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CASE REPORT

First case of acute cholestatic hepatitis attributed to oseltamivir in a young girl with AH1N1 influenza

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Abstract

Oseltamivir caryboxylase is a potent inhibitor of the enzyme neuramidase of the influenza virus particle and it is active against both influenza A and B viruses. Oseltamivir is indicated for therapy or post-exposure prevention of influenza A and B. Side effects are uncommon and include mild nausea, gastrointestinal upset, dizziness and headache. Despite its widespread use, oseltamivir has not been associated with clinically apparent liver injury. To the best of our knowledge, this is the first case report in the literature linking the development of acute hepatitis to the consumption of oseltamivir in a patient suffering from influenza H1N1 infection.

Introduction

Oseltamivir is a prodrug of oseltamivir carboxylate, a potent and selective inhibitor of the neuraminidase glycoprotein essential for replication of influenza A and B viruses. Oseltamivir (F. Hoffmann-La Roche, Ltd., Basel, Switzerland) is the antiviral agent most frequently used for the treatment and prevention of influenza (1), with gastrointestinal events being the most commonly reported side effects. Increase of liver transaminase levels is a frequent observation during human influenza infection, due to variability in pre-existing levels of immunity from past influenza infections and to genetic differences among subjects (2). Influenza-associated hepatitis occurs due to the formation of inflammatory foci that include apoptotic hepatocytes, antigen-specific CD8+ T cells, and Kupffer cells (2). In patients with influenza infection, hepatic involvement may be common, can present in diverse ways and may have important implications for morbidity. Despite widespread use, there is little evidence that oseltamivir, when given orally, causes liver injury, either in the form of serum enzyme elevations or clinically apparent liver disease (1).

We present the first case of an 18-year female patient who presented worsening of

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liver function tests after she was started on Oseltamivir.

A 18-year-old woman presented to our hospital on February 5th, 2019, with fever, asthenia, and dry cough. There was no history of alcohol consumption or food allergies. The patient had no prior history of liver disease. On admission, she was conscious, alert, and maintaining saturation on room air. Her initial laboratory results showed mild thrombocytopenia (103,000/μl), and hyponatremia (128 mg/dL). Her total leukocyte count, liver functions, and coagulation profile were within normal limits. Chest X-ray showed bilateral homogenous opacities in all lung fields. Real-time polymerase chain reaction for pandemic influenza A (H1N1) was reported to be positive. Her antibiotic regimen included intravenous ceftriaxone along with oral oseltamivir.

Four days after starting the drug, the patient developed mixed hepatocellular and cholestatic liver injury with jaundice and pruritus, fatigue and nausea, followed by anorexia, abdominal discomfort (liver pain) and then dark urine. Levels of serum aspartate amino transferase (SGOT), serum alanine amino transferase (SGPT), alkaline phosphatase and total bilirubin levels increased to 1,280 U/L, 1,600 U/L, 330 U/L and 3.5 mg/dL from baseline values of 32 U/L, 40 U/L, 150 UTL, 1.8, respectively (reference ranges; SGOT: 1-34 U/L; SGPT: 25-65 U/L; alkaline phosphatase: 50-136 U/L, bilirubin 0.4 – 1.2 mg/dL). Peak levels were documented on the sixth day after starting of oseltamivir (SGOT: 1,425 U/L; SGPT: 1,950 U/L; alkaline phosphatase: 530 U/L; bilirubin 5.3 mg/dL with direct bilirubin 3.2 mg/dL). Patient was not taking other concomitant hepatotoxic medications and did not have any underlying liver dysfunction.

