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## Safety of octreotide in hospitalized infants

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### Abstract

**Background**—Octreotide is used off-label in infants for treatment of chylothorax, congenital hyperinsulinism, and gastrointestinal bleeding. The safety profile octreotide in hospitalized infants has not been described; we sought to fill this information gap.

**Methods**—We identified all infants exposed to at least 1 dose of octreotide from a cohort of 887,855 infants discharged from 333 neonatal intensive care units managed by the Pediatric Medical Group between 1997 and 2012. We collected laboratory and clinical information while infants were exposed to octreotide and described the frequency of baseline diagnoses, laboratory abnormalities, and adverse events (AEs).

**Results**—A total of 428 infants received 490 courses of octreotide. The diagnoses most commonly associated with octreotide use were chylothorax (50%), pleural effusion (32%), and hypoglycemia (22%). The most common laboratory AEs that occurred during exposure to octreotide were thrombocytopenia (47/1000 infant-days), hyperkalemia (21/1000 infant-days), and

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leukocytosis (20/1000 infant-days). Hyperglycemia occurred in 1/1000 infant-days and hypoglycemia in 3/1000 infant-days. Hypotension requiring pressors (12%) was the most common clinical AE that occurred during exposure to octreotide. Necrotizing enterocolitis was observed in 9/490 (2%) courses, and death occurred in 11 (3%) infants during octreotide administration.

**Conclusion**—Relatively few AEs occurred during off-label use of octreotide in this cohort of infants. Additional studies are needed to further evaluate the safety, dosing, and efficacy of this medication in infants.

## Keywords

octreotide; safety; infant; drug toxicity

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## 1. Introduction

Octreotide is a somatostatin analog that inhibits the release of growth hormone, glucagon, and insulin [1]. It decreases pancreatic secretion, gallbladder contraction, and gastrointestinal tract motility, and reduces intestinal blood flow by vasoconstriction of the splanchnic vessels [2,3]. Through these effects on the gastrointestinal tract, octreotide reduces fat absorption and lymphatic flow in the thoracic duct [2].

In adults, it is labeled for use in the treatment of acromegaly, carcinoid tumors, and vasoactive intestinal peptide tumors [4]; additionally, octreotide is often used off-label for several other indications, including acute esophageal variceal bleeding, tumor growth stabilization, tumor linkage, treatment of idiopathic pulmonary fibrosis, and acute pancreatitis [5–9]. Although octreotide is not labeled for use in children, case reports, case series, and cohort studies document the use of octreotide in children for several indications, including pancreatitis, chylothorax, and gastrointestinal bleeding [10–19]. In infants, the most common indication is treatment of congenital chylothorax, chylothorax secondary to thoracic surgery, congenital hyperinsulinism, and gastrointestinal bleeding [12–14]. Evidence of octreotide efficacy in this population is limited to small case series and retrospective studies [12,15,20].

The safety profile of octreotide has not been described in infants. In adults, the most frequent side effects are gastrointestinal events, glucose regulation disorders, hypothyroidism, and biliary tract abnormalities [4,21]. Based on small studies in children, side effects associated with octreotide include hyperglycemia, hypoglycemia, hypertension, hyperbilirubinemia, diarrhea, abdominal cramping and pain, and necrotizing enterocolitis (NEC) [12,15,16,22,23]. In the present study, we describe the safety profile of octreotide in a cohort of hospitalized infants.

## 2. Methods

### 2.1. Study design and setting

We identified all infants discharged from 333 neonatal intensive care units managed by the Pediatrix Medical Group from 1997 to 2012 who were exposed to at least one dose of octreotide. We used a database that prospectively captures information from daily progress

notes, laboratory results, admission and discharge notes, and maternal information. Notes are generated by clinicians using a computer-assisted tool on all infants cared for by the Pediatrix Medical Group. For this study, we captured demographic data, discharge data, daily medications, dosing information, laboratory values, and diagnoses.

## 2.2. Definitions

Octreotide exposure was defined as any day an infant was receiving the drug. Exposure was evaluated at the day level and at the course level. An octreotide course was defined as the uninterrupted interval from start day of octreotide to end day of octreotide. If the first day of the next octreotide course was >1 day after the last day of the previous course, the next interval was considered a new course.

