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International Journal of Pharmaceutical Research & Allied Sciences, 2016, 5(1):238-247

Research Article

ISSN : 2277-3657
CODEN(USA) : IJPRPM

Clinical use of long-acting somatostatin analogue (octreotide) in patients with congenital hyperinsulinism – A review

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ABSTRACT

Congenital hyperinsulinism (CHI) is the most frequent cause of profound hypoglycemia in neonates and infants. The management of this disorder has been a therapeutic challenge for clinicians because the delay in diagnosis and poor glycemic control can lead to severe neurological damage, intellectual disability and even death. Diazoxide is a first-line treatment for patients with CHI. It inhibits insulin secretion from the pancreatic β-cells, acting as a KATP channel agonist. However, diazoxide has been largely unresponsive in neonates with severe CHIs. As a result, these patients undergo either subtotal pancreatectomy or focal lesion resection, which carry a high risk of developing juvenile diabetes and exocrine pancreatic insufficiency. The only alternative that has been successful in maintaining euglycemia in diazoxide-unresponsive patients is octreotide, an analogue of the natural hormone somatostatin. While the drug is generally well tolerated by children with CHI, a number studies have reported some severe adverse effects following the therapy, including hepatitis, cholelithiasis, necrotizing enterocolitis, long QT syndrome, and growth retardation. This review provides an overview on the safety and effectiveness of octreotide in the management of CHI and discusses whether the serious side effects can outweigh the potential benefits of octreotide.

***Keywords**: Congenital hyperinsulinism; Somatostatin analogue; Octreotide; safety; Efficacy.*

INTRODUCTION

Congenital hyperinsulinism (CHI), also called persistent hyperinsulinemic hypoglycemia (PPH), is a condition characterized by persistently low plasma glucose levels in infants and children due to inappropriately high insulin secretion from the pancreatic β-cells [1-4]. The exact cause of CHI is not yet known. It may arise sporadically with no family history but may also be inherited in an autosomal recessive manner [4]. Both sporadic and inherited cases have been reported in the literature. However, mutations in essential genes, such as the K_{ATP} channel genes (ABCC8 and KCNJ11), that regulate insulin secretion have been identified as the most leading cause of CHI, accounting almost 50% of all known cases [5, 6].

The importance of early recognition, rigorous assessment and immediate treatment is critical for patients with CHI. The delay in diagnosis and the absence of adequate management can cause severe neurological damage and intellectual disability [2, 4]. CHI can even lead toa life-threatening eventifglycemia is not maintained within normal ranges for a prolonged period. The management of hypoglycemia initially starts with high glucose infusion until the diagnosis is set.Once CHI is diagnosed, the responsiveness to dietary modifications and medical treatment is evaluated [1].

A therapeutic trial with oral diazoxide is usually tried for a few days. Diazoxide serves as an agonist of the K_{ATP} channel and keeps it in open configuration, thereby inhibiting insulin secretion from the pancreatic β-cells [7]. However, diazoxide is mainly effective in patients with syndromic CHI; in neonates with severe form of CHI, it mostly presents an unresponsive profile [8, 9]. In diazoxide-unresponsive patients, clinical decisions need to be made regarding pancreatectomy or resection of the focal lesion [10], which carry a high risk of developing insulin-dependent diabetes mellitus and exocrine pancreatic insufficiency [11, 12].

The only alternative that can be compared to a near-total pancreatectomy is octreotide, an analogue of the natural hormone somatostatin [13-15]. Octreotide is usually used as a second-line treatment in patients with CHI. It works in a similar manner to diazoxide, inhibiting the secretion of insulin from the pancreatic β-cells, but through a different mechanism [16]. Although octreotide is generally well tolerated in infants and children with CHI, a number of small studies and case reports have reportedsome minor to serious side effects following the therapy, including diarrhea, abdominal cramping and pain, hepatitis, necrotizing enterocolitis (NEC), tachyphylaxis, biliary sludging,pituitary hormone suppression, and growth stasis [16-20]. In this review, we describe the safety and efficacy of octreotide in CHI patients and discuss whether the serious side effects have the potential to outweigh the benefits.

MATERIALS AND METHODS

We conducted a computerized, electronic search of articles on the use of octreotide in patients with congenital hyperinsulinism. We searched PubMed, Cochrane Library, and Science-Direct, with no language restrictions, using the search terms octreotide, and somatotropin combined with the term congenital hyperinsulinism and hyperinsulinemic hypoglycemia. The strings were coupled with additional search terms to find current, appropriate information in our particular areas of interest. We used filters to exclude certain publication types such as letters, commentaries, and dual papers.

