Development of resistance to a long-acting somatostatin analogue during treatment of two patients with metastatic endocrine pancreatic tumours

S. W. J. Lamberts¹, G. F. F. M. Pieters², H. J. Metselaar¹, G. L. Ong¹,
H. S. Tan³ and J.-C. Reubi³

Department of Medicine (III) and of Clinical Endocrinology¹,
University Hospital Dijkzigt, Erasmus University Rotterdam,
Department of Medicine², University of Nijmegen, Department of Medicine³, Canisius-Wilhelmina Hospital Nijmegen,
Department of Surgery¹, University Hospital Dijkzigt, Erasmus University Rotterdam, Rotterdam, The Netherlands,
and Sandoz Research Institute³, Bern Switzerland

Abstract. Two patients with metastatic endocrine pancreatic tumours initially responded well to therapy with the long-acting somatostatin analogue SMS 201-995. In the first patient with an insulinoma both the number of hypoglycemic attacks and the increased insulin levels decreased initially, but returned to pretreatment intensity and concentrations within 9 days after the start of therapy with 200—300 µg SMS 201-995 daily. After a short interruption, no effect was observed of re-institution of therapy at a dose of 400 µg SMS 201-995 daily. In the other patient with a metastatic vipoma both diarrhoea, hypokalemia and plasma VIP levels reacted initially well to SMS 201-995 treatment with 300 µg per day, but resistance to therapy developed after 2 weeks. An increase in the dose of the analogue to maximally 600 µg/day was followed by a transient improvement, but finally both the volume of diarrhoea and the levels of vasoactive intestinal polypeptide were higher than those before the start of therapy. Conclusions: Development of resistance to SMS 201-995 both with regard to the clinical effect and to the inhibitory effect on tumour hormone secretion can be expected in some patients with metastatic endocrine pancreatic tumours. On the basis of our clinical observations down-regulation of somatostatin receptors is suggested to be one of the mechanisms of this development.

Endocrine pancreatic tumours (apudomas) are in general slowly growing malignancies. In most cases morbidity and mortality are caused by hypersecretion of the tumoural peptide hormones (Bloom & Polak 1980). Metastases are present in most patients at the moment of diagnosis and surgical debulking, arterial embolization of the tumour and cytotoxic drugs like streptozotocin are considered to be the first lines of therapy (Bloom & Polak 1980; Bonfils 1985): The new somatostatin analogue SMS 201-995 (Sandoz, Basel, Switzerland) was recently shown to be of additional value in these patients because chronic therapy with this drug both suppressed hormone release and alleviated clinical symptoms caused by these peptides in the majority of patients with endocrine pancreatic tumours and metastatic carcinoids (Wood et al. 1985; Maton et al. 1985; Santangelo et al. 1985; Wohrmann et al. 1985; Kvdols et al. 1986, 1987).

In a few patients with vipomas, glucagonomas and carcinoids, mild worsening of symptoms and increasing tumour-related hormone concentrations were observed during long-term therapy for over a year with SMS 201-995 (Anderson & Bloom 1986; Kvols et al. 1986), but doubling the dose of the analogue reversed these problems in most patients (Anderson & Bloom 1986).

In the present study we describe 2 patients with a metastatic endocrine pancreatic tumour (one pa-
Glucose, insulin and glucagon levels before and during treatment with SMS 201-995 in patient No. 1 with a malignant metastatic insulinoma. Asterisks indicate the number of hypoglycemic attacks. On day 1 SMS 201-995 was administered at a dose of $3 \times 100 \mu g$ and from day 2 till 10 at a dose of $2 \times 100 \mu g$. After discontinuation of therapy for one day, the analogue was restarted at a dose of $4 \times 100 \mu g$ daily. Fasting plasma glucose, insulin and glucagon concentrations on different days are shown.

