JPPT | Case Report

Drug-Induced Hepatitis in an Adolescent During Concomitant Use of Azithromycin and Lisdexamfetamine Dimesylate

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This case report describes a 14-year-old male with signs and symptoms of drug-induced hepatotoxicity after receiving azithromycin and lisdexamfetamine dimesylate. The patient was admitted to the hospital and a liver biopsy revealed findings suggestive of drug-induced hepatitis. In this patient, it is unclear whether 1 agent individually or a combination of azithromycin and lisdexamfetamine was the cause of hepatitis. Although hepatotoxicity has been reported with azithromycin and other macrolide antibiotics in adults, such a condition has yet to be reported in pediatrics. In light of this report, providers should be aware of a potentially rare reaction of acute hepatitis when combining azithromycin and lisdexamfetamine in pediatric patients.

ABBREVIATIONS ADHD, attention deficit hyperactivity disorder; CBC, complete blood count; CMP, comprehensive metabolic panel

KEYWORDS adolescent; azithromycin; hepatitis; lisdexamfetamine dimesylate; pediatrics

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Introduction

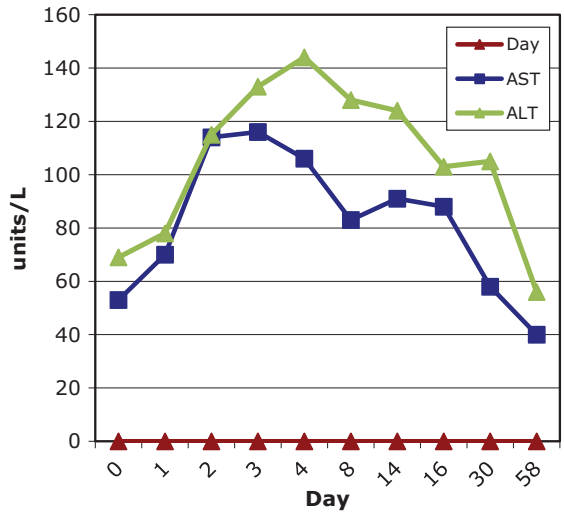
Attention-deficit hyperactivity disorder (ADHD) affects 5 million children between the ages of 3 and 17 years (8%), with males (11%) more than twice as likely as females to be diagnosed. Also, 11% of children between 12 and 17 years of age are diagnosed with ADHD.[1] In the treatment of ADHD, clinicians should develop an individualized treatment program that may include behavior therapy and medications to improve target outcomes.[2] Medications remain a staple in the treatment of ADHD, but they do not come without risks of adverse events. Lisdexamfetamine dimesylate, approved by the US Food and Drug Administration in 2007, was developed to treat ADHD and was proven to be safe and effective in children.[3] Lisdexamfetamine is an inactive prodrug that is metabolized to dextroamphetamine. Dextroamphetamine is a central nervous system stimulant that has been a component of ADHD medications since 1996. Eosinophilic hepatitis has recently been reported in an adolescent receiving lisdexamfetamine dimesylate for the treatment of ADHD.[4] Azithromycin is a macrolide antibiotic commonly used to treat respiratory infections. Common side effects of azithromycin include nausea, vomiting, diarrhea, and abdominal cramps. Hepatotoxicity has been reported in children and adults with the use of macrolides.[5–10] Recently, a child was admitted with acute hepatitis with a history of concomitant use of azithromycin and lisdexamfetamine dimesylate. Study findings indicated a drug- or toxin-induced hepatitis as the likely etiology of this patient's symptoms.

Case Description

A 14-year-old white male presented with chief complaints of increasing abdominal pain, vomiting, and jaundice. Four days prior to presentation, the patient experienced flu-like symptoms of chills, fatigue, muscle aches, and fever up to 101°F to 102°F and was seen by his primary care physician where laboratory work was completed. The laboratory values revealed a mildly elevated white blood cell count, and diagnosis of pneumonia was made by the primary care physician. The patient was started on a 5-day course of azithromycin (500-mg tablet on day 1; 250-mg tablet on days 2–5). His symptoms showed no improvement, and he had a gradual onset of generalized, increasing abdominal pain. On the night prior to hospital presentation, the patient's mother noticed yellowing of his skin, and on the morning of presentation, the patient had 2 episodes of vomiting. He was brought to the emergency department experiencing intermittent right-upper-quadrant pain with tenderness to palpation. His laboratory work included a comprehensive metabolic panel (CMP), serum acetaminophen concentration, a urinalysis, and a complete blood count with differential (CBC). All CMP values were within normal limits except for a slightly elevated serum creatinine of 0.8 mg/dL (0.2–0.7 mg/dL), increased

