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Octreotide for the Management of Chylothorax in Infants and Children

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Chylothorax may occur spontaneously in the neonatal population or in the postoperative setting after thoracic duct injury or disruption of lymphatic channels. Following damage to the thoracic duct, chyle, a mixture of triglycerides, fatty acids, proteins, immunoglobulins, and lymphocytes, may accumulate in the pleural space, resulting in a chylothorax. The loss of fluid through excessive chyle drainage may result in nutritional, electrolyte, and immunologic complications.[1]

A number of therapeutic interventions have been used to reduce chyle production and promote resolution of a chylothorax. Initial management typically includes restriction or temporary cessation of enteral feedings. Enteral feedings high in medium-chain triglycerides (MCT), such as Portagen®, or parenteral nutrition may be used. These strategies alone are not successful in all patients. MCT formulas have been shown to produce resolution of chylothorax in approximately one-third of patients after two weeks, while parenteral nutrition typically results in resolution in 75 to 80% of cases by that time. In resistant cases, pleurodesis, ligation of the thoracic duct, or placement of drains and pleuroperitoneal shunts may be considered.[1,2] In the last several years, octreotide has become another option for management of patients with chylothorax. This issue of *Pediatric Pharmacotherapy* will review the pharmacology of octreotide and the reports of its use in the pediatric population.

Mechanism of Action

Octreotide is a long-acting synthetic analog of endogenous somatostatin. Like somatostatin, it is a potent inhibitor of growth hormone, glucagon, and insulin. It suppresses the release of leutenizing hormone in response to gonadotropin releasing hormone and inhibits the secretion of thyroid stimulating hormone. In addition, octreotide has a number of effects on the gastrointestinal system, including a decrease in splanchnic blood flow and inhibition of serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide. Octreotide has also been shown to inhibit gallbladder contractility and decreases bile acid secretion.[3,4]

In an animal model of chylothorax, octreotide administration has been shown to result in a shorter time to chylous fistula closure and cessation of chyle drainage. Although the exact mechanism by which the drug exerts its effects has not been defined, it is believed that the multiple effects of octreotide on the gastrointestinal tract and the reduction in splanchnic blood flow reduce thoracic duct flow and decrease the triglyceride content of chyle.[1]

Pharmacokinetics and Pharmacodynamics

After administration by either subcutaneous or intravenous (IV) routes, octreotide is rapidly absorbed from the injection site. Peak serum concentrations are typically reached within 30 minutes after injection. The estimated volume of distribution in adults is 13 to 14 L. Octreotide is approximately 65% protein bound, primarily to lipoprotein. It is both metabolized and excreted unchanged. The elimination half-life in adults is 1.7 hours, compared to 1 to 3 minutes for endogenous somatostatin. The duration of action is approximately 12 hours, but is highly variable. Elimination is prolonged in patients with renal dysfunction. In patients undergoing hemodialysis, octreotide clearance is reduced by 50%. The pharmacokinetic profile of octreotide has not been studied in the pediatric population.[3,4]

Use in Postoperative Chylothorax

Over a dozen case reports have been published describing the use of octreotide in infants and children with chylothorax, most in the postoperative setting. In 2001, Cheung and colleagues published the first report of using octreotide for the treatment of postoperative chylothorax in infants.[2] The two patients, a 3 month-old who underwent an atrial switch operation and a 15 month-old who had closure of a ventricular septal defect and resection of infundibular muscle, both developed chylothorax after initiation of enteral feedings. Conservative treatment with parenteral nutrition and a MCT formula failed to resolve the chylous drainage. Both patients were initially given subcutaneous octreotide at a dose of 10 mcg/kg/day, divided into three doses. After titration, the effective dose was 40 mcg/kg/day in the first patient and 20 mcg/kg/day in the second. Drainage was significantly reduced within 72 hours of initiating therapy. Treatment continued for 8 days in the first patient, until resolution of the chylothorax, followed by a weaning of the dose over 4 days. In the second patient, treatment lasted for 5 days, with weaning over 3 days. Neither patient experienced a recurrence.

Also that year, Pratap and coworkers published their experience with octreotide in six children with postoperative chylothorax.[5] The patients, ranging in age from 1 to 10 years, had all undergone cardiac surgery. Initial management included use of a MCT formula in three patients and parenteral nutrition in one. After dietary management failed, octreotide was initiated as a continuous infusion at a dose of 1 to 4 mcg/kg/hr. Duration of therapy ranged from 5 to 9 days. Pleural drains were removed within 5 days.

Rosti and colleagues reported two similar cases the following year, using octreotide infusions of 0.5 to 1 mcg/kg/hr.[6] Time to discharge was shorter in the octreotide-treated children (13 and 15 days) than in a previous group of patients treated with dietary or surgical methods (average 25.5 days). Another case was reported by Al-Zubairy and Al-Jazairi describing their use of octreotide in a 5 month old with trisomy 21 who developed a chylothorax after atrioventricular canal repair.[7] An octreotide infusion of 3.5 mcg/kg/hr reduced chylous drainage from 7.14 ml/hr prior to initiation to 0.83 ml/hr on day 4 of treatment. Therapy was discontinued after 4 days with no significant reaccumulation.

