Delayed Hypotension and Bradycardia in Guanfacine ER Overdose

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Introduction

Attention deficit hyperactivity disorder (ADHD) has a prevalence rate of 7.2% in children and is primarily treated with either stimulants or non-stimulant medications (1, 3). Due to parental concern for side effects and risk for diversion, many parents opt for the non-stimulant treatment options for their child's ADHD.

Guanfacine ER, is an extended release selective α2A-adrenergic receptor agonist used initially to treat high blood pressure. It was then approved in 2009 to treat ADHD in children and adolescents 6 to 17 years of age (2).

Overdoses of guanfacine ER are rarely reported in the literature. Patients usually present with hypotension and bradycardia; symptoms can range from respiratory depression to coma (4). The average half-life of guanfacine HCL ER is 17 hours, and overdose symptoms generally resolve around 24 hours. However, due to its lipophilicity the ER formulation can lead to delayed onset of symptoms, especially in obese patients.

We discuss a young female with a BMI of 41.7 who overdosed on guanfacine ER, and subsequently developed hypotension and bradycardia about 48 hours post-ingestion.

Case Report

An 18-year-old female (BMI of 41.7) presented to the ED ~24 hours after intentional overdose on 25 tablets of 3mg guanfacine ER. Her PMH was significant for attention deficit hyperactivity disorder, a history of developmental delay, depression, and oppositional defiant disorder.

At initial presentation to the ED (24.8 hrs post ingestion), her temperature was 99° F, heart rate (HR) 53 and blood pressure (BP) 131/81. Poison control was contacted and suggested supportive care. She was then transferred to the inpatient psychiatric unit for further evaluation and treatment.

During her initial inpatient interview, she complained of dizziness, lightheadedness, and nausea. Vitals taken immediately after the interview (38.9 hrs post ingestion) showed a BP of 90/55 and pulse of 69. On recheck in the late afternoon, she still felt dizzy and lightheaded. At that time (46.7 hrs post ingestion), her BP was 81/50 and pulse was 50.

She was transferred back to the ED for further medical evaluation and stabilization. While in the ED, she was given 2L of normal saline and her BP two hours later (48.7 hrs post ingestion) was 108/57 with HR 69. She was then admitted to the medicine service for further monitoring and treatment. She continued to be bradycardic and hypotensive while on the medical floor requiring a total of 3L of normal saline. At 71.4 hrs post ingestion, HR was 80 and BP 103/68. She continued to have periods of hypotension until approximately 85 hours post ingestion.

The psychiatry consult team recommended holding her psychotropic medications until her vital signs became stable. Cardiology was consulted and recommended pseudoephedrine if the patient became hypotensive. The patient remained on the medical floor for a few more days and was then cleared for discharge home with follow-up outpatient psychiatric care.

Results

Patient Data

BMI	41.7 kg/m^2
Height	5 ft 5 in
Weight	113.8 kg

Patient's Vital Signs (Psychiatry Unit)						**ED**
Date/ Hours Post Ingestion	Day 1 24.8	Day 2 36.3	Day 2 38.9	Day 2 46.7	Day 2 46.8	Day 2 48.44
Temp (F)	99.0	98.6				98.1
Pulse	53	69	47	50	46	69
BP	131/81	92/56	90/55	81/50	80/43	108/57

Patient's Vital Signs (Medical Floor)								
Day/ Hours Post Ingestion	Day 3 55.5	Day 3 56.4	Day 3 58.5	Day 3 61.5	Day 3 66.8	Day 3 71.0	Day 3 71.1	Day 3 71.4
Temp (F)	98.2	98.1	98.4	97.5	98.4	99.0		
Pulse	53	47	58	44	43	48	61	80
BP	104/51	83/54	90/45	105/63	99/62	112/71	88/54	103/68

Patient's Vital Signs (Medical Floor)				
Day/ Hours Post Ingestion	Day 4 79.8	Day 4 83.0	Day 4 85.9	Day 4 91.0
Temp	98.1	98.1	98.2	98.1
Pulse	70	65	61	66
BP	84/43	91/57	109/50	134/75

