

Leading article

New somatostatin molecule for management of endocrine tumours

The use of somatostatin in the management of hormone secreting tumours, particularly those located in the digestive tract, has often been proposed, and this as early as 1974.^{1 2} At that time, natural S14 was the only molecular form available and its inhibitory activity towards both endocrine and exocrine gastroenteropancreatic secretions was well demonstrated.

Therapeutic implications in the field of hormone hypersecretion, particularly when of tumoural origin, were thus envisaged: confirmation was repeatedly obtained that consequences of exaggerated hormone secretion(s) can be decreased or suppressed by somatostatin without harmful unwanted effects. Clinical benefits usually resulted more from the decrease in target organ response(s), than from decrease in circulating hormone concentrations.^{1 3 4}

Application of scattered, although important acute data to long term management were unfortunately hindered by the apparently insurmountable problem of duration of action: S14, S28 and a variety of synthetic molecular forms mostly with D amino-acids substitutes had such short term activity (scale of minutes after single injection) that only prolonged infusion of somatostatin allowed meaningful therapeutic results to be obtained.

The new molecular form, SMS 201–995 (or minisomatostatin), with its very specific structural rearrangement (octapeptide with 2 D amino acid substitutions) gives us the opportunity to overcome the problems of short duration of action and particularly the requirement of administration by infusion. Although it is not a very long acting substance, SMS 201–995 gives therapeutic efficacy with two daily injections, that is under conditions no different from those commonly used for insulin in diabetes.

If, as documented by the paper by Wood *et al.*,⁵ in this issue of *Gut* somatostatin like biological activities are obtainable for prolonged periods, therapeutic potential is now to be assessed in acute and chronic conditions. Strictly designed prospective studies should be envisaged for SMS 201–995 applied in complex management schemes and for assessment of the benefit over known therapeutic agents.

We are thus faced with a series of questions and difficulties of clinical relevance, which can be put forward on the basis of theoretical and practical considerations.

The safety of a new therapeutic agent is of critical importance for the performance of adequate studies on efficacy. In the case of somatostatin, particularly when used over months or years, the risk of severe effects appearing in the long run is not negligible. Somatostatin has an exceptionally wide spectrum of activities: gastrin, secretin, CCK, insulin,

glucagon are all inhibited by somatostatin in terms of release and target organ stimulation. Interestingly enough, in antagonistic hormone couples such as gastrin and secretin, or insulin and glucagon, both hormones are inhibited, but not to the same extent. Most of these hormones are feedback regulated and these adaptive systems are also disturbed by somatostatin. Some other organs, such as the smooth muscle of the gut and the blood vessels are targets for somatostatin, without obvious or apparently specific hormone interactions. In addition, somatostatin is an important factor in the regulation of growth hormone secretion.

On the whole, as large doses of somatostatin (or somatostatin-like material) are necessary to counteract excessive hormone secretion from a tumour, one should expect many unwanted effects in the treated patients, specially in the long term. The data presented by Wood *et al*⁵ underline the excellent tolerance of SMS 201–995 by each patient, signs of visceral blood flow imbalance being observed in only one.

It is difficult, however, to determine whether in the treated patients the severity of the initial symptoms does not mask for a time secondary functional changes of uncertain importance, such as disturbances of gut motor activity.^{6,7}

This apparently good tolerance is comparable with what has been observed in somatostatinomas, which usually give rise to slight symptoms compared with other endocrine tumours. In reference to this condition⁸ attention should be given to possible pancreatic insufficiency and gall stones. These have not been so far described in patients receiving minisomatostatin, but may be expected from prolonged treatments.

Is the SMS 201–995 molecule itself harmless? Tolerance studies in animals which at present indicate no damaging effect, even with high doses and prolonged administration, are encouraging. The structural changes which differentiate SMS 201–995 from natural somatostatin, however, make it foreign to the human body, with the potential risk of raising antibodies. At least theoretically, therefore, the danger of loss of efficacy of this synthetic compound exists, let alone the problems of allergy, or production of antibody with cross reactivity inducing inactivation of natural somatostatin.

Tests needed for safety control are difficult to define a priori. In prolonged administration of high dosages the very wide range of targets for somatostatin makes controls theoretically indispensable, but in practical terms very difficult.

In the group of patients reported in this issue⁵ multiple hormone dosages were used, but Bloom *et al*, have exceptional expertise in the field. Furthermore, the control period lasted only seven days at the start of the study. In long term therapeutic conditions, it seems to us that exocrine and endocrine pancreatic secretions should be accurately checked. In addition to gall bladder radiographs or ultrasonography we suggest that stool analysis (fat, hydration, enzymes) could be a good and informative variable for screening for possible damaging effects of the treatment.

The danger of specific nutrient malabsorption one could expect from fundamental studies of somatostatin actions on small bowel epithelium seems more theoretical.⁹

If unwanted effects do occur the next question is whether they arise as a direct consequence of administration of somatostatin, or whether perma-

ment changes have taken place which may persist after discontinuation of the treatment.