Fig. 1.
tient with an insulinoma and one with a vipoma) who developed resistance to SMS 201-995 with regard to its initial suppressive effects on hormone secretion and on the related symptoms, shortly after the start of medical therapy and in whom an increase in the dose of the analogue resulted in no (first patient) or in only transient improvement (second patient).

Patients and Methods

Plasma insulin and vasoactive intestinal peptide determinations were carried out with routine commercial radioimmunoassay kits. Statistical analysis was performed using Student's t-test.

Case reports

Patient No. 1. A 71-year-old man was admitted to the hospital because of attacks of unconsciousness and aggressive behaviour. He appeared hypoglycemic with fasting glucose levels between 0.8 and 4.0 mmol/l. The serum insulin levels were inappropriately elevated between 181 and 204 mU/l. A computerized tomography (CT)-scan revealed a tumour in the head of the pancreas with a diameter of 5 cm and hepatomegaly with multiple hypodense lesions. A biopsy of the liver confirmed the clinical diagnosis of metastatic malignant insulinoma.

Treatment with SMS 201-995 was started at a dose of 100 µg three times daily sc on the first day. Glucose levels became elevated, reaching a level of 14.5 mmol/l (Fig. 1). Therefore the dose of SMS 201-995 was lowered from the second day on to 100 µg twice daily. Initially the clinical response to this treatment was very good: the hypoglycemic attacks, which occurred daily in this patient, remained completely absent for 7 days. Thereafter hypoglycemic attacks reappeared. The initially favourable clinical response was accompanied by a clear increase in glucose levels and decreases of insulin and glucagon levels, but later, despite continuation of SMS 201-995 treatment, insulin levels rose and glucose levels gradually decreased (Fig. 1). After 9 days of treatment, SMS 201-995 administration was discontinued. On day 10, more hypoglycemic attacks occurred, whereas insulin levels reached pretreatment values. Therefore treatment with SMS 201-995 was re-instituted on day 11 at a higher dose (four times daily 100 µg sc). Now the effect of the treatment was much less impressive in comparison to the first institution of SMS 201-995 therapy. One or more attacks of hypoglycemia daily remained present and circulating blood glucose levels gradually decreased. Unfortunately no plasma insulin and glucagon levels were measured at this stage of the study. After discontinuation of SMS 201-995 therapy the patient underwent ligation of the hepatic artery, which was followed by treatment with 5-fluorouracil and streptozotocin.

Patient No. 2. A 75-year-old woman presented elsewhere in 1979 with diarrhea, achlorhydria, severe hypokalemia and high plasma levels of vasoactive intestinal polypeptide (VIP) (1250 ng/l; normal less than 100 ng/l). The primary tumour was located in the head of the pancreas. Two large metastases with a diameter of 8 cm each were found at echographic examination in both lobes of the liver. A biopsy of the tumour confirmed the diagnosis of apudoma. The patient refused both a laparotomy for tumour debulking and cytotoxic therapy with streptozotocin. There was invalidating watery diarrhea with profound hypokalemia and acidosis. A trial with SMS 201-995 administered sc was started at a gradually increasing dose from 50 to 300 µg daily (Fig. 2). In the ensuing 2 weeks of therapy a marked clinical improvement occurred. The amount of loose stools reduced from a mean of 1510 ± 497 ml/day (mean ± sd) to a mean of 868 ± 190 ml/day and became less watery. In parallel, a gradual normalization of serum potassium was observed, which...
made additional oral substitution therapy unnecessary. There was an increase in general well-being and an increased appetite. After 22 days of therapy diarrhea suddenly increased overnight, whereas hypokalemia (2.0 mmol/l) and acidosis (bicarbonate 12 mEq/l) reappeared within a few hours. An increase in the dose of SMS 201-995 to a maximum of 600 µg per day resulted in a transient decrease in diarrhea, whereas potassium supplementation could be stopped again. The accompanying improved sense of well-being deteriorated, however, suddenly for a second time, concurring with diarrhea and hypokalemia which were even worse than observed before the start of SMS 201-995 treatment. Echoscopic control of the size of the primary tumour and its liver metastases did not show evidence of tumour growth. Plasma VIP levels before treatment were 2375 ± 93 ng/l (mean ± se; N = 4). Concomitantly with the decrease in stool-volume, plasma VIP levels initially fell (−33%), but in parallel with the subsequent increase in diarrhea they rose thereafter by 91% to levels which were significantly higher than the pretreatment plasma levels (P < 0.05; Fig. 2). The increase in the dose of SMS 201-995 to 600 µg/ day resulted again in a decrease of plasma VIP levels by 26%, concomitantly with a decrease in stool-volume. However, after a further 2 weeks of therapy a rebound rise of plasma VIP levels was once again observed. Postprandial blood glucose levels were normal before SMS 201-995 therapy. They became elevated and remained in the diabetic range during treatment, and normalized immediately after stopping the drug. In a plasma sample taken during therapy with 600 µg SMS 201-995 daily, the plasma SMS concentration measured 3 h after the sc administration of 200 µg of the analogue amounted to 9.6 ng/ml (personal communication: Prof E. del Pozo, Sandoz, Basel, Switzerland).