We defined octreotide indication by a diagnosis recorded prior to or during the octreotide course that matched reported indications for octreotide in the available literature [14,19,20,24,25]. All concomitant medications administered were captured during octreotide exposure.

Available laboratory and clinical information was collected while infants were exposed to octreotide. An adverse event (AE) was attributed to octreotide if it occurred between the start of octreotide exposure through the end of exposure. Laboratory abnormalities were classified as an AE or a serious adverse event (SAE) based on pre-specified cut-off values. Diagnoses included as AEs were NEC, focal intestinal perforation, intraventricular hemorrhage, periventricular leukomalacia, seizure, hypotension requiring pressors, and rash.

## 2.3. Statistical analysis

Standard summary statistics were used to describe demographic characteristics. Laboratory AEs were described on both the course level (number and percentage of courses with at least one abnormal laboratory result) and the infant-day level (number of days with abnormal labs per 1000 infant-days on octreotide); clinical AEs and concomitant medications were presented at the course level. At the course level, diagnoses, lab abnormalities, and concomitant medication that occurred more than once during the same course were only counted once. Octreotide use over time was described by the proportion of infants that received at least one course of octreotide out of the total number of infants in the database for each year during the study period. Dosing information was described if available.

All analyses were performed using SAS statistical software version 9.3 (SAS Institute Inc., Cary, NC, USA). The study was approved by the Duke University Institutional Review Board.

## 3. Results

Of the 887,855 infants discharged during the study period, 428 (0.05%) received 490 courses of octreotide. Infants exposed to octreotide had a median birth weight of 2290 g (interquartile range; 1110, 3090), median gestational age (GA) of 33 weeks (28, 37), and 314 (74%) were <37 weeks GA. On the first day of octreotide exposure, the median

postnatal age was 27 days (11, 63), 225 (53%) infants were receiving mechanical ventilation, and 68 (16%) infants were receiving inotropes (Table 1).

During the study period, the proportion of hospitalized infants given octreotide ranged from <0.1/1000 infants to 0.8/1000 infants (Figure 1). Octreotide use increased after 1998 but has remained relatively constant since 2005, with octreotide use ranging from 0.6/1000 infants to 0.8/1000 infants. Octreotide exposure varied greatly by site and ranged from 0.1 to 12/1000 infants (Figure 2).

The most common indications for octreotide use were chylothorax (245/490 [50%]), pleural effusion (158/490 [32%]), and hypoglycemia (110/490 [22%]) (Table 2). The most common concomitant medications included vancomycin (259/490 [53%]), gentamicin (220/490 [45%]), furosemide (217/490 [44%]), fentanyl (165/490 [34%]), and midazolam (154/490 [31%]) (Table 3).

Dosing information was available for 78/490 (16%) of the courses. Infants received the drug by continuous infusion in most of the courses (60/78 [77%]). The median dose by continuous infusion was 2 mcg/kg/hour (1, 6), and the median dose by intermittent administration was 7.5 mcg/kg/day (2, 20).

The most common laboratory AEs that occurred during exposure to octreotide were thrombocytopenia (47/1000 infant-days), hyperkalemia (21/1000 infant-days), and leukocytosis (20/1000 infant-days). The most common laboratory SAEs during exposure to octreotide were elevated blood urea nitrogen (5/1000 infant-days), elevated direct bilirubin (5/1000 infant-days), elevated gamma-glutamyl transpeptidase (5/1000 infant-days), and leukocytosis (5/1000 infant-days). Hyperglycemia >250 mg/dl occurred in 1/1000 infant-days (1%) and hypoglycemia <40 mg/dl in 3/1000 infant-days (2% of octreotide courses) (Table 4).

