Drugs in Focus: Octreotide Use in Children With Gastrointestinal Disorders

*Emmanuel Mas, †Osvaldo Borrelli, ‡Ilse Broekaert, §J. Martin de-Carpi, ||Jernej Dolinsek, ¶Erasmo Miele, #Corina Pienar, **C. Ribes Koninckx, ††Ruth-Anne Thomassen, ‡‡Mike Thomson, §§Christo Tzivinikos, and ||||Marc A. Benninga

ABSTRACT

Octreotide, a somatostatin analogue, has been used for more than 20 years in children with gastrointestinal bleeding, chylothorax or chylous ascites, intestinal lymphangiectasia, pancreatitis, intestinal dysmotility, and severe diarrhoea; however, until now, there is a lack of randomised clinical trials evaluating the efficacy of this compound in childhood. Hence, we aimed to review the literature in order to determine the evidence of its use and safety in children, using PubMed from 2000 to 2021 with the search terms ''octreotide'' and ''children'' and ''bleeding or chylous ascites or chylothorax or acute pancreatitis or lymphangiectasia or diarrhoea or intestinal dysmotility''.

Key Words: bleeding, children, chylous ascites, diarrhoea, ocreotide, somatostatin

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Learning Points

- Octreotide, a somatostatin analogue, has been used for more than 20 years in children with gastrointestinal bleeding, chylothorax or chylous ascites, primary intestinal lymphangiectasia, pancreatitis, intestinal dysmotility, and intractable secretory diarrhoea.
- Octreotide can be administered intravenously or subcutaneously, but not orally due to its digestion by pancreatic enzymes.
- Octreotide decreases lymphatic, splanchnic, hepatic, and portal blood flow, and modulate the motility of the stomach and small bowel.
- Octreotide can decrease the production of gastrointestinal (GI) peptides as well as the secretion of pancreatic enzymes and hormones. In addition, octreotide can decrease fluid secretion and stimulate absorption of water and electrolytes, hence improving chronic secretory diarrhoea.
- The level of evidence of paediatric studies is low. It is important to be cautious on octreotide's indication, efficacy, and dose, because no randomised controlled trials have been performed in children.
- Based on adult experience, and children case series, GI bleeding is the main indication of octreotide.

Somatostatin, discovered 40 years ago, is a peptide that is abundant in the gastrointestinal (GI) tract and exerts several biological activities. Synthetic agonists were developed, such as octreotide, with a longer half-life to allow the use for clinical practice. Today, octreotide is used for the treatment of several GI disorders, including GI bleeding, chylothorax and chylous ascites, primary intestinal lymphangiectasia, pancreatitis, intestinal dysmotility, and severe secretory diarrhoea. The aim of this paper is to provide information regarding the use, mode of delivery and safety of this agent in different GI disorders.

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From the *Unité de Gastroentérologie, Hépatologie, Nutrition, Diabétologie et Maladies Héréditaires du Métabolisme, Hôpital des Enfants, CHU de Toulouse; IRSD, Université de Toulouse, INSERM, INRAE, ENVT, UPS, Toulouse, France, the †Department of Paediatric Gastroenterology, Neurogastroenterology and Motility Unit, Great Ormond Street Hospital, London, UK, the ‡Department of Paediatrics, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany, the §Department of Paediatric Gastroenterology, Hepatology and Nutrition, Hospital Sant Joan de Déu, Barcelona, Spain, the ||Department of Paediatrics, University Medical Centre Maribor, Maribor, Slovenia, the ¶Department of Translational Medical Science, Section of Paediatrics, University of Naples ''Federico II'', Naples Italy, the #Department of Paediatrics, 2nd Paediatric Clinic, ''Victor Babes'' University of Medicine and Pharmacy, Timisoara, Romania, the **Paediatric Gastroenterology, La Fe University Hospital, Valencia, Spain, the ††Department of Paediatric Medicine, Division of Paediatric and Adolescent Medicine, Oslo University Hospital, Oslo, Norway, the ‡‡Centre for Paediatric Gastroenterology, Sheffield Children's Hospital NHS Foundation Trust, Sheffield, UK, the §§Department of Paediatric Gastroenterology, Al Jalila Children's Specialty Hospital, Dubai, UAEFrom the ||||Department of Paediatric Gastroenterology and Nutrition, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands.

