INDUCED BY MEDICATION HEPATOTOXICITY IN AN AMBULATORIAL PATIENT: CASE REPORT

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ABSTRACT

Background: Drug-induced hepatitis, also called toxic hepatitis or DILI (Drug Induced Liver Injury), accounts for about 2% of hospitalization cases of jaundice and liver damage is involved in 3-10% of all adverse drug reactions. Cases of hepatic injury associated with ibuprofen use are rare and the frequency of idiosyncratic hepatotoxicity is small. **Objective**: To report a case of hepatic injury induced by ibuprofen identified in a medium complexity outpatient clinic. **Case report**: A 48-year-old female patient was admitted to a Specialized Care Center in the southwestern state of Bahia for a consultation with an orthopedist complaining of low back pain, and ibuprofen and sodium dipyrone were prescribed to relieve symptoms. After 15 days of treatment, the patient returns to the service complaining of arthralgia in the upper limbs, right hand edema, jaundice, coluria, fecal suppura, asthenia and intense pruritus. From the investigation of the presented case, viral and autoimmune etiologies were ruled out. Ultrasonography of the total abdomen showed a slight abnormal texture of the liver and gallstones in motion, being suggestive of choledocholithiasis. After evaluation of causality and application of RUCAM, the reaction was classified as highly probable. **Conclusions**: The hepatic injury shown by the patient has a strong causal relationship with the use of ibuprofen.

Keywords: Hepatotoxicity, drug induced hepatic injury, ibuprofen.

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INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAID) are the mostly worldwide used drugs. They are often prescribed for headaches and musculoskeletal pain treatment and are well known as one of the drugs that induces idiosyncratic hepatotoxicity (or liver toxicity) the most [1].

Drug-induced hepatotoxicity accounts for approximately 2% of the cases of hospitalization for jaundice, with liver damage being involved in 3-10% of all Adverse Drug Reactions (ADR). It is believed that approximately 50% of all acute liver failure cases are related to drugs, which are associated to a 90% mortality rate [2].

Many drugs routinely used in the clinic may present liver injury as an undesirable side effect, with hepatotoxicity being the leading cause of fatal ADR and the most frequent reason for withdrawal of drugs from the Market [2]. Drug-induced liver injury (DILI) may seem rare in the context of liver diseases, but they are frequent in liver diseases reference centers.

Among all NSAIDs, ibuprofen is probably the one with the greatest liver safety profile. The cases of liver injury associated with the use of ibuprofen are rare and the frequency of idiosyncratic hepatotoxicity is small [1].

CASE REPORT

The patient, who was a 48 years old black woman with complaints of arthralgia, was admitted to a Specialized Care Center located in the southwestern region of the State of Bahia and referred to an orthopedist. After clinical assessment, a drug treatment with ibuprofen and dipyrone sodium was prescribed (D1). In pharmacological anamnesis, it was evidenced that the patient used hydroxyzine, for allergic rhinitis, omeprazole 20 mg, and simethicone drops. She reported neither the use of other therapies, including supplements and herbal medicine, nor the use of alcoholic beverages and illicit drugs.

After 15 days (D15) of treatment, the patient returned to the Care Center for medical assistance, with complaints of joint pain in the upper limbs, edema in the right hand, jaundice, dark urine, insomnia, asthenia and intense itching. Clinical examinations showed that she had mild splenomegaly. The biochemical analysis showed an increase in the transaminases and bilirubin levels (Table 1). Total abdomen ultrasound examination (Figure 1) suggested a discrete change in the liver texture, with an ill-defined focal area of about 4.6 cm in the right lobe and moving gallstones measuring 1 cm, thus indicating choledocolithiasis. In Total Abdomen Magnetic Resonance Imaging (TAMRI), the liver showed usual dimensions, borders, and intensity, with no dilatation of the bile ducts. The gallbladder showed a small nodule, with bile apparently compressed in its inside, which did not correspond to the image described in the ultrasonography, with no liquids or collections in the peritoneal cavity and absence of adenomegalies.

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Table 1. Biochemical parameters of patient after used ibuprofen

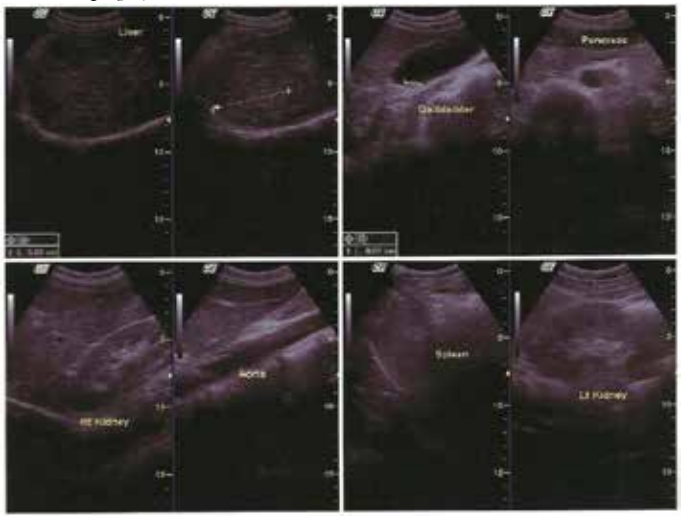
Dosed enzymes	DILI recognition D15	D30	D45	D133
AST (IU/L) ULN < 46	127	115.5	72	31
ALT (IU/L) ULN < 69	286	210.4	91	26
FA (IU/L) ULN < 126	-	102.3	378	90
TB (mg/dL) ULN < 1.2	-	6.07	1.67	0.8
Cr (mg/dL) ULN < 1,5	0.9	-	-	-
R factor (IU/ml)	-	< 8	-	-
Anti-Smooth Muscle Antibodies	-	Negative	-	-
Hepatitis A	-	Negative	-	-
Hepatitis B	-	Negative	-	-
Hepatitis C	-	Negative	-	-

Captions: AST (Aspartate transaminase), ALT (Alanine Transaminase), AP (Alkaline phosphatase), TB (Total Bilirubin), Cr (Creatinine), R Factor (Rheumatoid Factor).