This leads to a new problem of immediate and delayed consequences when stopping the treatment in case of bad tolerance, poor efficacy, or for any other purpose: that is to say, rebound phenomena. Dramatic rebound after stopping of somatostatin (S14) infusions has been recorded in the form of worsening of diarrhoea in VIPoma, harmful hypercalcemia in parathyroid adenoma, flush and diarrhoea in serotonin-secreting carcinoids.^{3 10 11} Rebound can be also limited to hormone hypersecretion without clinical relevance.

This risk of rebound when using long acting SMS 201–995 is not to be dismissed (as suggested by the cases of VIPoma of Woods series);⁵ we tested progressive reduction in somatostatin S14 dosage in a case of VIPoma undergoing hormone infusion, and observed rebound of diarrhoea similar to that present after abrupt discontinuation of the treatment.¹²

Obviously with a new substance whose efficacy has been pharmacologically documented in animals and humans, clinical application needs controls adapted to specific problems. In the case of hormone secreting tumours, two aspects should be considered: (1) symptomatic improvement, (2) controls of the pathophysiological chain involved in the disease.

Concerning the first point, some possible effects are well known: healing of ulcer and suppression of diarrhoea in gastrinoma; decrease in stool volume with easy control of systemic electrolyte and water imbalances in VIPoma; improvement of skin lesions in glucagonoma;¹³ decrease in number and/or intensity of flushes in serotonin secreting carcinoids.¹⁴

As mentioned in Wood's paper,⁵ there are individual variations in sensitivity to SMS 201–995, yet some discrepancies exist compared with what was observed with natural somatostatin. This may be due to the latter's more flexible adaptation of the dose to symptomatic response. Hence, quantitation of symptoms should be systematically attempted in as accurate and objective a manner as possible.

Concerning the second point, assessment of efficacy creates problems because responses of circulating hormones are not the most relevant variable: a number of studies with S14 showed that target organ responses are most closely correlated with the clinical responses. These responses reflect both actions of somatostatin, that is to say inhibition of hormone release from the tumour, and inhibition of hormone activity at the receptor level. For instance, in the Zollinger Ellison Syndrome treated with S14 500 $\mu\text{g}/\text{kg}/\text{h}$, serum gastrin decreases by 40%, but acid secretion is totally inhibited.¹⁵ Similar observations were made in VIPoma¹⁶ and carcinoid tumours.¹⁷

Finally, in experimental designs for testing SMS 201–995 in hormone-secreting tumours, variables representative of the end of the pathophysiological chain (target organ activity), rather than of the early link represented by circulating hormone concentrations, should be measured. Obviously this is easily done with 24-hour intragastric pH profiles in gastrinoma,¹⁸ but difficulties arise in VIPoma, because measurement of small bowel absorption and secretion needs sophisticated and invasive techniques¹⁹ which cannot be done repeatedly. We noticed that in carcinoids suppression of diarrhoea was not associated with decrease of

urinary excretion of 5 HIAA.⁵ Similar observations were made in another series,¹⁷ with unchanged concentration of blood serotonin. This makes studies of intestinal absorption and motor activity mandatory for correct appreciation of SMS 201-995 efficacy.^{17 20}

Concerning hormones with metabolic activity, glucose tolerance studies reflecting action of insulin and glucagon do not seem relevant. Although plasma glucagon is strongly decreased by SMS 201-995 in the patients described,⁵ skin lesions were not modified by the treatment and this discrepancy makes assessment of the therapeutic value difficult. Personal experience with PTH in parathyroid adenoma has shown that a correct appreciation of therapeutic efficacy and dangers of somatostatin can only be ascertained by measurement of serum calcium.³ We believe that for prolonged treatment with SMS 201-995 the same kind of global reference should be obtained, when hormones with metabolic activities are concerned.

It will probably be long before the therapeutic usefulness of SMS 201-995 for hormone secreting tumours can be precisely known. This is because of the rarity of these diseases, the diversity of the clinical and pathophysiological aspects, the spontaneous variations in severity of the syndromes and the occurrence of unexpected stabilisations, or even regressions.

For the present, each new case has experimental value. The rule adopted by Wood *et al*⁵ to treat only patients resistant to conventional management schemes must be accepted. The final assessment of SMS 201-995 should not be limited to its inhibitory activity on exocrine and endocrine secretions. For instance, somatostatin could be used for slowing gut motor activity and thus improving bioavailability of other active drugs; anti-trophic effect of somatostatin²¹ could diminish the parietal cell mass in the Zollinger Ellison syndrome, as well as the number, or the activity of other endocrine cells. Diarrhoea could appear as the main symptomatic indication, whatever the kind of tumour involved.

In conclusion it should be stressed that because of the wide spectrum of actions, the precise limits of usefulness of SMS 201-995 remain to be defined.

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