Address correspondence and reprint requests to Marc A. Benninga, Department of Paediatric Gastroenterology and Nutrition, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands (e-mail: M.A.Benninga@amc.uva.nl) and Emmanuel Mas, MD, PhD, Unité de Gastroentérologie, Hépatologie, Nutrition, Diabétologie et Maladies Héréditaires du Métabolisme, 330, avenue de Grande-Bretagne, TSA 70034, 31059 Toulouse cedex 9, France (e-mail: mas.e@chu-toulouse.fr).

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Search Strategy

We identified articles on PubMed using the search terms ''octreotide'' and ''children'' and ''bleeding or chylous ascites or chylothorax or acute pancreatitis or lymphangiectasia or diarrhoea or intestinal dysmotility'' from 2000 to 2021. In addition, we included studies performed in adults, even before 2000, to complete the knowledge of case reports, case series and small studies available in children.

Mechanism of Action

Octreotide is a synthetic octapeptide, showing higher resistance to degradation than the natural tetradecapeptide somatostatin. Consequently, octreotide has a longer half-life than somatostatin, that is, 1–2 hours compared to 2–3 minutes, respectively. As somatostatin and octreotide have the same effects, the latter is preferred in clinical practice due to its longer half-life. Octreotide can be administered intravenously or subcutaneously, but not orally due to digestion by pancreatic enzymes (1).

Somatostatin is particularly abundant in the GI tract and there are two active peptides of either 14 or 28 amino acids, which are both encoded from the somatostatin-1 gene (2). The somatostatin-14 sequence is highly conserved across species and contains the biological activity site. Somatostatin-14 is the main form, even within the GI tract, but significant amounts of somatostatin-28 are also present in the small intestine, largely produced by enteroendocrine cells. In the GI tract, somatostatin is mainly found in the mucosa, localised in epithelial endocrine cells or in neurons of both submucosal and myenteric plexus. Its secretion is regulated by nutritional factors, low pH, gut regulatory peptides, and by both sympathetic and parasympathetic nervous systems. Five somatostatin receptors have been characterised (sst1–sst5) (2). All somatostatin receptors are expressed in the GI tract, and a receptor selectivity of somatostatin actions has been reported. For example, sst2 is involved in inhibition of gastric acid secretion, inhibition of gastric emptying, modulation of intestinal motility, modulation of epithelial function and blood flow, stimulation of ion transport and inhibition of chloride secretion by colonic epithelial cells, and inhibition of glucagon secretion, whilst sst5 is involved in inhibition of pancreatic amylase release and inhibition of glucagon secretion (2).

Octreotide may decrease lymphatic, splanchnic, hepatic, and portal blood flow, and modulate the motility of the stomach and small bowel (3). Octreotide can decrease the production of GI peptides as well as the secretion of pancreatic enzymes and hormones (1). In addition, octreotide can decrease fluid secretion and stimulate absorption of water and electrolytes, hence improving chronic secretory diarrhoea (2). Lanreotide, a newer alternative, shows a much longer half-life, and may be administered on a weekly or monthly basis with equal benefit.

Gastrointestinal Bleeding

In adults, there is documented efficacy for the use of octreotide in association with endoscopic procedures for the treatment of oesophageal variceal bleeding in cirrhotic patients (4). As shown in randomised controlled trials that studied sclerotherapy alone or in combination with octreotide (5) and band ligation alone or in combination with octreotide (6), octreotide significantly decreased bleeding recurrence (5,6). The dosage was 25 μg/h intravenously for 5 days (5) and 50 μg/h intravenously for 5 days (6), respectively. The consensus conference of Baveno VI recommends starting vasoactive drugs (terlipressin, somatostatin, octreotide) before endoscopy, in combination with endoscopic therapy, and to continue up to 5 days post-GI bleed (4). In children, octreotide has been used to control acute variceal (7–10) and non-variceal GI bleeding (7,9,11,12). One small study suggests that octreotide is more effective in controlling GI bleeding in children with portal hypertension than in those without (9) (Table 1). It is generally used via bolus application, with a dose ranging from 1 to 2 μg/kg over 30 minutes, followed by a maintenance dose of $2\,\mu g\,kg^{-1}\,h^{-1}$. Doses up to $5\,\mu g\,kg^{-1}\,h^{-1}$ are often needed, especially in significant GI bleeding requiring circulatory support, red cell transfusion and urgent upper GI endoscopic assessment/treatment. Generally, the infusion should not cease until a repeat endoscopy has ascertained complete cessation of ongoing bleeding. In one study, octreotide was safely used to augment endoscopic haemostasis at a dose of $2\,\mu g\,kg^{-1}\,h^{-1}$ starting 1 hour before endoscopy and subsequently tapered down to $1\,\mu g\,kg^{-1}\,h^{-1}$ after 2–3 days (8). Ideally, a referring hospital should start octreotide before the patient's transfer to a referral centre with endoscopic therapeutic experience, with a bolus of 1–2 μg/kg and a maintenance dose of $2\,\mu g\,kg^{-1}\,h^{-1}$. For prophylactic endoscopy, a maintenance dose of $2\,\mu g\,kg^{-1}\,h^{-1}$ should be started 1 hour before endoscopy without bolus, and continued up to 5 days. In children, placebo-controlled studies or at least registries are required to confirm octreotide use in GI bleeding.