Discussion

- Guanfacine ER is often prescribed for ADHD due to its perceived safety and low side effect profile. Overdoses are rarely reported in the current literature but can present as a wide range of symptoms including: respiratory depression, mild sedation to coma, hyporeflexia, bradycardia, and hypotension (4-5). The usual half-life of guanfacine ER is 17 hours, about the time a patient with a healthy weight would start experiencing hemodynamic effects of overdose.
- Our patient, a morbidly obese female (BMI of 41.7), was cleared medically as she had no signs of hypotension in the first 24 hours after overdose. She did not have any signs of hemodynamic instability until ~48 hours post-ingestion. This delayed presentation of overdose symptoms is attributed to her weight and increased lipophilicity of the drug, causing delayed absorptive effects and delayed presentation of hypotension and bradycardia.
- Lipophilicity, the ability of a substance to dissolve in fats and oils, . plays a vital role in how drugs are absorbed and distributed in the body. Pharmacokinetics of lipophilic medications can be altered by excess body fat, resulting in greater storage in fatty tissues in obese individuals, and subsequently larger volume of distribution (7-8).
- Lipophilic medications at steady state are stored in fatty tissues, and may be released slowly over time , leading to a prolonged effect and increasing risk of side effects, causing toxicity or adverse reactions. In addition, medications are excreted from the body through different means such as through the liver or through the kidney. In general, the degree of obesity is important to consider when looking at the effect of drugs in obese patients.
- Obese patients often have secondary hepatic or renal complications, which can also affect the clearance of lipophilic medications (8-10). This has the potential to further contribute to delayed onset of action and increased risk of side effects.

Conclusion

- Medical professionals must be aware of the potential for delayed overdose symptom onset and offset in morbidly obese patients treated for ADHD. We recommend increasing medical observation time from 24 hours to 48-72 hours post overdose ingestion, obtaining orthostatic BP and HR before medically clearing for inpatient psychiatric admission, obtaining EKG on presentation, and repeat EKG with worsening signs and symptoms of toxicity, and if on the inpatient psychiatry unit, increase the frequency of vitals .
- More research and guidance is needed to define safety protocols and studies into the lipophilicity of guanfacine ER and its effects on pharmacokinetics in obese pediatric and adult populations, given recently growing rates of obesity.

References

1. Thomas R, Sanders S, Doust J, et al: Prevalence of attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. Pediatrics 135(4):e994–1001, 2015
2. Cruz MP. Guanfacine Extended-Release Tablets (Intuniv), a Nonstimulant Selective Alpha(2A)-Adrenergic Receptor Agonist For
3. Attention-Deficit/Hyperactivity Disorder. *P T*. 2010;35(8):448-451.
4. Fein D; Hafeez Z; Cavagnaro C. An Overdose of Extended-Release Guanfacine. Pediatric Emergency Care 29(8):p 929-931, August 2013. DOI: 10.1097/PEC.0b013e31829ec525
5. Walton J, Byrum M, Shumaker A, Coury DL. Prolonged bradycardia and hypotension following guanfacine extended release overdose. *Journal of Child and Adolescent Psychopharmacology*. 2014;24(8):463-465. doi:10.1089/cap.2014.0022
6. Strange BC. Once-daily treatment of ADHD with guanfacine: patient implications. *Neuropsychiatric Disease and Treatment*. 2008;4(3):499-506. doi:10.2147/ndt.s1711
7. Bruno, CD, Harmatz, JS, Duan, SX, Zhang, Q, Chow, CR, Greenblatt, DJ. Effect of lipophilicity on drug distribution and elimination: Influence of obesity. *British Journal of Clinical Pharmacology*. 2021; 87: 3197– 3205. https://doi.org/10.1111/bcp.14735
8. Hanley MJ, Abernethy DR, Greenblatt DJ. Effect of obesity on the pharmacokinetics of drugs in humans. *Clinical Pharmacokinetics*. 2010;49(2):71-87. doi:10.2165/11318100-000000000-00000
9. Knibbe CA, Brill MJ, van Rongen A, Diepstraten J, van der Graaf PH, Danhof M. Drug disposition in obesity: toward evidence-based dosing. *Annual Review of Pharmacology and Toxicology*. 2015; 55:149-167. doi:10.1146/annurev-pharmtox-010814-124354
10. Chen K, Luo P, Yang G, et al. Population pharmacokinetics of omeprazole in obese and normal-weight adults. *Expert Review of Clinical Pharmacology*. 2022;15(4):461-471. doi:10.1080/17512433.2022.2075343

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