All articles relevant to the topic were extracted for further evaluation. We also examined and scrutinized the reference lists of the selected papers for pertinent articles. The most relevant articles were retrieved in full. Based on the level of evidence, the extracted data were analyzed to review, discuss the most appropriate information on our areas of interest. This review also cites some classic literature to illustrate certain earlier findings and developments.

RESULT AND DISCUSSION

Pharmacology of Octreotide:

Somatostatin is a naturally produced polypeptide in the body that is found abundantly throughout the nervous and gastrointestinal systems [21]. Somatostatin is known as the hypothalamic release-inhibiting hormone and has broad-spectrum inhibitory effects on the gastrointestinal and endocrine systems. Apart from regulating the release of growth hormone, glucagon, insulin, gastrin and other hormones from various systems, itsneurotransmission modulating action in the central nervous system is well described [14, 16]. However, the use of somatostatin in many of the clinical conditions,where it would be of therapeutic value, has been limitedbecause of its short half-life (less than 3 minutes) and the need for intravenous administration [22]. As a result, steps have been taken to make synthetic analogues of somatostatin that are more potent and have a prolonged half-life.

Octreotide (Sandostatin, Novartis) is the first analogue of somatostatin that was approved for clinical use [23]. It made medical treatment possible for many of the difficult-to-treat conditions where a therapeutic benefit of somatostatin was envisaged. Octreotide binds to the SSTR2, SSTR3 and SSTR5 receptors and mimics the pharmacologically of somatostatin [14, 16]. It is 1.3 times stronger than somatostatin in regulating the release of gastrointestinal and endocrinological hormones [23] and has an elimination half-life of 100 minutes after subcutaneous administration. It also degrades more slowly than somatostatin.

Octreotidecan be administered either alone or as an adjunctive therapy. The drug is primarily indicated for the treatment of acromegaly, diarrhea and flushing caused by carcinoid tumors, and profuse watery diarrhea associated with vasoactive intestinal peptide secreting tumors. However, it has some off-label uses as well (**Table 1**). In addition,

a long-acting release (LAR) formulation of octreotide (Sandostatin LP, Novartis) has also been developed for once-monthly intramuscular administration [24, 25]. LAR octreotide is as safe and effective as subcutaneous octreotide but comes with a better pharmacokinetic profile and a considerably longer half-life (up to 4-6 weeks) [26].

Table 1. Off-label Uses of Octreotide

Pancreatic fistula
Dumping syndrome
Pituitary macroadenoma
AIDS-related diarrhea
Ileostomy-related diarrhea
Chemotherapy-related diarrhea
Chylothorax

Source: Lamberts et al. [16] and Tylor [27]

Octreotide Therapy for Patients with CHI

Octreotide is generally considered as a second-line treatment in patients with CHI [28].Although no country has, so far, officially recommended its use for CHI, it has been used in the treatment of CHI since 1986 [29]. The drugis most frequently used for both long- and short-term management of diazoxide-unresponsive CHI patients. In patients with CHI, octreotide primarily works by inhibiting the insulin release from the pancreatic β-cells. Numerous mechanisms have been thought to play a role in the inhibition of insulin secretion, including activation of ATP sensitive potassium channels at the β-cell membrane, decrease in the intracellular translocation of calcium and suppression of the insulin gene promoter activity [15, 16].

Octreotide is administered either by subcutaneous injections every 6 to 8 hours per day or using the insulin pump therapy (continuous subcutaneous infusions) [30]. The standard dose of octreotide in neonates and children with CHI ranges between 5 mcg/kg per day and 20 mcg/kg per day. To avoid daily subcutaneous administrations, CHI patients can also take the once-monthly intramuscular dose of LAR octreotide [15]. Once administered intramuscularly, the serum concentrations of sustained-release octreotide remain considerably low for the first 7 days and thereafter increase rapidly to reach a plateau, which continues to be relatively constant ranging from 14 to 42 days [31]. This pharmacokinetic profile of LAR octreotide assures a steady-state serum concentration for at least 28 days. However, the use of LAR octreotide is not recommended in infants with CHI because the dose may need to be carefully titrated several times a week. In addition, there is a potential risk of developing necrotizing enterocolitis in neonates receiving octreotide, which may require the therapy to be stopped abruptly [32].