Octreotide also seems beneficial for GI bleeding from angiodysplasia. In an adult, cohort study, the recurrence of GI bleeding significantly decreased in 32 patients treated with octreotide 50 μg subcutaneously twice daily for 1 to 2 years (13). In 98 adult patients with chronic GI bleeding from angiodysplasia, the use of long-acting octreotide reduced the need for red blood cell transfusions, bleeding episodes and hospitalisation stays (14). They received octreotide 100 μg tid for 28 days, followed by 20 mg long-acting octreotide for 6 months (14). These patients were classified, according to the presence/absence of overt bleeding, the level of haemoglobin and the necessity of one or more cycle of therapy, as full responders (40.8%), relapsers (32.6%), and poor responders (26.5%).

In children, experience with octreotide in vascular malformations is limited to case reports of angiodysplasia secondary to congenital heart disease with right heart failure (Table 1) (12); however, long-acting octreotide seemed also to be effective in achieving haemostasis in children with portal hypertension (15). Nine children (median age of first GI bleeding: 21 months, range: 1 month–14.5 years), who were refractory to four endoscopic treatments (sclerotherapy or banding ligation), each of them followed by intravenous infusion of octreotide (50 μg/h independent of weight, tapered down over 24–48 hours after the bleeding ceased), were started on intramuscular long-acting octreotide at a dose of 2.5–20 mg once a month. Long-acting octreotide treatment may have contributed to a reduction in the number of GI bleeding episodes in all children and cessation of bleeding in seven of nine.

Chylothorax and Chylous Ascites

Chylothorax is defined as a pleural effusion with a fluid triglyceride level >1.1 mmol/L (without fasting) and a white cell count >1000/μL consisting of >80% lymphocytes. The pathophysiological mechanisms underlying chylothorax include increased transpleural filtration pressure, impaired lymphatic drainage, and/or increased permeability of lymphatic vessels (16). Congenital chylothorax is caused by intrinsic abnormalities of the lymphatic system, while acquired chylothorax mainly occurs after cardiothoracic surgery. This rare clinical entity is often associated with a syndrome, of which Noonan syndrome is the most common one (17).

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TABLE 1. Description of octreotide treatment in patients with gastrointestinal bleeding, chylothorax and chylous ascites, primary intestinal lymphangiectasia, and pancreatitis

