Severe hepatitis due to percutaneous diclofenac

Hépatite sévère due à l’application de diclofenac percutané

Although it is rare, diclofenac, a nonsteroidal anti-inflammatory drug, may cause severe liver damage, sometimes with a fatal outcome. We report the first case of a patient who developed severe reversible liver damage after a percutaneous administration of diclofenac.

Observation

A 52-year-old woman, known to have gastroesophageal reflux, dyslipidemia and for the last four years very mild primary biliary cirrhosis, developed progressive weakness combined with icterus in September 2004. Her daily treatment for the past four years had been ursodeoxycholic acid 900 mg, omeprazol 20 mg and atorvastatin 20 mg. She had recently received percutaneous diclofenac for lumbar and sciatic pain. Laboratory tests showed an increase in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels of 1672 IU/L (n < 36 IU/L) and 2012 IU/L (n < 37 IU/L) respectively, marked cholestasis with a total bilirubin of 184 μmol/L (n < 21 μmol/L) and direct bilirubin of 121 μmol/L (n < 3.4 μmol/L), γ-glutamyl transpeptidase (γGT) level of 280 IU/L and alkaline phosphatase (ALP) level of 123 IU/L, a spontaneous prothrombin time of 57%, as well as an increase in C-reactive protein at 47.7 mg/L (n < 5 mg/L). One year before, laboratory tests had shown AST 87 IU/L, ALT 87 IU/L, γGT 108 IU/L and ALP 82 IU/L. Abdominal ultrasound followed and cholangio magnetic resonance imaging did not show any suspicious nodules, gallstones or bile duct obstruction. Liver biopsy showed severe acute hepatitis with large areas of converging necrosis, sometimes panlobular and with reticular collapse. There was no major fibrosis in the portal spaces, but they contained inflammatory infiltrate of lymphocytes, eosinophils and neutrophils, and biliary cholangitic lesions. There was no significant plasmocytic infiltrate, eliminating an autoimmune origin. This mixed biliary and hepatocellular picture, as well as the presence of polymorphonuclear eosinophils, suggested a toxic or medicinal origin. Thus all medications were stopped and the patient began to recover. Four days later, the results were as followed: AST 993 IU/L, ALT 1321 IU/L, γGT 179 IU/L and ALP 109 IU/L. On February 2005, she had the same results as she had before the onset of the hepatitis, with AST 71 IU/L, ALT 85 IU/L, γGT 123 IU/L and ALP 94 IU/L. Her usual treatment (ursodeoxycholic acid, omeprazol, atorvastatin) was then reintroduced, with no relapse. One month later, we observed the following results: AST 54 IU/L, ALT 103 IU/L, γGT 118 IU/L and ALP 82 IU/L.

There was no evidence of a viral attack. All serology results remained negative: IgM hepatitis A virus, anti-body to hepatitis C virus, hepatitis B surface antigen and antibody to hepatitis B core antigen, cytomegalovirus IgG below 4 and IgM were all negative, as well as Epstein-Barr virus (virus capsid antigen [VCA] below 20 and EB virus nuclear antigen [EBNA] 481) which demonstrates a past infection. Autoimmune assessment values were the same as during the previous test. The patient was known to have and had been followed for four years for a mild primary biliary cirrhosis with positive anti mitochondrial antibodies and liver biopsy. Analyses showed anti mitochondrial antibody 40 (n < 20), smooth muscle antibody below 40, antibody to liver—kidney microsomes (anti-LKM1) below 10, antinuclear antibody 1280 (n < 160) with antinucleosome 21 (n < 21), Ro antibody (SSA) below 20, La antibody (SSB) below 20, antineutrophil cytoplasmic antibody (RNP) below 20, anti-Smith antibody (anti-Sm) below 20 and antineutrophil cytoplasmic antibody negative.

Comment

It was likely that percutaneous diclofenac was responsible for the severe hepatic damage in this case. The reintroduction of the patient’s usual treatment was not followed by a relapse.

