Ranitidine-Induced Delirium in a 7-Year-Old Girl: A Case Report

Roberta Esteves Vieira de Castro, MD, MSc, PhD,[a,b] Carolina da Cunha Sousa, MD,[b]
Maria Clara de Magalhães-Barbosa, MD, MSc, PhD,[c] Arnaldo Prata-Barbosa, MD, MSc, PhD,[c] Elie Cheniaux, MD, MSc, PhD[a,d]

Ranitidine is a histamine-2 blocker commonly prescribed in PICUs for the prophylaxis of gastrointestinal bleeding and stress ulcers. However, it can be associated to central nervous system side effects, such as delirium, in adults. We present the first case of a child presenting delirium possibly caused by anticholinergic toxidrome secondary to the use of ranitidine, resolving after drug discontinuation. With this case report, we reinforce that a wide variety of clinical conditions can trigger delirium and that the best therapeutic approach is to minimize risk factors.

Upper gastrointestinal bleeding and stress ulcers are recognized complications in PICUs.[1] Histamine-2 (H2) receptor antagonists (H2 blockers) are commonly prescribed as prophylaxis,[2] and ranitidine is 1 of the most commonly used.[3] Generally, these drugs are well tolerated, but central nervous system (CNS) side effects have been reported.[4] In adults, these effects are less frequent with ranitidine compared with other H2 blockers. However, ranitidine is an anticholinergic drug[4–6] that has been linked to anticholinergic toxidrome and delirium in adults.[7]

We report the case of a child with asthma admitted to the PICU for bronchospasm, who presented delirium possibly caused by anticholinergic toxidrome secondary to ranitidine, resolving after its discontinuation. To the best of our knowledge, this is the first case reported in children.

CASE PRESENTATION

We followed the CARE guidelines for case reports.[8] A 7-year-old white girl with asthma (34 kg) was admitted to the emergency department and transferred to the PICU after a 2-day history of nasal congestion and cough, without fever, that progressed to dyspnea and the need for oxygen therapy (Fig 1). She did not report intercrisis treatment, previous hospitalization, or previous or family history of neurologic or psychiatric disorders. She was hemodynamically stable, had no neurologic abnormalities, and presented with tachypnea, bilateral expiratory wheezes, and a Wood-Downes score to assess asthma severity equal to 4, indicating a mild asthmatic crisis. The Pediatric Risk of Mortality-2 score was 0.5%. Blood laboratory test results were normal (Table 1), except for a slight increase in C-reactive protein (CRP). The hematocrit was at the upper limit, which probably reflected some degree of dehydration. However, the patient did not require intravenous fluid administration. A chest radiograph revealed a retrocardiac opacity with pulmonary atelectasis appearance.

Inhaled salbutamol (700 μg) every 3 hours and methylprednisolone (2.0 mg/kg per day) were prescribed. Intravenous ranitidine (4.0 mg/kg per day, every 8 hours) was initiated for upper gastrointestinal bleeding and stress ulcer prophylaxis as part of the

abstract

[a]Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil; [b]Hospital Vitória, Americas Medical City, Rio de Janeiro, Brazil; [c]Instituto D'Or de Pesquisa e Ensino, Rio de Janeiro, Brazil; and [d]Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil

Dr Castro conducted the diagnosis, conceptualized and designed the study, drafted the manuscript, and reviewed and revised the manuscript; Dr Sousa conducted the diagnosis, conceptualized and designed the study, and reviewed and revised the manuscript; Drs de Magalhães-Barbosa, Prata-Barbosa, and Cheniaux critically reviewed the manuscript concerning important intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DOI: https://doi.org/10.1542/peds.2018-2428

Accepted for publication Oct 3, 2018

Address correspondence to Roberta Esteves Vieira de Castro, MD, MSc, PhD, Departamento de Pediatria, Hospital Universitário Pedro Ernesto, Blvd 28 de Setembro, 77, 2°andar, Vila Isabel 20551-030, Rio de Janeiro, Brazil. E-mail: roberta.castro@uerj.br

