

Octreotide therapy for chylothorax in infants and children: A brief review

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Objectives: We review physiology and pharmacology relating to the use of octreotide for chylothorax in infants and children. We review the published experience of octreotide dosing in this context.

Data Source: Systematic review of the literature, including PubMed (English-only journals), citations from relevant articles, major textbooks, and personal files.

Conclusions: Octreotide has been used as a successful therapeutic adjunct in a small number of neonatal cases and a larger

number of pediatric cases. No consensus has been reached as to the optimal route of administration, dose, duration of therapy, or strategy for discontinuation of therapy. We suggest using higher doses (80–100 $\mu\text{g}/\text{kg}/\text{day}$) and initiating therapy early rather than using a low initial dose with upward titration. Duration of therapy required to elicit a significant response may vary between patients. (*Pediatr Crit Care Med* 2006; 7:576–579)

KEY WORDS: chylothorax; octreotide

Chylothorax is a disorder with a variety of causes and is often difficult and complex to manage. Depending on the etiology, conservative measures may not be adequate in a significant number of cases. Adjunctive use of the somatostatin analogue octreotide for chylothorax has been reported. However, experience with this substance is limited, and there is no consensus as to (1) whether it provides a benefit beyond traditional supportive and/or surgical therapies, (2) in which clinical scenarios it provides the greatest benefit, and (3) which dosing regimens are optimal. We present a synthesis of the current state of knowledge regarding the use of octreotide in chylothorax, with particular attention to congenital chylothorax. This work was approved by the University of Illinois Institutional Review Board.

DISCUSSION

Etiology and Pathophysiology

Chylothoraces are caused by developmental anomalies of the lymphatics, by

traumatic injury, or by obstruction of the lymphatic system, notably of the thoracic duct. Often the precise etiology may not be certain, particularly with congenital lesions.

Congenital, or primary, chylothorax is the most common type of pleural effusion seen during the neonatal period (1). Congenital chylothorax may present as acute respiratory distress at the time of birth or may develop subacutely during the first week of life. No specific etiology is identified in the majority of cases (2). Chylothorax is associated with syndromes known to involve abnormal development of the lymphatic system (3, 4). Nonimmune hydrops fetalis (NIHF) is associated with congenital chylothorax (5, 6) and may result from external compression of the duct by an intrathoracic space-occupying lesion such as congenital diaphragmatic hernia (7) or neuroblastoma (8). Kessel et al. (9) report an association between NIHF and hypothyroidism in a term infant presenting with congenital chylothorax. These authors cite decreased adrenergic stimulation of lymphatics, due to hypothyroxinemia, as the etiology of chylothorax (and hydrops) in this patient. Alternatively, massive protein losses into the chylous effusion may produce hydrops secondary to low intravascular oncotic pressure (10).

Traumatic injury to the thoracic duct is an often-encountered cause of chylothorax in the pediatric intensive care setting. Penetrating injury to the chest,

neck, or abdomen may lead to rupture of the duct. Additionally, blunt trauma or sudden hyperextension of the cervical spine—particularly after a meal, when the thoracic duct is more distended (11)—may lead to ductal rupture. Neck hyperextension during delivery has even been implicated as a cause of congenital chylothorax (1). Most traumatic injury to the duct is iatrogenic (11). Direct injury may potentially occur during any surgery in the vicinity of the mediastinum or involving the lower neck. Specific examples include repair of aortic coarctation, ligation of patent ductus arteriosus, and placement of extracardiac systemic-to-pulmonary shunts, esophageal procedures, and tumor resection. Beghetti and associates (12) recorded a mean interval of 7 days (range, 1–25 days) between surgical procedure and detection of chylous effusion. Chylothorax is a rare complication of central venous catheterization (11) and is thought to arise from thrombotic occlusion of the superior vena cava (SVC) rather than from direct trauma to the thoracic duct.

Conditions leading to thoracic duct obstruction or high SVC pressure are the last major etiological group. In addition to SVC thrombosis, other processes of neoplastic, inflammatory, or infectious origin may ultimately lead to internal (more common) or external (less common) occlusion of the SVC and/or the thoracic duct, with ensuing leakage of lymphatic fluid from the duct into the

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pleural space. Additionally, procedures such as the Fontan, which produce an increase in SVC pressure, are associated with chylothorax (12).

Diagnosis

The two primary findings used to diagnose chylous effusion are lymphocytic pleocytosis and elevated triglyceride levels. Beghetti et al. (12) define chylous effusion as having the following characteristics: >1,000 leukocytes/mL (>70% lymphocytes); triglycerides, >100 mg/dL; protein, >20 g/L; sterile culture; milky appearance; and positive Sudan III (a fat-soluble dye) staining of the fluid from enterally fed patients. Without enteral fat intake, it may be difficult to differentiate between chylous and nonchylous effusion.

