Case Report

Acute liver injury due to atomoxetine – A potential lethal outcome of a ubiquitous drug

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ABSTRACT

Atomoxetine is a selective norepinephrine reuptake inhibitor used for the treatment of attention-deficit hyperactivity disorder (ADHD). It's ubiquitous these days and considered a very safe drug in pediatric practice. However, drug-induced liver injury is a rare but potentially lethal side effect of the drug. We report a 7-year-old boy, a case of ADHD on atomoxetine, who presented with acute liver injury. The boy was initially unresponsive to the treatment but his condition drastically improved after withdrawal of atomoxetine. A derangement of liver function due to atomoxetine often responds only to complete stoppage of the drug.

Key words: Atomoxetine, attention-deficit hyperactivity disorder, drug-induced liver injury

Drug-induced liver injury (DILI) in children is most commonly linked to the use of acetaminophen, antibiotics, or anticonvulsants and discontinuation of the offending agent often resolves the injury [1]. Atomoxetine, a non-stimulant approved for the treatment of attention-deficit hyperactivity disorder (ADHD), has a warning for occurrence of DILI due to the case reports after its United States Food and Drug Administration (USFDA) approval [2]. DILI due to atomoxetine is primarily an idiosyncratic reaction, but hypersensitivity has also been reported [3]. With atomoxetine being ubiquitous these days, it is important to sensitize the primary care pediatrician about this potentially lethal side effect of the drug. We report a 7-year-old boy, a case of ADHD on atomoxetine, who presented with acute liver injury.

CASE REPORT

A 7-year-old boy, weighing 34 kg, a case of ADHD, was admitted to the intensive care unit with complaints of jaundice, pain abdomen, and non-bilious vomiting of 4 days duration. He was on atomoxetine 20 mg twice daily for ADHD for the past 6 months. On examination, he was dehydrated with pulse – 110/min, blood pressure – 98/70 mmHg, respiratory rate – 28/min, oxygen saturation – 97%, and had icterus. Liver was enlarged 3 cm below right costal margin with a span of 10 cm, soft, and minimally tender. There was no evidence of hepatic encephalopathy. Other system examination was essentially normal.

Laboratory investigations revealed a normal hemogram with raised liver enzymes, aspartate aminotransferase (AST) – 400 IU/L, alanine aminotransaminase (ALT) – 980 IU/L, alkaline phosphatase – 302 IU/L, total serum bilirubin (TSB) – 6.8 mg/dl (conjugated – 6 mg/dl, unconjugated – 0.8 mg/dl), total serum protein – 6.8 g/dl (albumin – 3.8 g/dl), and international normalized ratio (INR) – 1.28. Hepatic serology was negative for hepatotropic viruses. Ultrasonography was suggestive of hepatosplenomegaly with minimal ascites and mild bilateral pleural effusion.

Immediate intravenous fluid replenishment was done and care for hepatitis was initiated in the form of injectable (Inj) N-acetyl cysteine, Inj Vitamin K, and syrup lactulose. As a part of ongoing therapy, atomoxetine was continued. There was an increasing trend of liver enzymes noted in subsequent days (AST – 890 IU/L, ALT – 1342 IU/L, and INR – 1.8) with ALT >AST and the child was noted to be irritable. At this point of time, atomoxetine was withheld, in view of suspected drug-induced hepatitis. Drug levels of atomoxetine could not be afforded by the parents.

Child responded well after stopping atomoxetine. Repeat investigations done on day 10 of admission revealed fall in TSB (2.7 mg/dl) and liver enzymes (AST/ALT – 250/572 IU/L, normalized INR) and he was finally discharged after 21 days with near normal laboratory parameters. After recovery, atomoxetine was replaced with methylphenidate which was gradually increased to a maintenance dose of 20 mg twice daily. He was

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asymptomatic during the follow-up evaluation over the next 2 months.

DISCUSSION

DILI in children is not as common as adults. A 2010 case analysis on adverse drug reactions (ADRs) in children found that only 1% of ADRs were attributed to hepatic events [4]. However, DILI comprises around 20% of cases of acute liver failure in children [5]. The same percentage rises to 52% when the entire population is considered [6]. DILI in children is most commonly linked to the use of acetaminophen, antibiotics, or anticonvulsants and discontinuation of the offending agent often resolves the injury [1].

The 2019 American Academy of Pediatrics guidelines currently recommend atomoxetine as a second-line treatment for ADHD behind stimulants [7]. Atomoxetine, a selective norepinephrine reuptake inhibitor, was the first non-stimulant approved for ADHD in children (>6 years) and adults. The medication is generally considered both safe and effective and is associated with only a few adverse effects. However, it comes with a black box warning of suicidal ideation in children and teenagers. The other side effects are hepatic damage, cardiovascular issues such as increased blood pressure and heart rate, sudden cardiac death in children with underlying heart defects, dyspepsia, nausea, vomiting, fatigue, rash, decreased appetite, and weight loss [2]. The USFDA included a warning for hepatotoxicity in 2004 after case reports emerged about ADRs in children on atomoxetine for ADHD. The DILIN Prospective Study in 2011 found that atomoxetine was the most common central nervous system drug involved in DILI in children [8].