Discussion

Recently the somatostatin analogue SMS 201-995 was shown to be effective both on the clinical symptomatology and hormonal hypersecretion in patients with (metastatic) endocrine pancreatic tumours secreting VIP (Wood et al. 1985; Maton et al. 1985; Anderson & Bloom 1986), glucagon (Wood et al. 1985; Maton et al. 1985), gastrin (Kvols et al. 1987), and in carcinoids (Kvols et al. 1986). In some cases evidence was presented of an arrest of tumour growth or even an actual shrinkage of these tumours (Kvols et al. 1986; Wood et al. 1985). After the initial positive reports it became gradually clear that during long-term therapy with SMS 201-995, a mild worsening of the symptoms and an increase in the initially suppressed circulating tumour-related hormone concentrations occurred in a minority of patients, especially in those with a vipoma or glucagonoma (Anderson & Bloom 1986; Kvols et al. 1987) and less frequently in those with metastatic carcinoids (Kvols et al. 1986). However, an increase in the dose of the somatostatin analogue resulted in further clinical improvement and (often incomplete) lowering of hormone levels in most patients (Anderson & Bloom 1986). In this regard it is interesting to note that an impressive improvement of the clinical symptoms occurred in our vipoma patient during the first period of SMS 201-995 therapy, despite the fact that circulating VIP levels had decreased only by less than 50% and remained greatly elevated. Especially in patients with insulinomas, the primary effect of SMS 201-995 on blood sugar concentrations and insulin levels was described to be virtually absent (Verschoor et al. 1986; Schrezenmeir et al. 1986) or beneficial only in therapeutic trials with the drug for a few days to periods of months (Verschoor et al. 1986; Lewis et al. 1986; Kvols et al. 1987). The lack of uniformity in the primary inhibitory responses to SMS 201-995 of insulin secretion in insulinoma patients seems to a considerable extent to be influenced by the variability between patients in the affinity and the number of somatostatin-14 receptors in these tumours (Reubi et al. 1987).

Actual development of resistance to SMS 201-995 as seen in our second patient were described in 2 vipoma patients (Koelz et al. 1987). It was concluded that the need to increase the dose of the analogue might be due to desensitization or perhaps progression of tumour growth (Anderson & Bloom 1986; Koelz et al. 1987). It was also suggested that the beneficial effect of the somatostatin analogue in some cases of diarrhea might be due to a direct effect on the gut not involving a decrease in the secretion of VIP (Wood et al. 1985). If this last suggestion is true, beneficial effects of SMS 201-995 might also be expected in patients with severe diarrhea of other causes including cholera.

