Pediatric Tizanidine Toxicity Reversed with Naloxone a case report

doaa emad emad (dr.doaa.bader@gmail.com)
: Royal Commission for Jubail and Yanbu
ahmad adam
: Royal Commission for Jubail and Yanbu
mohamed shaban
Royal Commission for Yanbu Medical Center: Royal Commission Medical Center
bader alyahya
King Saud University Medical City

Case report

Keywords: tizanidine, naloxone, toxicology, pediatric

Posted Date: June 9th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-577939/v1

Abstract

Background

Tizanidine, an α-2 adrenoreceptor agonist, is widely prescribed for the management of spasticity in adults. Case reports for pediatric tizanidine overdose are limited. Here, we report a case of pediatric tizanidine toxicity that was reversed with naloxone.

Case presentation

A three year-old male presented to the emergency department with lethargy, bradycardia, and bradypnea after accidental ingestion of multiple tizanidine tablets. Improvements in the level of consciousness, respiratory and heart rates were observed post intravenous naloxone administration of 0.05 and 0.1 mg/kg respectively.

Conclusions

This case report provides additional epidemiologic data on childhood tizanidine poisoning and further documentation on the use of naloxone as a viable antidote for centrally acting α-2 receptor agonists.

Background

Tizanidine hydrochloride is a centrally acting imidazoline derivative with α-2 adrenoreceptor agonist properties. It is widely prescribed for the management of spasticity-related conditions including multiple sclerosis, cerebral palsy, spinal cord injuries, and regional musculoskeletal pain syndromes [1–3].

There is paucity of case reports for tizanidine overdose or toxicity especially in children. Here, we describe a case of pediatric tizanidine toxicity that was reversed with naloxone.

Case Presentation

A previously healthy 3-year-old male (14 kg) presented to the emergency department with an hour history of lethargy, decreased level of consciousness, and difficulty breathing. He was found near scattered tablets of tizanidine (4 mg each) about an hour prior to presentation and had become pale and drowsy over the ensuing 30 minutes warranting emergency care. The exact amount of ingested tablets was unknown but his parents indicated 4–5 missing tablets.

Upon examination, the toddler appeared ill and lethargic. His pupils were constricted at 2mm and his level of consciousness was reduced with a Glasgow Coma Scale (GCS) score of 10/15. His temperature was 36.2^{o}C, blood pressure was 93/44 mm Hg, heart rate was 56/min (reference range 80–120/min), respiratory rate was depressed to 10/min (reference range 20–30/min), and oxygen saturation was 99% in room air. Serum glucose concentration was 133 mg/dl. Breathing and heart sounds were normal. There was no murmur. The abdominal exam was normal. Electrocardiogram showed sinus bradycardia. His

venous blood gas showed (pH 7.32, Pco2 45.5, HCO_3 23.6). Renal function test, liver function test and urine analysis, were all within the normal ranges.

The child was admitted into the pediatric intensive care unit where he was connected to a non-invasive mechanical ventilation machine (BiPAP - PEEP 5, PIP 10 rate 20, FIO^2 30) for approximately 90 minutes. The child became increasingly sleepy and miosis worsened to “pin-point”, the respiratory rate was 7 breaths per minute prompting a trial of naloxone of 0.05 mg/kg intravenously, which resulted in spontaneous regaining of consciousness 60 seconds post administration and to which the child removed the BiPAP mask. His heart and respiratory rates were increased to 90/min and 16/min respectively.

However, 40 minutes after the initial dose of naloxone, both heart and respiratory rates depressed to 60/min and 10/min respectively. A second dose of naloxone of 0.1 mg/kg was administered intravenously to which the child became fully alert (GCS score of 15) 60 seconds post administration. Both heart and respiratory rates were increased to 90/min and 12/min respectively. His pupils increased to 4 mm and were equally reactive.

The child remained in the pediatric intensive care unit for 6 hours and was then transferred to the pediatric ward for observation for further 12 hours. He was hence discharged without complication. His blood pressure and heart rate at the time of discharge were 90/94 mm and 125/min respectively. There were no subsequent hospital visits related to this event four months post discharge.

Discussion

Tizanidine hydrochloride is a centrally acting imidazoline derivative with α-2 adrenoreceptor agonist properties. Physiologically, tizanidine activates presynaptic α-2 adrenoreceptors within the central nervous system thereby inhibiting the release of excitatory neurotransmitter norepinephrine via negative feedback mechanism[7].

Common side effects of tizanidine include somnolence, dry mouth, asthenia, and dizziness. Reports of overdose often describe hypotension and bradycardia[1,4]. Currently, there is no known antidote for tizanidine intoxication and treatment options are limited to endotracheal intubation as well as administration of intravenous fluids and vasopressors as necessary[5,6].

Central α-2 receptor agonists toxicity has been well-documented in numerous case series and case reports[8,9], with effects ranging from central nervous system depression, bradycardia, hypotension, miosis, and hypothermia. They have also been suggested as a “one pill can kill” drug when adult doses are unintentionally ingested by children[10].

Retrospective investigations of unintentional pediatric exposures to central α-2 receptor agonists have indicated a significant increase of tizanidine intoxication over an 11-year period[8]. Treatment of these exposures varied between atropine, IV fluids, naloxone, and vasopressors, illustrating that one specific therapy was not highly effective.

Acute intoxication with central α-2 receptor agonists presents a recognizable clinical entity with signs and symptoms that largely resemble opiate intoxication, prompting the use naloxone hydrochloride as a reversal agent for this type of poisoning. The therapeutic mechanism of naloxone is thought to work by competing with endogenous opioids leading to an increase in sympathetic tone[5].

