JPPT | Case Report

# Liver, Renal, and Cardiovascular Failure After Unintentional Overdose of Tizanidine in a 2-Year-Old Child

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Tizanidine is a central alpha-2 adrenergic receptor agonist indicated for the treatment of spasticity in adults; however, its use in the pediatric population is considered off-label. In adults, the dose is gradually titrated until the desired reduction in muscle tone is achieved. Hypotension is a frequent adverse effect, but impaired liver function is not characteristic of alpha-2 adrenergic agonist overdose. We report a 2-year-old male affected with spastic quadriplegia (treated with clonazepam and tizanidine) and dysphagia (he was fed by nasogastric tube). Two days before admission caregivers ran out of clonazepam so they increased the tizanidine dose from 0.15 mg/kg/day to 1.6 mg/kg/day. Simultaneously his nasogastric tube fell out; therefore, he was unable to maintain proper oral nutrition and hydration. He presented to the emergency department hemodynamically unstable, with impaired consciousness and signs of severe dehydration. Blood tests revealed hepatic dysfunction without cholestasis and renal dysfunction. He was transferred to the pediatric intensive care unit. Treatment was mainly supportive, apart from tizanidine discontinuation. Metabolic and infectious diseases were ruled out so he was finally diagnosed as having liver, renal, and cardiovascular failure after tizanidine overdose, worsened by dehydration. His clinical status improved, and after 3 weeks he was discharged from the hospital, receiving clonidine instead of tizanidine to treat spasticity. Tizanidine overdose can result in serious complications that can be worsened because of patient comorbidities.

**KEYWORDS** drug overdose; liver failure, acute; muscle spasticity; tizanidine; toxicology

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## Introduction

Tizanidine is a central alpha-2 adrenergic receptor agonist indicated for the treatment of spasticity. The effect of this drug is attributed to the increase in the pre-synaptic inhibition of motor neurons.[1] The use of tizanidine in the pediatric population is considered off-label. In adults suffering from spasticity, the dose must be adjusted progressively; it should not exceed 36 mg per day, and the optimal therapeutic response is usually achieved with 12 to 24 mg per day divided into 3 or 4 doses administered at regular intervals.[2] In studies[3-7] including children with cerebral palsy tizanidine has been used at different doses with a good safety profile and therapeutic efficacy (Table).

At the usual doses, the most frequent adverse effects reported on the drug label are hypotension, bradycardia, drowsiness, dizziness, dryness of the mouth, fatigue, and slight and transient increases in transaminase concentrations.[2] Each adverse effect has been described with a frequency that ranges from 1% to 10% in treated patients. Because of alpha-2 agonist effects, hypotension is a frequent and dose-dependent adverse effect.[8] On the other hand, the frequency of hepatitis or liver failure is unknown, and published cases are very scarce.[2]

The most common adverse effects in the pediatric population are psychiatric and neurological symptoms such as enuresis, insomnia, aggression, anxiety, somnolence, and headache. Few cases of mild and transient increase in transaminase concentrations have been reported,[9] but they resolved spontaneously.

In children, unintentional overdose of alpha-2 agonists like clonidine, guanfacine, or tizanidine can cause neurological symptoms, respiratory depression, hypotension, and bradycardia, but impaired liver function is not characteristic of alpha-2 agonist overdose.[10] We report a case of unintentional tizanidine overdose in a 2-year-old male with liver, renal, and cardiovascular failure. Written informed consent for publication of this case was obtained from his parents.

## Case Report

We present a 2-year-old Caucasian male diagnosed with bilateral periventricular nodular heterotopia, spastic quadriplegia, neurodevelopment delay, and a suspected interstitial pneumopathy without oxygen requirements. At home he received clonazepam (0.3–0.4 mg twice daily) and tizanidine (0.15 mg/kg/day, 2 mg/day, for 1 year) to treat spasticity and montelukast (4 mg/day) to prevent recurrent wheezing. He was fed by nasogastric tube secondary to dysphagia, so medica-