Reference	Indication	Number of children	Bolus	Starting dose	Maximum dose	Duration	Efficacy
Eroglu (9)	GIB	21 with PH (35 episodes) 12 without PH (14 episodes)	Most of them	1–2 $\mu g\,kg^{-1}\,h^{-1}$		w PH = 50 h (19 h–7 d) wo PH = 42.8 h (3 h–36 d)	Complete response: 71% w PH, 50% wo PH
Duche (8)	Biliary atresia GIB	36, primary prophylaxis (22 mo) 30, secondary prophylaxis (24 mo)		2 $\mu g\,kg^{-1}\,h^{-1}$, started 1 h before endoscopy			Well tolerated No death
Koul (10)	GIB w PH	18; 9.89 y (5 mo–21 y)	Some of them 1.27 ± 0.76 μg/kg	Mean 1.44 ± 1.19 $\mu g\,kg^{-1}\,h^{-1}$	Max 1.68 ± 1.38 $\mu g\,kg^{-1}\,h^{-1}$		Haemostasis achieved
Al-Hussaini (7)	GIB	11 (7 of whom w PH)	Most of them Mean 2.2 ± 1 $\mu g\,kg^{-1}\,h^{-1}$ (1–5)	Mean 2.2 ± 1 $\mu g\,kg^{-1}\,h^{-1}$ (1–5)			72% decrease of packed blood cell requirement
Puri (12)	GIB	2, angiodysplasia	1 μg/kg	1 $\mu g\,kg^{-1}\,h^{-1}$	50 μg BID to 150 μg TID SC	Long-acting octreotide, 10 mg monthly for 2 y	No recurrence
Bellini (19)	Neonatal chylothorax	88		Median of 2 $\mu g\,kg^{-1}\,h^{-1}$ (range 0.3–15)	Median of 10 $\mu g\,kg^{-1}\,h^{-1}$ (range 1–20) in congenital and 4 $\mu g\,kg^{-1}\,h^{-1}$ (range 1–15) in postoperative ones	Congenital = 19d Postoperative = 9.5 d	Overall 47% Congenital = 53.3% Postoperative = 33.3%
Roehr (50)	Chylothorax (postoperative 26), congenital (6), spontaneous (3))	35, treated by somatostatine (10) or octreotide (25)			Median of 2.8 $\mu g\,kg^{-1}\,h^{-1}$ continuous IV (range 0.2–10) Median of 40 $\mu g\,kg^{-1}\,d^{-1}$ SC (range 2–68)	IV, median of 7 d (range 3–34) SC, median of 17 d (range 8–43)	Effective in 5–6 d in all octreotide patients
Bialkowski (18)	Congenital chylothorax	27, treated by somatostatine (2) or octreotide (7)			3–8 $\mu g\,kg^{-1}\,h^{-1}$ IV in three divided doses 7–10 $\mu g\,kg^{-1}\,h^{-1}$ continuous IV	21 d (10–45)	No efficacy
Chan (20)	Postoperative chylothorax	30, 18 of them treated by octreotide		10 $\mu g\,kg^{-1}\,d^{-1}$ SC in three divided doses	40 $\mu g\,kg^{-1}\,d^{-1}$		83%
Al-Hussaini (7)	Postoperative chylothorax	3			8.3–14 $\mu g\,kg^{-1}\,d^{-1}$		Effective
Caverly (21)	Postoperative chylothorax	19			1–8 $\mu g\,kg^{-1}\,h^{-1}$ IV 4–17 $\mu g\,kg^{-1}\,d^{-1}$ SC in two divided doses		Decrease = 74% Cessation = 63% Only IV
Pessotti (22)	Postoperative chylothorax and chylous ascites	Three chylothorax, one chylous ascites		1 $\mu g\,kg^{-1}\,h^{-1}$	4 $\mu g\,kg^{-1}\,h^{-1}$		In few days
Matsuura (24)	Post-LTX chylous ascites	6, 4 of them treated by octreotide		0.5 $\mu g\,kg^{-1}\,h^{-1}$	1–4 $\mu g\,kg^{-1}\,h^{-1}$		Cessation in 1 mo
Zaki (29)	Neonatal chylothorax and chylous ascites	Nine chylothorax (3 congenital, 2 idiopathic, 4 post-operative or – intercostal drainage) Two chylous ascites (1 congenital, 1 post-operative NEC)		1 $\mu g\,kg^{-1}\,h^{-1}$ IV (n = 9) 11 and 25 $\mu g\,kg^{-1}\,d^{-1}$ TID (n = 2)	4–10 $\mu g\,kg^{-1}\,h^{-1}$ 24 and 117 $\mu g\,kg^{-1}\,d^{-1}$	17.5 d (7–26) in successful resolutionates with	Complete resolution 4/11 (36%)
Yang (27)	Post-abdominal surgery chylous ascites	4, 2 treated by octreotide		1 $\mu g\,kg^{-1}\,h^{-1}$	2 $\mu g\,kg^{-1}\,h^{-1}$		Cessation in 7 d vs 24–30 d
Al Sinani (30)	PIL (Hennekam syndrome)	2			100 μg BID SC		Effective
Sari (32)	PIL	6, <2 y			15–20 μg/kg BID SC	6–37 mo	Decrease (3) or cessation (3) of albumin infusions
Prasad (31)	PIL	28, 6 treated by octreotide			100 $\mu g/m^2$ in two divided doses SC	20.5 d (5–90)	
Al-Hussaini (7)	Pancreatitis (pseudocysts and/or ascites)	4			2 $\mu g\,kg^{-1}\,d^{-1}$ IV BID 2 or 7.5 $\mu g\,kg^{-1}\,d^{-1}$ SC TID or 10 $\mu g\,kg^{-1}\,d^{-1}$ BID		Effective: pseudocysts resolution in 12 ± 2d and/or drains removed <7 d
Wu (33)	Pancreatitis (L-asparaginase induced)	4			0.3 $\mu g\,kg^{-1}\,h^{-1}$ IV	5.3 d (range 4–7)	Effective: median duration of pain 5 d (range 4–6) and increased pancreatic enzymes 7.5 d (range 4–11)
Sakaguchi (34)	Pancreatitis (L-asparaginase recurrence prevention)	7			0.1–0.2 $\mu g\,kg^{-1}\,h^{-1}$ IV		Efficacy = 43%
Tokimasa (35)	Pancreatitis (L-asparaginase recurrence prevention)	3			2.5–4 $\mu g\,kg^{-1}\,d^{-1}$ SC once daily		Efficacy = 100%