Efficacy of Octreotide

Octreotide has shown some efficacy in both short- and long-term management of CHI (Table 2). It helps achieve and maintaineuglycaemia in children and neonates with CHI and provides a successful treatment strategy in combination with frequent daytime and continuous overnight feedings.The drug also allows the cessation of diazoxide therapy and the weaning of intravenous glucose infusions [33-36].Tachyphylaxis may hamper the therapeutic efficacy of octreotide. It usually shows up within the first 24-48 hours after initiation of the treatment and may occur because of glucagon suppression. If symptoms of tolerance to octreotide appear, a higher dose (15-50 mcg/ kg/ day) may be tried. However, this should be administered with appropriate caution, as it may suppress the glucagon and growth hormone secretion, making hypoglycemia paradoxically worse [3, 4].

In both pre- and post-operative CHI cases, treatment with octreotide has been found helpful to stabilize the plasma glucose levels sufficiently [17, 30]. In patients who responded poorly to octreotide and required undergoing a surgery,

the drug was still considered a useful short-term adjunct to therapy in the preoperative period [13, 17, 29, 30, 33]. Postoperatively, in patients who had recurrent hypoglycemia, long-term octreotide therapy was reported to be beneficial to maintain normoglycemia and avoid further surgery [13, 17, 30, 34].

In infants with severe, early-onset CHI, octreotide therapy is consideredas an alternative to avoid near total pancreatectomy. Glaser et al. [36] reported eight CHI patients, who had a long-term treatment with octreotide, did not require undergoing pancreatectomy. The patients were given three or four daily doses of octreotide either by subcutaneous injections or subcutaneously via an insulin infusion pump. In another study on 16 diazoxide-unresponsive infants with a similar octreotide dosage regime, four patients (25%) continued the therapy for up to 4.3 years without pancreatectomy [13]. Recently, in a study of 15 Japanese infants with CHI, 3 patients were reported to achieve spontaneous remission with subcutaneous octreotide infusion and 8 continued on octreotide for months to years without a surgical intervention [30].In addition, Demirbilek et al. [17]in a recent study reported that 12 out of 28 CHI patients non-responsive to diazoxide were treated successfully with long-term octreotide therapy without the need of a surgery.

However, it is not yet understood why some patients were able to avoidpancreatectomy with long-term subcutaneous octreotide administration and some did not.Interestingly,Yorifuji et al. [30] found that CHI patients with monoallelic KATP-channel mutations are more likely to achieve spontaneous remission with octreotidetherapy.The authors suggested that because patients with biallelic mutations require large doses of the drug for a longer period of time, the long-term management of CHI is difficult, and thus they might need a partial resection of the pancreas. In contrast to these findings, Demirbilek et al. reported no statistically significant difference betweengenetic mutations in 12 patients who did not undergo surgery.The responsiveness to octreotide was similar in these patients regardless of themonoallelic or biallelic paternal mutations.Taken together, it can be said that more research is warranted to have a clear understanding on the role of genetic mutations in CHI.

Furthermore, the efficacy of LAR octreotide is also demonstrated in a recent study done by Sang et al. [15]. The once monthly intramuscular dose of the drug simplified medical care for the children with CHI and was efficient in maintaining euglycaemia without affecting the normal growthanddevelopment.A clear improvement in the overall quality of life of the CHI patients and their families was also reported in the trial.The one limitation of the study was the average age of the participants, which was 4.7 years. This means that the severity oftheir CHI was already improved with the daily subcutaneous octreotide. Therefore, the successful outcomes of LAR octreotide in these children cannot be applied to all diazoxide-unresponsive CHI patients.

Lastly, a downside of subcutaneous octreotide therapy is that the reports on its efficacy cannot be generalized for all CHI patients. This is because, although its effectiveness in stabilizing plasma glucose concentrations has been established by a number of studies, the efficacy is demonstrated only in a small number of patient populations, especially in diazoxide-unresponsive neonates and children [13, 17, 30, 33-36]. Perhaps this may be due to the fact that diazoxide has been the mainstay of medical therapy in CHI patients and is the less expensive treatment option than octreotide.