The most common clinical AE that occurred during octreotide exposure was hypotension requiring pressors in 57/490 (12%) courses (Table 5). Rash was present in 7/490 (1%) courses, and surgical NEC occurred in 1/490 (0.2%) course. There were 10/428 (2%) infants with gastrointestinal events: 9 with NEC, and one with focal intestinal perforation. Dosing information was available for 3 infants who had NEC. One infant received 10 mcg/kg/day from day of life (DOL) 71–79 and had NEC on DOL 141. The second infant received a continuous infusion of 10 mcg/kg/hour from DOL 6–17 and had NEC on DOL 17. The third infant received 1 mcg/kg/hour from DOL 1–55 and had NEC on DOL 50. A total of 79/428 (19%) infants ever exposed to octreotide died while in the hospital, and 11/428 (3%) died during octreotide use.

## 4. Discussion

In our cohort of hospitalized infants, octreotide use was rare but increased over time. Octreotide use coincided with several AEs, and most AEs identified were laboratory abnormalities. AEs are defined by the U.S. Food and Drug Administration (FDA) as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related [26]. AEs associated with octreotide use in our population could be

related with the drug or with the underlying disease; however, we do not have the ability to determine causation from these data. Concomitant medications could also be responsible for the AEs, as well as the interaction between the different drugs.

Hypoglycemia and hyperglycemia are expected adverse reactions caused by octreotide action on insulin/glucagon balance [4]. Octreotide has a potent inhibitory effect on growth hormone secretion and a transient inhibitory effect on insulin and glucagon secretion [27]. Hyperglycemia and hypoglycemia are commonly described AEs in retrospective studies and case reports in children receiving octreotide [15,28–30]. However, in our cohort, hyperglycemia and hypoglycemia occurred in only 1/1000 and 3/1000 infant-days, respectively.

Thrombocytopenia was identified as an AE associated with octreotide in post-marketing reports [4]. In our study, thrombocytopenia was the most common laboratory AE, occurring in 47/1000 infant-days. Severe thrombocytopenia ( $<30,000/\text{mm}^3$ ) occurred in 1/1000 infant-days. Although our results could be a drug-related AE, thrombocytopenia is not uncommon in hospitalized, critically ill infants and is usually associated with septicemia [31]. Premature infants have higher incidence of thrombocytopenia ( $>10\%$ ), and 73% of infants in our cohort were  $<37$  weeks GA [31]. The majority of infants in our cohort were critically ill; 52% were receiving mechanical ventilation, and 14% were receiving inotropes when the first use of octreotide occurred.

Biliary abnormalities (gallstones, sludge without gallstones, and biliary duct dilation) are AEs reported with octreotide use on the FDA label [4]. Gallbladder stasis is increased and intestinal transit is prolonged after octreotide use [32,33]. Octreotide also alters hepatic bile composition, decreasing bile pH and increasing the risk of cholesterol and calcium bilirubinate precipitation [33]. In children, previous single-center retrospective studies did not report biliary abnormalities associated with octreotide [30,34,35]. However, a case report described a 33-week-GA infant receiving octreotide for congenital hyperinsulinism who developed cholelithiasis after five weeks of treatment [36]. In our study, only one infant had cholelithiasis, which was diagnosed on DOL 113. This infant received octreotide from DOL 4–55.

Octreotide reduces intestinal blood flow by vasoconstriction of the splanchnic vessels, causing concern that it may increase the risk of NEC [3]. Infants with NEC requiring surgery have mortality higher than 50% [37]. Short- and long-term morbidities associated with NEC include intestinal failure, short bowel syndrome, intestinal strictures, and neurodevelopment impairment [23,38]. Two case reports described NEC occurring within 72 hours after octreotide initiation. The first was an infant with 2600 g birth weight who received octreotide for treatment of chylothorax diagnosed two weeks after a coarctation repair; the second, a 22-day-old, full-term infant who received octreotide for persistent hypoglycemia treatment [22,39]. However there is a concern that octreotide may be associated with NEC, we observed an incidence of only 2% (10/428) of NEC in our infants exposed to octreotide, which is similar to a previously described cohort of hospitalized infants (1.2% [6460/560,227]) [35].