BID = bis in die, d = day, GIB = gastrointestinal bleeding, h = hour, IV = intravenous, mo = month, PH = portal hypertension, PIL = primary intestinal lymphangiectasia, SC = subcutaneous, TID = ter in die, w = with, wo = without, y = year.

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Table 1 depicts the use of octreotide in children with congenital chylothorax (incidence 1:24,000) or chylothorax that developed after cardiothoracic surgery (3.8% incidence) (7,17–21). The incidence of postoperative chylothorax was higher in children undergoing Fontan procedures, heart transplantation, and tetralogy of Fallot repair (11%) compared to other type of cardiac operations (22), and was typically observed around 6–9 days after surgery (19,22).

Octreotide treatment was initiated in children not responding to nutritional management, when lymphatic leak persisted for >2 weeks or if the amount of lymphatic fluid leak was >10 mL kg^{-1} day^{-1} (19). A systematic review was performed to assess the efficacy and safety of octreotide in neonates with congenital and acquired chylothorax (18). Octreotide was mainly given intravenously (84/88, 95.5%) and by continuous infusion (82/84, 97.6%) and was used in 57 neonates with congenital chylothorax and in 27 with postoperative chylothorax (18). In the majority of neonates, the starting dose of octreotide was 2 μg kg^{-1} h^{-1} without bolus. It was increased according to therapeutic response to a median maximum dose of 10 μg kg^{-1} h^{-1} (range: 1–20) in congenital chylothorax and to 4 μg kg^{-1} h^{-1} (range: 1–15) in post-operative patients ($P = 0.002$). It is difficult to give strong recommendations regarding the maximum dosage of octreotide because the data available are based on small case series that were pooled in this review, explaining the large ranges of maximum doses (18). The total duration of octreotide therapy was longer in congenital chylothorax (median 19, range 4–47 days), than in postoperative chylothorax (median 9.5, range 1–41 days).

Octreotide treatment in children after abdominal surgery and chylous ascites is not widely reported (Table 1) (21,23–26). Chylous ascites is characterised by the accumulation of triglycerides -rich peritoneal fluid with a milky or creamy appearance due to intestinal tract/mesentery leakage. The diagnosis of chylous ascites can be made if more than three of the five following criteria are present: milky appearance; triglyceride level >110 mg/dL (or triglyceride ascites/serum ratio >1); cholesterol ascites/serum ratio <1; cell count >1000/μL with negative culture; and/or a predominance of lymphocytes (23). After liver transplantation, chylous ascites occurs in about 6% of children (23,24) in whom risk factors for chylous ascites were young age and low weight and height ($P < 0.005$). Chylous ascites did not influence patient or graft survival, but it was associated with a prolonged length of hospital stay (24). Chylous ascites can also occur up to 2 years after cardiac transplantation in children (27). It is also rarely reported after a Nissen fundoplication (25). When conservative management was not effective or if ascites flux was more than 20 mL kg^{-1} day^{-1} octreotide treatment was started (23). Octreotide use was also reported in case reports of congenital chylous ascites (Table 1, Supplemental Digital Content, *http://links.lww.com/MPG/C507*). A case series of 11 neonates with congenital and postoperative chylothorax and chylous ascites found a complete resolution of chylous effusions after a median of 17.5 days in 36% (28), using a starting dose of 1 μg kg^{-1} h^{-1} with a daily increase of 1 μg kg^{-1} h^{-1} depending on the response, up to a maximum of 10 μg kg^{-1} h^{-1} (median 8, range 4–10).