Her physical exam was remarkable for jaundice and scleral icterus, without any stigmata of liver disease. The patient had no known exposure to any other systemic medications or inciting factors other than oseltamivir. Ultrasound exam of the liver and biliary tract was normal. Oseltamivir-induced liver injury was suspected, and the drug was discontinued. Diagnostic tests ruled out other causes of cholestasis, including infectious and immunologic conditions. There were no serum markers for hepatitis A, B, C and E viruses. No anti-tissue antibodies were found. Clinical and laboratory test value outcome became favorable two weeks after cessation of administration of oseltamivir. The use of the Naranjo adverse drug reaction probability scale indicated a probable relationship (score of 7/8) between the patient's development of acute hepatitis and oseltamivir administration. Although there are a few reported cases of drug-induced liver disease related to oseltamivir and concomitant non steroidal anti-inflammatory drugs, this case is believed to be the first reported case of livery injury not associated with other concomitant drug as ibuprofen or paracetamol. Although oseltamivir is generally safe, health practitioners must be aware of association with liver injury, as the diagnosis of liver injury is one of exclusion and requires a high index of suspicion.

Discussion

Influenza is a viral infection that attacks the respiratory system and is caused by three types of RNA viruses called influenza types A, B and C, belonging to the family Orthomyxoviridae. In the majority of cases, flu is not serious, however for some people there can be severe complications. This is more likely for the children, the elderly, and for individuals with other longstanding illness that can undermine their immune system. Elevation of liver transaminase levels may be a frequent observation during influenza; however, the incidence of liver involvement effect and the etiology underlying the liver damage have been investigated in only a

few studies (3), and very few studies have characterized the nature and extent of liver involvement in affected patients. One hundred and thirty-one patients (58%) had abnormal liver tests in an observational study of liver tests conducted on patients with influenza A H1N1 in Shanghai during the 2009 pandemic (4), however, a severe hepatic dysfunction and acute liver failure (ALF) associated with influenza virus infection have been rarely reported in both children (5) and adult patients (6).

Hypoxic hepatitis, requiring a pre-existing, chronic condition that reduces oxygen supply to the liver, followed by an acute event that further decreases hepatic oxygen supply, can be an important causative factor for ALF associated with influenza virus infection (6). Polakos NK *et al.* provided evidence formally linking influenza-associated liver pathology to the accumulation of influenza-specific CD8+ T cells, and they showed that Kupffer cells are essential in this process (2). The process of CD8+ T-cell infiltration of the liver in influenza infection can itself lead to clinically significant hepatitis, despite the lack of detectable virus in the liver, by a mechanism described as "collateral damage" (2). Hepatic changes may be a consequence of a significant immune response that in combination with moderate hypoxia, caused by influenza respiratory illness, may lead to hepatocellular injury and finally result in different clinical and laboratory features (7). Oseltamivir is a selective neuraminidase inhibitor, frequently used for the treatment and prevention of influenza. Oseltamivir is a prodrug which needs conversion to the active form, oseltamivir carboxylate, and is absorbed by the gastrointestinal tract on oral administration, with a bioavailability of 80%. Oseltamivir is excreted via the kidneys and there is less potential for drug interactions. Oseltamivir is well tolerated and in treatment studies modestly reduces the time to first alleviation of symptoms, but it causes nausea and vomiting and increases the risk of headaches and renal and psychiatric syndromes. In prophylactic studies oseltamivir reduces the proportion of symptomatic influenza, representing a useful therapeutic alternative in providing household prophylaxis or adjunctive prophylaxis in high-risk vaccinated patients during an outbreak of the disease or for use in patients in whom vaccination is ineffective (8).

In a recent study, publicly available data from patients who have taken oseltamivir in the *real life* have been collected (9). Among all types of side effects that were described in this study, the neuropsychiatric symptoms and body pain were the most important, followed by dermatologic manifestations (9).

Spectrum of adverse reactions to oseltamivir include sudden onset type reactions, delayed onset and/or prolonged type reactions. The sudden onset type reactions appear very shortly after the first dose of oseltamivir, and disappear rapidly, even if oseltamivir is continuously taken. Gastrointestinal, central nervous system, psychiatric symptoms, and respiratory suppression are included in this group of adverse reactions. It is possible that there exist target receptors or enzymes that oseltamivir carboxylate specifically acts on different molecular targets. Delayed onset type reactions include disorders of various organs and systems such as renal, metabolic, cardiac, hepatic, haematological, immune, nervous, psychiatric, and general systems (fatigue or malaise). Most of the reactions of this type appear at least a few days after commencement of oseltamivir intake, and the duration of these reactions may be prolonged. Some reports suggest that reduction of human endogenous sialidase (neuraminidase) activity by oseltamivir carboxylate may cause delayed onset type adverse reactions to neuraminidase inhibitors. It may be possible that oseltamivir carboxylate exhibits intrinsic antiinflammatory effects and the possibility of a direct alterations of neurons and heart muscles excitability (10).