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

To cite: Castro REV de, Sousa C da C, de Magalhães-Barbosa MC, et al. Ranitidine-Induced Delirium in a 7-Year-Old Girl: A Case Report. *Pediatrics.* 2019;143(2):e20182428

hospitalization protocol. The patient evolved with improvement of the respiratory symptoms, with bronchospasm reduction and weaning from the oxygen therapy. However, about 30 hours after admission, psychomotor agitation was observed during ranitidine administration, which resolved spontaneously after the end of the infusion. The patient presented a new psychomotor agitation episode during the sequential ranitidine dose administration, becoming combative, inattentive, and displaying hallucinations and evident disorganized thinking. She was confused and shouted that the nursing technician was attacking her and was going to kill her. This behavior was reported as atypical by her sister. At that moment, she was in ambient air but with normal oxygen saturation. A provisional and possible delirium diagnosis was made. Applying the gold standard criteria from the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*,[9] we concluded that the patient presented delirium. The ranitidine infusion was discontinued, and this drug was replaced by omeprazole. Antipsychotics were not administered. Some hours later, the child returned to her baseline mental status, and the condition was resolved. There were no new episodes. The next day she was released to the ward and was discharged 2 days later.

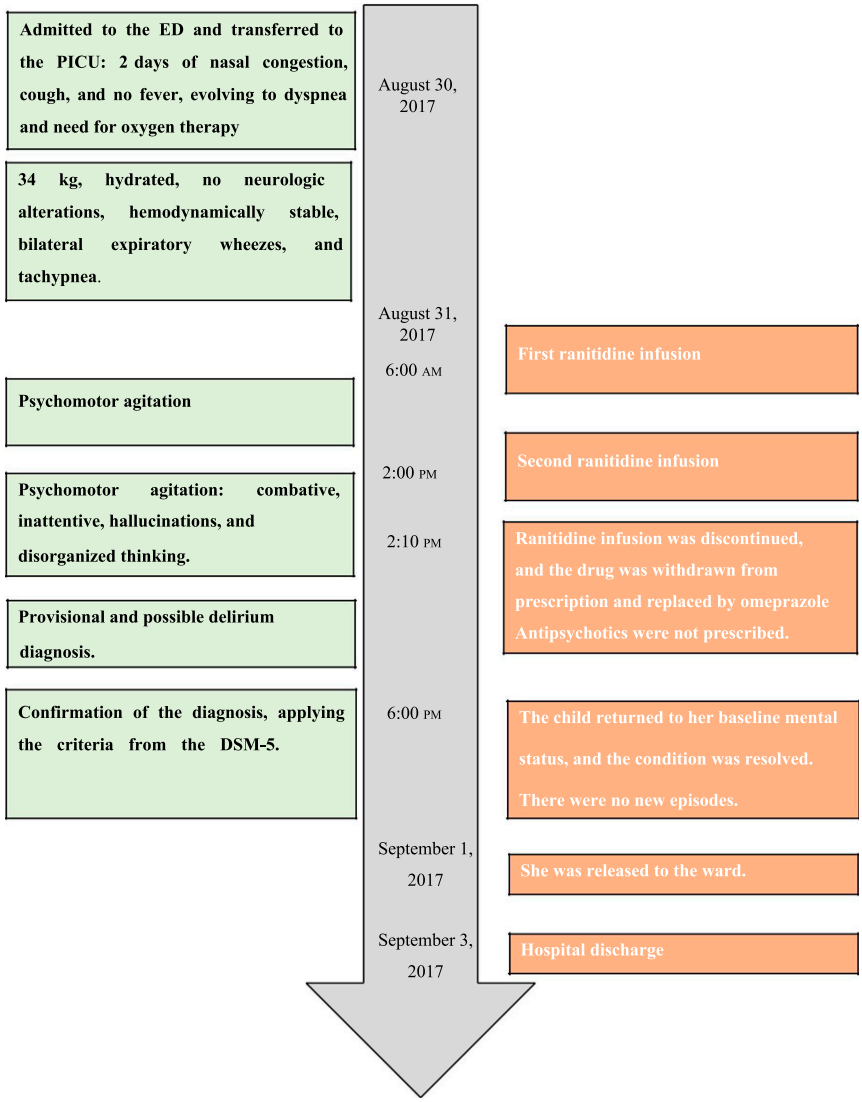

FIGURE 1

A 7-year-old white girl with asthma with no intercrises treatment, previous hospitalization history, or family neurologic and/or psychiatric disorders. DSM-5, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; ED, emergency department.

