Case Report ISSN 2639-9334

Gastroenterology, Hepatology & Digestive Disorders

Acute Hepatitis with the Tramadol-Paracetamol Combination; About an Observation at The Regional University Hospital Center of Ouahigouya in Burkina Faso and Review of the Literature

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Received: 03 Jun 2024; **Accepted:** 21 Jul 2024; **Published:** 02 Aug 2024

Citation: Zoungrana SL, Ouattara ZD, Tapsoba A, et al. Acute Hepatitis with the Tramadol-Paracetamol Combination; About an Observation at The Regional University Hospital Center of Ouahigouya in Burkina Faso and Review of the Literature. Gastroint Hepatol Dig Dis. 2024; 7(4): 1-3.

ABSTRACT

Introduction: *Idiosyncratic drug hepatotoxicity called drug-induced liver injury (DILI) is a major problem in modern hepatology. However, it remains underdiagnosed and relatively rare. We report a case of acute hepatitis due to tramadol associated with paracetamol in a hospital setting in Ouahigouya (Burkina Faso).*

Case History: *a 20-year-old male gardener presented, following hospitalization in July 2023, with clinical cholestasis syndrome after taking tramadol and paracetamol as an adjuvant to anti-malaria treatment. No pathological history was found. There was no notion of alcohol consumption or taking hepatotoxic medication before hospitalization. The clinical examination revealed flamboyant jaundice, the biology revealed syndromes of cholestasis, cytolysis and hepatocellular insufficiency. The markers of viral hepatitis A B, and C as well as those of autoimmunity were negative. The hepatobiliary and other abdominal organs ultrasound was normal. Therapeutically, we stopped tramadol and paracetamol. The evolution was favorable after 15 days with first a normalization of clinical parameters and a clear improvement in biological parameters, then their normalization 1 month after hospitalization.*

Conclusion: *We report a documented observation of "mixed" acute hepatitis (cytolytic and cholestatic) in connection with the concomitant use of tramadol and paracetamol, with a favorable outcome in the absence of re-exposure to the drug after 45 days.*

Keywords

Acute hepatitis, Tramadol-paracetamol, Ouahigouya, Burkina Faso.

Introduction

Idiosyncratic drug hepatotoxicity called drug-induced liver injury (DILI) is a major problem in modern hepatology. It is the most common cause of drug withdrawal on the market. However, it remains relatively rare and underdiagnosed, especially in our practice context. In fact, its incidence reaches approximately 1 case/100,000 prescriptions. Although antibiotics are the substances most frequently involved [1], other medications are also involved to a lesser degree. We report a case of acute hepatitis due to tramadol associated with paracetamol in a hospital setting in Ouahigouya (Burkina Faso).

Case History

A 20-year-old man, a gardener, was hospitalized in our department on July 26, 2023 with a malaria syndrome consisting of a fever of 38°5 C, asthenia, headaches and aches, and vomiting lasting for 72 hours. He had consulted a health facility where oral anti-malaria treatment had been prescribed to him. It is because of the persistence of the symptoms that he goes to the medical emergency where antimalarial treatment based on artemisinin will be undertaken in the face of the positivity of the thick drop. Symptomatic parenteral treatment with tramadol and paracetamol

is also administered to the patient when headaches and fever persist. During hospitalization, the patient presented with clinical cholestasis syndrome (made of mucocutaneous jaundice, associated with slight pruritus, dark urine and discolored stools) 5 days after taking tramadol combined with paracetamol. There was no evidence of consumption of alcohol or other hepatotoxic medications (phytotherapy or pharmaceutical medications) in the days and weeks preceding the onset of jaundice.

We did not find any medical history in this patient, particularly chronic viral hepatopathy B or C, chronic alcohol poisoning, or smoking.

Clinical examination on admission revealed flamboyant jaundice, hepatomegaly, and splenomegaly. There was no hepatic encephalopathy or any other abnormality.

The biological assessment revealed cytolysis with AST at 1212.1 IU/l (30.3N) and ALT at 305.60 IU/l (6.7N), cholestasis with total bilirubin at 144.4 µmol /l (7N) including 90.5 µmol/l of direct bilirubin (10.52 N). Alkaline phosphatase levels were 244.7 IU/l (1.6N), prothrombin level 42%. Urea was elevated at 32.3 mmol/l as well as creatinine at 454 µmol/l reflecting functional renal insufficiency. Thick drop for malaria research was positive.

Tests for HBs antigen, anti-HBc antibody, anti-HAV IgM, anti-HCV antibody and hepatitis C virus RNA by PCR were negative. HIV 1 and 2 serologies, as well as dengue fever, were negative. Tests for antinuclear antibodies, anti-smooth muscle antibodies, and anti-LKM1 antibodies were negative.

Hepatobiliary ultrasound revealed homogeneous hepatomegaly, without signs of gallbladder and/or bile duct lithiasis. Homogeneous splenomegaly was also found as well as signs of right-sided nephritis associated with slight peritoneal fluid effusion.