Two additional case reports have recently been published in the *Annals of Thoracic Surgery*.[8,9] Tibballs and colleagues described a term infant with complex congenital heart defects who developed a chylothorax four days after cardiac surgery (two days after the initiation of enteral feedings).[8] When insertion of a drain and cessation of enteral feeds did not produce a reduction in chylous flow, octreotide was initiated at a dose of 3 mcg/kg/hr. The infusion was gradually increased to 5 mcg/kg/hr with drainage stopping within the next day. Therapy was continued for a total of three days. Fluid accumulation resumed after 48 hours, but octreotide was not restarted because of the decision to redirect care. The patient expired within the next week.

In that same issue, Hamdan and Gaeta described their patient, a 3 month old with hypoplastic left ventricle, double outlet right ventricle, transposition of the great arteries, and pulmonary obstruction.[9] Surgery to create bilateral cavopulmonary connections was complicated by the development of bilateral chylothoraces on postoperative day 6, shortly after starting enteral feeds. The patient underwent surgical ligation of the shunt and mechanical pleurodesis, but continued to have pleural drainage, electrolyte imbalances, and repeated infections. On postoperative day 28, octreotide was started at an infusion rate of 0.5 mcg/kg/hr. The infusion was gradually increased to 2 mcg/kg/hr, with a drop in pleural drainage from 270 ml/day to an average of 2 to 11 ml/day. Enteral feedings were resumed during treatment. On day 37, therapy was switched to 20 mcg/kg/day, divided and given as three separate IV doses. Therapy was concluded on postoperative day 67, without reaccumulation of the effusions.

In addition to its use during cardiac surgery, octreotide has also been used in chylothorax occurring after surgical repair of congenital diaphragmatic hernia and gastroschisis.[10,11] In each report, a single infant is described who was successfully treated with octreotide after failing conservative therapy with chest tube insertion and the administration of MCT formula or parenteral nutrition.

Use in Spontaneous and Congenital Neonatal Chylothorax

Four case reports of octreotide in the management of neonatal chylothorax have been published in the *Journal of Perinatology*.[12-15] In 2003, Goto and colleagues reported their treatment of a chylothorax in a 467 gram neonate born at 26 weeks gestational age.[12] The patient was placed on mechanical ventilation immediately after birth. At 16 days of age, a pleural effusion was noted. On day of life 23, a week after initiating enteral feeding, the previously clear effusion became white. A

change to a MCT formula failed to reduce chylous flow, so at 36 days, octreotide was initiated as an infusion at 0.3 mcg/kg/hr. Chest tube drainage stopped the following day. Octreotide was continued for a total of 3 days, with resolution of the effusion.

In 2004, similar cases were reported by Coulter and Sivasli and colleagues.[13,14] The patient described by Coulter, a 906 gram, 26-week infant, developed a pleural effusion on day of life 65.[13] Drainage and restriction to parenteral nutrition failed to reduce chylous flow. Octreotide was initiated at 4 mcg/kg/day, given subcutaneously, but was switched to the IV route and increased to 24 mcg/kg/day (1 mcg/kg/hr) before drainage decreased. Therapy was discontinued after 28 days. In the case by Silvasli et al, a 2.1 kg, 34 week infant was treated for a spontaneous chylothorax with IV octreotide at 3.5 mcg/kg/hr.[14] Chest tube drainage cleared within 72 hours. Octreotide was gradually tapered off over 2 days, without reaccumulation of the effusion.

Also this year, Young and colleagues reported a rare case of congenital chylothorax diagnosed *in utero* in a 3.7 kg term neonate.[15] When severe respiratory distress developed despite drainage, octreotide was initiated at a dose of 40 mcg/kg/day given subcutaneously. The dose was eventually increased to 70 mcg/kg/day and continued for a total of 17 days, with resolution of the chylothorax.

Use in Radiation-induced Chylothorax

Octreotide has also been used successfully in a 12 year old male with bilateral pleural effusions attributed to radiation for a mediastinal mass resulting from non-Hodgkin's lymphoma.[16] After failure of conservative treatments over a 2 month period, octreotide was initiated with an infusion of 0.35 mcg/kg/hr. The dose was reduced to 0.215 mcg/kg/hr after the patient developed hypoglycemia. Drainage was reduced from an average of 380 ml/day to zero within 3 days of starting octreotide. Therapy was continued for 2 weeks, with no reaccumulation.

