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Use of Octreotide Acetate for Control of Symptoms in Patients with Islet Cell Tumors

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Gut tumor syndromes are rare, occurring in less than two cases per million population per year: Insulinomas are most common and gastrinomas are less common; all the others are extremely rare. Conventional treatment of the symptoms caused by these tumors has included surgery, hepatic arterial embolization, and chemotherapy; some patients with Zollinger-Ellison syndrome (ZES) have been treated with specific agents such as gastric antisecretory drugs. The development of octreotide, a synthetic, long-acting analogue of the natural peptide somatostatin, has offered an alternative to such therapies. Octreotide has a half life of >100 minutes and inhibits both physiological- and tumor release of many peptides. It also has direct effects on the gut that modify secretion and motility. Octreotide has been shown to be particularly useful for the symptoms of tumors producing vasoactive intestinal peptide (VIP), and of the carcinoid syndrome. It is also useful in patients with glucagonomas, with growth hormone-releasing hormone producing tumors, and in some patients with Cushing's syndrome and unresectable insulinomas. Octreotide is effective in patients with ZES, but alternative therapies such as omeprazole are more effective, safer, and more convenient for those patients. Side effects of octreotide have not been troublesome in these patients, but the incidence of long term effects is still not entirely clear. Octreotide has proved to be a significant advance in the treatment of patients with islet cell tumors.

The various types of islet cell tumors that give rise to a number of clinical syndromes are indistinguishable histologically and are classified according to the major circulating tumor product and clinical findings. They include those that produce principally insulin (insulinomas), gastrin (gastrinomas), vasoactive intestinal peptide (VIPomas), glucagon (glucagonomas), somatostatin (somatostatinomas), serotonin (carcinoids and the carcinoid syndrome), growth hormone-releasing hormone (GHRHomas) [1–6], ACTH, (ectopic Cushing syndrome), or homoral hypercalcemic factors [1, 2, 6]. Rarely, islet cell tumors produce solely neurotensin (neurotensinomas) or pancreatic polypeptide (PPomas), which give rise to no clinical syndrome [1] and are grouped with those tumors classified by light microscopy as being neuroendocrine in type but that produce no detectable products and are referred to as "nonfunctioning tumors" [1]. Many neuroendocrine tumors release more than one peptide (e.g., VIP and PP or gastrin and ACTH) and may contain one or more other peptides detectable by immunocytochemistry. In these cases, the tumors are usually classified by the dominant clinical syndrome.

Of the islet cell tumors, insulinomas are the most common, occurring about 0.9 cases per million people per year, gastrinomas 0.4 cases, and all other islet cell tumors fewer than 0.2 cases per million per year [7]. Although carcinoids are more common than all the islet cell tumors, most occur in the ileum, jejunum, and lung [6]; and islet cell tumors giving rise to the carcinoid syndrome are rare. Any of the islet cell tumors can occur as a sporadic tumor or as part of familial multiple endocrine neoplasia type 1 (MEN-I). As islet cell tumors are often slow-growing, treatment of the symptoms caused by the release of biologically active products into the circulation is of considerable importance. Indeed these tumors can produce severe symptoms when the tumor is still localized, and patients may die from the consequences of peptide production rather than tumor progression. Conversely, the abolition of paraneoplastic symptoms can leave the patient feeling well despite extensive hepatic metastases.

Treatment Alternatives for Symptoms Due To Islet Cell Tumors

Except in the late stages, most clinical manifestations of islet cell tumors are due to the circulating agents. Thus treatments are directed at reducing their effects by reducing production and release into the blood, reducing tumor bulk, interfering with the action of the circulating agents on the target organ, or reducing the plasma concentration of agents by pharmacologic means.

Surgery, either to completely remove the primary tumor or to reduce tumor bulk in those with metastatic disease, may reduce the concentration of circulating peptides and thereby reduce symptoms.