**Table.** Reports on the Optimal Dosage of Tizanidine to Treat Spasticity or Dysfunctional Voiding in the Pediatric Population

| Reference | Design | Age | Tizanidine Dosage |
|---|---|---|---|
| Vasquez-Briceno[3] | Randomized clinical trial; tizanidine (n = 19) or placebo (n = 30) | All ages | 0.05 mg/kg/day* |
| Dai[4] | Retrospective; tizanidine (n = 33); baclofen (n = 31) | >2 yr | 0.3–0.5 mg/kg/day, divided four times daily* |
| Brin[5] | Case series (n = 30) | All ages | 1 mg for children <10 yr and 2 mg for children ≥10 yr, divided three times daily* |
| El-Hefnawy[6] | Randomized open-labeled trial in dysfunctional voiding; tizanidine (n = 20); doxazosin (n = 20) | 4–12 yr | 2 mg/day before bedtime† |
| Palazón García[7] | Retrospective analysis of patients treated according to a protocol (n = 45) | 18 mo–7 yr<br>7–12 yr<br>>12 yr | 1 mg/day as a single dose*<br>2 mg/day divided twice daily*<br>4 mg/day divided twice daily* |

* Treatment of Spasticity
† Dysfunctional Voiding

tions were also administered via this route. A complete blood test with liver and renal function 1 month prior to the hospital admission was within normal limits.

Two days before admission, the nasogastric feeding tube fell out and it was not replaced. As a result, the oral route was then used to administer drugs (with the same dosage form as used via the nasogastric feeding tube), food, and liquids; he experienced some difficulty with this because of his dysphagia. On the last 2 days prior to the admission, the patient's parents also ran out of clonazepam, and they decided to increase the dose of tizanidine up to 1.6 mg/kg/day (4 mg every 4 hours; patient weight = 15 kg) to improve spasticity.

The patient presented to the emergency department with altered mental status, respiratory distress, and fever. The provider's physical examination revealed an ill-looking child with decreased level of consciousness, hypotonia, and a Glasgow coma score of 7 points (eye = 3, verbal = 2, motor = 2). He had clinical signs of dehydration, with sunken eyes and dry mucous membranes. Respiratory examination revealed normal breath sounds, with oxygen saturation by pulse oximetry of 100%. His heart sounds were normal, capillary refill was >2 seconds, blood pressure was 65/33 mm Hg, and cardiac rate was 100 beats/min. Abdomen palpation was normal.

Laboratory tests at diagnosis showed the following: metabolic acidosis with high lactic acid concentrations (pH 7.11, lactic acid 4 mmol/L); renal dysfunction (urea 152 mg/dL, serum creatinine 3.28 mg/dL, uric acid 20.1 mg/dL, glomerular filtration rate 10.5 mL/min/1.73 $m^2$); hepatic dysfunction without cholestasis (aspartate transaminase 2691 units/L, alanine transaminase 2261 units/L, prothrombin time international normalized ratio 2.08, fibrinogen 1.4 g/L, albumin 3.7 g/dL); sodium 155 mmol/L; chloride 119 mmol/L; phosphate 9.6 mg/dL; and magnesium 2.6 mg/dL. Procalcitonin was elevated (153 ng/dL), but C-reactive protein was normal (0.5 mg/dL). The urine output was low, with an elevated urine osmolarity of 327 mOsm/kg after initial intravenous fluid resuscitation.

In the emergency department he received fluid resuscitation with 30 mL/kg of 0.9% normal saline and 40 mL/kg of a solution containing 0.16 mmol/mL of sodium bicarbonate. Hypotension persisted despite initial fluid resuscitation, with a blood pressure of 49/36 mm Hg and a heart rate of 109 beats/min. He was transferred to the pediatric intensive care unit to initiate vasoactive drugs. An adverse effect of tizanidine overdose was suspected, and the offending agent was discontinued. He required vasoactive drug treatment with noradrenaline and dobutamine for 4 days. Echocardiogram was normal. Kidney function, urine output, dyselectrolytemia, and metabolic acidosis improved within 24 hours after intravenous fluid resuscitation.

Hepatic function worsened during the first days, with a maximum aspartate transaminase and alanine transaminase values of 18,372 units/L and 12,723 units/L respectively, and a minimum fibrinogen of 1.3 g/dL and an albumin of 2.8 g/dL. At admission, the indocyanine green clearance test, a non-invasive dynamic liver function test, showed a clearance of 11%/min, indicating hepatic dysfunction.[11] He received vitamin K and antithrombin. A metabolic disorder was suspected initially; because of this he received medical treatment until it was ruled out. Hepatic function improved within 5 days with medical treatment. He received cefotaxime as empiric therapy until infection was ruled out; the dose was adjusted according to glomerular filtration rate.

The patient was discharged to home after 3 weeks; blood tests before discharge showed normal blood cell count, normal hepatic and renal function, and no

alteration in acid-base balance and electrolytes.