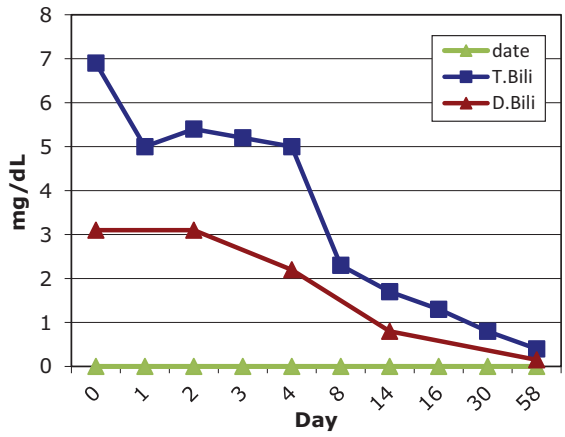
aminotransferase concentrations (Figure 1), as well as increases in total and direct bilirubin concentrations (Figure 2). The serum acetaminophen concentration was less than 10 mcg/mL. The urine sample was noted to be orange, contained a large amount of bilirubin, and trace ketones. The CBC was unremarkable and the white blood cell count upon admission was $10.1{10}^{9}$/L. His home medications, which were not restarted upon admission, included lisdexamfetamine dimesylate (50 mg daily), loratadine (10 mg daily), albuterol as needed, and a 5-day course of azithromycin. The azithromycin was discontinued after the patient had received 4 days of treatment. Past medical history was significant for ADHD and asthma, but negative for hospitalizations and surgeries. The patient reported no illicit drug use and alcohol. Family history was negative for chronic liver disease and hematologic disorders.

Figure 1. Serum aminotransferase concentrations during our patient's clinical course.



ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Figure 2. Serum bilirubin concentrations during our patient's clinical course.