Side Effects of Octreotide

Octreotide is generally well tolerated by both neonates and children with CHI [2-7].However, as with all therapeutic agents, there are some side effects of octreotide as well(see table 3). The short-term adverse effects resulting from octreotide therapy include nausea, elevation of transaminases, abdominal pain, gastrointestinal problems, diarrhea and white stool [2, 13, 17, 21, 36]. These symptoms appear within a few hours following the first subcutaneous administration of the drug. The severity of these adverse reactions is dose-dependent. They are generally transient and require no additional interventions, as they often subside spontaneously within the first two weeks, despite ongoing treatment with octreotide [16]. The long-term side effects of octreotide include cholelithiasis or cholesterol gallstones,dilated gall bladder, pituitary hormone suppression,and growth retardation [17, 21, 36].

Table 2. Efficacy of Octreotide in Patients with CHI

Citation, country	Study group	Study type	Key results	Conclusion
Bruining et al. (1986), Netherlands [29]	A female newborn infant with PPH	Case report	Administration of octreotide infusion (30-50 mcg/24-hour) was sufficient to suppress insulin secretion to almost undetectable.	Octreotide may be useful in the treatment of hyperinsulinism in neonates.
Sullivan et al. (1988), New Zealand [33]	A diazoxide-unresponsive infant (male) with PPH	Case report	Administration of subcutaneous octreotide infusion stabilized the blood glucose levels and decreased the intravenous glucose requirements within the first 24 hr.	Twice daily subcutaneous administration of octreotide in infants with PPH may replace the need of a surgery.
DeClue et al. (1990), United States [34]	One diazoxide-unresponsive infant	Case report	Postoperatively, octreotide stabilized blood glucose levels for up to 22 months.	Octreotide is a useful treatment to stabilize hypoglycemia associated with CHI.
Glaser &Landaw (1990), Israel [35]	9 diazoxide-unresponsive infants with PPH	Case series	All patients responded to octreotide; however, the responses varied and were unpredictable. In 5 out of 9 infants, relatively normal feeding schedules were instituted with subcutaneous octreotide therapy without recurrence of hypoglycemia.	Long-term octreotide treatment can be an alternative to surgery.
Glaser et al. (1993), Israel [36]	8 diazoxide-unresponsive patients	Case series	8 patients with CHI of infancy were treated with subcutaneous octreotide therapy without pancreatectomy.	Octreotide may help avoid partial pancreatectomy in some CHI patients.
Thornton et al. (1993), United States [13]	16 diazoxide-unresponsive infants	Case series	Octreotide stabilized plasma glucose levels in 9 out of 16 infants; of these, only four were able to avoid surgery with long-term octreotide therapy.	Octreotide may be useful in the acute or long-term management of CHI.
Yorifuji et al. (2013), Japan [30]	15 diazoxide-unresponsive patients (8 males and 7 females)	Case series	One patient underwent 90% pancreatectomy, 2 were cured by partial resection, 3 achieved spontaneous remission with subcutaneous octreotide infusion, and the remaining 9 patients continued on octreotide therapy.	Long-term, octreotide therapy is a feasible alternative to surgery, especially for CHI patients with monoallelic KATP-channel mutations
Demirbilek et al. (2014), United Kingdom [17]	28 diazoxide-unresponsive patients (17 males and 11 females)	Prospective cohort study	12 (42.8%) out of 28 CHI patients avoided surgery with long-term octreotide therapy. Of the remaining 16 patients in whom a pancreatectomy was performed, 11 were subsequently treated with octreotide to maintain euglycaemia.	Octreotide is a safe and effective alternative for CHI patients non-responsive to diazoxide

Gallstones resulting from long-termtreatment with octreotide are thought to form due to poor gallbladder emptying, suppression of intestinal motility, inhibition of prokinetic peptides release, and increased production of deoxycholic acid [16]. The formation of gallstones in acromegalic adult patients was shown to correlate with the duration of octreotide therapy [41]; however, in pediatric patients with CHI,no such correlation was found with the dose and duration of the drug [17]. The incidence of octreotide-induced gallstonesis up to 20 to 30 percentin patients with

acromegaly [16]. Of the CHI patients who were treated long-term with the drug, 11(19.64%) were reported to develop gallstones [13, 17, 30, 36, 42], which is considerably consistent with the frequencyinacromegaly.Ursodeoxycholic acid (UDCA) has been the choice of therapy to treat gallstones or biliary sludge due to octreotide [17, 36, 43, 44]. Demirbilek et al. demonstrated complete resolution of gallstones in 50% CHI patients within a short period of UDCA therapy. The authors also reported no recurrences of cholelithiasis even if the doses and duration of treatment with octreotide were increased.