For those with inoperable metastatic tumors, chemotherapy or hepatic arterial embolization (both of which reduce tumor bulk) have been used and in some cases have reduced symptoms [1, 2, 4, 5, 7–9]. A different approach is possible in patients with Zollinger-Ellison syndrome (gastrinomas) by blocking acid secretion by the parietal cell on which gastrin acts, with histamine H_2-receptor antagonists or the H^+K^+-ATPase inhib-

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itor omeprazole [4, 10]. No drugs are available that compete with the actions of other circulating peptides, although antidiarrheal drugs may be of limited use in some patients with VIPomas [1, 2].

A third approach to the management of the symptoms produced by neuroendocrine tumors is to reduce the amounts of circulating biologically active products by pharmacologic means. Administration of the naturally occurring peptide somatostatin to normal volunteers reduced basal and stimulated plasma concentrations of many circulating peptides [11–15] and inhibited gastric and pancreatic secretion, intestinal absorption, and motility by a direct action [15]. Infusions of somatostatin infusions have been shown to produce biochemical and sometimes symptomatic improvement in patients with the carcinoid syndrome [16, 17], VIPoma [18–21], insulinoma [21–27], gastrinoma [13, 21, 28], and glucagonoma [21, 29–31]. However, natural somatostatin has a half-life in the circulation of about 3 minutes [32] and therefore has limited clinical utility. The development of the long-acting somatostatin analog octreotide acetate (Sandostatin, SMS 201-995) made this approach possible.

Octreotide Acetate

Octreotide acetate is a cyclic octapeptide that retains the four amino acids of the biologically active region and the cystine bridge of native somatostatin 14. The substitution of the L-isomers with D-isomers of tryptophan and phenylalanine residues, and the reduction of the threonine to an alcohol derivative, rendered the peptide more resistant to peptidases [33]. After subcutaneous injection, peak plasma concentrations of octreotide are observed within 60 minutes, and the half-life is 70 to 113 minutes [34, 35]. Like native somatostatin 14, octreotide has been found to inhibit meal-stimulated secretion of other pancreatic hormones and gallbladder contraction [35, 36]. In addition, both natural somatostatin and octreotide inhibit bile output [36, 37]. However, octreotide has a somewhat different spectrum of activity from native somatostatin in that octreotide is relatively more potent in terms of inhibiting growth hormone release.

Because islet cell tumors are rare, no controlled trials of octreotide have been performed in patients with these tumors. In early studies most patients were given 50 μg every 12 hours, increasing up to 600 μg/day, at which point the drug was stopped if no symptomatic response was achieved. Subsequently the dose limit was raised to 1500 μg/day. Although octreotide has been used principally for symptom relief, various somatostatin analogs, including octreotide, have antitumor activity in animal models [38, 39]. In some longer-term studies in humans, the effect of octreotide on tumor size has been studied. These data are discussed in another review in this volume [40].

Use of Octreotide in Patients with Islet Cell Tumors

Insulinomas

All the symptoms of insulinomas are due to the release of excessive amounts of insulin, with resultant low blood glucose and transient episodes of neuropsychiatric disturbance associated with palpitations and sweating. Insulinomas, unlike other islet cell tumors, are usually localized at the time of diagnosis and in about 90% of cases are benign. Thus most insulinomas are best treated by surgical resection, which is usually curative [5].

Nevertheless, in studies designed to investigate the action of octreotide in this syndrome more than 30 patients with insulinomas have been given octreotide prior to surgery in short-term studies [41, 42]. Typically, octreotide was given at 50 μg or more every 12 hours. Effects on plasma insulin and glucose were not consistent, and in some patients the hypoglycemia was made worse, possibly because the release of counterregulatory peptides were suppressed more profoundly than release of the tumor-produced insulin. Thus in patients with insulinomas who are waiting to undergo surgery, octreotide is not reliable for maintaining blood glucose concentrations and should not be used.

A few patients with unresectable insulinomas have been given octreotide long term in an attempt to control blood glucose. In these reports hypoglycemia was well controlled in most patients, despite a return of insulin concentrations to pretreatment levels in some cases. Symptoms recurred with time in about 30% of the patients, and some but not others responded to an increase in octreotide dose. Thus octreotide has proved useful in some cases, but diazoxide and chemotherapy are alternatives in this circumstance. The place of octreotide in treating patients with unresectable tumor has yet to be clearly defined.

