elevation of alanine aminotransferase similar to previous analyses was observed. Neither of these two cases presented hyperbilirubinemia or changes in the biochemical indices of cholestasis and did not present either symptoms or decompensation of their liver disease. The details of the analyses performed during the episode compared with previous and posterior registries of each case are shown in Table 1.

DISCUSSION

To our knowledge this is the first report on the consumption of products containing glucosamine and/or chondroitin sulfate in patients with chronic liver disease. The frequent intake observed in the population studied is substantial (23 out of 150 patients, that is 15%), with 2 cases of possible toxicity among 23 patients who acknowledged current or past intake. This represents hepatic toxicity of almost 9% in patients with chronic liver disease reporting consumption of these drugs. The two cases with liver damage coinciding with the treatment had chronic hepatitis C.

Review of the literature has shown several cases of alleged hepatotoxicity by glucosamine and chondroitin sulfate (Table 2). In 2007 one case of hepatitis with elevations in alanine aminotransferase and total bilirubin of 6- and 10-fold, respectively above normal values was reported in a patient who had taken glucosamine at the therapeutic doses for 4 wk prior to presenting jaundice and pruritus[4]. Other etiologies were ruled out with a complete study of the patient, and liver biopsy showed findings compatible with drug-induced hepatitis. Another report identified 3 cases of probable hepatotoxicity. The first was a patient with severe cholestatic hepatitis who developed fulminant liver failure resulting in death after having taken glucosamine for 4 wk. The second case was a woman who had consumed a glucosamine/

Table 1 Results of the liver function tests in cases of hypertransaminasemia related to glucosamine consumption

	1-yr prior to consumption	During consumption	1-yr after consumption
AST (UI/L) (normal < 40)			
Case 1	25	182	71
Case 2	36	161	36
ALT (UI/L) (normal < 40)			
Case 1	33	282	85
Case 2	53	162	37
GGT (UI/L) (normal < 40)			
Case 1	32	150	77
Case 2	18	31	15
AP (U/L) (normal < 290)		229	219
Case 1	240	183	213
Case 2	144		
Total bilirubin (mg/dL) (normal < 1.2)			
Case 1	0.3	0.8	0.4
Case 2	0.8	0.9	0.9

The results of the two cases are compared with analyses performed 1-yr prior to and after the episode. AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma Glutamyl transpeptidase; AP: Alkaline phosphatase.

chondroitin compound and presented anorexia, jaundice and cutaneous rash with persistence of biochemical alterations 6 mo after the onset of the symptoms. During the follow up the patient developed signs of hepatic dysfunction, and liver biopsy showed chronic portal hepatitis. The third case was a patient presenting an asymptomatic elevation in transaminases after having consumed a compound containing glucosamine for 6 mo. Complete recovery was achieved on discontinuation of the drug[5]. Two cases of probable hepatotoxicity were described in 2010 in relation to the consumption of a dietetic supplement (move free advanced) which contained glucosamine and chondroitin sulfate. The first of these cases presented diarrhea with an elevation in aminotransferases and alkaline phosphatase and the second showed a slight increase in aminotransferases with no specific symptoms. Neither case presented jaundice nor features of hepatic failure and the two patients improved 7 and 12 wk after withdrawal of the product[6].

The two cases attended by one of us (AP) were patients with no previous liver disease in whom a relationship was observed between the consumption of glucosamine and alterations in liver function tests. One was a 28-year-old woman who presented features of acute hepatitis with jaundice and pruritus at one month of starting treatment with glucosamine because of rough discomfort in both knees after minor trauma. Blood tests improved slightly on discontinuation of treatment with glucosamine with the subsequent disappearance of the symptoms. Viral, alcoholic, metabolic and autoimmune etiologies of the disease were ruled out. A liver biopsy performed one year later due to the persistence of biochemical alterations showed signs of chronic hepatitis. The other patient was a 56 year-old woman who had persistent transaminase values 3-fold greater than normal. All the potential causes of liver diseased were discarded and transaminase values normalized on withdrawal of glucosamine. The treatment was prescribed to improve initial symptoms of osteoarthrosis.