Management

Conservative management of chylothorax consists of pleural fluid drainage, supportive ventilation, supplementation of fluid loss, and elemental diet or total parenteral nutrition (12, 13). A diet rich in medium chain triglycerides (MCTs) is often used, because MCTs enter directly into the portal circulation, bypassing the lymphatics, and therefore do not increase flow in the thoracic duct. The MCT-rich diet, however, has not been universally accepted (14). Brodman (15) summarized 34 cases of chylothorax and found that MCT diets were ineffective. Vain et al. (16) proposed the use of MCT oil initially and suggested that if chylous effusion reaccumulates or enteral intake is not tolerated, then enteral feedings should be withheld for 2 wks (16). In the absence of enteral feeding, absorption of gastrointestinal secretions from the gut is prevented, thereby reducing the volume of fluid potentially available for absorption into the thoracic duct (17). The use of an MCT-rich enteral diet, parenteral nutrition, thoracostomy tube drainage, and assisted ventilation led to successful resolution of chylothorax in 80% of cases (12), where improvement was defined as drainage of <10 mL/(kg/day) and failure as drainage >10 mL/(kg/day) after 4 wks of medical treatment.

Chylothorax in infancy presents a unique management challenge. When antenatal diagnosis is possible, therapies such as antenatal thoracentesis (18), pleuroamniotic shunt placement (19), or pleurodesis with the *Streptococcus pyo-*

genes-derived sclerosant OK-432 (Picibanil) (20, 21) may prevent pulmonary hypoplasia, improve respiratory function in the immediate postnatal period, and prevent severe asphyxia (13). Many newborns with chylothorax have not been fed, so withholding enteral feedings is not an option. Additionally, the basal rate of chyle production during the neonatal period has been estimated at 1.8 mL/kg/hr (22), which easily may exceed 25% of total maintenance fluid requirements for a newborn. Thoracostomy tubes are often necessary to maintain lung expansion and therefore to permit adequate lung function. However, an infant with persistent chylothorax and indwelling thoracostomy tubes may become quickly dehydrated (and protein-depleted) if fluids are not replaced aggressively.

Traditional management techniques are inherently suboptimal. Supportive therapies may fail or may take longer than 14 days to allow for resolution of lymphorrhoea. Chylous fluid is rich in lymphocytes (predominantly T-lymphocytes), small-molecular-weight proteins (albumin, globulins, fibrinogen, prothrombin), and triglycerides (11). The patient may suffer from the effects of lost fluid, immunoglobulins, protein, clotting factors, or electrolytes. Thus, patients are at risk for marked immunocompromise (14, 23), third-spacing due to lowered serum oncotic pressure (10), and significant electrolyte disturbances, the most common of which are hyponatremia, acidosis, and hypocalcemia (24). Surgical therapies include direct repair of the thoracic duct, duct ligation below the diaphragm (via thoracoscopy or open thoracotomy), mechanical pleurodesis, chemical pleurodesis, pleurectomy, and pleuroperitoneal shunt placement (11). These techniques are invasive and are generally not considered as viable for critically ill infants.

Somatostatin and Octreotide

The only pharmacologic agents that have been used successfully to manage chylothorax are somatostatin and its analog, octreotide. Somatostatin is a widely-distributed polypeptide hormone that has a host of modulatory effects on gastrointestinal and endocrine function. Most of these effects are inhibitory and have been extensively reviewed elsewhere (25).

The mechanisms by which somatostatin and octreotide inhibit thoracic duct flow are not well known. Octreotide may

act directly on somatostatin receptors in the splanchnic circulation to reduce lymph fluid production (26–28). Thoracic duct lymphatic flow depends on splanchnic vascular tone as well as gastric motility (29). Octreotide decreases the volume of gastric, pancreatic, and biliary secretions (17), therefore reducing the volume and protein content of fluid within the thoracic duct (17).

Nakabayashi and coworkers (29) were the first group to clinically demonstrate a reduction in lymphatic flow through the thoracic duct after administration of somatostatin. Ulibarri et al. (30) subsequently reported that somatostatin, when administered to an adult patient with chylothorax, resulted in diminution of the chylous effusion. Somatostatin has subsequently been used with success in adults, infants, and children with chylothoraces, although pediatric data come primarily from patients who developed chylothorax as a complication of cardiothoracic surgery (25, 27, 31).

Octreotide is a synthetic analogue of somatostatin with nearly identical therapeutic properties. Somatostatin has fallen out of favor in recent years because octreotide has a comparatively longer half-life, has greater potency, is synthetic, and can be administered either as an intravenous infusion or subcutaneously (25). Octreotide is >60% lipoprotein bound in plasma, undergoes first-order kinetics, has a relatively short elimination half-life (100 ± 5 mins, in adults), and undergoes extensive hepatic metabolism (30% to 40%) (32). After subcutaneous injection, peak concentration is achieved after 20–30 mins and is 20% to 40% of the peak concentration achieved after intravenous injection (32). These pharmacokinetic data are derived from adult studies, and no specific pharmacokinetic data are available regarding this drug in infants and children.