There have been multiple case reports over the past decades describing naloxone as a viable agent for acute α-2 receptor agonists toxicity. For example, a single 0.1 mg dose of naloxone was described to resolve tetrahydrozoline toxicity in a 36-month-old toddler within 30 seconds of administration[11]. A similar case also described one-time 0.1 mg dose of naloxone resolved symptoms of tetrahydrozoline toxicity in a 25-day-old infant[12].

Successful naloxone therapy was also documented in unintentional pediatric clonidine and guanfacine exposures[13–15]. However, it should be noted that the use of naloxone remains controversial with multiple reports describing inefficacy[7,16].

Despite the abundant documentation regarding the use of naloxone for pediatric clonidine, brimonidine, guanfacine and tetrahydrozoline poisonings, there are limited reports for its use in pediatric tizanidine poisoning. To such effect, this case report provides additional epidemiologic data on childhood tizanidine poisoning and further documentation on the use of naloxone as a viable antidote for centrally acting α-2 receptor agonists.

Abbreviations

GCS Glasgow Coma Scale

Declarations

Patient consent

Consent to publish the case report was obtained from patient's parents. This report does not contain any personal information that could lead to the identification of the patient.

Ethics approval and consent to participate

The ethnics committee at The Royal Commission Medical Center, Yanbu approved this case report for publication

Consent for publication

An informed consent was obtained from the child's parents

Availability of data and materials

The data is available in the patient’s medical record

Competing interests

The Authors declare that they have no competing interest

Funding

None

Authors' contributions

BA: Treated the patient as a toxicology consultant, reviewed and edited the manuscript.

DB: Initial patient admission, treatment and ICU supervision, analysis and interpretation of the patient data and contributor in writing the case presentation.

AA: Manuscript writing and editing.

MS: Initial patient admission, treatment and ICU supervision.

Acknowledgements

Not applicable

Authors' information (optional)

References

1. Malanga G, Reiter RD, Garay E. Update on tizanidine for muscle spasticity and emerging indications. *Expert Opin Pharmacother*. 2008;9(12):2209-2215. doi:10.1517/14656566.9.12.2209.
2. Chang E, Ghosh N, Yanni D, Lee S, Alexandru D, Mozaffar T. A review of spasticity treatments: Pharmacological and interventional approaches. *Crit Rev Phys Rehabil Med*. 2013;25(1-2):11-22. doi:10.1615/CritRevPhysRehabilMed.2013007945.
3. Kamen L, Henney HR, Runyan JD. A practical overview of tizanidine use for spasticity secondary to multiple sclerosis, stroke, and spinal cord injury. *Curr Med Res Opin*. 2008;24(2):425-439. doi:10.1185/030079908X261113.
4. Spiller HA, Bosse GM, Adamson LA. Retrospective review of tizanidine (zanaflex®) overdose. *J Toxicol - Clin Toxicol*. 2004;42(5):593-596. doi:10.1081/CLT-200026978.
5. Ahmad SA, Scolnik D, Snehal V, Glatstein M. Use of naloxone for clonidine intoxication in the pediatric age group: Case report and review of the literature. *Am J Ther*. 2015;22(1):e14-e16. doi:10.1097/MJT.0b013e318293b0e8.

6. Sinha Y, Cranswick NE. Clonidine poisoning in children: A recent experience. *J Paediatr Child Health*. 2004;40(12):678-680. doi:10.1111/j.1440-1754.2004.00491.x.
7. Lowry JA, Brown JT. Significance of the imidazoline receptors in toxicology. *Clin Toxicol*. 2014;52(5):454-469. doi:10.3109/15563650.2014.898770.
8. 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. doi:10.1016/j.jpeds.2013.08.038.
9. Eddy O, Howell JM, Love JN. Are one or two dangerous? Clonidine and topical imidazolines exposure in toddlers. *J Emerg Med*. 2003;25(3):297-302. doi:10.1016/S0736-4679(03)00206-3.
10. Michael JB, Sztajnkrycer MD. Deadly pediatric poisons: Nine common agents that kill at low doses. *Emerg Med Clin North Am*. 2004;22(4 SPEC. ISS.):1019-1050. doi:10.1016/j.emc.2004.05.004.
11. Holmes JF, Berman DA. Use of naloxpne to reverse symptomatic tetrahydrozoline overdose in a child. *Pediatr Emerg Care*. 1999;15(3):193-194. doi:10.1097/00006565-199906000-00008.
12. Katar S, Taskesen M, Okur N. Naloxone use in a newborn with apnea due to tetrahydrozoline intoxication. *Pediatr Int*. 2010;52(3):488-489. doi:10.1111/j.1442-200X.2010.03040.x.
13. Spiller HA, Klein-Schwartz W, Colvin JM, Villalobos D, Johnson PB, Anderson DL. Toxic clonidine ingestion in children. *J Pediatr*. 2005;146(2):263-266. doi:10.1016/j.jpeds.2004.09.027.
14. Tsze DS, Dayan PS. Treatment of Guanfacine Toxicity With Naloxone. *Pediatr Emerg Care*. 2012;28(10):1060-1061. doi:10.1097/PEC.0b013e31826ce9f1.
15. Kappagoda C, Schell DN, Hanson RM, Hutchins P. Clonidine overdose in childhood: Implications of increased prescribing. *J Paediatr Child Health*. 1998;34(6):508-512. doi:10.1046/j.1440-1754.1998.00301.x.
16. Banner W, Lund ME, Clawson L. Failure of Naloxone to Reverse Clonidine Toxic Effect. *Am J Dis Child*. 1983;137(12):1170-1171. doi:10.1001/archpedi.1983.02140380030009.