Although idiosyncrasy is the reason behind DILI due to atomoxetine, there are case reports of autoimmune hepatitis after atomoxetine use [3]. Idiosyncrasy is dependent on factors such as age, genetic makeup, nutritional conditions, concomitant medications, and underlying diseases [9]. In most cases, the affected children begin to show symptoms within weeks of initiating therapy. Symptom onset in case reports ranged from 1 month to 23 months from drug initiation [10]. This variability in timing of symptom onset highlights the possible need for routine monitoring of liver function of patients on atomoxetine starting within the 1st month of treatment. In one case, a 14-year-old male taking atomoxetine developed acute liver injury within 3–4 months of instituting therapy and recovered after it was stopped. When rechallenged with atomoxetine, he again developed liver failure within 5 weeks. The patient's liver function tests normalized only after complete discontinuation of the drug [10]. Hence, once diagnosed to be having atomoxetine-induced liver injury, the drug should not be restarted and a change of drug class seems prudent.

There is currently no diagnostic tool to diagnose DILI in children and we have to rely on liver enzymes as a guide for the same [9]. Biomarkers currently in research include glutamate dehydrogenase, keratin 18, sorbitol dehydrogenase, glutathione S-transferase, bile acids, cytochrome P450, osteopontin, high mobility group box-1 protein, fatty acid-binding protein 1, cadherin 5, and genetic testing [11]. The liver toxicity knowledge base by the USFDA comprises roughly 1000 drugs and provides data on drugs for DILI studies and can be accessed for research [12]. Hence, till the time a definitive biomarker can be established clinical suspicion remains the key especially if drug levels are not available. Even if drug levels could be done, further research is required to define a level of toxicity for drugs.

CONCLUSION

Stimulants are considered the first-line therapy for ADHD and have superior efficacy over non-stimulant choices that are USFDA approved for ADHD. Considering the variability of DILI symptom onset, routine monitoring of LFTs is recommended during therapy, especially within the first 30 days of treatment. If a patient presents with symptoms of hepatotoxicity, or if an increase in liver enzymes is observed subsequent to atomoxetine use, prompt discontinuation of atomoxetine is recommended and the drug should not be restarted.

REFERENCES

1. Murray KF, Hadzic N, Wirth S, Bassett M, Kelly D. Drug-related hepatotoxicity and acute liver failure. J Pediatr Gastroenterol Nutr 2008;47:395-405.
2. Strattera (Atomoxetine Hydrochloride) Capsules Label, FDA; 2020. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021411s035lbl.pdf. [Last accessed on 2020 Jul 16].
3. Lim JR, Faught PR, Chalasani NP. Severe liver injury after initiating therapy with atomoxetine in two children. J Pediatr 2006;148:831-4.
4. Ferrajolo C, Capuano A, Verhamme KM, Schuemie M, Rossi F, Stricker BH, *et al*. Drug-induced hepatic injury in children: A case/non-case study of suspected adverse drug reactions in VigiBase. Br J Clin Pharmacol 2010;70:721-8.
5. Amin MD, Harpavat S, Leung DH. Drug-induced liver injury in children. Curr Opin Pediatr 2015;27:625-33.
6. Lee WM. Acute liver failure in the United States. Semin Liver Dis 2003;23:217-26.
7. Wolraich ML, Hagan JF, Allan C, Chan E, Davison D, Earls M, *et al*. Clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Pediatrics 2019;144:e20192528.
8. Molleston JP, Fontana RJ, Lopez MJ, Kleiner DE, Gu J, Chalasani N, *et al*. Characteristics of idiosyncratic drug-induced liver injury in children: Results from the DILIN prospective study. J Pediatr Gastroenterol Nutr 2011;53:182-9.
9. Shi Q, Yang X, Greenhaw JJ, Salminen AT, Russotti GM, SalminenWF. Drug-induced liver injury in children: Clinical observations, animal models, and regulatory status. Int J Toxicol 2017;36:365-79.
10. Stojanovski SD, Casavant MJ, Mousa HM, Baker P, Nahata MC. Atomoxetineinduced hepatitis in a child. Clin Toxicol 2007;45:51-5.
11. Fu S, Wu D, Jiang W, Li J, Long J, Jia C, *et al*. Molecular biomarkers in drug-induced liver injury: Challenges and future perspectives. Front Pharmacol 2020;10:1667.
12. Thakkar S, Chen M, Fang H, Liu Z, Roberts R, Tong W. The liver toxicity knowledge base (LKTB) and drug-induced liver injury (DILI) classification for assessment of human liver injury. Expert Rev Gastroenterol Hepatol 2018;12:31-8.

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