Taking our cases and those reported in the literature into account several characteristics may be pointed out. Firstly, all the cases had consumed compounds with glucosamine or chondroitin sulfate at the recommended therapeutic doses with no warning on the possible influence of doses within the range of the risk of hepatotoxicity. Neither was any other possible cause of liver damage identified. Suspicion of a toxic etiology in our cases was based on the infrequency of episodes of important elevations in transaminase values in chronic hepatitis C with no concomitant cause as well as regression on drug discontinuation. Jaundice was the most frequent initial symptom of hepatic compromise in the published cases but some cases presented asymptomatic alterations in liver biochemistries, one being severe hepatic failure and another developed chronic liver disease.

The mechanisms involved in the drug-induced hepatotoxicity are not clear. It is of note that the raw material used in compounds containing glucosamine are obtained from biopolymers of shells from marine invertebrates (shrimps, crabs, lobsters) and chondroitin sulfate is taken from cow trachea cartilage and shark cartilage in Japan[7]. One of our cases and two of those reported in the literature simultaneously presented hypersensitivity reactions and thus, hypersensitivity may have been the contributory mechanism, at least in one of the cases. Responsibility of additives contained in the glucosamine preparations used for our patients seems unlikely, because neither aspartame, sorbitol, citric acid or polietilenglicol have been related to liver injury.

Glucosamine is a precursor to glycosaminoglycan, which is believed to play a role in the growth of cartilage and its repair. Chondroitin is part of a large proteoglycan molecule that gives cartilage flexibility and is thought to inhibit enzymes that break down cartilage. Glucosamine is used in the treatment of osteoarthritis, a disease resulting from the articular hyaline cartilage degeneration which leads to the loss of cartilage. Osteoarthritis is very prevalent in general population, particularly in elder subjects. It causes significant morbidity due to pain and functional disability of joints, and increased health care costs as well[8]. The reason for the use of glucosamine or chondroitin sulfate in these patients lies in the belief that osteoarthritis is associated with a deficiency in key natural substances and these products provide a substrate for the synthesis of cartilaginous matrix. In addition, they provide protection against enzymes which degrade the cartilage[7]. Some randomized placebo-controlled trials using glucosamine showed a decrease of the symptoms of osteoarthritis in the group receiving glucosamine in comparison with the control group, but this not found in others[8-11]. No side effects related to the liver were observed in these trials. In the 2005 Cochrane review it was reported that in studies older and of lesser quality the effect of placebo was greater, while pain relief was

Table 2 Summary of the cases reported in the literature on hepatotoxicity by glucosamine and/or chondroitin sulfate

Ref.	Age (yr) Sex (F/M)	Drug consumed	Length of consumption	Latency	Jaundice	Peak in AST/ ALT (IU/L)	Hypersensitivity	Hepatic failure	Follow-up
Ossendza *et al*[4]	52/M	Glucosamine	3 wk	4 wk	Yes	263/63	Pruritus, eosinophilia	No	Complete recovery
Smith *et al*[5]	64/M	Glucosamine/ chondroitin sulfate	4 wk	5 wk	Yes	-/1461	-	Yes	Death
	57/F	Glucosamine	4 wk	5 wk	Yes	-/1130	Pruriginous rash	No	Chronic hepatitis
	55/F	Glucosamine	6 mo	8 mo	No	-/175	-	No	Complete recovery
Linnebur *et al*[6]	71/F	Glucosamine/ chondroitin sulfate	7 wk	3 wk	No	600-700/ 00-500	-	No	Complete recovery
	85/F	Glucosamine/ chondroitin sulfate	3 wk	3 wk	No	54/37	-	No	Complete recovery
Authors' cases	71/F	Glucosamine	1 yr	NA	No	182/282	-	No	Liver tests return to pretreatment (basal) values
	77/F	Glucosamine	3 mo	NA	No	161/162	Pruriginous rash	No	Liver tests return to (basa) values

M: Male; F: Female; AST/ALT: Aspartate aminotransferase/ alanine aminotransferase; NA: Not available.

similar in patients receiving glucosamine or placebo in studies of better quality[12]. In Europe the different compounds containing glucosamine or chondroitin alone or in combination require a medical prescription, but in North America they may be purchased as a supplement without prescription, thus adding an extra risk of potential adverse effects because the drugs are taken without any medical judgment or are poorly purified.

