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Octreotide use and safety in infants with hyperinsulinism

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Abstract

Background—Octreotide is a synthetic peptide analog of naturally occurring somatostatin. Octreotide is used off-label in children <6 years of age for hyperinsulinism, chylothorax, and gastrointestinal bleeding. There is a lack of controlled data on efficacy or potential adverse events from this off-label use.

Methods—Three pediatric hospitals participated in this study. Patients were hospitalized January 2007–December 2010 and administered octreotide for congenital hyperinsulinism (CHI) at least 1 day. Variables assessed included octreotide dosage, patient demographics, medical interventions, concomitant medicines, serious adverse events (SAEs) including necrotizing enterocolitis (NEC), and mortality.

Results—The 103 patient sample had a median gestational age of 38 weeks. During the study period, two patients died: one from NEC and the other from cardiomyopathy/sepsis. There were 11 other SAEs in the 101 surviving patients.

Conclusion—This study highlights potential risks in administering octreotide off-label. This study, like several other published studies, has highlighted NEC in a full-term infant treated with octreotide. It is important to study the efficacy and the safety of octreotide for hyperinsulinism. In the interim, it might be prudent to prescribe octreotide in CHI neonates only in the absence of other risk factors for NEC.

Keywords

hyperinsulinism; octreotide; necrotizing Enterocolitis; infants; safety; pharmacoepidemiology; pharmacoepidemiology

INTRODUCTION

Congenital hyperinsulinism (CHI) is the most common cause of persistent hypoglycemia in neonates, infants, and children. ¹ Currently, diazoxide is the only drug approved by the US

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CONFLICT OF INTEREST

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Food and Drug Administration (FDA) for the treatment of this condition in children. If diazoxide fails, second-line treatment options for children are limited.² In addition, the management of pediatric CHI is complex and frequently requires interventions that put patients at high risk for complications including fluid overload, heart failure, sepsis, thrombosis, and necrotizing enterocolitis (NEC).

Octreotide (brand name Sandostatin) is a synthetic long-acting peptide analog of naturally occurring somatostatin.¹ Octreotide is frequently used as a second-line therapy for children who are not responsive to diazoxide or as a first-line therapy in areas of the world where diazoxide is not available.³ In addition to its insulin-inhibitory effects, octreotide has other effects including suppression of luteinizing hormone response to gonadotropin releasing hormone, decrease in splanchnic blood flow, and inhibition of serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide release.⁴ Octreotide is also used in adults to suppress growth hormone, to inhibit severe diarrhea and flushing with carcinoid tumors, and to decrease severe watery diarrhea associated with vasoactive intestinal polypeptide tumors. Off-label use of octreotide in children has been reported for conditions such as treatment of chylothorax, congenital hyperinsulinism, and gastrointestinal bleeding.⁵ Octreotide has been used in the treatment of newborns, infants, and children with hyperinsulinemic hypoglycemia since the 1980s⁶ and is currently broadly used around the world for the management of children with diazoxide-unresponsive CHI.³ Octreotide's off-label use in pediatric clinical practice has been discussed at the FDA's Pediatric Advisory Committee (PAC) starting in 2007. However, one of the first reports in the literature of octreotide-related NEC was in 2010.⁷

The FDA's PAC reviews drug use and safety in children two to three times per year according to pediatric safety labeling changes that have occurred in the previous 18 months. Octreotide was discussed at two meetings on 11 April 2007 and on 18 November 2008. At the first meeting, the PAC discussed the usage and safety data on octreotide in children and noted instances of NEC and hypoxia in octreotide-treated children. After noting that pediatric octreotide usage was increasing, particularly in neonates, the PAC recommended a 1-year update focusing on observed adverse events. At the 2008 meeting, the PAC recommended a change in octreotide's labeling information to include information about serious pediatric adverse events and to acknowledge that no causal association has been established. The PAC also recommended that FDA continue its standard ongoing safety monitoring. In January 2010, octreotide's labeling was changed to reflect the PAC's recommendations: "No formal controlled clinical trials have been performed to evaluate the safety and effectiveness of Sandostatin in pediatric patients under age 6 years. In post-marketing reports, serious adverse events, including hypoxia, necrotizing enterocolitis, and death, have been reported with Sandostatin use in children, most notably in children under 2 years of age. The relationship of these events to octreotide has not been established as the majority of these pediatric patients had serious underlying co-morbid conditions."⁸ The PAC recommended that FDA perform a study on off-label use of octreotide in children.