Gastrinomas

Gastrinomas produce Zollinger-Ellison syndrome (ZES) characterized by elevated plasma concentrations of gastrin and gastric acid hypersecretion, giving rise to peptic ulceration, diarrhea, or both. In this syndrome the incidence of metastatic disease is probably 30% to 50% at the time of diagnosis, and in those patients with no metastatic disease surgical resection cures only about 40% to 50% [4]. Thus there are a considerable number of patients with ZES who require long-term therapy to control symptoms. Because hypersecretion of gastric acid causes all the clinical manifestations of this syndrome, histamine H_2-antagonists, or the H^+K^+-ATPase inhibitor omeprazole, if given in sufficient dose, can reduce acid outputs to safe levels and render the patients asymptomatic [4, 10].

Despite the availability of these powerful antisecretory drugs, the effect of octreotide has been described in more than 50 patients with gastrinomas [42]. Octreotide lowered plasma gastrin concentrations and reduced gastric acid secretion. The temporal and dose relations between inhibition of plasma gastrin and acid secretion indicate that octreotide inhibits acid secretion, at least in part, by a direct action on the stomach. This action is similar to the effect of octreotide on acid secretion in normal volunteers. No systematic data are available on symptomatic responses in patients with ZES because acid hypersecretion was usually controlled by concomitant oral H_2-antagonists or omeprazole therapy, but some patients who were given octreotide were able to reduce their intake of H_2-antagonists. Nevertheless, because the symptoms of gastrinoma can be effectively and safely controlled by oral medication alone, there is no current indication for octreotide for the control of symptoms of this syndrome.

VIPomas

Tumors producing vasoactive intestinal peptide (VIP) cause watery diarrhea, hypokalemia, hypochlorhydria, hypophosphatemia, and sometimes hypercalcemia, together with increased plasma concentrations of VIP. Usually the patients have extensive metastatic disease at the time of presentation, and virtually all patients become entirely resistant to conventional antidiarrheal drugs. Furthermore, chemotherapy is only transiently useful in these patients.

More than 20 reports of VIPomas treated with octreotide (100–450 μg/day) have been published [42]. All the patients responded initially with a reduction in diarrhea, and the beneficial effects of octreotide were usually evident within 12 hours. In more than 80% of patients the immediate beneficial effects of octreotide were striking and persisted with continued treatment; but in about 15% the beneficial effect of octreotide lasted only a few days, and subsequently increasing the dose as high as 1200 μg/day did not produce a therapeutic response. Over several months many patients whose symptoms were initially controlled with low doses of octreotide required an increase in dose to control their symptoms, and others required the addition of steroids. One patient became resistant to octreotide after treatment for more than 1 year. Plasma concentrations of VIP fell during therapy in nearly all patients but fell to within the normal range in only about 30%. However, symptomatic relief of the diarrhea was not always related to changes in plasma concentrations of VIP, and in some patients octreotide was effective despite plasma concentrations of VIP that cause secretory diarrhea when VIP is infused into normal volunteers. It may be that the molecular size of circulating VIP during octreotide therapy changes to a larger, less biologically active form, or that octreotide has a direct effect on the gut to reduce fluid secretion or both. In patients with VIPomas, octreotide clearly represents a therapeutic advance; and because approximately 85% of these patients respond to the drug, having failed other therapies, this drug will become first line therapy in this syndrome.

Glucagonomas

The glucagonoma syndrome is characterized by an elevated plasma concentration of glucagon, a unique migrating erythematous rash, anorexia, weight loss, mild glucose intolerance, and on occasion diarrhea, neuropsychiatric symptoms, and venous thrombosis.