A preparation for cutaneous applications must be as hydrophilic as they are lipophilic, highly water soluble and have a high affinity for lipids as with diclofenacum epo- luminum. The direct local penetration calculated for all nonsteroidal anti-inflammatory drugs is 3–4 mm under the application site, with a distribution to the deeper tis-
sues by the systemic blood circulation [1]. There may be high individual variations in cutaneous absorption, mainly due to different permeability and hydration of the skin [2].

Each plaster (14 × 10⁻³ kg) contains 182 × 10⁻⁶ kg of diclofenacum epolaminum (corresponding to a concentration of 1.3% of diclofenacum epolaminum and 1% of diclofenacum natricum, respectively). After a cutaneous application of a plaster of diclofenac, the plasma concentration at the steady-state is characterized by a plateau concentration (concentration maximum average 0.05 μmol/L and time maximum average 5.4 ± 3.7 h). In comparison, 50 mg of diclofenacum natricum taken orally has an average plasma concentration of 5 μmol/L, two hours after intake [3]. There are few mechanisms of hepatic toxicity. One is an immune-mediated liver injury with a reaction involving T cells. There are also reactive metabolites, the 4-OH— and the 5-OH—diclofenac, that can potentially be oxidized to a β-benzoquinone imine, known to be implicated in redox cycling and in producing oxidative stress. Another important pathway is glucuronidation, resulting in acyl glucuronide with toxicological consequences. In addition to these mechanisms, an immunological reaction is also involved. Some patients had fever, rash or eosinophilia associated with liver injury and there is a rapid reaction when readministering the diclofenac.

As liver damage cannot be reproduced in animals and because a dose—response relationship does not exist, there must be an individual sensitivity which would suggest an idiosyncratic toxicity [4]. The causes of this individual sensitivity are probably genetic factors, as well as acquired factors induced by the environment. In about 15% of the patients treated with diclofenac, the value of one or several hepatic enzymes might increase during treatment. In 2.5% of the cases, a moderate increase is observed less than eight times the upper limit of normal, while in 1% it is more than eight times the upper limit of normal [3]. The typical histopathological picture is hepatic necrosis (generally diffused). The presence of liver disease (primary biliary cirrhosis) in our patient might have favored the toxic reaction.

Until the 1990s, the efficacy of percutaneous applications of nonsteroidal anti-inflammatory drugs had not been determined. Since 2000, several articles have been published showing the effectiveness of the drug with a significant local effect, but without systemic side effects [5]. In the literature, four cases have been reported of gastrointestinal hemorrhage associated with topical application of diclofenac [6]. Other drugs, such as topical minoxidil, also provoked an increase in aminotransferase levels [7]. The onset of severe hepatitis due to a topical application of diclofenac, has not been reported.

Conclusion

In conclusion, our observations suggest that the secondary effects of percutaneous applications of nonsteroidal anti-inflammatory drug on the liver should not be overlooked. A careful assessment should be made in patients with a previous history of liver disease.

References


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Hépatite à la doxycycline

Doxycycline induced hepatitis

Introduction

La doxycycline est un antibiotique de la famille des tétracyclines, dérivé semi-synthétique de l’oxytétracycline ou de la méthyacycline, très lipophile d’où une excellente pénétration tissulaire. Ses effets secondaires sont similaires à ceux des autres membres de la même famille, avec notamment des réactions de photosensibilisation cutanée. Si l’hépatotoxicité des tétracyclines, et en particulier de la minocycline et de la chlorotétracycline, a été bien décrite, les observations d’hépatite associée à la doxycycline sont peu nombreuses. Nous rapportons ici un cas d’hépatite aiguë à la doxycycline, survenue lors du traitement d’une actinomycose pulmonaire.

Observation

Un homme de 37 ans était hospitalisé en janvier 2007 pour une fièvre et une asthénie d’apparition récente. Il était suivi