Van die Redaksie/Editorial

Somatostatin analogues and their clinical application

Somatostatin was detected accidentally in 1968 by Krulich during investigations into the distribution of growth hormone-releasing factors in rat hypothalami.[1] Concurrently, Hellman and Lernmark[2] discovered a substance in extracts of pigeon pancreatic islets that inhibited insulin release. These separate observations proved to be related several years later, with the chemical identification of this potent inhibitor of hormone release.[3] Somatostatin, so called because of its original description as a somatotrophin release-inhibiting factor (SRIF), is synthesised in many tissues, including the central nervous system, hypothalamus, peripheral nervous system, pancreatic islet cells (D cells) and epithelial, glandular and neuronal cells of the gastro-intestinal tract. In these tissues a single gene encodes a large peptide, pre-prosomatostatin, which is cleaved to form the large precursor prosomatostatin, which in turn is subsequently processed to two much smaller biologically active forms, somatostatin-14 and somatostatin-28. When secreted, somatostatin enters the circulation and acts at a distant site in an endocrine fashion, or it may act locally, exhibiting paracrine and autocrine functions. Infusion of the peptide in man causes numerous effects, including inhibition of endocrine secretions (growth hormone, thyroid-stimulating hormone, insulin, glucagon and all the gut hormones, e.g. gastrin, vaso-active intestinal polypeptide and cholecystokinin) and exocrine secretions (gastric acid, pancreatic enzymes and pancreatic bicarbonate). The hormone has also been shown to reduce splanchnic blood flow, intestinal absorption, gastric emptying and gallbladder contraction.[4,5]

The native peptide's obvious pharmacological potential has been restricted by a number of factors, including (*i*) its multiple simultaneous effects on different physiological functions, especially the inhibitory effect on insulin secretion; (*ii*) its short duration of action due to rapid clearance of the hormone from plasma; (*iii*) the need to administer the peptide intravenously; and (*iv*) the rebound hypersecretion of hormones (tumorous and non-tumorous) that occurs after infusion of SRIF.[6]

A major advance in overcoming these obstacles was achieved with the development of a cyclic 8 amino-acid analogue (SMS 201-995), now marketed as octreotide (Sandostatin).[7] This analogue is 45 times more active in its growth hormone release-inhibitory effects, 11 times more active in its glucagon release-inhibitory effects and only 1,3 times more active than the natural peptide in its insulin release-inhibitory effects. In addition, it has a long circulatory half-life of 90 - 115 minutes, causing a prolonged inhibitory effect in target organs, it can be administered subcutaneously (even orally with higher doses), and it does not cause rebound hypersecretion of hormones following administration.

The analogue has now been used in the treatment of a number of endocrine and gastro-enterological disorders. In acromegaly octreotide causes persistent reduction of growth hormone concentration by more than 50% in 86% of patients, with normalisation of somatomedin-C concentration in 36%.[8] In addition, excessive sweating, headache, paraesthesiae and tiredness markedly decrease within the first weeks of therapy, while longer periods of treatment lead to reduced soft-tissue swelling and improvement of facial coarsening. Improved glycaemic and blood pressure control has been reported in some patients with insulin-resistant diabetes and severe hypertension.[9] Slight shrinkage of tumours has also been documented in up to 50% of patients treated.[8]

Octreotide has been used with variable success to treat patients with neuro-endocrine tumours of the gut. In the carcinoid syndrome, up to 90% of patients reported significant improvement of symptoms (flushing and diarrhoea) during therapy.[10] The analogue effectively controls the diarrhoea and severe metabolic abnormalities associated with tumours secreting vaso-active intestinal polypeptide (VIPomas) in over 80% of cases.[11] Clinical and/or biochemical responses to therapy have also been reported in some patients with glucagonomas, insulinomas, and gastrinomas.[12] In persistent hyperinsulinaemic hypoglycaemia of infancy (nesidioblastosis), octreotide effectively controls hypoglycaemia without the need for parenteral glucose in up to 90% of cases reported.[13]

Octreotide has been used to treat a variety of non-malignant gastro-intestinal disorders. Up to 80% of patients with small-bowel fistula respond to therapy, with reduction in output and closure of the fistula within 1 - 2 weeks.[14,15] Similarly, reduced output from and subsequent closure of pancreatic fistula have been reported in 85 - 100% of patients within 6 days of therapy.[16] Preliminary reports of successful treatment of pancreatic ascites and pancreatic pseudocysts are also encouraging.[17]

Somatostatin's effects on splanchnic blood flow have led to its use in peptic ulcer and variceal haemorrhage, with small studies reporting initial control of bleeding in approximately 80% of cases.[17] Treatment with the drug in other conditions, including biliary fistula[18] and dumping syndrome,[19] has been investigated, but its use is not justified at this stage, except where failure to respond to conventional therapy has been documented or as part of a clinical trial.