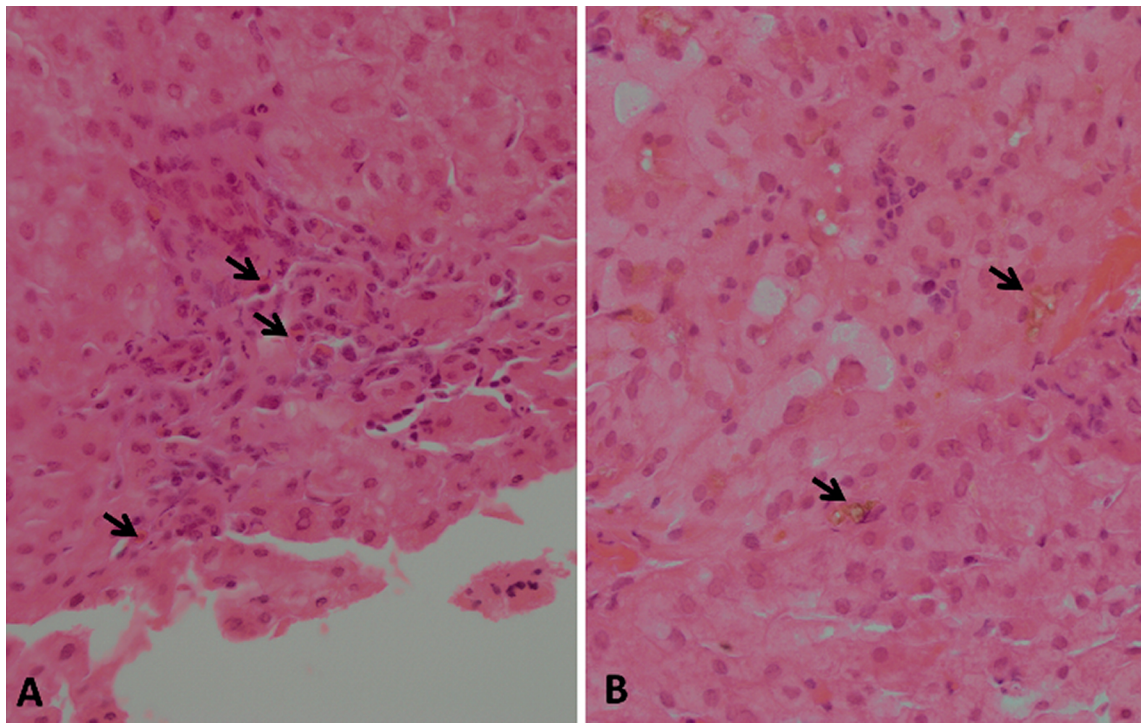


D. Bili, direct bilirubin; T. Bili, total bilirubin.

The patient was admitted to the hospital owing to worsening hepatitis. Numerous tests were conducted including a hepatitis panel, Epstein-Barr virus, cytomegalovirus, anti-liver/kidney microsomal antibody, anti–smooth muscle antibody, ceruloplasmin, alpha-1 antitrypsin, and HIV enzyme-linked immunosorbent assay. The hepatitis blood panel consisted of hepatitis A IgM antibody, hepatitis B surface antigen, hepatitis C core-IgM antibody, and hepatitis C antibody. All test results were negative. A core liver biopsy was performed on day 8 of admission, revealing marked centrilobular cholestasis and mixed portal inflammation, including several eosinophils. No fibrosis was noted and there was no histologic evidence of alpha-1 antitrypsin deficiency. The findings were strongly suggestive of drug/toxin-induced hepatitis (Image A and B). An immunoperoxidase staining for adenovirus was negative and no viral cytopathic changes were identified. The patient received symptomatic treatment during his hospital stay, which included intravenous fluids for rehydration, ibuprofen for pain or fever, hydroxyzine for itching due to cholestasis, polyethylene glycol 3350 for constipation, and acetaminophen for pain after the liver biopsy. The patient was discharged 9 days after admission with improved abdominal pain and was instructed to resume home medications.

The patient resumed lisdexamfetamine dimesylate 4 days after discharge and 15 days after initial symptom onset. The dose of lisdexamfetamine was taken in the morning on the day prior to readmission and the patient awoke that night with multiple episodes of vomiting that were preceded by episodic, diffuse abdominal pain. He also reported loose stools, fatigue, and diffuse abdominal tenderness with palpation. Multiple family members reported having similar symptoms recently including vomiting, diarrhea, and abdominal pain. Of note, the patient's mother was documented to be home with acute gastroenteritis on the day of the patient's initial discharge from the hospital. The patient was readmitted the day after his symptoms reappeared owing to dehydration. Lisdexamfetamine dimesylate was discontinued upon readmission to the hospital, and the patient was treated with intravenous fluids. Laboratory work upon readmission included CMP and CBC with differential, which resulted in several laboratory values being elevated. The elevated laboratory values included serum creatinine, total bilirubin, aminotransferases, and white blood cell count. He was discharged 4 days after admission and returned for follow-up visits at the outpatient clinic. Within 2 months of the initial admission, the patient's serum aminotransferase concentrations normalized.

Image. (A) A portal area shows increased inflammatory infiltrate. Numerous eosinophils are noted (arrows). (B) The hepatocytes showed no significant abnormality. However, centrilobular cholestasis was evident (arrows).



Discussion

Eosinophilic hepatitis is a type of hypereosinophilic syndrome characterized by acute or chronic liver injury and hypereosinophilia. The most common drug causes include tetracyclines or semisynthetic penicillins.[11] However, there have been several reports implicating various drugs as the causative agent, resulting in eosinophilic hepatitis.[12–15] There are case reports of hepatotoxicity in adults and adolescents receiving azithromycin,[5–10] but to our knowledge no reports involving the concurrent use of lisdexamfetamine dimesylate and azithromycin.

To date, there has only been 1 other report of eosinophilic hepatitis in an adolescent taking lisdexamfetamine dimesylate. The previous case report of eosinophilic hepatitis occurred in a 14-year old male who was only taking 1 medication, lisdexamfetamine dimesylate, for the treatment of ADHD.[4] In this case, the patient began experiencing scleral icterus, generalized jaundice, and worsening abdominal pain 3 days before presentation. Additionally, this patient had biochemical markers of hepatic injury, including elevated bilirubin, aspartate aminotransferase, and alanine aminotransferase (see Figures 1 and 2). This was first suspected to be autoimmune hepatitis, and the patient was started on steroids while continuing to receive lisdexamfetamine dimesylate. When the patient did not improve, a liver biopsy was performed that showed eosinophilic hepatitis indicative of drug-induced liver injury. Lisdexamfetamine dimesylate was discontinued in this patient, and within 2 months the patient's blood aminotransferase concentrations had normalized and when a repeated liver biopsy was performed 4 months after the initial biopsy, no abnormalities were found.

Similarly, in our patient other tests were performed to rule out other causes of hepatitis. The azithromycin was stopped because the patient had completed 4 of 5 days of antibiotics, and owing to the potential for the azithromycin contributing to the current presenting symptoms, the physician decided that the risk outweighed the benefit from completing the last day of therapy. On reinitiation of lisdexamfetamine dimesylate 4 days after hospital discharge, the patient presented to the hospital again the following day with similar symptoms. Concurrently, other family members were exhibiting gastrointestinal symptoms, but because it could not be determined if the lisdexamfetamine dimesylate was also a potential contributing agent, the decision to stop the medication was made. The Naranjo Algorithm score for the probability of an adverse drug reaction with lisdexamfetamine was calculated as 7 owing to the reemergence of symptoms upon the patient restarting the medication (see Table 1).[16] A total score