DISCUSSION

This is probably the first report of pediatric delirium associated with ranitidine infusion. Delirium is defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* as a disturbance of attention and awareness that can no longer be well explained by preexisting or evolving dementia. This disorder develops over a short period, with a tendency to fluctuate throughout the day, and is a direct physiologic consequence of another medical condition, substance intoxication or withdrawal, exposure to a toxin, or multiple etiologies.[9] Thus, delirium may occur in different scenarios,[10] and it is crucial to consider its diagnosis because it is associated with high morbidity and mortality.[11]

We hypothesized that the ranitidine infusions triggered the episodes of delirium. However, one of the great challenges in health research is to attribute causality between 2 events. Classically, 9 conditions, known as "Hill Criteria," are required to define a causal association: strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experimental evidence, and analogy.[12,13] Although no strength of association and no experimental evidence are provided in this case, some of the other Hill Criteria are present and can be used to support that hypothesis. Consistency is reinforced by similar reports in adults.[7] Specificity is observed (the supposed causal factor

of ranitidine was followed by the occurrence of the effect of delirium) more than once. After switching to omeprazole, the patient did not present further episodes. Temporality is a strong criterion because both delirium episodes began during ranitidine infusion, corroborating that the cause preceded the onset of effect. Concerning plausibility, coherence, and analogy, the current state of knowledge reveals that loss of cholinergic neuromodulation can lead to cognitive and attentional deficits.[14] Several studies indicate anticholinergic drugs as risk factors for delirium and the role of anticholinergic burden in delirium pathophysiology.[5,14–17] Anticholinergic toxidrome is described after exposure to anticholinergic drugs, including H2 blockers,[16,17] which antagonize peripheral and central muscarinic receptors, producing anticholinergic toxoids. One CNS manifestation of these drugs is delirium.[15] Unfortunately, the literature on anticholinergic toxidrome and its relationship to delirium is limited to adult populations, and, thus, the magnitude of its occurrence in childhood is still unknown.[17] The fact that many risk factors described in the literature are lacking in this case gives further support to the hypothesis of a causal relationship between ranitidine and delirium. Important predisposing factors include the severity of the underlying disease, male sex, visual and hearing impairment, dehydration, malnutrition, low albumin, and past alcohol, substance, and/or cigarette abuse or multiple psychoactive drugs. In children, an age <2 years and preexisting developmental delay are quoted in the literature as relevant predisposing factors.[6,10,18] Precipitating factors include electrolyte imbalances, metabolic disturbances, hypoxia, shock, anemia, hypothermia or fever, severe acute illness, surgery, physical restraints, sedative hypnotics (such as benzodiazepines), opioids, and infections.[6,10]

Patient blood tests revealed normal electrolytes, normal venous blood gases, and normal hepatic and renal function. At the time of the delirium episode, oxygen saturation was 98% in ambient air, and she did not return to oxygen therapy at any time until hospital discharge. The severity of the acute illness was low, and the patient did not require volumetric expansion or vasoactive drugs. No sedative or opioid drugs were prescribed, and the patient needed no physical restraint. Bacterial infection was excluded because the patient had no history of fever or hypothermia, presented normal leukogram, negative blood culture results, and no evidence of pneumonia on physical examination or on the chest radiograph. No clinical signals of CNS infection were detected, and a lumbar puncture was not indicated. The slight increase in CRP was attributed to the asthma exacerbation.[19]

TABLE 1 Laboratory Values at Admission to the PICU (and References)

	Laboratory Result	Reference
Complete blood count		
Hemoglobin, g/dL	16	12 to 16
Hematocrit, % of g/dL	48	36 to 48
Platelets, per mm^3	365 000	150 000 to 550 000
WBC count, per mm^3	11 900	4000 to 11 000
Blood chemistry		
Albumin, g/dL	4.8	3.5 to 5.0
ALP, U/L	170	94 to 499
ALT, U/L	19	5 to 26
AST, U/L	17	19 to 49
Bilirubin direct, mg/dL	0.3	<0.5
Bilirubin indirect, mg/dL	0.6	0.1 to 0.7
BUN, mg/dL	35	11 to 36
Calcium, mg/dL	9.6	8.8 to 10.7
Chlorine, mEq/L	106	98 to 107
Creatinine, mg/dL	0.73	0.2 to 0.8
CRP, mg/dL	0.96	<0.5
GGT, U/L	17.9	9 to 29
Glucose, mg/dL	189	70 to 99
Potassium, mEq/L	4.2	3.4 to 4.7
Sodium, mEq/L	139	138 to 145
Coagulogram		
APTTV, in	36.8	28 to 38
INR	1.19	0.8 to 1.20
Prothrombin activity, %	75	70 to 100
Venous blood gases		
pH	7.31	7.32 to 7.42
Pco_2, mm Hg	49	38 to 50
Po_2, mm Hg	45	20 to 50
Bicarbonate, mmol/L	24.7	22 to 29
Base excess, mmol/L	−2.2	−3.0 to +3.0
So_2, %	76	55 to 75
Blood cultures	Negative	—