More than 10 patients with this syndrome (all with metastatic disease) have been described who were given octreotide in doses of 100 to 450 μg/day [42]. In all patients who had the rash at the time therapy was started, the rash resolved within a few days. However, two patients were also taking zinc, which has been shown to ameliorate the rash in some patients with this syndrome. Weight loss, abdominal pain, and diarrhea were alleviated in the patients with these symptoms, but octreotide had little effect on diabetic control. Plasma concentrations of glucagon fell in nearly all patients but remained above the normal range in all but one. In one well studied patient given octreotide, the rash resolved with no change in plasma concentrations of glucagon, amino acids, or zinc, suggesting that octreotide may have had a direct action on the skin. This case is consistent with the finding that octreotide can improve psoriasis in some patients. Octreotide continued to be effective long term in all the patients with glucagonoma, although the plasma concentration of glucagon returned to pretreatment levels in at least two, and two other patients required an increase in dose. Ideally, controlled studies should be performed to establish the efficacy of octreotide in improving the rash, but in the absence of such studies it seems reasonable to use the drug in patients in whom the rash does not respond quickly to simple measures.

Carcinoid Syndrome

Although islet cell tumors producing the carcinoid syndrome are rare, presumably they respond to octreotide, as do the more typical carcinoids arising in the intestine or lung. Like other tumors producing the carcinoid syndrome, virtually all pancreatic tumors described have been accompanied by extensive metastases at the time of presentation.

More than 100 cases of the carcinoid syndrome, mainly associated with intestinal primaries but often due to primary tumors of unknown site, have been reported that have been treated with octreotide [41, 42] in doses of 50 μg q12h to 500 μg q8h. In more than 90% of the patients treated, the symptoms (flushing, diarrhea, or both) improved during therapy. In addition, urinary levels of 5-hydroxyindoleacetic acid (5-HIAA), a marker of 5-hydroxytryptamine production, fell in two-thirds of patients but did not become normal in any. In many patients in whom octreotide produced initial symptomatic relief, the effects persisted for many months with no change in dose. In those who developed recurrent symptoms on therapy, an increased dose controlled symptoms in some but not others. Two patients have been reported in whom octreotide was useful or life-saving in carcinoid crisis. One patient received a continuous infusion of octreotide 50 μg/hour with a good response, and the other patient in whom other resuscitative measures had failed was successfully resuscitated only when 100 μg octreotide was administered intravenously.

Chemotherapy is not effective for symptom relief in the carcinoid syndrome; hepatic arterial embolization is effective but has significant risks; and interferon therapy, although promising, has many side effects. Octreotide has proved useful for ameliorating symptoms in most patients with this syndrome and thus is a significant advance in therapy. Octreotide should be available whenever there is a risk of precipitating a carcinoid crisis.

Tumors Producing Growth Hormone-Releasing Hormone

Islet cell tumors producing growth hormone-releasing hormone (GHRH) stimulate a normal pituitary to release excessive amounts of growth hormone, causing acromegaly, which often proves to be resistant to medical therapy and recurs despite pituitary surgery, irradiation, or both.

Several patients with GHRHomas in the abdomen (in all but one case associated with metastases) have received octreotide [42]. Interestingly, several of the patients presented initially with ZES and developed signs of acromegaly only later. Except in the patients who underwent a curative surgical resection of the tumor, these patients received octreotide long term. All the

patients described had a good initial symptomatic response with reduction in hyperhidrosis in the adult patients and arrest of growth and onset of menarche in a prepubescent girl with gigantism. In at least one patient the pituitary became smaller as measured by computed tomographic (CT) scan. Octreotide reduced plasma concentrations of GHRH and growth hormone but did not to reduce GHRH into the normal range. Thus octreotide probably acts in part directly on the pituitary to reduce growth hormone secretion. Because all these patients with GHRHomas derived symptomatic relief from octreotide when they had become resistant to other modes of therapy, octreotide will continue to be used in patients with this rare syndrome who cannot be cured surgically.

Cushing's Syndrome

Islet cell tumors may produce ACTH and ectopic Cushing's syndrome either as an isolated syndrome or, more often, associated with ZES [3]. By the time the diagnosis is made, all these patients have hepatic metastases, and in nearly all cases the tumors are aggressive and carry a poor prognosis [4].