Table 2. Results of the lab exams, patient's protein electrophoresis in D15.

Dosed enzyme	%	g/dL
Albumin	56.2	4.22
Alpha 1	3.7	0.28
Alpha 2	13.5	1.01
Beta 1	7.2	0.54
Beta 2	4.4	0.33
Gamma	15	1.13
Total Protein		7.5
Albumin/Globulin Ratio	1.28	

Figure 1. Image obtained from the patient's total abdomen ultrasonography



Other possible causes of liver injury were excluded: possible clinical similarities (acute viral hepatitis or autoimmune hepatitis, table 01. For drug interaction assessment, Micromedex solutions was used and no interaction with the therapy in use was evidenced [3]. In order for the condition to be resolved, the use of ibuprofen was was discontinued", and started ursodeoxycholic acid and cholestyramine. Three months later, the patient had recovered, showing normal liver function (D133).

For causality evaluation, two experts were consulted, one physician and one pharmacist. The RUCAM (Roussel Uclaf Causality Assessment Method) causality scales were used, and a final result of 8 (eight) points was obtained, which means a highly probable reaction [4].

DISCUSSION

DILI diagnosis occurs through the following steps: a) the establishment of a causal relationship; b) the exclusion of alternative causes for diagnosis, e.g. viral disease, autoimmune diseases, alcoholism; c) improvement of the condition after drug suspension; d) reexposure to the suspected agent, when it occurs; and e) associated risk factors [5,6,7].

The literature reports that the risk of NSAIDs-induced hepatotoxicity is very small (1 to 10 per 100,000 individuals exposed), and that Ibuprofen has a higher incidence among NSAID. The reported case is a mixed-type liver injury. Cholestatic or mixed injuries due to ibuprofen use correspond to 42% of injuries, which are accompanied by jaundice in most cases [5,8].

In this case, the diagnostic hypothesis of drug-induced hepatitis is quite plausible, since ibuprofen toxicity is justified by several of the aspects established in the literature. Initially, the temporal relationship of 15 days between the use of the drug and the appearance of the symptoms is similar to other studies [9,10].

Viral etiologies, such as hepatitis HAV, HBV and HCV, were excluded. These etiologies are especially present as a diagnostic suspicion in the Brazilian population, but according recent studies the frequency of viral hepatitis was decrease [11,12]. The autoimmune disease, also excluded as an alternative cause, the results of autoantibodies was negative, and patient had negative history of alcohol abuse.

Regarding the other medicines that the patient reported using, omeprazole, hydroxyzine, and simethicone (with the first being the only of continued use) were discarded as the cause of DILI. Hepatotoxicity secondary to omeprazole is also uncommon: although the type of liver damage may be compatible with the one described herein, the time of use and appearance of the event is much higher than what is reported in other studies [13]. With respect to the concomitant use of dipyrone, its association with liver damage is infrequent [14]. In addition, the patient had already used dipyrone prior to the event, showing no symptoms of toxicity.

Although there was no previous exposure to ibuprofen, which is one of the main evidences for the confirmation of DILI, hepatic function tests normalized after treatment discontinuation. The damage was resolved within 115 days after the start of the reaction, an amount of time compatible with the type of damage, in this mixed case [5].

Regarding the risk factors, the female sex presents a more frequent correlation, which suggests a greater susceptibility of women to drug-induced liver diseases. This fact reinforces the exposed results. The patient was 48 years old, considering the age group, elderly patients present a higher incidence of drug-induced liver disease, and the reactions tend to be more severe for them [15].

The treatment of hepatotoxicity due to herbal remedies consists of product discontinuation and hepatic function monitoring[16]. Ursodeoxycholic acid (UDCA) has hydrophilic and protective properties regarding membranes of hepatocytes. It is also a choleretic and immunomodulating agent, and is used in diseases associated with cholestasis [17]. In this case, for treatment of liver injury, the patient had use of UDCA and cholestyramine.

The application of the RUCAM scale showed a final score of eight points, which means that drug-induced hepatic damage is highly probable. Although algorithms are not mandatory for the diagnosis of DILI, their application becomes relevant, for it considers the main criteria for causality imputation in hepatic damage and greater specificity, as already described in the literature [18].

Final Considerations

The case reported is a DILI, probably due to ibuprofen. Although it is an infrequent reaction, hepatoxicity by ibuprofen may affect secondary care patients. In addition, the evaluation of drug-induced liver injuries is a problem that brings about reflection regarding the clinical practice and the performance of the country's regulatory agencies. Thus, the maintenance of pharmacovigilance actions in secondary care services becomes imperative, in order to detect and know best the safety profile of medicines used by the Brazilian population.

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Conflict of Interests

The authors declare that they do not have conflicts of interest.

Author's Contributions

NMBLP and GM: Conception and project or analysis and interpretation of data. NMBL and GOSJ: Article writing or critical review relevant to intellectual content. RPFF: Final approval of the version to be published. NMBLP, GM and GOSJ: responsible for all aspects of the work in ensuring the accuracy and integrity of any part of the work.

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