A potential biological mechanism for NEC after use of octreotide is the decrease of splanchnic blood flow contributing to a general lack of adequate gastrointestinal blood flow. Because NEC occurs almost exclusively in premature infants,⁹ it is important that any study

of octreotide use in children and incidence of NEC as a potential adverse drug event focus on fullterm infants.

METHODS

Through a pediatric hospital and FDA collaboration known as Kidnet, we collected a retrospective convenience sample of patient medical records for 103 children admitted to a hospital setting who were primarily diagnosed with hyperinsulinism and treated with octreotide.

Three tertiary care pediatric hospitals participated in this study: Children's Hospital of Philadelphia, Children's National Medical Center, and Mattel Children's Hospital University of California Los Angeles. Records were extracted by medical personnel associated with each institution. If no personnel from the site were available, FDA provided personnel. All charts abstracted were de-identified electronic medical records (EMRs). Pharmacy records identified drug use and dates of drug use. Institutional Review Boards approved the protocol at all the participating clinical sites and at the FDA before the study commenced.

The data collection form for this study was kept as simple as possible and was clinically based including demographic information, drug use information, medical interventions, other drug exposures, and adverse event information. Patients in the sample were hospitalized between January 2007 and December 2010, were administered octreotide for CHI for at least 1 day, and were <7 years of age during the study period. Patients with preexisting NEC were excluded so as not to bias study results.

The main outcomes of our study were mortality and other serious adverse events (SAEs) including NEC. The outcome of NEC was defined as the diagnosis in the EMR and surgical or and/or radiographic evidence of pneumatosis intestinalis with or without perforations. Cause of death was determined by the death certificate or autopsy report in the patient record. In general, exclusions to the SAE category were clinical entities that existed before the drug was started. No other criteria for exclusion were utilized. A regulatory definition was used for SAEs: "Any adverse drug experience... that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect...".¹⁰ Because the study was small and uncontrolled, and the detail of physician attribution of causality was weak, we did not include causality in the analysis.

Patient records were extracted on a paper form, which was then manually entered into a Microsoft Access database. Descriptive statistical analysis was performed in Microsoft Excel exported from the Microsoft Access database, then entered into Stata 12 (StataCorp LP, College Station, TX, USA).

RESULTS

In our sample, there were 103 children diagnosed with hyperinsulinism and were exposed to octreotide. During the study period, 101 infants survived with 96 discharged home. Two

patients died: one from NEC and the other from cardiorespiratory failure secondary to cardiomyopathy, chronic lung disease, and sepsis. For the overall study, patient gender was evenly split, while the majority of the patients were White/Caucasian (Table 1).

Most of the patients were born at a gestational age greater than 36 weeks. Patient birth weights were mostly between 3 and 4 kg (Table 2). The median age in days at first exposure to octreotide was 15 weeks ranging from 1 to 313 weeks. There were three patients under 32 weeks gestational age. Octreotide was administered intravenously to two of these patients and subcutaneously to the other.

Other treatments for the hyperinsulinism diagnosis besides octreotide were diazoxide, glucagon, and pancreatectomy. Sixty-four patients were given diazoxide in addition to octreotide. Of these, 34 had diazoxide administered before octreotide began while 23 had diazoxide administered at the same time or after octreotide began. The remaining did not record the date of diazoxide administration. The dosage of diazoxide was not recorded for this study. Pancreatectomy was documented in 20 patients. Of the 20, the date of the pancreatectomy was recorded for six patients. All of those six received their pancreatectomy after octreotide therapy began.

Serious adverse events were documented in 10 patients who survived the study period and two who died (patients may have experienced more than one SAE): hyperglycemia (three), thrombosis (two), complications of G-tube placement (one), hypoxia (three), hypotension (one), hypoglycemia (three), intussusception (one), hypoglycemic seizure (one), lipohypertrophy at injection sites (one), and NEC (one) (Table 3). Neither of the patients with thrombotic SAEs received glucagon. CHI patients do have the risk of thrombosis from indwelling catheters. The probability of experiencing an SAE was no different in the premature infants (<36 weeks gestational age) compared with the full-term infants (>36 weeks gestational age) ($p = 0.74$).

