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A Case Report of a Drug-Induced Liver Injury (DILI) Caused by Sodium Alendronate: A Study of Causality Assessment Method.

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ABSTRACT

Drug-induced liver injury (DILI) is an uncommon but potentially lethal adverse drug reaction. Among the methods of causality assessment used for the diagnosis of DILI, the RUCAM (Causality Assessment Method Roussel Uclaf) remains the most widely used worldwide. The causality of the hepatic adverse reaction related to the use of the drug was evaluated by the application of the RUCAM algorithm in a patient treated with Sodium Alendronate, and diagnosed with Paget's disease. The RUCAM scales were applied, which characterized Alendronate as highly probable causing the DILI developed by the patient.

Keywords: Alendronate; Drug-induced Liver Injury; DILI; Adverse Reactions.

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INTRODUCTION

Drug-induced liver injury (DILI) is an uncommon adverse reaction, with a frequency ranging from 1 in 10,000 to 1 in 100,000 cases of adverse drug effects, but potentially lethal [1, 2], being the cause of fulminant liver failure in 13% to 30% of cases [3]. However, the DILI notification is still very low, which is why the mechanisms of liver toxicity of some drugs are still unknown and is also the most frequently cited reason for withdrawal of medications from the marketplace [4].

The diagnosis of DILI is still a challenging issue in clinical practice and depends on the exclusion of other causes. Abnormal liver enzymes detected on laboratory tests, in the absence of most common liver diseases, should always lead the clinician to suspect DILI [5]. Given the inconsistent presentation of DILI, a major challenge is establishing a causative relationship between the hepatic injury and the drug in question. An important tool in the elucidation of causality is the Roussel Uclaf Causality Assessment Method (RUCAM) algorithm, a well-validated clinical scoring system, which is now the preferred version to be used in cases of DILI [3,6].

Alendronate, a Bisphosphonate, is used in the treatment and prevention of osteoporosis in women who have undergone menopause and also to treat osteoporosis in men. The drug is also used to treat osteoporosis in patients who are taking corticosteroids and to treat Paget's disease of bone, a condition involving cellular remodeling and deformity of one or more bones. Alendronate works by preventing bone breakdown and increasing bone density (thickness). This drug is FDA (Food and Drug Administration-US) and ANVISA (National Health Surveillance Agency in Brazil) approved for the treatment of postmenopausal osteoporosis, prevention of postmenopausal osteoporosis, steroid-induced osteoporosis, male osteoporosis and Paget's disease.

There are many reports of hepatotoxicity associated with medications, but Alendronate is generally not counted among these drugs. Up to the present, five cases of hepatotoxicity induced by Alendronate have been reported [7-11]. Considering that bisphosphonates are absorbed by the bone matrix and rapidly eliminated by renal excretion, hepatic metabolism is minimal, and thus it is unexpected that they may be associated with hepatotoxicity.

According to the scientific literature, no reports of hepatotoxicity have been found in patients with Paget's disease treated with Alendronate. Thus, in this first report related to the occurrence of DILI caused by Alendronate in a patient from the rheumatology outpatient clinic with Paget's disease.

This study aims to report a case rare liver dysfunction preceded by the use of Sodium Alendronate and to assess the causality of the adverse reaction according to the Causality Assessment by Naranjo's Method [12] and Roussel Uclaf (RUCAM) [3,6].

CASE REPORT

A 76-year-old Caucasian man was admitted to the rheumatology outpatient clinic with urinary retention. At this time, he reported progressive bone pain and deformity in the right lower limb, making it difficult to walk. In addition, he reported back pain about six years after a fall down and denied fracture. After evaluation by rheumatologists, an X-ray evidenced bone changes, then a scintigraphic examination confirmed the diagnosis of polyostotic Paget's disease of the bone in sternal manubrium, left humerus, L1, L3, L4, right hemipelvis, right femur and proximal left femur diaphysis. Thus, he started drug treatment with alendronate 70 mg weekly. During outpatient follow-up, partial regression of the focal areas was observed on scintigraphy. In a clinical consultation, the patient reported worsening pain on movement and consequently remained at rest. On this occasion, the weekly dose of Alendronate was increased by the prescriber to 210 mg. After five months of this adjustment in therapy, there was a change in laboratory and ultrasound tests. On ultrasound examination, the liver was enlarged with rounded edges and smooth surfaces. In addition, he had the following laboratory alterations: Gamma-glutamyltransferase (GGT) 1,141 U/L, Alkaline Phosphatase (ALP) 312 U/L, Aspartate Transaminase (AST) 63 U/L and Alanine Transaminase (ALT) 156 U/L.