Although octreotide use has increased over time (Figure 1), the frequency of its use is still relatively low, with <0.1% of hospitalized infants exposed to octreotide. This may be true not only because safety and efficacy studies are lacking but also because of the low incidence of the diagnoses for which octreotide is used. The diagnosis most commonly associated with octreotide use in our cohort was chylothorax, and, in our database, the overall incidence of chylothorax was 0.08%.

Our study has several strengths, including a relatively large sample size compared with previous reports in infants. We had information on a day-level for each infant receiving octreotide in our database. We were also able to collect information on concomitant medications and diagnoses, in addition to associated laboratory AEs. Limitations of this cohort study include our inability to infer causality with reported AEs and our inability to include a comparison group of infants given the uniqueness of infants who are exposed to octreotide. We also did not have access to cause of death.

## 5. Conclusion

Octreotide is an understudied drug used off-label in critically ill infants. Relatively few AEs occurred during off-label use of octreotide in this cohort of infants. Additional studies are needed to further define the safety, dosing, and efficacy of octreotide in this population.

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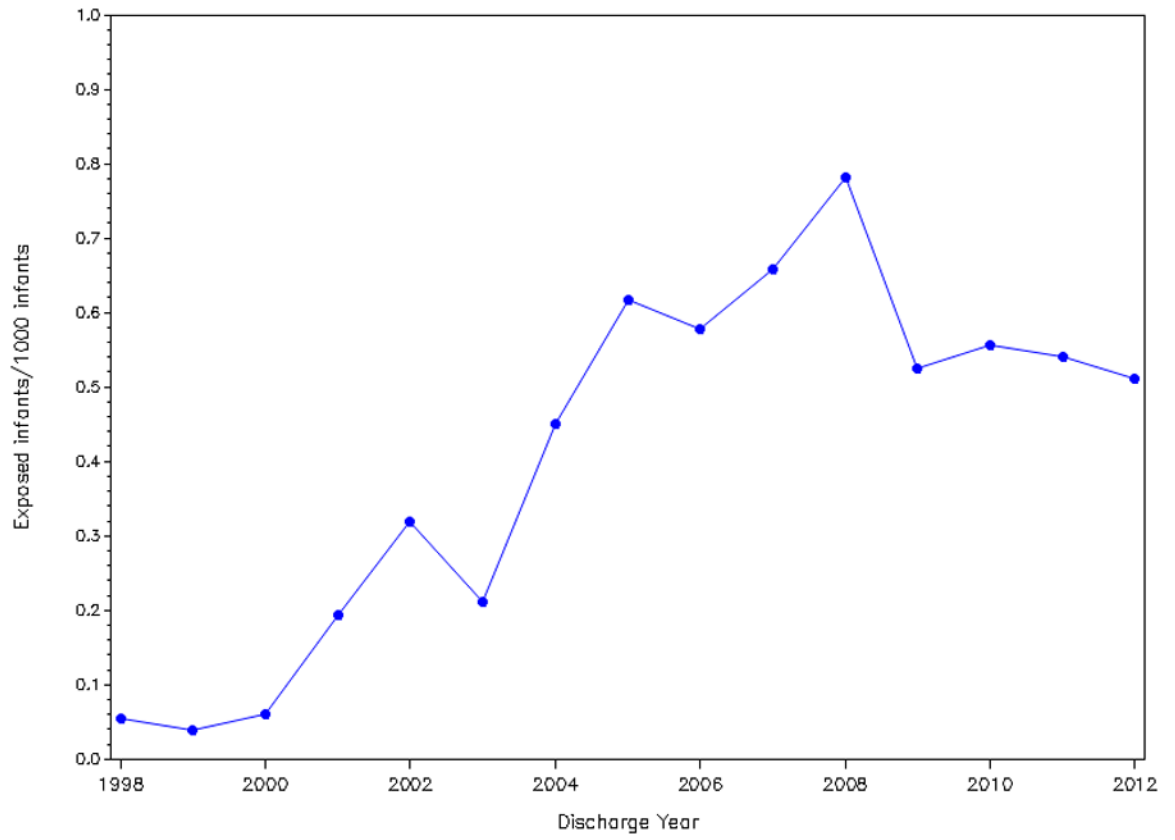
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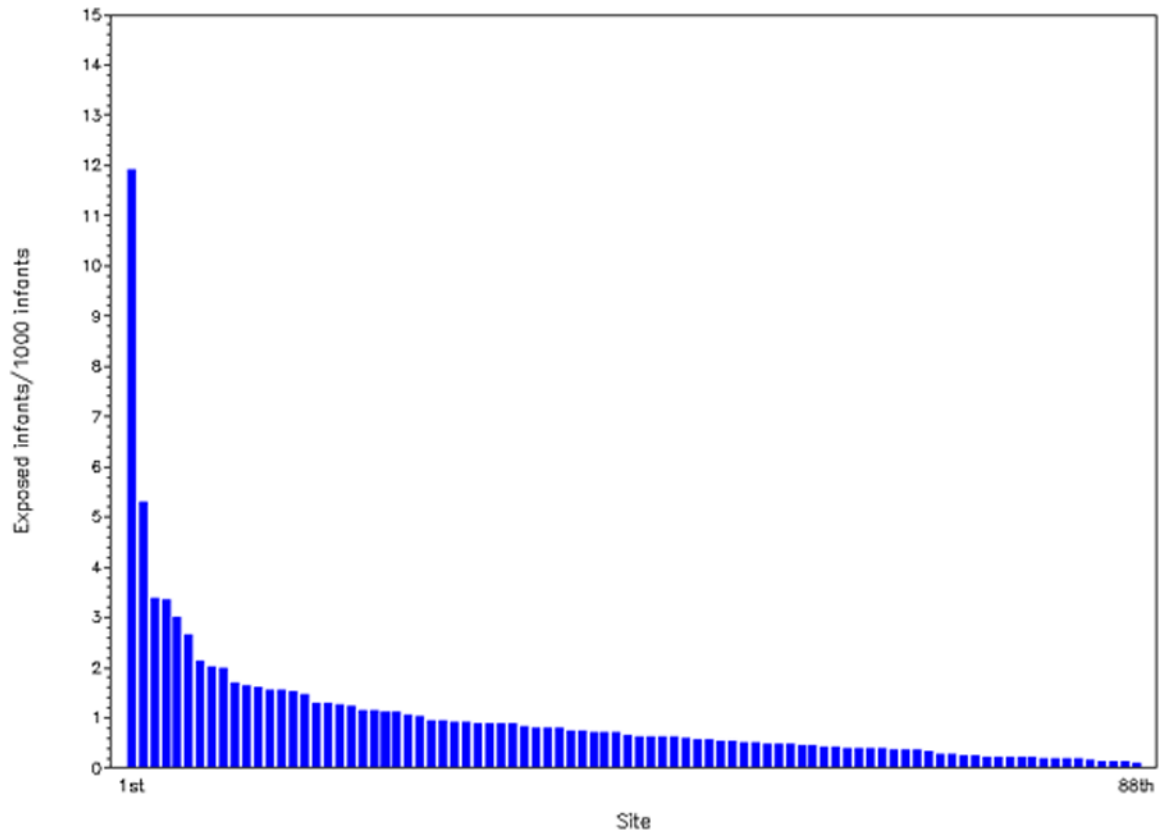
**Fig. 1.**  
Octreotide use over time.

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**Fig. 2.**  
Octreotide use by site.

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**Table 1****Demographics\***

	<b>N = 428</b>
Gestational age (weeks)	33 (28, 37)
Birth weight (g)	2290 (1110, 3090)
Delivery by Cesarean section, n (%)	277 (66)
Male, n (%)	233 (55)
Race/ethnicity, n (%)	
White	199 (49)
Black	68 (17)
Hispanic	121 (30)
Other	20 (5)
Inborn, n (%)	269 (63)
Postnatal age (days)	
On first octreotide day	27 (11, 63)
Weight (g)	
On first octreotide day	3050 (2290, 3815)
Mechanical ventilation, n (%)	
On first octreotide day	225 (53)
Inotropes, n (%)	
On first octreotide day	68 (16)
Length of stay (days)	62 (32, 115)
Any major congenital anomaly	239 (56)
Congenital heart disease	112 (26)

\* Data presented as median (interquartile range), unless otherwise specified.