Discussion

The diagnosis of drug-induced liver disease is difficult because the relationship between drug exposure and liver damage is not always obvious. However, there are several scores allowing toxicity to be attributed to a drug with objective criteria including the RUCAM score [1,2]. In this observation, the diagnosis of DILI is probable for the tramadol-paracetamol combination with RUCAM (roussel-Uclaf causality assessment method) imputability score rated at 5:

- Time for jaundice to appear: 5 days, compatible with DILI = 1 point;
- Clinical course (after withdrawal of treatment): suggestive of DILI = 2 points;
- Risk factors (alcohol or age over 55): none = 0 points;
- Concomitant medication: compatible with the time to onset of liver damage but medication with little hepatotoxicity (artemisinin) = -1;
- Alternative diagnosis of non-drug origin: alternative diagnosis excluded (no hepatitis A, B or C; no lithiasis or biliary tract disease on ultrasound; no recent hypotension) = 2 points;
- Hepatotoxicity of the drug: potentially hepatotoxic drug = 1 point;
- Response to drug re-exposure: the patient was not re-exposed to the drug = 0 points.

Epidemiologically, the incidence of DILI remains largely underestimated. Drug hepatotoxicity, all substances combined (drugs, phytotherapies), fluctuates between 1 case/10,000 and 1 case/100,000 exposed people [1]. A large prospective French study over three years reported an incidence of 14 cases/100,000 people treated [3]. Another study subsequent to the one mentioned above, however, reported that 1% of hospitalized patients developed such a pathology during their stay [4]. Analgesics are clearly the most often incriminated, representing up to 45.5% of cases [5]. Among these, paracetamol, tramadol and especially the tramadol-paracetamol combination are involved. The hepatotoxic substances involved in our case are tramadol and paracetamol. Under surveillance since 2012, Tramadol®, a painkiller, is the subject of a new warning. Indeed, according to a study carried out by pharmacology researchers from several University Hospital Centers in France and published in the journal Thérapie [6], this treatment would have negative effects on the liver. This was a pharmacovigilance study over a period of 4.5 years with 1512 reports of serious adverse effects (SAEs), some of which were "unexpected" such as cholestatic hepatitis.

The liver damage would be of the cholestatic type when tramadol appeared to be the only suspected drug; and of cytolytic type when tramadol was combined with paracetamol. Our patient received these two molecules as part of his treatment and the liver damage was rather mixed with significant cytolysis predominating. The authors suggest that tramadol has its own hepatotoxicity and that it could also potentiate the hepatotoxicity of paracetamol. Depending on age and sex, there are variable susceptibilities to medications. For example, in a study that focused on an antibiotic, co-amoxicillin, the "cholestatic/mixed" profile appeared in people over 55 years of age, while the "hepatocellular" profile predominated in younger people [1]. This phenomenon still remains misunderstood. Women are more likely to suffer from hepatocellular damage [5]. In our observation, the patient was young (20 years old) and presented a more "cytolytic/mixed" type profile. Clinically, the diagnosis is not easy because of the variability of clinical and paraclinical manifestations. In fact, there are no specific signs of drug-induced hepatitis. The diagnosis is therefore based on a precise, exhaustive and chronological examination of medication intake. This is usually a recently introduced medication, and it is important to collect all prescriptions. The first manifestations appear between 5 and 90 days after the start of treatment. They range from the absence of symptoms to acute liver failure, including jaundice. In this observation, the diagnosis of idiosyncratic acute mixed hepatitis is based on the following elements:

1) Occurrence of acute liver damage after initiation of treatment with tramadol-paracetamol
2) Absence of evidence for stone migration;
3) Elimination of acute hepatitis A, B, or C;
4) Absence of evidence for autoimmune hepatitis.

The biological assessment pointed towards "mixed" acute hepatitis

(cholestatic and cytolytic) due to:

- ALT/Alkaline Phosphatase ratio=1.2 (<2) reflecting the cholestatic profile;
- ALT > 2 times the upper limit of normal, reflecting the cytolytic profile.

On the physiopathological level, the genesis of the disease is complex, drug metabolites undergo and generate a host of biochemical reactions, depending on the genetic polymorphism specific to each patient. The evolution of the clinical and biological picture was favorable after stopping tramadol and paracetamol. After 15 days, the jaundice had completely resolved and the biological assessment almost normalized. These results were maintained 45 days after stopping exposure to both drugs. Several studies [7-9]. Attest to the favorable evolution of "cholestatic" forms and "mixed" forms in the absence of re-exposure to the drug(s) in question.

Conclusion

We report a documented observation of "mixed" acute hepatitis (cytolytic and cholestatic) in connection with the concomitant use of tramadol and paracetamol, with a favorable outcome in the absence of re-exposure to the drug after 45 days. We must therefore not forget the need to carry out further investigations in cases of jaundice in the context of taking medication, particularly an analgesic such as tramadol, whether or not associated with paracetamol, to establish accountability and allow appropriate care and follow-up preventive measures.

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