There are a few detailed reports of the effects of octreotide in patients with islet cell tumors producing ectopic Cushing's syndrome [42, 43]. Octreotide in doses of 150 μg q12h to 100 μg q8h produced clinical improvement in skin changes, blood pressure, diabetes, and hypokalemia in most cases. In cases where data were given, ACTH fell to within normal limits, as did urinary free cortisol; and in the 4 patients who also had ZES, plasma gastrin concentrations also fell. Octreotide continued to be effective for several months in all but one case. These results suggest that octreotide produces striking improvements in the ectopic ACTH syndrome. However, not all cases have responded (Maton, unpublished observations). Tumors producing ectopic ACTH and that respond to octreotide differ from the normal pituitary (where octreotide does not reduce ACTH secretion [44, 45]) but are similar to the effects of natural somatostatin and octreotide on inhibition of pituitary ACTH secretion in pathologic states such as Nelson's syndrome [46], adrenal insufficiency [47], or Cushing's disease [46].

Nonfunctioning and Other Islet Cell Tumors

A number of patients with pancreatic tumors of the islet cell type but with no specific endocrine syndrome have been given octreotide [42]. The tumors in these patients produced pancreatic polypeptide, neurotensin, calcitonin, glucagon, or no detectable peptide; all had metastasized. The patients' symptoms were nonspecific and included weight loss, abdominal pain, diarrhea, itching, and fatigue. Octreotide is said to have produced symptomatic improvement in 3, had no effect in 1, and made 1 worse. However, judging symptomatic response in such circumstances is highly subjective. There was no consistent effect on plasma concentrations of pancreatic polypeptide, glucagon, calcitonin, or neurotensin. One patient with an islet cell tumor that produced a parathormone-like peptide with resulting hypercalcemia responded to octreotide for at least 11 months [10, 48]. One patient with a somatostatinoma received two doses of 200 μg of octreotide. Fasting plasma concentrations of somatostatin were not changed, but the postprandial rise of plasma somatostatin was abolished [49].

In patients with nonfunctioning islet cell tumors there is no indication that octreotide should be used for symptomatic relief. For other rare endocrine syndromes produced by islet cell tumors, octreotide may be worth trying if there are specific markers to monitor the effects of the drug on the syndrome.

Side Effects of Octreotide

The reports of adverse effects of octreotide therapy have been accumulated mainly from studies in patients with pituitary tumors. Side effects include nausea with and without vomiting, pain at the injection site (which can be minimized by warming the solution), diarrhea or constipation, and abdominal pain [41, 50]. Most of these side effects are mild and transient. In only a small number of cases have these problems been sufficiently severe to cause patients to stop therapy.

The side effects of long-term octreotide treatment are similar to the clinical syndrome observed in patients with somatostatinomas. The excess somatostatin produced by these islet cell tumors induces mild diabetes mellitus, cholelithiasis, malabsorption, and weight loss [51]. Although several investigators have reported abnormal glucose tolerance in patients receiving octreotide, frank diabetes is rare [52–55]. Increased fecal fat excretion is an inconsistent finding reported in some patients on prolonged treatment [56, 57], although it is almost certainly universal in patients taking high doses. No clinically significant abnormalities related to the fat malabsorption have been identified.

Particularly in patients with acromegaly, the use of octreotide has been associated with the development of biliary sludge, cholesterol crystal formation, and microlithiasis detected by gallbladder ultrasonography [41, 50, 56]. True gallstones have also been observed, and acute cholecystitis and cholangitis occurring during the course of octreotide treatment have also been reported [58, 59]. Cholelithiasis probably results from octreotide-induced changes in bile composition and the inhibition of gallbladder contraction [60, 61]. More prospective studies are required to determine the frequency and consequences of these findings and to determine whether interventions to prevent gallbladder disease are necessary [62].

Elevation of hepatic transaminases with octreotide treatment has been reported on occasion [41]. An unexpected finding of moderate to severe gastritis has been observed in acromegalics on long-term octreotide treatment [60]. Although patients were not examined prior to drug treatment, these findings again raise concerns over the long-term use of octreotide. In an unrelated report, a patient with acromegaly and a nonsecreting pancreatic tumor developed melena after 6 months of octreotide treatment that recurred on subsequent challenge with the drug [63].