Review of the literature reveals significant heterogeneity in octreotide dosing regimens. Dosing regimens from published case reports are summarized in Table 1. Therapy duration ranges from 3 to 27 days (33, 34). Subcutaneous, intravenous bolus, and intravenous infusion are all modes of administration that have been used. Some groups used more than one modality in a given patient. Intravenous infusion dosing ranged from 0.3 to 10 $\mu\text{g}/\text{kg}/\text{hr}$ (7–240 $\mu\text{g}/\text{kg}/\text{day}$). In fact, the dose required to elicit a significant reduction in lymphorrhoea was quite variable. Some authors began treatment with a lower dose and tapered upward, and some authors tapered down the

Table 1. Octreotide dosing regimens reported in the literature

Reference	No. of Patients	Dose Used, $\mu\text{g} \cdot \text{kg}/\text{day}$	Route	Total Duration of Therapy, Days	Duration of Taper, Days
36	1	84-168	IV infusion	14	3
25	2	24	IV infusion	3-7	Unclear
27	2	10-40	SC	15	4
28	1	10	SC	<10	Unclear
33	1	7	IV infusion	3	Unclear
43	1	84	IV infusion	8	3
2	1	84	IV infusion	4	Unclear
34	1	84	IV infusion	27	3
38	1	72-120	IV infusion	5	2
44	1	12-48	IV infusion and q8h bolus	21	Unclear
45	1	20-40	SC	16	Unclear
37	1	4-24	SC, IV	12	7
39	7	60	IV infusion	10	None
41	1	48-96	IV infusion	3	None
46	1	7	IV infusion	11	8
47	2	12-24	IV infusion	7	3-4
48	1	12	IV infusion	5	None
49	1	72	IV infusion	4	None
36	1	12-240	IV infusion	10	Unclear
40	3	40-96	SC, IV	7-14	0-3

IV, intravenous; SC, subcutaneous.

dose at the end of therapy. Tapering upward was a clearly effective maneuver in some studies (35, 36). Tapering was usually longer, on the order of 7 days (37), if chylous effusion recurred. There was no apparent consensus about how long therapy should be continued after cessation of lymphorrhea. In the majority of cases where therapy was started at moderate to higher doses (with the exception of Goto et al. [33], a reduction in chest tube output to <10 mL/day was typically observed after approximately 3 days of therapy. In 13 of the 17 reports appearing in Table 1, chylothorax resolved within 6 days from commencement of octreotide therapy (most within 3 days). The range of time for chylothorax resolution in these 17 reports is 16 hrs to 18 days (38, 39). Recurrence of chylothorax was noted in two patients after successful treatment and withdrawal of octreotide (38, 39). One patient died (38) and the other responded to a second course of octreotide (39). It is not clear from the existing data whether a more brisk response or a need for shorter therapy was noted in patients with intravenous administration, in comparison with subcutaneous dosing. Additionally, it is difficult to ascertain whether constant infusion rather than bolus dosing is more effective.

Our own experience with octreotide in three cases is consistent with that reported in the literature. We have treated two patients with congenital chylothorax and one with postneonatal chylothorax that likely occurred as a complication of ductal ligation surgery. The time for res-

olution of chylothorax ranged from 1 day to 12 days, with the congenital lesions responding more quickly. Additionally, the dosing required to elicit a response was variable (Table 1).

Octreotide appears to be very well tolerated, even at the highest dosing ranges used. No significant side effects were noted in any of those studies included in Table 1. Potential adverse effects include cholelithiasis, liver impairment (including cholestasis), renal impairment, transient glucose intolerance (35, 38), hypothyroidism (39), and necrotizing enterocolitis (41). The possible association between octreotide and necrotizing enterocolitis, recently described by Mohseni-Bod et al. (42), is intriguing, because reduced flow in both arterial and lymphatic vasculature of the gut may be one mechanism by which octreotide reduces lymph production (27, 29, 38, 42).

Thus, the experience with somatostatin and octreotide in the management of pediatric chylothorax is still quite limited. Only a small number of case reports exist, and no consensus has been reached as to the optimal route of administration, dose, duration of therapy, or strategy for discontinuation of therapy.

CONCLUSION

We derive several conclusions from our review of the literature. First, octreotide is relatively safe, even at very high doses used for as long as 3 wks. Second, use of octreotide earlier in a patient's

clinical course may reduce fluid and electrolyte complications of chylothorax and may enable earlier removal of thoracostomy tubes. Third, earlier use of higher doses (i.e., on the order of 80 to 100 $\mu\text{g}/\text{kg}/\text{day}$) in theory may be preferable to a gradual upward tapering of the dose. Octreotide is associated with few adverse effects, and potential adverse effects can be easily monitored with simple laboratory tests and are easily treated. Additionally, the fact that some patients required titration of the dosage upward suggests a dose-response relationship, with higher doses being more effective. Furthermore, rapid cessation of lymphorrhea is a desired clinical outcome, and higher doses of octreotide may be beneficial in this regard. Fourth, the benefit of tapering the dose at the end of therapy intuitively makes sense but is not substantiated. Fifth, the best route of administration (i.e., subcutaneous, intermittent intravenous, or continuous intravenous) is unclear. Sixth, the possible association between octreotide and necrotizing enterocolitis should be noted when using octreotide in neonates. Last, a prospective, multicentered controlled trial of various octreotide dosing ranges vs. conventional therapy is needed.

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