ALP, alkaline phosphatase; ALT, alanine aminotransferase; APTTV, activated partial thrombin time; AST, aspartate transaminase; BUN, blood urea nitrogen; GGT, γ-glutamyl transpeptidase; INR, international normalized ratio; So_2, venous oxygen saturation; WBC, white blood cell; —, not applicable.

One can argue that other precipitating factors, such as admission to the PICU, the presence of invasive devices, and multiple drug therapy,[6,10] were present and could have contributed to the delirium episodes. The patient had a peripheral venous access and received inhaled salbutamol and methylprednisolone. Salbutamol can stimulate the CNS, leading to anxiety, insomnia, motor restlessness, and delirium.[20,21] Corticosteroids induce both CNS side effects[22] and stress responses, so clinicians are recommended to avoid steroids when a potential delirium mindset ocurrs.[6] We believe that these factors may have contributed to elicit the delirium

episodes, although the synchrony between both episodes and the ranitidine infusions was striking in this case.

Prevention is the most effective way to reduce delirium incidence. Understanding the risk factors is critical because they can, to some extent, be controlled and managed.[6] Key strategies include modification of environmental, iatrogenic, and patient-related factors. Treatment relies on the prevention of risk factors, early diagnosis, clinical monitoring, and, if possible, resolution of the underlying disease.[23–25] Reserving pharmacological treatment for when nonpharmacological alternatives have been exhausted is recommended in the literature.[25–27] We used no drugs to treat the delirium episodes in this case.

CONCLUSIONS

This case report suggests that a widely prescribed drug in the PICU, such as ranitidine, may induce delirium episodes. The case also reinforces that a great variety of clinical conditions can trigger this event. Therefore, clinicians must be always alert for the presence of predisposing factors and the need to control precipitating factors for delirium.

ACKNOWLEDGMENT

We acknowledge our dear friend Dr Grace Kelly Paranhos (in memoriam) for assistance with the diagnosis.