**Table 2****Octreotide indications**

	Courses, n (%) <sup>*</sup> N = 490
Chylothorax	245 (50)
Pleural effusion	158 (32)
Hypoglycemia	110 (22)
Gastrointestinal hemorrhage	48 (10)
Bloody stools	25 (5)
Pericardial effusion – acute	13 (3)
Lymphangiectasia	3 (1)
Congenital lymphedema	1 (0.2)

\* Multiple diagnoses per course were allowed; thus, sum of % >100.

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**Table 3****Concomitant medications**

	<b>Courses, n (%) N = 490</b>
Vancomycin	259 (53)
Gentamicin	220 (45)
Furosemide	217 (44)
Fentanyl	165 (34)
Midazolam	154 (31)
Morphine	133 (27)
Albumin	112 (23)
Albuterol	96 (20)
Ampicillin	94 (19)
Dopamine	93 (19)
Ranitidine	81 (17)
Acetaminophen	65 (13)

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Table 4

Laboratory adverse events and serious adverse events

	Adverse Events		Serious Adverse Events	
	Courses, n (%) N=490	Days (/1000 infant-days) N=7793	Courses, n (%) N=490	Days (/1000 infant-days) N=7793
<b>Serum electrolytes</b>				
Hyperglycemia > 250 mg/dL	6 (1)	7 (1)	0	0
Hypoglycemia < 40 mg/dL	11 (2)	22 (3)	3 (1)	3 (0.4)
Hyponatremia > 150 mmol/L	15 (3)	23 (3)	1 (0.2)	1 (0.1)
Hyponatremia < 125 mmol/L	19 (4)	27 (4)	1 (0.2)	1 (0.1)
Hyperkalemia > 6 mmol/L	98 (20)	161 (21)	11 (2)	15 (2)
Hypokalemia < 3 mmol/L	63 (13)	102 (13)	12 (2)	19 (2)
Hypercalcemia > 12.5 mg/dL	2 (0.4)	4 (1)	2 (0.4)	3 (0.4)
<b>Renal dysfunction</b>				
Elevated BUN > 70 mg/dL	41 (8)	126 (16)	19 (4)	42 (5)
Elevated creatinine > 1.7 mg/dL	15 (3)	49 (6)	7 (1)	8 (1)
<b>Liver dysfunction</b>				
Elevated AST > 500 U/L	6 (1)	9 (1)	1 (0.2)	1 (0.1)
Elevated ALT > 500 U/L	2 (0.4)	3 (0.4)	0	0
Elevated GGT > 100 U/L	40 (8)	91 (12)	22 (4)	39 (5)
Direct bilirubin > 5 mg/dL	49 (10)	117 (15)	16 (3)	39 (5)
<b>Complete blood count</b>				
Leukocytosis > 25,000/mm <sup>3</sup>	56 (11)	152 (20)	15 (3)	38 (5)
Leukopenia < 5000/mm <sup>3</sup>	41 (8)	80 (10)	1 (0.2)	1 (0.1)
Thrombocytopenia < 100,000/mm <sup>3</sup>	88 (18)	368 (47)	9 (2)	11 (1)
Thrombocytosis > 600,000/mm <sup>3</sup>	22 (5)	35 (5)	2 (0.4)	3 (0.4)

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

**Table 5****Clinical adverse events**

	<b>Courses, n (%) N=490</b>
<b>Gastrointestinal</b>	
Necrotizing enterocolitis–medical	8 (2)
Necrotizing enterocolitis–surgical	1 (0.2)
Focal intestinal perforation	1 (0.2)
<b>Neurologic</b>	
Intraventricular hemorrhage	2 (0.4)
Periventricular leukomalacia	2 (0.4)
Seizure	4 (1)
<b>Cardiovascular</b>	
Hypotension requiring pressors	57 (12)
<b>Dermatologic</b>	
Rash	7 (1)
<b>Any clinical adverse event</b>	<b>70 (14)</b>

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