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Somatostatin in gastroenterology

For unresectable hormone secreting neuroendocrine tumours, secretory diarrhoeas, and bleeding varices

Somatostatin was isolated from ovine hypothalamus in 1973, and eight years later a long acting analogue, octreotide, was synthesised. More than 1000 clinical applications have since been suggested for these paninhibitory peptides, particularly in gastroenterology. The enormous clinical potential in the gastrointestinal tract for a universal inhibitor and the remarkable non-toxicity of the agents fuelled this enthusiasm. Although a lack of randomised controlled trials with sufficient numbers of subjects hampered clinical progress, the recent publication of several large, well controlled trials has helped to delineate a role for somatostatin and its analogues in gastroenterology. In clinical practice octreotide is preferable to the native compound because of its longer half life, which permits intermittent subcutaneous administration. Recently an orally active somatostatin analogue has been described.[1]

Octreotide is useful in the management of unresectable hormone secreting neuroendocrine tumours, particularly carcinoids and vipomas.[2] It inhibits both the secretion and the effect of the active agent. For example, in vipomas characterised by profuse secretory diarrhoea, octreotide reduces the diarrhoea by inhibiting the secretion of vasoactive intestinal polypeptide and by directly reducing intestinal secretion. Responsiveness often falls—perhaps because of down regulation of somatostatin receptors on tumour cells or the emergence of a receptor negative clone. The absence of a consistent antiproliferative effect may be related to the poor affinity of octreotide for some of the somatostatin receptor subtypes found on these tumours. Nevertheless, the high density of somatostatin receptors on most gastrointestinal neuroendocrine tumours has allowed tumours to be localised with in vivo scintigraphy with labelled octreotide.[3]

In clinical practice these peptides have probably had their greatest impact in the management of bleeding varices, gastrointestinal fistulas, and complications of pancreatic surgery. Somatostatin reduces splanchnic arterial blood flow, portal flow, and gastric mucosal blood flow. In addition, it inhibits the secretion of gastric acid and pepsinogen and stimulates the secretion of gastric mucus. For these reasons the efficacy of these agents on upper gastrointestinal haemorrhage has received considerable attention. The effectiveness of somatostatin or octreotide in variceal bleeding has been tested in over a dozen published controlled trials. In the largest (120 patients) and most carefully designed study, somatostatin 250 μg per hour (equivalent to octreotide 25 μg per hour) for five days was better than placebo in controlling bleeding and reducing transfusion requirements.[4] Other studies have shown that somatostatin or octreotide is as effective as vasopressin infusion, balloon tamponade, or emergency sclerotherapy.[5,6] No study has shown a beneficial effect on mortality. Importantly, somatostatin and octreotide have fewer cardiovascular side effects than vasopressin and are cheaper on a cost per hour basis at least in Australia. In contrast (and somewhat surprisingly), somatostatin and octreotide provide no benefit in bleeding from peptic ulcer.[7]

Because of their inhibitory effects on pancreatic secretion the peptides have been suggested as treatment for pancreatic fistulas, pancreatic ascites, and possibly also pseudocysts, but there have been no controlled trials.[8] Disappointingly, four controlled trials (in a total of 375 patients) have failed to show benefit in acute pancreatitis.[9] Furthermore, a recent large randomised controlled trial failed to show any benefit of octreotide on the pain and pancreatitis after endoscopic retrograde cholangiopancreatography. In fact, failure of sphincteric cannulation was more common in the treatment group, and the authors suggested that any potential benefit of octreotide in suppressing pancreatic secretion may be offset by its effect on the sphincter of Oddi, where it increases basal tone and the frequency of phasic contractions.[10] More encouraging are the data from two large multicentre European trials suggesting that perioperative and postoperative octreotide reduces the rate of local complications after major pancreatic surgery.[11,12]

Because of their inhibitory effects on intestinal secretion the agents have been used in cases of enterocutaneous fistulas. One controlled trial compared total parenteral nutrition and octreotide with total parenteral nutrition alone. Both regimens were similarly effective, but fistulas closed faster with octreotide.[13]