ABBREVIATIONS

CNS: central nervous system
CRP: C-reactive protein
H2: histamine-2

REFERENCES

1. Reveiz L, Guerrero-Lozano R, Camacho A, Yara L, Mosquera PA. Stress ulcer, gastritis, and gastrointestinal bleeding prophylaxis in critically ill pediatric patients: a systematic review. *Pediatr Crit Care Med*. 2010;11(1):124–132
2. Krag M, Perner A, Møller MH. Stress ulcer prophylaxis in the intensive care unit. *Curr Opin Crit Care*. 2016;22(2):186–190
3. Araujo TE, Vieira SM, Carvalho PR. Stress ulcer prophylaxis in pediatric intensive care units. *J Pediatr (Rio J)*. 2010;86(6):525–530
4. Mauran A, Goze T, Abadie D, et al. Mania associated with ranitidine: a case report and review of literature. *Fundam Clin Pharmacol*. 2016;30(4):294–296
5. Rudolph JL, Salow MJ, Angelini MC, McGlinchey RE. The anticholinergic risk scale and anticholinergic adverse effects in older persons. *Arch Intern Med*. 2008;168(5):508–513
6. Page VJ, Ely EW. *Delirium in Critical Care*. 2nd ed. Cambridge, United Kingdom: Cambridge University Press; 2015
7. Picotte-Prillmayer D, DiMaggio JR, Baile WF. H2 blocker delirium. *Psychosomatics*. 1995;36(1):74–77
8. Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, Riley D; CARE Group. The CARE guidelines: consensus-based clinical case report guideline development. *J Clin Epidemiol*. 2014;67(1):46–51
9. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013
10. Maldonado JR. Delirium: neurobiology, characteristics and management. In: Fogel BS, Greenberg DB, eds. *Psychiatric Care of the Medical Patient*. 3rd ed. New York, NY: Oxford University Press; 2015:823–907
11. Brahmbhatt K, Whitgob E. Diagnosis and management of delirium in critically ill infants: case report and review. *Pediatrics*. 2016;137(3):e20151940
12. de Araújo LFSC, Dalgalarrondo P, Banzato CEM. On the notion of causality in medicine: addressing Austin Bradford Hill and John L. Mackie. *Rev Psiquiatr Clín*. 2014;41(2):56–61
13. Fedak KM, Bernal A, Capshaw ZA, Gross S. Applying the Bradford Hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology. *Emerg Themes Epidemiol*. 2015;12:14
14. Field RH, Gossen A, Cunningham C. Prior pathology in the basal forebrain cholinergic system predisposes to inflammation-induced working memory deficits: reconciling inflammatory and cholinergic hypotheses of delirium. *J Neurosci*. 2012;32(18):6288–6294
15. Crispo JA, Willis AW, Thibault DP, et al. Associations between anticholinergic burden and adverse health outcomes in Parkinson disease. *PLoS One*. 2016;11(3):e0150621
16. Cowan K, Landman RA, Saini A. Dexmedetomidine as an adjunct to treat anticholinergic toxidrome in children. *Glob Pediatr Health*. 2017;4:2333794X17704764
17. Madden K, Burns MM, Tasker RC. Differentiating delirium from sedative/hypnotic-related iatrogenic withdrawal syndrome: lack of specificity in pediatric critical care assessment tools. *Pediatr Crit Care Med*. 2017;18(6):580–588
18. Patel AK, Bell MJ, Traube C. Delirium in pediatric critical care. *Pediatr Clin North Am*. 2017;64(5):1117–1132
19. Camargo N. *Estudo Transversal e Longitudinal da Associação Entre Asma e Proteína C Reativa: Interferência da Obesidade Nos Valores da Proteína C Reativa em Asmáticos* [master's thesis]. Botucatu, Brazil: Universidade Estadual Paulista, Faculdade de Medicina de Botucatu; 2008. Available at: http://hdl.handle.net/11449/92121. Accessed July 7, 2018
20. Durandal Montaño JR. Trastornos psiquiátricos inducidos por medicamentos.*Revista Científica Ciencia Médica*. 2011;14(1):21–24
21. Cahill A, Pearcy C, Almahmoud K, et al. Don't call me crazy! Delirium occurs outside of the intensive care unit. *J Trauma Acute Care Surg*. 2018;84(1):66–69
22. Ciriaco M, Ventrice P, Russo G, et al. Corticosteroid-related central nervous system side effects. *J Pharmacol Pharmacother*. 2013;4(suppl 1):S94–S98

23. Faria RS, Moreno RP. Delirium in intensive care: an under-diagnosed reality [in Portuguese]. *Rev Bras Ter Intensiva*. 2013;25(2):137–147

24. Smith CD, Grami P. Feasibility and effectiveness of a delirium prevention bundle in critically ill patients. *Am J Crit Care*. 2016;26(1):19–27

25. Kotfis K, Marra A, Ely EW. ICU delirium - a diagnostic and therapeutic challenge in the intensive care unit. *Anaesthesiol Intensive Ther*. 2018;50(2): 160–167

26. Barr J, Fraser GL, Puntillo K, et al; American College of Critical Care Medicine. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med*. 2013; 41(1):263–306

27. Thom RP, Mock CK, Teslyar P. Delirium in hospitalized patients: risks and benefits of antipsychotics. *Cleve Clin J Med*. 2017;84(8):616–622

Ranitidine-Induced Delirium in a 7-Year-Old Girl: A Case Report

Roberta Esteves Vieira de Castro, Carolina da Cunha Sousa, Maria Clara de Magalhães-Barbosa, Arnaldo Prata-Barbosa and Elie Cheniaux

Pediatrics 2019;143;
DOI: 10.1542/peds.2018-2428 originally published online January 11, 2019;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Ranitidine-Induced Delirium in a 7-Year-Old Girl: A Case Report

Roberta Esteves Vieira de Castro, Carolina da Cunha Sousa, Maria Clara de Magalhães-Barbosa, Arnaldo Prata-Barbosa and Elie Cheniaux

Pediatrics 2019;143;
DOI: 10.1542/peds.2018-2428 originally published online January 11, 2019;