The patient denied ingestion of natural products or teas and reported alcohol consumption occasionally. Analyzing the drugs in use that could be the causative agent by the potential for

hepatotoxicity, Alendronate was considered the suspect, and it was immediately suspended. Then the laboratory changes was quickly reversed, but GGT and ALP remained high.

After nine months of Alendronate's discontinuation, the blood rates of GGT (282 U/L) and ALP (216 U/L) remain increased. Serology for viral hepatitis and total abdomen ultrasound were requested to investigate the persistence of such changes. The ultrasound showed suggestive signs of steatosis and serology for viral hepatitis was negative.

The patient presented an evolution of Paget's disease, with the development of symptomatic secondary osteoarthritis in the right knee. He presented a comminutive fracture of the neck of the right femur after fall, and surgery was required. The treatment with Alendronate 70 mg/week was resumed. In continuous clinical evaluations, after four years of identification and suspension of the probable liver injury agent, GGT (158 U/L) and ALP (450 U/L) did not return to baseline levels.

This study was approved by the Research Ethics Committee of the State University of Maringá, Maringá, Paraná, Brazil (CAAE: 57956016.2.0000.0104).

DISCUSSION

The diagnosis and notification of the adverse events induced by drugs (ADR) are important for the early detection and reduction of damages to patients affected by DILI, whereas changing the course of liver injury in 50% of the cases in which the drug was suspended and decreasing the liver enzyme levels [4,5]. Liver injury is defined by increased serum activities of ALT of at least 5 times the upper limit of normal (ULN) and/or of ALP of at least 2 times ULN, provided that ALP is of hepatic origin [3,4]. DILI may progress to acute liver failure, rapidly leading to death, whereas the early detection and well managed, it evolves favorably with the suspension of medication and support measures for the symptoms.

The most frequently reported adverse reactions after the use of Alendronate are gastrointestinal, such as esophageal ulcers, dyspepsia symptoms, gastritis, and esophagitis, observed after dosages varying from 5 to 10 mg daily [9,13].

In the present report, possibly due to the rapid identification of the causative agent, there was no evolution of the case for urgent/emergency care, however, this is not always a reality. A prospective study observed within a six-month period an incidence of 4.2% of hospital emergencies as adverse drug events, of which 90% were confirmed as ADRs [14]. Thus, as a way to make the decision about the causality of the drug reaction more objective and to prevent further damage to the patient, causal algorithms were created. The causality of the adverse event related to the use of the drug could be evaluated by the application of the Naranjo and RUCAM algorithms. The Naranjo algorithm was one of the precursors, but its general character does not allow contemplating the specificity of DILI. The RUCAM was the first and most widely used algorithm specific for DILI [15].

The RUCAM algorithm is an important tool for clinical practice and can be applied by physicians, pharmacists and nurses. The method consists of seven axes in the decision strategy, in which the answers correspond to numerical values whose sum results in the total score. This score can assign a definitive diagnosis of DILI without re-administration of the same to the patient [3]. The application of the algorithm allows for greater accuracy in confirming the suspected adverse reaction and was conveniently applied for the evaluation of hepatotoxicity by Sodium Alendronate.

On the RUCAM scale, initially the ratio R was calculated, in which R = [ALT/ULN] ÷ [ALP/ULN] [4,5]. The values applied were those found at the peak of the DILI manifestation, with ALT: 156 U/L and ALP: 311 U/L, so the established value was 0.88. This value characterizes the lesion as cholestatic, because the classification is based on hepatocellular (R> 5.0), cholestatic (R <2,0) or mixed (R = 2,0-5,0). Subsequently, the sum of the values attributed to each question culminated in score 11, which defines the adverse reaction as defined as highly probable as to causality.