Adverse Effects

The most common adverse effects reported after octreotide use in adults include: arrhythmias (9%), injection site pain or hematoma (7.5%), headache (6%), nausea, vomiting, constipation, or diarrhea (5-10%), hyperglycemia or hypoglycemia (1-2%), dizziness, fatigue, weakness, flushing, edema, pruritus, alopecia, joint pain, biliary sludge, fat malabsorption, blurred vision, and symptoms of an upper respiratory tract infection or urinary tract infection (1 to 4%). Hypersensitivity reactions, including anaphylactic shock, have been reported, but appear to be rare. The frequency of some adverse effects varies with the disease state being treated. For example, bradycardia, hyperglycemia, and hypothyroidism occur more often in patients being treated for acromegaly.[3,4]

In the pediatric cases published to date, adverse effects have been uncommon. Hyperglycemia and hypoglycemia have each been reported in one patient.[13,15] Earlier this year, Mohseni-Bod and coworkers reported a case of necrotizing enterocolitis (NEC) in a neonate treated with octreotide.[17] The patient developed a chylothorax two weeks after repair of a coarctation of the aorta. When the effusion failed to resolve with an MCT formula, octreotide was initiated at 2 mcg/kg/hr and then titrated to 4 mcg/kg/hr. Within 72 hours, the patient developed fever, abdominal distension, and bloody stools. Radiographic and laboratory tests were consistent with NEC. Both octreotide and enteral feedings were discontinued, and the patient recovered over the next two weeks. Although causality was not established, this case highlights the need to monitor gastrointestinal function in infants receiving octreotide.

Drug Interactions

Concomitant administration of octreotide and cyclosporine may result in reduced cyclosporine serum concentrations.[3,4] The mechanism of this interaction appears to be a reduction in intestinal absorption of cyclosporine in patients receiving octreotide. Monitoring cyclosporine concentrations should minimize the risk of inadequate immunosuppression.

Octreotide has been shown to prolong the QT_c interval in some patients at therapeutic doses. Although there are no studies demonstrating an additive effect, it is recommended that patients not receive other agents which can prolong the QT_c interval, such as azole antifungals, cisapride, or macrolide antibiotics during octreotide administation.[4]

The manufacturer does not recommend mixing octreotide and parenteral nutrition solutions. Although infusions of octreotide appear physically stable when mixed with parenteral nutrition solutions, the mixture may result in the formation of a glycosyl octreotide conjugate, resulting in a reduced effect. Simultaneous Y-site administration is acceptable.[4]

Dosing

For the management of chylothorax in infants and children, two approaches have been used.

Octreotide may be administered subcutaneously at 20 to 70 mcg/kg/day, divided and given as three separate doses, or as an IV infusion starting at a dose of 1 to 4 mcg/kg/hr and titrating as needed to 10 mcg/kg/hr. The duration of therapy is typically determined by the reduction in the volume of pleural drainage. In the cases reviewed, duration of treatment ranged from 3 to 29 days, with a mean of 11 days. Octreotide was usually weaned over a 2 to 4 day period while the patient was monitored for reaccumulation of the effusion.[2,5-16] Patients receiving octreotide for prolonged periods should be monitored for malabsorption of dietary fats, and if necessary, supplemented with IV fat emulsion to prevent essential fatty acid deficiency.

Availability and Cost

Octreotide (Sandostatin®; Novartis) is available as an injection in 0.05 mg/ml, 0.1 mg/ml, 0.2 mg/ml, 0.5 mg/ml, and 1 mg/ml concentrations.[3,4] The average wholesale price (AWP) for Sandostatin® is $8.53 for a 0.05 mg/ml 1 ml amp, $16.60 for the 0.1 mg/ml 1 ml amp, and $79.87 for the 0.5 mg/ml 1 ml amp. The 0.2 mg/ml and 1 mg/ml strengths are available in 5 ml multi-dose vials, with an AWP of $170.72 and $842.01, respectively.

Summary

For infants and children who develop a chylothorax, octreotide offers an additional mode of treatment. In conjunction with chest tube insertion and restriction or elimination of dietary fats, octreotide has been shown to reduce chylous drainage and may shorten the length of hospitalization. Controlled trials are needed to substantiate the results seen in these cases and to further explore the safety of this regimen in the pediatric population.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 9/24/04:

1. Azacitidine (Vidaza®) was added to the Inpatient Formulary for the treatment of patients with myelodysplastic syndrome, refractory anemia, or chronic myelomonocytic leukemia.
2. Imatinib (Gleevec®), a protein-tyrosine kinase inhibitor used in patients with CML, was added to both Inpatient and Outpatient Formularies, with restriction to the FDA approved indications.
3. Porfimer sodium (Photofrin®) was added, with restriction to use in Barrett's esophagus.
4. The use of lansoprazole suspension is now restricted to pediatric patients. Pantoprazole suspension will be available for adults requiring an oral liquid proton pump inhibitor.
5. The restrictions on pemetrexed (Alimta®) were amended to include use as a second-line agent for locally advanced or metastatic non-small cell lung cancer.
6. Thalidomide (Thalomid®) was added to the Outpatient Formulary.

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