One patient developed NEC in this study. This patient was female with non-syndromic CHI who spent 4 days in the neonatal intensive care unit, admitted at 2 weeks of age. Her birthweight was 3.5 kg (4.1 kg at the time of treatment with octreotide) with a gestational age of 39 weeks. She was diagnosed with CHI and was given diazoxide 2 days before admission. Patient comorbidities included patent ductus arteriosus (PDA), respiratory distress, and heart block type 1. She was treated with intravenous dextrose, continuous intravenous glucagon, and diazoxide. Diazoxide treatment began 2 days before octreotide started and continued after octreotide began. Other concomitant medications for this patient included dopamine, gentamicin, vancomycin, fentanyl, furosemide, atropine, cisatracurium, calcium gluconate, potassium chloride, and sodium bicarbonate. Octreotide was started the day of admission with a regimen of 4 mcg/kg administered three times per day subcutaneously with a total duration of 3 days throughout the admission. The patient had four SAEs identified: hypoxia, hypotension, hyperglycemia, and NEC, all beginning 3 days after admission. Her hyperglycemia was considered to be an adverse effect caused by therapy (glucose/glucagon) for her CHI. The patient died from NEC, which was verified by a pathology report: “abdominal distension; small bowel discolored, thinned, and friable with

pneumatosis intestinalis and multiple perforations. Serosanguinous ascites fluid included fecal material.”

We have calculated an estimate in our sample of the occurrence of NEC before octreotide use and after octreotide use in the setting of no event recurrence: before = 0/103 (95%CI 0.0000 to 0.0352) and after = 1/103 (95%CI 0.0002 to 0.0529). The estimate of NEC in full-term infants in the general population, from the literature,^{11,12} is 0.0001 95%CI 0.0000 to 0.0001.

DISCUSSION

From our sample of 103 mostly full-term infants diagnosed with hyperinsulinism and administered octreotide, 12 experienced an adverse event. One patient developed NEC and later died. Laje *et al.*⁷ found a rate of 2% of NEC in neonates administered octreotide for hyperinsulinism at a single center. Four of the 197 neonates who developed NEC in the Laje study did not have risk factors for developing NEC other than octreotide. Reck-Burneo *et al.*¹³ published a case study of a full-term 22 day neonate that presented with nausea and vomiting 3 days after starting octreotide therapy for hyperinsulinism. After multiple surgeries, bowel function was preserved and the infant’s life was saved. This case was notable for the onset of NEC right after octreotide was started, suggesting that octreotide may indeed have contributed to the outcome. Another case of fulminant NEC after several weeks of initiation of octreotide in an older infant was recently reported.¹⁴ Therefore, there is precedent for octreotide being reported as a risk factor for NEC.

In a previous study of children with hyperinsulinism treated with octreotide, elevation of liver enzymes was the most common adverse event (almost 50%).¹⁵ This was not noted in our study, possibly due to the lack of long-term follow-up data for our patients. It is possible that the overall low rate of SAE reporting (especially hypoglycemia and hyperglycemia) was due to data extraction error and not due to very low rates of select SAEs.

Mortality is the most significant aspect of the SAEs in our sample. One infant died of cardiomyopathy, which has not previously been reported to be associated with pediatric octreotide use. The cause of death for the patient who developed NEC is explored here. This patient was a full-term infant with a PDA. The presence of a PDA, which can cause decreased blood flow both in the gastrointestinal tract as well as in other areas of the body, suggests that there was a predisposing condition that may have contributed to the NEC. Therefore, the cause of NEC in this patient was clearly multifactorial.

One limitation of this study is that the sample size is small for detecting certain adverse events such as NEC. In addition, we did not have access to the level of clinical detail that would be optimal as the scope of this study was limited to certain adverse events of interest and octreotide usage information. For instance, if there were follow-up questions about a patient, the approved study protocol did not allow the authors to go back into patient records for additional details.

