

# Case report on alimentary tract hemorrhage and liver injury after therapy with oseltamivir

## A case report

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### Abstract

**Rationale:** Oseltamivir-induced alimentary tract hemorrhage and liver injury are rarely reported in children and adult individuals. In this study, we described the clinical features and outcomes of oseltamivir-induced alimentary tract hemorrhage and liver injury in a child.

**Patient concerns:** Here, we present a case of a 6-year-old Asian boy with hematemesis and elevated alanine aminotransferase (ALT) (80 U/L) and aspartate aminotransferase (AST) (69 U/L) levels on day 2 of oseltamivir administration. The presence of alimentary tract hemorrhage and liver injury was diagnosed. The ALT level reached 1931.3 U/L, accompanied by an increase in total bilirubin (TBIL) to 53.3  $\mu\text{mol/L}$  on day 15 after oseltamivir administration. Additional tests were performed to determine the presence of viruses that can cause hepatitis and autoantibodies, and the results from these tests were all negative.

**Diagnosis:** Drug-induced liver injury was considered.

**Interventions:** This patient was treated with compound glycyrrhizin and reduced glutathione and glucocorticoid.

**Outcomes:** The liver enzymes recovered within 6 weeks without any symptoms of liver-related diseases after treatment with glucocorticoid. This treatment therefore helps reduce ALT and TBIL levels and protects the liver from further injury.

**Lessons:** Oral oseltamivir is widely used to treat influenza and the adverse effects of this drug were mostly mild. However, clinicians should always be alert for oseltamivir-induced alimentary tract hemorrhage and liver injury when prescribing oseltamivir for children.

**Abbreviations:** ALT = alanine aminotransferase, AMA = antimitochondrial antibody, ANA = antinuclear antibody, ASMA = antismooth muscle antibody, AST = aspartate aminotransferase, CMV = cytomegalovirus, DILI = drug induced liver injury, EBV = Epstein–Barr virus, HIV = human immunodeficiency virus, LKM = liver-kidney microsomes antibody, RUCAM = Roussel Uclaf Causality Assessment Method, SLA/LP = soluble liver antigen antibody/hepatopancreatic antigen antibody, TBIL = total bilirubin.

**Keywords:** alimentary tract hemorrhage, drug-induced liver injury, oseltamivir

## 1. Introduction

Influenza is a vital contributing cause of hospitalization and mortality in children aged <5 years.<sup>[1]</sup> Oseltamivir is a neuraminidase inhibitor that was licensed by the US Food and Drug Administration (FDA) in 1999 to treat influenza. In the nearly 2 decades, the most commonly reported adverse effects of oseltamivir were nausea and vomiting,<sup>[2,3]</sup> whereas the severe or

rare adverse effects include psychiatric manifestations,<sup>[4–8]</sup> tongue swelling,<sup>[9]</sup> enterorrhagia,<sup>[10–13]</sup> dyskinesia,<sup>[14]</sup> bradycardia,<sup>[15]</sup> glaucoma, transient myopia,<sup>[16]</sup> and Stevens–Johnson syndrome.<sup>[17]</sup> However, alimentary tract hemorrhage and liver injury after oseltamivir treatment have been rarely reported.

### 1.1. Consent statement

Informed consent was obtained from the patients for the publication of this study.

## 2. Case report

A 6-year-old Asian boy was admitted into hospital due to severe liver injury. The boy had no prior history of diseases, surgery, and medication. Two weeks ago, the boy had a fever (39.5°C) and was given ibuprofen (0.1 g, twice to 3 times daily). However, the boy still had frequent fever and thus was taken to local hospital and received an empirical treatment of oseltamivir for influenza infection. According to the medication package insert, the boy should take a 5-day course of 60 mg of oseltamivir twice a day. On the second dose of oseltamivir, the boy began to experience hematemesis (approximately 5 ml). The liver function of the boy became abnormal with alanine aminotransferase (ALT) and aspartate aminotransferase (AST) values of 80 U/L (reference range: 9–50 U/L) and 69 U/L (reference range: 15–40 U/L), respectively. Oseltamivir treatment was suspended due to these circumstances. Three days before admission, ALT and AST

Editor: N/A.

Funding/support: This study was approved by the ethics committee of The First Hospital of Jilin University (Minquan Tan, Junqi Niu, Hangdong Zhang, and Chaoying Yan).

The authors have no conflicts of interest to disclose.

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Medicine (2018) 97:38(e12497)

Received: 2 May 2018 / Accepted: 22 August 2018

<http://dx.doi.org/10.1097/MD.00000000000012497>

**Table 1****Laboratory test values of patient with oseltamivir-induced liver injury.**

Variable	Reference range	Before admission		Hospital day							0.5 mo after discharge
		14 d	3 d	1 d	2 d	3 d	4 d	6 d	8 d	11 d	
ALT, U/L	9–50	80	1113	1874.2	1931.5	1773.5	1567.9	1039.4	1097.1	588	14.4
AST, U/L	15–40	69	748	1083.7	816.4	714.5	605.4	518.7	599.6	138.8	29.2
TBIL, $\mu\text{mol/L}$	6.8–30.0	6.9	19.68	39.8	53.3	74.8	84	65	81.9	35.5	17.2
DBIL, $\mu\text{mol/L}$	0.0–8.6	3.04	9.41	23.9	33.5	43.5	52.3	42.2	53.4	19.7	7.7
IBIL, $\mu\text{mol/L}$	5.1–21.4	3.86	10.27	15.9	19.8	31.3	31.7	22.8	28.5	15.8	9.5
TBA, $\mu\text{mol/L}$	0–10	2.5	35.6	235.3	284.3	80.7	153.6	110.9	110.9	10	4.7