Unresolved Issues

Despite the fact that octreotide has been used for several years, the reasons for differing drug requirements in different patients, and the incidence and reasons for resistance to the drug are not clear. Most neuroendocrine tumors have receptors for somatostatin [64, 65] (see review elsewhere in this volume), and so presumably octreotide has a direct action on such tumors to reduce secretion of the marker peptide. Whether the differences in symptomatic response is due solely to differences in somato-

statin receptor number or affinity or to some other mechanism is not yet known, and the relative contributions of reduction in peptide secretion and direct effects on the target organ in different syndromes are not established. Furthermore, the effects of many months of octreotide therapy for symptoms due to islet cell tumors have not been well studied, although one study of 7 patients treated for 13 to 54 months (mean 29 months) found that patients required increasing doses after 4 to 5 months, became entirely resistant to octreotide after 24 ± 3 months of therapy, and died within 5 months of stopping the drug [66]. This report suggests that the effects on islet cell tumor symptoms may last only a few months or years, but more long-term data are required.

Résumé

Les auteurs présentent les avantages et les inconvénients de l'octréotide acétate dans le traitement de certaines tumeurs insulaires du pancréas telles que les insulinomes, les gastrinomes, les VIPomes et les glucagonomes. L'utilité de ce médicament dans le traitement du syndrome carcinoïde, du syndrome de Cushing et des tumeurs à ACTH et les effets secondaires de l'octréotide acétate sont abordés.

Resumen

Los diferentes tipos de tumores derivados de las células insulares del páncreas, que producen variados síndromes clínicos, son imposibles de distinción histológica y se clasifican mas bien según su principal producto tumoral circulante y según los hallazgos clínicos. Tales tumores incluyen los que producen principalmente insulina (insulinomas), gastrina (gastrinomas), péptido intestinal vasoactivo (vipomas), glucagón (glucagonomas), somatostatina (somatostatinomas), serotonina (carcinoides y el síndrome carcinoide), hormona liberadora de hormona del crecimiento (HLHComas, o GHRHomas en inglés), ACTH (síndrome de Cushing ectópico) o factores humorales hipercalcémicos. Raramente los tumores de células insulares secretan solamente neurotensina (neurotensinomas) o polipéptido pancreático (PPomas), que no producen síndromes clínicos, y se agrupan con aquellos tumores que se clasifican como de tipo neuroendocrino por microscopía de luz pero que no liberan productos detectables y que se conocen como "tumores no funcionantes". Muchos neoplasmas neuroendocrinos secretan más de un péptido (por ejemplo VIP y PP o gastrina ACTH) y pueden contener uno o más péptidos detectables por inmunocitoquímica. En tales casos los tumores se clasifican según el síndrome clínico dominante. Cualquiera de los tumores de células insulares puede presentarse como tumor esporádico o como parte del síndrome familiar de neoplasia endocrina múltiple tipo I. Puesto que los tumores de células insulares con frecuencia son de crecimiento lento, el tratamiento de los síntomas que produce la liberación de productos biológicamente activos a la circulación es de importancia; en efecto, tales neoplasmas pueden producir síntomas severos cuando todavía no han dado metástasis, y los pacientes pueden sucumbir como consecuencia de los péptidos más que por el crecimiento tumoral. Por otra parte, la abolición de los síntomas paraneoplásicos puede lograr el bienestar del paciente, aún en presencia de metastasis extensas.

Los autores presentan los pros y contras del uso del acetato de octreótido en casos de tumores de células insulares específicos, incluyendo insulinomas, gastrinomas, VIPomas y gloucagonomas. Además, discuten la utilidad de este agente en el síndrome carcinoide, el síndrome de Cushing y en tumores productores de hormona liberadora de hormona del crecimiento. Se revisan los efectos colaterales del octreótido y otros asuntos pertinentes aún no resueltos.

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