As surgery for peptic ulcer disease becomes rarer so too does the dumping syndrome. Most patients with this syndrome can be adequately managed by dietary means, but there exists a small subset of patients severely disabled by their symptoms. Several placebo based trials have shown that somatostatin or octreotide given before eating benefits both early and late dumping.[14]

Somatostatin and octreotide reportedly improve secretory diarrhoeas other than those associated with neuroendocrine tumours. Control of secretory diarrhoea associated with the short bowel syndrome, ileostomy diarrhoea, idiopathic

secretory diarrhoea, diarrhoea associated with amyloidosis, and diabetic diarrhoea has been reported, but no controlled trials have been performed.[15] The agents have no effect on the diarrhoea of cholera. Octreotide has shown some promise in the management of refractory diarrhoea related to AIDS, especially in patients without identifiable pathogens.[16]

After years of mostly uncontrolled studies, a series of randomised controlled trials is defining the clinical applications of octreotide.[17] Nevertheless, analogues of somatostatin with special affinities for the different classes of somatostatin receptors are needed. Now that the sequences of many of the somatostatin receptor subtypes are being described,[18] the synthesis of analogues targeted for specific clinical applications should be possible.

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Cancer in adolescence

Special problems; special solutions

The pattern of cancer among adolescents differs from that among young children, yet the common carcinomas of adulthood are still extremely rare in adolescents. The annual incidence of cancer among people aged 13-19 in Western countries is 140-150 per million, with around 700 new cases a year in Britain. The most common cancers, in order of frequency, are lymphomas, tumours of the central nervous system, acute leukaemias, bone and soft tissue sarcomas, germ cell tumours, malignant melanoma, and thyroid carcinoma. The incidence of Hodgkin's disease and bone sarcoma peaks in adolescence or early adulthood. Although the overall incidence of cancer in this age group is stable, testicular cancer, malignant melanoma, other skin cancer, and thyroid cancer have become more common since the 1970s, while ovarian cancer has become less common.[1]

The aetiology of cancer in adolescents is poorly understood. A few cases arise as part of a genetic syndrome and even fewer can be attributed to established environmental risk factors (on the assumption that their aetiology is the same as that of similar cancers in children or adults).

The clinical needs of adolescents with cancer differ little from those of younger or older patients with similar cancers, and they therefore require multidisciplinary care. Many are treated in adult oncology departments and a few by paediatric oncologists. A diagnosis of cancer can be devastating for patients and their families at any age, but adapting to the effects of the disease and its treatment may be particularly hard for adolescents. They must cope with loss of personal control; changes in social relationships; prolonged absences from school, college, or a first job; and uncertainty about the future—all at a time when they are beginning to establish an identity apart from the nuclear family but are still heavily dependent on it. Even if establishing a separate adolescent unit may not be possible, provision for the particular emotional, educational, and social needs of these patients could undoubtedly be improved. Britain's first adolescent oncology unit opened in 1990 at the Middlesex Hospital, London, and most of its patients receive treatment for bone sarcomas. The unit emphasises a team approach not only to clinical management but also to provide the best possible emotional and psychological support for the patients and their families and for the unit's staff.[2]

Survival from cancer in adolescence varies widely among diagnostic groups. Thyroid carcinoma has an excellent prognosis. The outlook for most patients with Hodgkin's disease and germ cell tumours is also good, largely because of the development of effective chemotherapy. Survival from bone sarcomas has improved, again with advances in chemotherapy, though even now possibly only half the patients with these tumours will enjoy long, disease free survival. This has happened concurrently with the increasing success of limb reconstructive surgery,[3] which is justifiable on clinical and financial grounds, though its contribution to long term quality of life is not yet certain. For several types of cancer, notably sarcomas and germ cell tumours, the current aim is to maintain the high survival rate in subgroups with a good prognosis with less toxic treatment while intensifying treatment for those with poor prognostic features.