None of the studies performed was conclusive in determining the etiology of the disease. Infectious diseases studies were negative; they included blood and stool cultures, nasal swab and serologies for the following: hepatitis viruses; Epstein Barr virus; cytomegalovirus; enterovirus; herpesvirus 1, 2, and 6; human immunodeficiency virus; *Bartonella henselae* and *Bartonella quintana*; *Coxiella burnetii*; *Treponema pallidum*; and *Leptospira* species. The initial metabolic study showed a mitochondrial dysfunction that resolved with the improvement of hepatic function.

No specific treatment was provided; rather, only supportive therapy was given. Tizanidine was discontinued and the child made a complete recovery. Tizanidine was stopped at admission and at discharge; it was substituted with clonidine to treat spasticity. The rest of the treatment remains unchanged to date. The patient has routinely presented with normal blood pressure and hepatic and renal function at follow-up evaluations.

## Discussion

We present a 2-year-old child with cardiovascular, renal, and hepatic failure that can be attributed to tizanidine overdose exacerbated by dehydration. Tizanidine can cause liver damage at usual doses, leading to mild and asymptomatic elevation of transaminase concentrations or jaundice, although few cases of clinical hepatitis have been reported.[12-14]

Increase of transaminase concentrations more than 3 times the upper limit of the normal range—or 2 times if baseline concentrations were already high—can affect up to 5% of treated patients.[15] The incidence of clinical hepatitis or liver failure is unknown. In symptomatic cases, jaundice is common and usually appears 2 to 14 weeks after treatment initiation and resolves 1 to 2 months after discontinuation of the drug. The pathogenesis of tizanidine-induced hepatic injury is not known. No common features of immunoallergy or auto-immunity are seen in these patients. The injury is thought to represent a hypersensitivity or idiosyncratic reaction because hepatitis has been described in therapeutic range doses. The pattern of liver injury is usually mixed or cholestatic, although some cases of hepatocellular pattern have been reported.[16]

Clinicians ought to perform blood liver tests monthly during the first 4 months of treatment with tizanidine if the daily dose exceeds 12 mg or at any time during the treatment if nausea, anorexia, fatigue, or other symptoms suggesting hepatic impairment appear.[2] Treatment should be discontinued if transaminase concentrations are persistently above 3 times the upper limit of the normal range.[2] In the case reported, while receiving the therapeutic dose of tizanidine the patient's routine hepatic tests were normal, but after tizanidine overdose he presented with non-cholestatic liver failure. Even though cholestasis was not present, hepatotoxicity secondary to tizanidine overdose was suspected and the treatment was discontinued.

Apart from liver involvement, cardiovascular symptoms appeared, with hypotension and abnormally low heart rate according to the blood pressure. Hypotension due to alpha-2 agonist effects is frequent and dose-related.[8] A single dose of 8 mg of tizanidine causes hypotension in 2 out of 3 cases and reduces up to 20% systolic or diastolic blood pressure within 1 hour.[15] Occasionally, hypotension is associated with bradycardia. Symptoms like dizziness, syncope, and rarely circulatory collapse are secondary to tizanidine's cardiovascular effects. The risk can be reduced if the dose is carefully titrated and if clinicians are aware of hypotension symptoms. Tizanidine should be used with special caution in patients receiving antihypertensive drugs.[2,10]

Renal dysfunction has not been reported as an adverse effect of tizanidine. However, if the filtration rate is <25 mL/min, the dose must be titrated carefully because plasma concentrations can be up to 6 times higher than those in patients with normal renal function.[2]

We hypothesize that in this patient, liver failure can be explained as a result of hepatic ischemia caused by overdose-related hypotension and dehydration secondary to decrease in oral intake. Additionally, tizanidine direct liver toxicity can play a role in worsening liver function. Acute renal injury and low glomerular filtration rate are thought to be secondary to hypotension and dehydration because renal dysfunction, electrolytes, and urine output quickly improved after rehydration and hemodynamic stabilization. Decreased glomerular filtration ought to increase toxic exposition to tizanidine, worsening hepatic and cardiovascular symptoms during the first days. Liver function started to improve at the fifth day of admission, after drug withdrawal and once the hemodynamic and hydration status normalized.

At admission, the child was receiving montelukast, a drug described[17] as causing mild hepatotoxicity, usually with mixed pattern. Hypotension is not characteristic with montelukast, and hepatic and cardiovascular symptoms improved even though the drug was not discontinued.