A comprehensive assessment of the potential causes of liver damage during influenza should also include the potential effect of antiviral therapy, although oseltamivir-induced liver injury are rarely reported in children and adults. In conclusion, we have described the first reported case in the current literature of oseltamivir-induced acute cholestatic hepatitis all over the world. During pandemic influenza infection, hepatic complications may be seen in addition to the respiratory infection and physicians must recognize both the pulmonary and extrapulmonary complications, including liver involvement due to influenza itself and liver injury possibly due to antiviral treatment.

Riassunto

Primo caso di epatite acuta colestatica attribuita ad oseltamivir in una giovane ragazza con influenza AH1N1

L'oseltamivir carbossilasi è un potente inibitore dell'enzima neuramidasi del virus dell'influenza ed è attivo contro i virus dell'influenza A e B. Oseltamivir è indicato per la terapia o la prevenzione post-esposizione dell'influenza A e B. Gli effetti collaterali non sono comuni ed in genere consistono in lieve nausea, disturbi gastrointestinali, vertigini e mal di testa. Nonostante l'uso diffuso, l'oseltamivir non è stato associato a danno epatico clinicamente evidente. In base ai dati in nostro possesso, questo è il primo caso in letteratura che collega lo sviluppo di un'epatite acuta alla assunzione terapeutica di oseltamivir in una paziente affetta da influenza H1N1.

References

1. LiverTox: Clinical and Research Information on DrugInduced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Oseltamivir. [Updated 2014 Jan 24].
2. Polakos NK, Cornejo JC, Murray DA, et al. Kupffer cell-dependent hepatitis occurs during influenza infection. Am J Pathol 2006; **168**(4): 1169-78; quiz 1404-5.
3. Esper RC, Péres Bustos E, Arroyo SO, Saavedra JA, Uribe M. Liver involvement in severe human AH1N1. Ann Hepatol 2019; **9**: 107-111.
4. Yingying C. Abnormal liver chemistry in patients with influenza A H1N1. Liver Intern 2011; **31**(6): 902. doi: 10.1111/j.1478-3231.2011.02519.x.
5. Whitworth JR, Mack CL, O'Connor JA, Narkewicz MR, Mengshol S, Sokol RJ. Acute hepatitis and liver failure associated with influenza A infection in children. J Pediatr Gastroenterol Nutr 2006; **43**(4): 536-8.
6. Nonaka K, Matsuda Y, Kakizaki M, et al. Acute liver failure associated with influenza A virus infection: an autopsy case report. Jpn J Infect Dis 2019; **72**(5): 347-349. doi: 10.7883/yoken.JJID.2018.494.
7. Papic N, Pangercic A, Vargovic M, Barsic B, Vince A, Kuzman I. Liver involvement during influenza infection: perspective on the 2009 influenza pandemic. Influenza Other Respir Viruses 2012; **6**(3): e2-e5. doi: 10.1111/j.1750-2659.2011.00287.x
8. Jefferson T, Jonessen M, Doshi P, Spencer EA, Onakpoya I, Heneghan CJ. Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. BMJ 2014; **348**: g2545. doi: https://doi.org/10.1136/bmj.g2545.
9. Antipov EA. Pokryshevskaya EB. The effects of adverse drug reactions on patients' satisfaction: evidence from publicly available data on Tamiflu (oseltamivir). Int J Med Inform 2019; **125**: 30-6. doi: https://doi.org/10.1016/j.ijmedinf.2019.02.005.
10. Hama R. The mechanisms of delayed onset type adverse reactions to oseltamivir. Infect Dis (Lond) 2016; **48**(9): 651-60. doi: 10.1080/23744235.2016.1189592.

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