Despite its wide-ranging physiological effects, treatment with octreotide causes relatively few side-effects. The abdominal discomfort, loose stools and symptoms of malabsorption sometimes reported during the initial few weeks of therapy are usually transient. Long-term therapy has been associated with the development of gallstones in 10 - 25% of cases. Glucose intolerance has also been reported.[20] Resistance to treatment has been documented in a number of patients with metastatic neuro-endocrine tumours of the gut,[21] but no tachyphylaxis has been observed in acromegalics treated for more than 3 years.[22]

Thus the clinical introduction of this new long-acting SRIF analogue adds a new dimension to the medical therapy of a variety of conditions. While short-term treatment of a number of the non-malignant gastrointestinal disorders, e.g. fistula, is relatively cheap and cost-effective, long-term therapy for conditions such as acromegaly is expensive — the estimated cost of treatment with 300 μg daily is R45 000 per annum. In an attempt to avoid unnecessary and unjustified use of this drug, the Society for Endocrinology, Metabolism and Diabetes of Southern Africa (SEMDSA) and the South African Gastroenterological Society (SAGES) have established somatostatin subcommittees whose function is to approve and monitor long-term use of these SRIF analogues. Each subcommittee comprises representatives from the major teaching hospitals in South Africa. Guidelines for the use of SRIF analogues, together with dosage protocols, have been drawn up by these committees and are published in this issue of the *SAMJ* (p. 379). Used appropriately, octreotide should benefit many patients suffering from a wide range of mostly rare or uncommon conditions.

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Laparoscopic cholecystectomy

The 'gold standard' for treating patients with stones in the gallbladder is standard operative cholecystectomy. Only patients with symptomatic gallstones should be considered for cholecystectomy. Neither patients with 'silent' gallstones nor patients with so-called 'biliary dyspepsia', who happen to have stones in the gallbladder, should be subjected to cholecystectomy. Some would argue that young patients with small gallstones, or young otherwise fit diabetic patients, should be considered for cholecystectomy in the presence of 'silent' stones.[1] I do not subscribe to this view.

Laparoscopic cholecystectomy is a newly described procedure whereby the gallbladder can be removed without open laparotomy using a modern operating laparoscope with newly designed instruments inserted through portals in the abdominal wall. The operation was first performed in France in 1987. The patient is anaesthetised and has a pneumoperitoneum induced with carbon dioxide, and is then placed in the foot-down position to facilitate exposure. Laparoscopic cholecystectomy has captured the imagination of general surgeons and the lay public world-wide because of the reported advantages of removing the gallbladder without the necessity for an open operation. This could put pressure on surgeons to perform the procedure without adequate training or without the requisite instrumentation, which could have disastrous consequences and threaten a valuable operative procedure, particularly if morbidity — including damage to the common bile duct — or mortality were to occur.

The possibility of performing major surgery via a laparoscope is appealing. Gynaecologists have used the laparoscope for pelvic surgery for some years. General surgeons have been slow to follow. It is interesting that

a cholecystectomy performed through a laparoscope is associated with less metabolic response to trauma, probably because the trauma of laparotomy access is abolished, and it is usually not associated with the transient ileus that frequently accompanies standard operative cholecystectomy. As a result, the hospital stay is shortened to 1 or 2 days, which reduces the overall costs. In addition, most patients can return to work after 1 week rather than the usual 6 weeks. The procedure also has the advantage of avoiding a laparotomy scar.

On the other hand, laparoscopic cholecystectomy is a full operative procedure with all the attendant dangers and takes longer to perform than standard operative cholecystectomy. The general contraindications are the same as for open cholecystectomy or other major operative procedures. Specific contraindications include marked intra-abdominal adhesions or a thickened inflamed gallbladder wall, since these increase the hazards to the patient. It is also contraindicated in portal hypertension. All patients undergoing laparoscopic cholecystectomy should give consent for full operative cholecystectomy in case this becomes necessary. Estimates are that between 5% and 20% of patients are unsuitable for laparoscopic cholecystectomy. The procedure is best performed using modern television camera attachments for the laparoscope so that the surgeon and operating team are able to see the procedure on a television screen. This has the disadvantage of a two-dimensional picture of a three-dimensional operative procedure, which can be hazardous until expertise has been achieved. This, together with the limited access, increases the danger of damaging the common bile duct and of initiating major haemorrhage.

The problems and ethical dilemmas surrounding laparoscopic cholecystectomy were the subject of a major symposium at the combined Second World Congress of Endoscopic Surgery and the Annual Meeting of the Society of American Gastrointestinal Endoscopic Surgeons held in Atlanta, Georgia, USA, in March 1990. The full proceedings of this symposium have been published.[2] Questions of particular importance raised at the symposium were: (*i*) who should undertake laparoscopic cholecystectomy; and (*ii*) what training was required? The conclusion was that only fully trained general surgeons with expertise in biliary surgery should perform the procedure. Such surgeons require laparoscopic training, if they have not had this previously, and also need to learn to use instruments working from a television screen. At overseas institutions there are courses with workshops and seminars to assist general surgeons with biliary surgery training to acquire the necessary skills for laparoscopic work using the new instrumentation, including training in the animal laboratory. Similar training facilities will be essential in this country if we are to avoid the danger to patients in what is otherwise likely to be an important milestone in the development of abdominal surgery. It is totally inappropriate for anyone other than a fully trained surgeon with expertise in biliary surgery, who also has laparoscopic training, to undertake laparoscopic cholecystectomy. Laparoscopic training alone is inadequate, and if persons with laparoscopic expertise, but without training in biliary surgery, undertake laparoscopic cholecystectomy, they will jeopardise the procedure and render themselves liable to justifiable litigation.

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