Table 1. Naranjo Score for Probability of an Adverse Drug Reaction[16]

Question	Response	Score
Are there previous conclusive reports on this reaction?	Yes	+1
Did the adverse event appear after the suspected drug was given?	Yes	+2
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	Yes	+1
Did the adverse reaction appear when the drug was readministered?	Yes	+2
Are there alternative causes that could have caused the reaction?	Do not know	0
Did the reaction occur when a placebo was given?	Do not know	0
Was the drug detected in any body fluid in toxic concentrations?	No	0
Was the reaction more severe when the dose increased, or less severe when the dose was decreased?	Do not know	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	No	0
Was the adverse event confirmed by objective evidence?	Yes	+1
	Total score:	7

between 5 and 8 on the Naranjo Algorithm indicates a probable link between the adverse reaction and the offending medication.

Conclusions

With a score of 7 from the Naranjo Algorithm for determining adverse drug reactions, the case report described above represents a probable link between lisdexamfetamine dimesylate and eosinophilic hepatitis. The adverse drug reaction was confirmed with clinical evidence, appeared after starting the drug, improved upon its discontinuation, and reappeared after the drug was started again, indicating that this agent likely played a role in the adverse event. Whether this reaction was due to the combination of these agents or either agent alone, or whether there were additional external mitigating factors was unclear. Owing to the prevalence of ADHD and the use of lisdexamfetamine dimesylate for this condition and the use of azithromycin for acute respiratory infections in children and adolescents, clinicians should be made aware of the potential for liver injury with these agents.

Article Information

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Ethical Approval and Informed Consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and have been approved by the appropriate committees at our institution. However, given the nature of this study, informed consent was not required by our institution.

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References

1. Bloom B, Jones LI, Freeman G. Summary health statistics for U.S. children: National Health Interview Survey, 2012. *Vital Health Stat 10*. 2013;(258):1–81.
2. Subcommittee on Attention-Deficit/Hyperactivity Disorder; Steering Committee on Quality Improvement and Management; Wolraich M, Brown L, Brown RT, et al. ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics*. 2011;128(5): 1007–1022.

3. Biederman J, Krishnan S, Zhang Y, et al. Efficacy and tolerability of lisdexamfetamine dimesylate (NRP-104) in children with attention-deficit/hyperactivity disorder: a phase III, multicenter, randomized, double-blind, forced-dose, parallel-group study. *Clin Ther*. 2007;29(3):450–463.
4. Hood B, Nowicki MJ. Eosinophilic hepatitis in an adolescent during lisdexamfetamine dimesylate treatment for ADHD. *Pediatrics*. 2010;125(6):e1510–e1513.
5. Principi N, Esposito S. Comparative tolerability of erythromycin and new macrolide antibacterials in paediatric patients. *Drug Saf*. 1999;20(1):25–41.
6. Hopkins S. Clinical toleration and safety of azithromycin. *Am J Med*. 1991;91(3A):40S–45S.
7. Chandrupatla S, Demetris AJ, Rabinovitz M. Azithromycin-induced intrahepatic cholestasis. *Dig Dis Sci*. 2002;47(10):2186–2188.
8. Cascaval RI, Lancaster DJ. Hypersensitivity syndrome associated with azithromycin. *Am J Med*. 2001;110(4): 330-331.
9. Longo G, Valenti C, Gandini G, et al. Azithromycin-induced intrahepatic cholestasis. *Am J Med*. 1997;102(2):217–218.
10. Baciewicz AM, Al-Nimr A, Whelan P. Azithromycin-induced hepatotoxicity. *Am J Med*. 2005;118(12):1438–1439.
11. Nutman TB. Evaluation and differential diagnosis of marked, persistent eosinophilia. *Immunol Allergy Clin North Am*. 2007;27(3):529–549.
12. Cleau D, Jobard JM, Alves T, et al. Cholestatic hepatitis induced by amoxicillin-clavulanic acid combination: a case and review of the literature. *Gastroenterol Clin Biol*.1990;14(12):1007–1009.
13. Fix OK, Peters MG, Davern TJ. Eosinophilic hepatitis caused by lamotrigine. *Clin Gastroenterol Hepatol*. 2006;4(4):xxvi.
14. Owens RC Jr, Ambrose PG. Antimicrobial safety: focus on fluoroquinolones. *Clin Infect Dis*. 2005;41(suppl 2): S144–S157.
15. Pompili M, Basso M, Grieco A, et al. Recurrent acute hepatitis associated with use of cetirizine. *Ann Pharmacother*.2004;38(11):1844–1847.
16. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239-245.