In the present study we described 2 patients in whom development of resistance to SMS 201-995 occurred within 22 days after starting the analogue. This resistance involved both the inhibitory effect on hormone secretion (on insulin in patient No. 1 and on VIP in patient No. 2) and the clinical effect (reappearance of hypoglycemic attacks in patient No. 1 and of watery diarrhea with potassium loss in patient No. 2). An increase in the dose
of SMS 201-995 was of no value in patient No. 1 and was temporarily effective in patient No. 2, in whom the development of resistance to somatostatin analogue therapy even resulted in statistically higher VIP levels than before the start of treatment and a worsening of diarrhea.

There are several possible explanations of the occurrence of this development. 1. An accelerated enzymatic breakdown of SMS 201-995 might occur in some patients. This can be excluded, however, in patient No. 2 who had measurable circulating SMS levels 3 h after the sc administration of 200 µg of the analogue which at least in acromegalic patients is considered to be in the ‘therapeutic’ range (Christiansen et al. 1987). 2. A rapid growth of the primary tumours or its metastases might explain the secondary development of resistance of SMS 201-995 as observed during long-term administration for over one year in some endocrine pancreatic tumour patients (Anderson & Bloom 1986; Kvols et al. 1987). It is improbable, however, that this was the case during the short period of treatment in our 2 patients. Echoscopic control of the tumour in our second patient did not point to this possibility. 3. A third possibility is the development of antibodies to SMS 201-995 in these patients. However, in patient No. 2 hyperglycemia developed during therapy with the somatostatin analogue, which normalized immediately after stopping the drug. This implies that SMS 201-995 remained active in its inhibitory effect on insulin secretion in this patient even when hormone secretion by the vipoma had become insensitive to it. 4. The fourth and most likely explanation is down-regulation of somatostatin receptors on these endocrine pancreatic tumours during chronic SMS 201-995 therapy.

It was shown previously that repeated administration of high doses of SMS 201-995 induces desensitization or tachyphylaxis of its inhibitory effect on normal GH secretion in the rat (Lamberts et al. 1986) and of its inhibitory effect on the growth of transplantable PRL-secreting pituitary tumours (Lamberts et al. 1986). Prolonged somatostatin pretreatment in vitro also desensitizes its inhibitory effect on ACTH release by cultured mouse anterior pituitary tumour cells (Reisine & Axelrod 1986), whereas multiple sc injections of another somatostatin analogue were reported to induce in rats very rapidly tachyphylaxis of its suppressive effect on insulin, but not on glucagon secretion (Marki et al. 1982). It is currently unknown why this desensitization phenomenon or tachyphylaxis to SMS 201-995 therapy in man seems to be confined to endocrine pancreatic tumours (Lamberts 1986). In acromegalic patients both tumorous GH and insulin secretion by normal beta-cells remain highly sensitive to the analogue during long-term therapy with SMS 201-995, and the beneficial clinical effects persist (Lamberts et al. 1985). In addition, continuous infusion for 30 days with SMS 201-995 in a newborn with nesidioblastosis was highly effective in suppressing insulin secretion without signs or symptoms of development of resistance to therapy (Bruining et al. 1986).

The sudden escape phenomenon from therapy with SMS 201-995 as observed in the 2 patients described in the present study resulted in the recurrence of attacks of hypoglycemia and of diarrhea and hypokalemia. Especially in patients with (malignant) insulinomas this phenomenon might be dangerous. Therefore, close clinical control and careful instruction should be given to insulinoma patients during treatment with SMS 201-995. However, preliminary results from studies on the effects of chronic SMS 201-995 therapy in patients with endocrine pancreatic tumours and carcinoids fortunately show that the escape phenomena as observed in our 2 patients and those from Koelz et al. (1987) did not occur in more than 40 patients treated for 4 weeks to over 2 years with SMS 201-995 at dosages varying between 150—450 µg/day (Kvols et al. 1986, 1987).

References


Christiansen S E, Weeke J, Ørskov H et al. (1987): Continuous subcutaneous pump infusion of somatostatin


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Prof Steven W. J. Lamberts,
Department of Medicine (III),
University Hospital Dijkzigt,
NL-3015 GD Rotterdam,
The Netherlands.