Among the algorithms, we also applied the method proposed by Naranjo et al. (1981) [12]. By this Algorithm, the adverse reaction was classified as probable. A "probable" ADR is configured in a time sequence with a recognized response to the suspected drug and is confirmed by withdrawal thereof, but not by re-exposure to the drug.

Considering that the period between the medical prescription of Alendronate at the dose of 210 mg/week and the appearance of the liver lesions in the present study was five months, it is observed that the time for the development of the symptoms was in accordance with the reports in the literature [4,5]. However, even with the discontinuation of the probable causative agent, there was no complete restoration of serum enzymes that assess liver function after 4 years. The reversal of liver enzymes to normal values is occurring slowly due to the history of previous diseases (diabetes mellitus) and life habits (alcoholism, smoking, and sedentary).

It is extremely important to look at the drugs used simultaneously with the probable hepatotoxicity agent. When concomitant use of drugs occurs, the metabolic activity of cytochrome P-450 enzymes may undergo induction, inhibition, or substrate competition [16]. At the time of evaluations of drug interactions, no significant interactions were found. During a progression of the disease, there may be variations in the profile of the serum enzymes, in this way, the time at which the R-value is calculated is of extreme importance. Some clinicians use enzymatic values from the first analytical test showing elevations above normal to establish the R-value, while others use maximum values, which may or may not coincide with the initial analytical values. Thus, a lack of standardization for the calculation could interfere with the diagnosis of DILI and in the type of liver injury.

Therefore, the selection of a drug for the treatment of Paget's disease should be carefully considered. Most clinicians consider Calcitonin as second-line therapy for bisphosphonate intolerant. When compared to this class, Calcitonin is less effective in suppressing bone turnover, has a higher cost, and may develop resistance, but does not cause osteomalacia and is more effective in cicatrization of lytic lesions [17].

Up to the present, five cases of hepatotoxicity induced by Alendronate have been reported. In 1998, Lieverse [7] reported a 77-year-old woman who developed severe hepatitis under alendronate therapy. No other cause for hepatotoxicity was found, and the laboratory findings returned to normal after alendronate was stopped. In 2000, a 71-year-old woman was reported with elevated serum liver enzyme levels after two months of alendronate therapy [8]. After the withdrawal of the drug, the enzyme levels slowly returned to normal ranges. Similarly, in 2001, a 76-year-old woman presented with elevated serum liver enzymes three months after the start of Alendronate therapy, and again laboratory parameters returned to normal six weeks after withdrawal of the drug [9]. In 2002, similar hepatotoxicity was seen in a 71-year-old woman on alendronate therapy and this slowly resolved after the drug was stopped [10]. Finally in 2007 Yanik *et al*. (2007) described a 47-year-old postmenopausal woman who had been taking Alendronate 70 mg/week for osteoporosis. After two months of Alendronate therapy, she developed hepatotoxicity and behind the therapy was discontinued, the patient's hepatic enzyme levels slowly returned to normal. For all of these patients, no other possible causative factors for hepatotoxicity except Alendronate therapy were reported [11].

After analyzing the data from this clinical case, the Pharmacovigilance Commission of the hospital in question concluded that the use of Alendronate was the likely cause of the ADR presented by the patient and notified to the Brazilian Notification System in Health Surveillance (SNVS) [18].

CONCLUSION

The rapid and accurate detection of DILI is essential in clinical practice, however, it is a challenge as it presupposes a high index of suspicion and the exclusion of other differential diagnoses. The RUCAM algorithm is an important tool for clinical practice, plus it can be applied by doctors, pharmacists, and nurses. The application of this algorithm allows higher accuracy in the confirmation of the suspicion of the adverse reaction, and it was applied conveniently for evaluation of Alendronate hepatotoxicity.

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