Safety of Octreotide in Hospitalized Infants

Daniela Testoni[1,2], Christoph P. Hornik[1,3], Megan L. Neely[1,4], Qinghong Yang[1], Ann W. McMahon[5], Reese H. Clark[6], P. Brian Smith[1,3], on behalf of the Best Pharmaceuticals for Children Act – Pediatric Trials Network

[1] Duke Clinical Research Institute, Durham, NC; [2] Escola Paulista de Medicina – Universidade Federal de São Paulo, Brazil; [3] Dept. of Pediatrics, Duke University, Durham, NC; [4] Dept. of Biostatistics & Bioinformatics, Duke University, Durham, NC; [5] Office of Pediatric Therapeutics, Food & Drug Administration, Silver Spring, MD; [6] Pediatrix-Obstetrix Center for Research and Education, Sunrise, FL.

Background

- Octreotide is used off-label in infants for treatment of chylothorax, congenital hyperinsulinism, and gastrointestinal bleeding
- The safety profile of octreotide in infants is not well described
- Adverse events identified in pediatric case reports include abnormalities in glucose regulation and necrotizing enterocolitis
- We sought to describe the safety profile of octreotide in hospitalized infants

Methods

- We identified infants exposed to octreotide from a cohort of 804,172 infants discharged from 333 neonatal intensive care unites between 1997 and 2011
- We looked at daily laboratory and clinical information generated from clinical notes
- For infants exposed to octreotide we examined drug indication, infant characteristics, concomitant medications and use over time
- We described pre-specified adverse events (AE) that occurred during exposure to octreotide

Results

Table 1: Demographics and baseline characteristics (N = 384)

Gestational age (weeks)	33 (28, 37)
Birth weight (g)	2270 (1040, 3085)
Male, n (%)	209 (55)
Race/ethnicity, n(%)	
White	171 (47)
Black	63 (17)
Hispanic	117 (31)
Other	16 (4)
Inborn, n (%)	237 (62)
Postnatal age* (days)	28 (12,16)
Weight* (g)	3041 (2297, 3840)
Mechanical ventilation*, n (%)	199 (52)
Inotropes*, n (%)	55 (14)
Length of stay (days)	62 (32, 115)

Data presented as median (interquartile range), unless otherwise specified.
*On first octreotide day.

Results

- 384 infants received 441 courses of octreotide
- Median duration of octreotide course = 10 days (interquartile range; 4, 21)
- 70/383 (18%) infants exposed to octreotide died before discharge; 11/383 (3%) died during octreotide use

Table 2: Octreotide indications

	Courses, n (%) N = 441
Chylothorax	218 (49)
Pleural effusion	136 (31)
Hypoglycemia	100 (23)
Gastrointestinal hemorrhage	44 (9)
Bloody stools	23 (5)
Pericardial effusion	11 (3)
Lymphangiectasia	3 (1)
Congenital lymphedema	1 (0.2)

Multiple indications per course were allowed; thus, sum of % >100.

Table 3: Most common concomitant medications

	Courses, n (%) N = 441
Vancomycin	231 (52)
Gentamicin	196 (44)
Furosemide	191 (43)
Fentanyl	145 (33)
Midazolam	137 (31)
Morphine	116 (26)

Table 4: Laboratory adverse events

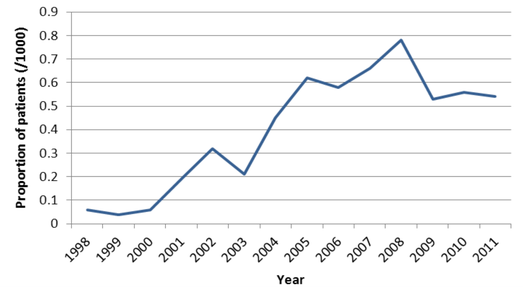
	Adverse Events		Serious Adverse Events	
Serum electrolytes		Courses, % N = 441		Courses, % N = 441
Hyperglycemia	> 250 mg/dl	1	> 400 mg/dl	0
Hypoglycemia	< 40 mg/dl	2	< 20 mg/dl	1
Hypernatremia	> 150 mmol/L	3	> 160 mmol/L	0.2
Hyponatremia	< 125 mmol/L	4	< 115 mmol/L	0.2
Hyperkalemia	> 6 mmol/L	21	> 7.5 mmol/L	5
Hypokalemia	< 3 mmol/L	12	< 2.5 mmol/L	2
Hypercalcemia	> 12.5 mg/dL	1	> 13.5 mg/dL	1
Renal dysfunction				
Elevated BUN	> 70 mg/dL	8	> 100 mg/dL	4
Elevated creatinine	> 1.7 mg/dL	3	> 3.0 mg/dL	2
Liver dysfunction				
Elevated AST	> 500 U/L	1	> 1000 U/L	0.2
Elevated ALT	> 500 U/L	0.2	> 1000 U/L	0
Elevated GGT	> 100 U/L	8	> 200 U/L	4
Direct bilirubin	> 5 mg/dL	11	> 10 mg/dL	4
Complete blood count				
Leukocytosis	> 25,000/mm^3	12	> 40,000/mm^3	3
Leukopenia	< 5000/mm^3	7	< 2000/mm^3	0.2
Thrombocytopenia	< 100,000/mm^3	18	< 30,000/mm^3	2
Thrombocytosis	> 600,000/mm^3	5	> 1,000,000/mm^3	1

BUN: blood urea nitrogen; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transpeptidase.

Table 5: Clinical adverse events

	Courses, % N = 441
Gastrointestinal	
Necrotizing enterocolitis	1
Focal intestinal perforation	0.2
Neurologic	
Intraventricular hemorrhage	1
Seizure	1
Cardiovascular	
Hypotension requiring pressors	12
Dermatologic	
Rash	2

Figure 1: Octreotide use over time



Conclusions

- Octreotide is an understudied drug used off label in critically ill infants
- For this population of sick hospitalized infants, incidence of AE was not higher than expected
- Additional studies are needed to further evaluate the safety, dosing and efficacy of octreotide in infants

References

1. U.S. Food and Drug Administration Web site. Sandostatin (octreotide acetate) injection. [pdf]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/019667s061lbl.pdf. Accessed October 22, 2013
2. Foo 2011, *Pediatr Neonatol*. 2011;52(5):297–301
3. Reck-Burneo 2008, *J Pediatr Surg*. 2008;43(6):1209–1210

Disclosures:

The authors have no financial relationships relevant to this article to disclose. Dr. Smith receives salary support for research from the National Institutes of Health (NIH), the U.S. Department of Health and Human Services, and the National Center for Advancing Translational Sciences of the NICHD.

Acknowledgments

This work was funded under NICHD contract HHSN27500016 for the Pediatric Trials Network. This work was also supported by the American Recovery and Reinvestment Act, DHHS-1R18AE000028-01) (P.B.S). Research reported in this publication was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under award number UL1TR001117. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Corresponding author:
P. Brian Smith, MD, MPH, MHS,
Duke Clinical Research Institute,
Box 17969, Durham, NC, 27715;
brian.smith@duke.edu
phone: 919-668-8951
fax: 919-668-7058