This sample is not intended to evaluate the efficacy of octreotide use in hyperinsulinism in infants. Rather, we show that the off-label use of octreotide in hyperinsulinism in full-term

infants and children has the potential risk for adverse events including NEC while its clinical benefit/risk ratio remains unestablished. Although there are some data^{3,16} on the use of octreotide in neonatal hyperinsulinism, we suggest that the efficacy and the safety of octreotide for hyperinsulinism need to be studied in the infant population with this new information.

In the interim, it might be prudent to prescribe octreotide in CHI neonates only in the absence of other risk factors for NEC.

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KEY POINTS

- There is off-label use of octreotide in infants with hyperinsulinism.
- The safety and efficacy of octreotide have not been demonstrated in the context of this use.
- A described adverse event associated with octreotide in infancy is NEC.

Table 1Demographics of infants receiving octreotide for hyperinsulinism ($N = 103$)

	No. of patients
Gender	
Female	51
Male	50
Not recorded	2
Race/ethnicity	
White	52
Other	31
Hispanic	13 *
Black	3
Asian	1
Not recorded	4
Location admitted	
Outside ICU	75
NICU	23
PICU	2
Not recorded	3
Octreotide route of administration	
Subcutaneous	53
Intravenous	45
Both	3
Not recorded	2

ICU, intensive care unit; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit.

*
One patient identified as both White and Hispanic.

Table 2Clinical information for infants treated with octreotide for hyperinsulinism ($N = 103$)

Variable	Median	Range	No. of patients
Gestational age	38 weeks	28–40 weeks	84
Birth weight	3.7 kg	1.0–5.6 kg	50
Age at study entry	15.2 weeks	0.9–313.2 weeks	103
Weight at study entry	6.4 kg	2.3–31.4 kg	103
Hospital length of stay	24.5 days	1–90 days	102
Octreotide daily dose	8.96 mcg/kg	1.33–96 mcg/kg	100
Octreotide duration	8 days	1–84 days	103
Gestational age breakdown			
28 to <31 weeks *			1
31 to <34 weeks			5
34 to <37 weeks			19
37 to <40 weeks			55
40 weeks			4
Not recorded			19

* 28-week gestational age infant was not administered octreotide until 93 days of age.

Table 3Patients with hyperinsulinism receiving octreotide that had a serious adverse event ($n = 12$)

	Gestational age	Birth weight	Age in weeks at admission	SAE specification	SAE days after admission	SAE days after octreotide	Octreotide dose (mcg/kg)	Times per day administered	Route of administration	Days administered	Cause of death
1	—	—	69.6	Complications of G-tube placement	24	23	5.95	2	Intravenous	14	N/A
2	—	—	30.45	DVT right basilic vein, treated Lovenox	6	3	3.06	1	Intravenous	1	N/A
3	37	—	7.29	Hyperglycemia	11	10	4.52	3	Intravenous	5	N/A
4	38	—	1.29	Hyperglycemia (8 days before admission), Hypoglycemia (2 days after admission)	2	1	1.66	3	Intravenous	12	N/A
5	36.6	3.9	4.35	Hypoglycemia	37	37	3.8	4	Subcutaneous + intravenous	60	N/A
6	—	—	4.35	Hypoglycemic seizure after octreotide stopped	7	7	3.18	3	Subcutaneous + intravenous	8	N/A
7	32	3.54	4	Hypoxia	66	65		4	Intravenous	3	Cardiorespiratory failure 2° to cardiomyopathy, chronic lung disease, and sepsis
8	—	4.63	0.86	Hypoxia	0	0	3.71	4	Intravenous	2	N/A
9	36	—	43.5	Intussusception	—	—	3.9	3	Subcutaneous	5	N/A
10	40	—	48	Lipohypertrophy, bilateral thighs injection sites	24	16	3.5	3	Subcutaneous	15	N/A
11	39	3.5	2.1	NEC, hypoxia, hypotension, hyperglycemia	3	3	4	3	Subcutaneous	3	NEC
12			34.8	Thrombosis, right leg site of old line	2	2	3.04	2	Intravenous	4	N/A

—, information not recorded; SAE, serious adverse event; DVT, deep vein thrombosis; NEC, necrotizing enterocolitis; N/A, not applicable.