ALT = alanine aminotransferase, AST = aspartate aminotransferase, DBIL = direct bilirubin, IBIL = indirect bilirubin, TBA = total biliary acid, TBIL = total bilirubin.

continued to increase to more than a dozen times. On the 2nd day in hospital, ALT increased to the peak of 1931.5 U/L with total bilirubin (TBIL) increasing to 53.3  $\mu\text{mol/L}$  (reference range: 6.0–30.0  $\mu\text{mol/L}$ ). In the course of illness, the boy complained of fatigue and his skin and sclera were slightly yellow. Imaging examination was performed, and the test exhibited negative results. Different tests were performed to determine the presence of the following different pathogens: antibodies to hepatitis A, B, C viruses; cytomegalovirus (CMV); Epstein–Barr virus (EBV); treponema pallidum; tubercle bacillus, and human immunodeficiency virus (HIV). Furthermore, tests for autoantibodies such as antinuclear antibody (ANA), antismooth muscle antibody (ASMA), and antimitochondrial antibody (AMA), liver-kidney microsomes antibody (LKM), soluble liver antigen antibody/hepatopancreatic antigen antibody (SLA/LP) were also performed and the results from all these tests were negative. The thyroid function of the boy showed no abnormalities, and the levels of ceruloplasmin were also normal. The boy recovered by treatment with hepatic protector such as compound glycyrrhizin, reduced glutathione, and glucocorticoid in 12 days. The boy's liver function level returned to normal after 2 weeks of discharge. The laboratory data of his liver function before and after admission are summarized in Table 1.

### 3. Discussion

The 6-year-old Asian boy first received oseltamivir. Although ibuprofen was previously administered to him before the alimentary tract hemorrhage and liver injury, the gastrointestinal injury due to ibuprofen was dose-related.<sup>[18]</sup> A meta-analysis of 8 randomized, double-blind placebo-controlled trials in patients aged  $\geq 12$  years who were exposed to multiple Over The Counter doses of ibuprofen (800 or 1200 mg/day for 1–10 days) was found to have no specific gastrointestinal adverse events rate in the ibuprofen and placebo group.<sup>[19]</sup> For hepatic safety, ibuprofen had the lowest incidence rate (at 1.6/100,000) of inducing liver injury among nonsteroidal anti-inflammatory drugs.<sup>[20]</sup> Liver injury would more likely to occur by taking ibuprofen for 6 to 9 times and combined with other potential hepatotoxicity medicines.<sup>[21]</sup> In this case, the boy weighing 27.5 kg only took 0.1 g of ibuprofen (3.64 mg/kg) 3 times. Moreover, the boy took ibuprofen before and has not observed any adverse effect. Therefore, ibuprofen is less likely to cause alimentary tract hemorrhage and liver injury. According to Roussel Uclaf Causality Assessment Method (RUCAM), a well-established tool commonly used to quantitatively assess causality in cases of suspected drug-induced liver injury (DILI), oseltamivir had a score of 7, which indicated a probable relationship of oseltamivir and liver injury. Thus, the liver injury in this case was probably caused by oseltamivir.

As inactive precursor drugs, oseltamivir phosphate can be converted into oseltamivir carboxylate by liver esterase. Oseltamivir carboxylate plays an important role in inhibiting influenza A and B viral neuraminidase. Although the adverse effects caused by oseltamivir were mostly mild, sudden onset-type reactions, including hypothermia, abnormal behavior, and sudden death, have been reported.<sup>[22]</sup> Delayed onset-type reactions were also reported including reduction of antibody production, renal disorders, hyperglycemias, psychiatric disorders, and QT prolongation.<sup>[23]</sup> Other adverse reactions were presented with pneumonia, wheezing, gastrointestinal bleeding, and hepatic and/or hematological impairment.<sup>[23]</sup> The mechanism of action by oseltamivir in gastrointestinal bleeding and hepatic impairment is still unknown. Yang et al.<sup>[24]</sup> found that the liver esterase activity of age < 1 year and immature animals (including humans) was lower than the mature individuals; this phenomenon may increase the blood concentration of nonactivated oseltamivir giving rise to toxic effects.<sup>[24]</sup>

DILI is an uncommon but important cause of liver disease that can arise after exposure to various kinds of chemical drugs, biological agents, and herbal and dietary supplements. The annual incidence of DILI is about 14 to 19/100,000 inhabitants.<sup>[25]</sup> This study was the first case of oseltamivir-induced liver injury in children. The boy developed liver injury after 2 doses with elevated levels of hepatic aminotransferase and bilirubin. Without permission from the boy's parents, we were not able to conduct liver biopsy test to investigate the changes in liver pathology. Given that no guideline or data on how to control DILI in children have been established, early recognition and withdrawal of the offending drug are some of the most important things that can be performed. Although oral oseltamivir is widely used to treat influenza and the adverse effects were mostly mild, clinicians should always be alert for oseltamivir induced liver injury when prescribing oseltamivir for children, especially when used empirically. In addition, the precise mechanism of oseltamivir causing liver injury is still unknown. Whether or not other neuraminidase inhibitors can also cause liver injury needs further investigation.

### Author contributions

**Investigation:** Na Zhou.

**Resources:** Lingli Qi, Chunyan Li.

**Writing – original draft:** Shengbo Fang.

**Writing – review & editing:** Shengbo Fang.

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