Primary Intestinal Lymphangiectasia

Children with primary intestinal lymphangiectasia generally present with diarrhoea, lymphopenia and hypogammaglobulinaemia. Ascites can be caused by hypoalbuminaemia or by lymphatic leakage into the peritoneum. These children are managed with a low-fat diet with medium chain triglycerides. Albumin infusions may be required. When this nutritional approach is not effective, octreotide, is one of the therapeutic options (29–31) (Table 1).

Pancreatitis

Since octreotide decreases the secretion of pancreatic enzymes, it has been used for the treatment of severe acute pancreatitis complicated by pseudocysts and/or ascites (7) and in that induced by L-asparaginase (32). It has been reported successful in the prevention of recurrence of L-asparaginase induced acute pancreatitis (33,34). Octreotide delivered either subcutaneously or intravenously was efficacious in treating acute pancreatitis, even in small dose regimens (Table 1). In adults, the use of octreotide in acute pancreatitis is controversial. A randomised controlled trial including 302 patients found that subcutaneous octreotide 100 or 200 μg kg^{-1} day^{-1} TID for 7 days did not reduce mortality and complications compared to placebo (35); however, octreotide treatment was associated with a decreased rate of complications (sepsis, ARDS), hospital stays, and mortality (36). The use of higher doses of octreotide, 50 μg/h for 3 days and then 25 μg/h for 4 days, was significantly more effective than a lower dose of 25 μg/h for 7 days (37). In patients with predicted severe acute pancreatitis, the incidence of severe acute pancreatitis was lower in the high dose group (37.5%) than in the low dose group (59.8%) ($P = 0.005$). At day 8, the number of patients with severe acute pancreatitis was reduced by 29.8% in the high dose group in comparison with the low dose group ($P = 0.004$). The use of high dose octreotide may also be beneficial in the prevention of acute pancreatitis following endoscopic retrograde cholangiopancreatography (38).

Intractable Secretory Diarrhoea

Intractable diarrhoea is defined as non-infectious diarrhoea lasting more than 14 days despite extensive hospital therapy (39). The effects of octreotide contributing to its possible anti-diarrhoeal action are the inhibition of GI motility, exocrine digestive secretions, and intestinal absorption. Its effectiveness has been reported in a child with epithelial dysplasia as well as in a child with short gut syndrome secondary to necrotising enterocolitis (7). Both showed a marked reduction of stool output and a decrease of parenteral nutrition requirement. The doses were 20 μg kg^{-1} day^{-1} three times daily and 4 μg kg^{-1} day^{-1} twice daily subcutaneously for 420 and 240 days, respectively.

Another therapeutic option could be lanreotide, a long-acting somatostatin analogue. Thirty-three adults with chronic idiopathic diarrhoea (55.2 ± 16.4 years old) received lanreotide subcutaneously at days 0, 28, and 56 (40). A response, defined by a more than 50% reduction of stools, was found in 42.4% and 51.5% of patients at days 28 and 56, respectively.

In addition octreotide was effective in 25 of 27 children (92%) with chemotherapy-induced diarrhoea and in 9 of 11 children with graft versus host disease associated diarrhoea (82%), either partially (defined as a decrease in diarrhoeal output by 50%) (36%) or completely (defined as no diarrhoea or return to baseline of bowel function) (45%) (41). The initiation and the maximum doses of octreotide were 4 ± 5 μg kg^{-1} day^{-1} (range: 1–23) and 9 ± 9 μg kg^{-1} day^{-1} (range: 1–45), respectively.