Since octreotideinhibitsthyrotropin-releasing hormone, growth hormone secretion, and pancreatic exocrinerelease, there has been a concern about the long-term effects of the drug on linear growth and growth parameters [13, 45]. In CHI patents, mild deceleration in linear growth due to octreotide therapy was observed [13, 17, 30, 36, 46]; of these, a majority of patients showed catch-up growth when the dose was decreased or the treatment discontinued. However, aclinically significant suppression of growth hormone or arrest in growth velocitydue to treatment with octreotidehas been extremely rare in patients with CHI [21].In addition, no pediatric patient with CHI has been reported to develop hypothyroidism in studies that evaluated the long-term consequences of octreotide [13, 17, 30, 36]. Taken together, the risk of growth retardation, poor target height and hypothyroidism due to octreotide is very low. Nevertheless, until the findings of large-scale longitudinal studies are published, it is necessary to regularly monitor the growth parameters of CHI patients who are on octreotide therapy.

Necrotizing enterocolitis (NEC), hepatitis and long QT syndrome are three of the more severe adverse effects of octreotidetherapy.Becauseoctreotide reduces splanchnic blood flow in a dose-dependent manner, it has been thought to cause NEC in patients with CHI [19, 32]. However, a casual correlation between NEC and the drug is yet not established.Welters et al. [21] recently stated that there might be an association between NEC and the dose of octreotide, as all CHI patients that developed NEC received a remarkably higher dose (mean dose: 21.5 ±4.7 mcg/kg per day) of the drug compared to those without NEC (mean dose: 14.9mcg/kg per day). Demirbilek et al. [17] on the other hand suggested that NEC occurs in young infants not because of octreotide therapy but due to otherrisk factors such as preterm, sepsis, history of cardiac surgery or anomalies, and fluid overload.

Octreotide-associated hepatitis occurswhenliver transaminases increase substantially in infants with CHI [17, 21]. Elevation of transaminases is a mild and transient side effect of octreotide, but it is reported to persist and elevate as high as 1000IU/L in those who developed hepatitis.However, the incidence of octreotide-induced hepatitis in patients with CHI is extremely rare; so far, only a few isolated case reports have reported it [20, 38-40].Furthermore, the possibility of developing prolonged QT interval due to octreotide treatment is also very low, because only one study has yet reported this event in a CHI infant [37]. Nevertheless, routine examination of liver function and monitoring of ECG are warranted before and during octreotide therapy.

In light of the above discussion, it can be said that most adverse effects associated with octreotide are minor. Although some serious complications due to octreotide treatment have been described in the literature [2, 17, 21], they are mainly reported in a limited number of case studies [19, 20, 32, 37-40]. Moreover, since large-scale, longitudinal studies are not done yet in pediatric patients with CHI to evaluate the safety profile of octreotide, it is unclear whether the reported serious side effects correlate with the drug. Hence, these reports cannot be considered as a matter of significant clinical importance for the majority of CHI patients. Nevertheless, as there are some evidences supportingthe incidence of severe adverse effects due to octreotide treatment, careful monitoring for NEC signs and routine clinical examinations of growth parameters, liver and thyroid function, and gallbladder ultrasounds should be performed to avoid further complications.

Table 3. Side Effects of Octreotide in Patients with CHI

Severity	Adverse Effects
Short-term (mild, transient)	• Nausea

	• Elevation of transaminases • Abdominal pain • Diarrhea • White stool • Malabsorption of fat • Flatulence
Long-term	• Cholesterol gallstones • Dilated gall bladder • Growth deceleration after 2 years • Pituitary hormone suppression
Severe	• Necrotizing enterocolitis • Hepatitis • Long QT syndrome

CONCLUSION

Octreotide is an essential medication that helps achieve and maintain euglycaemia. In our view, the efficacy of the drug in the management of CHI of infancy is clear.Although the use of octreotide in CHI patients is associated with some severe side effects, we did not find any evidencesthat suggest a strong correlation of them with the drug. Hence, we believe these adverse effects do not outweigh the potential benefits of octreotide and cannot be a reason to discourage its use. However, patients receiving octreotide treatment should be monitored closely for undue adverse events, irrespective of the dose and duration of the drug. Lastly, we emphasize that more research, particularly randomized controlled trials and large-scale long-term studies, is required to fully ascertain the safety, efficacy, and dosing of octreotide in infants with CHI.

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