We report a severe adverse effect of tizanidine overdose in a child. To the best of our knowledge, this is the first report describing a non-cholestatic hepatic failure following tizanidine overdose. Nonetheless, other factors, such as dehydration and hypotension, could also have contributed to the hepatic injury.

Tizanidine use in the pediatric population is considered off label. No clinical trials have been performed in children, so daily optimal dosing should be in accordance with previous cases reported in the literature and after considering patient comorbidities because they can increase the probability of adverse effects. It is also important to instruct caregivers not to alter the dose without first contacting their health care provider. Therefore, a careful dose titration and follow-up is recommended in children receiving tizanidine.

## 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. Given the nature of this report, ethics committee review was not required; however, we did obtain permission from the patient's parents to publish this case report.

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## References

1. Curtis DR, Leah JD, Peet MJ. Spinal interneurone depression by DS103-282. *Br J Pharmacol*. 1983;79(1):9–11.
2. Spanish Agency of Medicines and Medical Devices. Sirdalud® product information. Madrid, Spain: Spanish Agency of Medicines and Medical Devices; 2020. Accessed June 5, 2020. https://cima.aemps.es/cima/pdfs/es/ft/58313/FT_58313.html.pdf
3. Vasquez-Briceno A, Arellano-Saldaña ME, León-Hernández SR, Morales-Osorio MG. The usefulness of tizanidine. A one-year follow-up of the treatment of spasticity in infantile cerebral palsy. *Rev Neurol*. 2006;43(3):132–136.
4. Dai AI, Aksoy SN, Demiryürek AT. Comparison of efficacy and side effects of oral baclofen versus tizanidine therapy with adjuvant botulinum toxin type A in children with cerebral palsy and spastic equinus foot deformity. *J Child Neurol*. 2016;31(2):184–189.
5. Brin IL, Kurenkov AL, Gotlib V. The use of sirdalud in cerebral palsy in children. *Zh Nevrol Psikhiatr S Korsakova*. 1999;99(10):30–33.
6. El-Hefnawy AS, Helmy T, El-Assmy MM, et al. Doxazosin versus tizanidine for treatment of dysfunctional voiding in children: a prospective randomized open-labeled trial. *Urology*. 2012;79(2):428–433.
7. Palazón García R, Benavente Valdepeñas A, Arroyo Riaño O. Protocol for tizanidine use in infantile cerebral palsy. *Ann Pediatr (Barc)*. 2008;68(5):511–515.
8. Miettinen TJ, Kanto JH, Salonen MA, Scheinin M. The sedative and sympatholytic effects of oral tizanidine in healthy volunteers. *Anesth Analg*. 1996;82(4):817–820.
9. Henney HR III, Chez M. Pediatric safety of tizanidine: clinical adverse event database and retrospective chart assessment. *Pediatr Drugs*. 2009;11(6):397–406.
10. Wang GS, Le Lait MC, Heard K. Unintentional pediatric exposures to central alpha-2 agonists reported to the National Poison Data System. *J Pediatr*. 2014;164(1):149–152.
11. Quintero J, Miserachs M, Ortega J, et al. Indocyanine green plasma disappearance rate: a new tool for the classification of paediatric patients with acute liver failure. *Liver* Int. 2014;34(5):689–694.
12. De Graaf EM, Oosterveld M, Tjabbes T, Stricker BH. A case of tizanidine-induced hepatic injury. *J Hepatol*. 1996;25(5):772–773.
13. Afonso Pérez E, Pego Reigosa R, Lancho Seco A, Brañas Fernández F. Tizanidine-induced toxic hepatitis. *Med Clin (Barc)*. 1999;112(12):478–479.
14. Gill D, Allam F, Boyle J. Importance of medication reconciliation: tizanidine-induced hepatitis. *Am J Ther*. 2017;24(5):e623–e624. doi:10.1097/MJT.0000000000000497
15. McEvoy GK, Snow EK, Miller J, Kester L, eds. *AHFS Drug Information 2017*. Bethesda, MD: American Society of Health-System Pharmacists; 2017.
16. National Institute of Diabetes and Kidney Diseases. *LiverTox. Clinical and research information on drug-induced liver injury*. Bethesda, MD: National Institute of Diabetes and Kidney Diseases. 2012. Accessed June 5, 2020. https://livertox.nih.gov/
17. National Institute of Diabetes and Digestive and Kidney Diseases. Montelukast. In: *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury*. Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases. 2012. Accessed August 14, 2020. https://www.ncbi.nlm.nih.gov/books/NBK548264/