Intestinal Motility

In a small study in adults, octreotide has been found to stimulate intestinal motility in normal and in scleroderma patients (42). In scleroderma patients, it also reduced small intestinal bacterial overgrowth, which had a positive effect on abdominal symptoms. Seven female patients with systemic sclerosis with small bowel involvement not responding to prokinetics responded all to subcutaneous octreotide 100 μg twice daily or intramuscular long-

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TABLE 2. Side effects of octreotide treatment

Reference	Endocrine and metabolic	Intestinal	Systemic	Frequency
Roehr (50)	Blood glucose changes	Transient abdominal distension, emesis		
Bellini (19)	Hyperglycaemia, transient hypothyroidism	Mild abdominal distension, bloody stools, increase liver enzymes, necrotising enterocolitis	Pulmonary hypertension, severe hypotension	14.2%
Testoni (49)	Hyperglycaemia (1/1000 infant-days), hypoglycaemia (3/1000 infant-days),	Necrotising enterocolitis (2%)	Thrombocytopenia (47/1000 infant-days), hyperkalaemia (21/1000 infant-days), leukocytosis (20/1000 infant-days), hypotension requiring pressors (12%)	
Sari (32)		Pancreatitis		
Al-Hussaini (7)	Hyperglycaemia, hypoglycaemia		Bradycardia, hypertension	19%
Zaki (16,29)	Hypoglycaemia revealing a growth hormone deficiency; growth hormone deficiency, hypothyroidism		Bradycardia complicated by ventricular fibrillation with prolonged corrected QT time	
Koul (10)	Transient hyperglycaemia			
Ambartsumyan (46)	Hyperglycaemia	Cholecystitis (gallstones)	Anaphylactic reaction, hypertension	25%

acting octreotide 20 mg once a month (43). In children, an antroduodenal manometry study confirmed the efficacy of octreotide in improving intestinal dysmotility (44). Phase III of the motor migrating complex (MMC) was present in 13 of 23 children (mean age 7.4 years) before and in 21 of 23 after SC octreotide—this was dose-independent (0.5 μg/kg or 1.0 μg/kg). Six of eight children with paediatric intestinal pseudo-obstruction (PIPO) developed phase III MMC following octreotide administration, but it was unclear as to whether this transmitted into a clinical observable effect. Sixteen children with total parenteral nutrition-dependent PIPO, median age 5 years, were treated with octreotide (45). Octreotide was delivered at a median of 0.5 $\mu g\,kg^{-1}\,day^{-1}$ (range 0.2–1) in two divided doses via a central venous catheter for a median duration of 10 weeks (range 3–84), and 7 of 16 children (44%) were considered responders, as defined by an increase in enteral feeding of more than 10 $mL\,kg^{-1}\,day^{-1}$, and three of them were weaned from parenteral nutrition. There was an association between octreotide response and the presence of octreotide-induced phase III MMC. It is important to note that octreotide delays both the liquid and solid phase of gastric emptying; hence, in PIPO patients, a combined use with erythromycin is suggested, but the pro-motility effect of this class of antibiotics is subject to debate (46). Colonic motility does not improve after octreotide infusion in another small study of 13 children with chronic intractable constipation (47).

Safety

Adverse events were reported in several small studies (Table 2), but their incidence is difficult to quantify due to the small case numbers. Only one study aimed to assess the safety of octreotide in infants (48). They identified 428 infants (490 courses of octreotide treatment) out of 887,855 infants discharged from 333 neonatal intensive care units who received at least one dose of octreotide for chylothorax (50%), pleural effusion (32%), and hypoglycaemia (22%). Possible associated adverse events were hyperglycaemia (1/1000 infant-days), hypoglycaemia (3/1000 infant-days), hypotension requiring vasopressor treatment (12%), and necrotising enterocolitis (2%). Laboratory adverse events were thrombocytopaenia (47/1000 infant-days), hyperkalaemia (21/1000 infant-days), and leucocytosis (20/1000 infant-days). Death occurred in 11% of infants and was not directly attributable to the use of octreotide and all observed adverse events were independent of the dose and duration of octreotide treatment, making a cause-effect relationship un-evidenced (18). Of note, a higher rate of necrotising enterocolitis has been reported in neonatal chylothorax (7%), without significant difference between those treated or not with octreotide (11% vs 5%, $P = 0.15$) (49).

CONCLUSION

Several studies support the use of octreotide for the treatment of GI bleeding with or without portal hypertension, neonatal chylothorax and chylous ascites. Octreotide can also be considered for the treatment of primary intestinal lymphangiectasia, acute pancreatitis, severe intestinal dysmotility disorders, and severe chronic secretory diarrhoea. The safety profile seems beneficial and associated adverse events are not proven to be due to octreotide, but assessment of random glucose levels and blood pressure monitoring would seem sensible whilst on an octreotide infusion. Finally, registries of children treated with octreotide should be useful to improve our knowledge and to propose guidelines.

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