Mild forms of hepatotoxicity may remain undiagnosed because of the absence of clinical expression with laboratory analyses not being performed in patients complaining of joint pain before and during treatment with glucosamine or chondroitin sulfate. Our observations suggest that these products should be suspected as a possible cause for the analytical changes in patients receiving treatment with these drugs who show an alteration in transaminase values. In these cases, drug discontinuation seems justified taking into account their low or questionable therapeutic efficacy and the possibility of developing more severe liver damage with continued use.

REFERENCES

1 **Vista ES**, Lau CS. What about supplements for osteoarthritis? A critical and evidenced-based review. *Int J Rheum Dis* 2011; **14**: 152-158 [PMID: 21518314 DOI: 10.1111/j.1756-185X.2011.01619.x]

2 **Owens S**, Wagner P, Vangsness CT. Recent advances in glucosamine and chondroitin supplementation. *J Knee Surg* 2004; **17**: 185-193 [PMID: 15553585]

3 **Barclay TS**, Tsourounis C, McCart GM. Glucosamine. *Ann Pharmacother* 1998; **32**: 574-579 [PMID: 9606479 DOI: 10.1345/aph.17235]

4 **Ossendza RA**, Grandval P, Chinoune F, Rocher F, Chapel F, Bernardini D. [Acute cholestatic hepatitis due to glucosamine forte]. *Gastroenterol Clin Biol* 2007; **31**: 449-450 [PMID: 17483788 DOI: 10.1016/S0399-8320(07)89410-3]

5 **Smith A**, Dillon J. Acute liver injury associated with the use of herbal preparations containing glucosamine: three case studies. *BMJ Case Rep* 2009; **2009**: 1603 [PMID: 21887162 DOI: 10.1136/bcr.02.2009.1603]

6 **Linnebur SA**, Rapacchietta OC, Vejar M. Hepatotoxicity associated with chinese skullcap contained in Move Free Advanced dietary supplement: two case reports and review of the literature. *Pharmacotherapy* 2010; **30**: 750, 258e-262e [PMID: 20586134 DOI: 10.1592/phco.30.7.750]

7 **Kirkham SG**, Samarasinghe RK. Review article: Glucosamine. *J Orthop Surg (Hong Kong)* 2009; **17**: 72-76 [PMID: 19398798]

8 **Huskisson EC**. Glucosamine and chondroitin for osteoarthritis. *J Int Med Res* 2008; **36**: 1161-1179 [PMID: 19094424 DOI: 10.1177/147323000803600602]

9 **Simánek V**, Kren V, Ulrichová J, Gallo J. The efficacy of glucosamine and chondroitin sulfate in the treatment of osteoarthritis: are these saccharides drugs or nutraceuticals? *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* 2005; **149**: 51-56 [PMID: 16170388 DOI: 10.5507/bp.2005.004]

10 **Wabndel S**, Juni P, Tendal , Nuesch E, Villiger PM, Welton NJ, Reichenbach S, Trelle S. Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. *BMJ* 2010; **341**: c4675 [DOI: 10.1136/bmj.c4675]

11 **Sawitzke AD**, Shi H, Finco MF, Dunlop DD, Bingham CO, Harris CL, Singer NG, Bradley JD, Silver D, Jackson CG, Lane NE, Oddis CV, Wolfe F, Lisse J, Furst DE, Reda DJ, Moskowitz RW, Williams HJ, Clegg DO. The effect of glucosamine and/or chondroitin sulfate on the progression of knee osteoarthritis: a report from the glucosamine/chondroitin arthritis intervention trial. *Arthritis Rheum* 2008; **58**: 3183-3191 [PMID: 18821708 DOI: 10.1002/art.23973]

12 **Towheed TE**, Maxwell L, Anastassiades TP, Shea B, Houpt J, Robinson V, Hochberg MC, Wells G. Glucosamine therapy for treating osteoarthritis. *Cochrane Database Syst Rev* 2005; **18**: CD002946 [PMID: 15846645]

P- Reviewers Nakajima A, Philip A, Yukihiro S
S- Editor Zhai HH **L- Editor** A **E- Editor** Zhang DN

百世登

Baishideng®

Published by **Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai, Hong Kong, China
Fax: +852-65557188
Telephone: +852-31779906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

ISSN 1007-9327

Baishideng Publishing Group Co., Limited