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TREATMENT OF MALIGNANT MIDGUT CARCINOID TUMOURS WITH A LONG-ACTING SOMATOSTATIN ANALOGUE OCTREOTIDE

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Abstract

Treatment with the somatostatin analogue octreotide, SMS 201-995 (Sandostatin), has been carried out in a series of 23 patients with malignant midgut carcinoid tumours. The patients received initially 50 μg twice a day for six months, thereafter a median of 100 μg twice daily. Six of 22 evaluable patients (28%) showed objective tumour response lasting for 6 to 30 months. Stable disease was observed in 8 of the 22 patients (36%) and progressive disease in a further 8 patients (36%). A subjective response with decrease of diarrhoea or flushing was noted in 11 out of 22 patients (50%). Two out of 6 patients with objective response demonstrated a significant decrease of tumour size lasting for 6 and 30 months respectively. In order to maintain the clinical response, the dose had to be increased in all 6 responders. The adverse effects included development of diabetic blood glucose levels in 8 out of 22 patients (36%). Albumin-modified serum calcium levels were significantly reduced after treatment with octreotide 50 μg twice a day. One patient developed symptoms of hypocalcemia which was reversed by supplementation with calcium and D-vitamins. The somatostatin analogue SMS 201-995 has a beneficial effect in the treatment of patients with the carcinoid syndrome. However, the precise role of the drug in the long-term management of these patients has to be further investigated.

Key words: Carcinoid tumours, somatostatin analogue, U-5-HIAA.

Malignant carcinoid tumours of midgut type, e.g. ileal or jejunal carcinoids, are slowly progressive neoplasms with a median survival of about 2.5 years (1). Due to secretion of biologically active substances, such as serotonin and tachykinins, patients with midgut carcinoid tumours and liver metastatses present the carcinoid syndrome which has been a therapeutic challenge (2, 3). Clinically the syndrome is usually manifested by episodic flushing and diarrhoea and in the advanced stages by right heart failure. The severity of the carcinoid syndrome varies in patients from minor nuisance to life-threatening carcinoid crises (2).

Numerous treatment approaches have been tried including treatment with H_1 and H_2 receptor blockers (4), serotonin antagonists (5) and corticosteroids (6), but these agents have only occasionally and partly suppressed the endocrine-related symptoms.

Somatostatin is a powerful inhibitor of the release of a number of endogenous peptides such as growth hormone, insulin, glucagon and gastrointestinal peptides (7). Natural somatostatin 14 has been reported to be effective in blocking the carcinoid flush induced by pentagastrin reducing circulating levels of serotonin and controlling other symptoms associated with carcinoid syndrome (8). However, natural somatostatin has limited therapeutic application because of short half-life which necessitates continuous intravenous infusion.

An analogue of somatostatin with prolonged effect, the octreotide SMS 201-995, has been synthesized. The octapeptide has a half-life of about two hours and can be given as subcutaneous injections (9). It has been reported to be effective in the management of clinical syndromes associated with endocrine pancreatic tumours (10-12). It has recently also been reported to be effective in controlling the carcinoid syndrome (13). Since there are only few reports (Expert Reports M. J. Dunne 1986, Sandoz, Basle), with a limited number of patients, of long-term

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Table 1

Data of patients included in the long-term study with octreotide (SMS 201–995)

Pat. No.	Age	Sex	Dur.[1] dis. (years)	Liver metastases	Carc.[2] syndr.	U-5-HIAA[3] μmol/24 h Bef./after		Obj.[4] biochem. resp.	Duration of therapy (months)	Sympt. effect	Final daily dose (μg)	Adverse reaction	Comments
1	69	M	4	+	+	184	197	SD	9	+	100 × 2	Flatulence	
2	71	M	6	+	+	700	450	SD	12	–	100 × 2	Flatulence	
3	60	M	15	+	+	290	193	SD	12	+	100 × 2	Flatulence	
4	71	F	1.5	+	+	2 000	1 000	OR	12	+	150 × 2	Flatulence	Liver met. Reduct. size by 30%
5	74	F	3	+	+	280	135	OR	27	+	100 × 2	Steatorrhoea	
6	75	M	7	+	+	173	157	SD	2	–	50 × 2		Increased clin. symp.
7	76	F	7	+	+	510	820	PD	12	–	100 × 2		Increased clin. symp.
8	66	F	2	+	+	2 350	2 800	PD	8	–	50 × 2	Steatorrhoea	Died after 8 months
9	68	F	2	+	+	490	300	SD	12	+	100 × 2	Flatulence	
10	76	M	2	+	+	1 220	500	OR	14	+	200 × 2		Reduction of tumour size > 50%
11	62	M	1	+	+	872	590	SD	30	+	150 × 2		
12	58	M	1.5	+	+	1 010	1 480	PD	5	–	100 × 2		Died after 5 months
13	64	F	0.5	+	+	189	186	SD	6	–	50 × 2	Cholangitis	
14	55	F	0.5	–	+	110	325	PD	18	–	50 × 2		Refused higher doses
15	71	M	5	+	+	274	–	–	1	–	50 × 2	Severe bradycardia	Stopped therapy after 1 mo.
16	60	M	2	+	+	187	46	OR	24	+	100 × 2		30% reduction of
17	61	M	1	+	+	129	1 063	PD	12	–	200 × 2	Steatorrhoea	
18	69	M	5	+	+	1 160	1 413	PD	12	–	200 × 2	Steatorrhoea	
19	73	F	2	+	+	267	213	SD	15	+	100 × 2		
20	68	F	6	+	+	471	871	PD	4	–	100 × 2	Steatorrhoea	
21	68	F	5.5	+	+	726	615	PD	6	–	100 × 2	Steatorrhoea	Died after 9 months
22	58	M	10	+	+	442	119	OR	30	+	100 × 2		> 50% reduction of tumour size
23	77	F	5	+	+	547	214	OR	15	+	150 × 2		Died after 15 months; heart failure

1) Duration of disease from first recorded symptom.
2) Carcinoid syndrome include flushes and diarrhoea and increased U-5-HIAA levels.
3) After denotes of the U-5-HIAA level at the last follow-up.
4) Objective biochemical responses: OR = objective response; SD = stable disease; PD = progressive disease.

treatment with the somatostatin analogue SMS 201-995 in patients with carcinoid syndrome, we wanted to evaluate the clinical use and the adverse effects of the drug in a larger number of patients with midgut carcinoid tumours.

Material and Methods

Patients. Twenty-three patients (Table 1) were included in the study (12 men and 11 women, median age 68 years, range 55-77). The duration of carcinoid disease from first symptom to start of treatment with the analogue was median 2.5 years (mean 4 ± 3.5 (SD)). All patients had histologically verified carcinoid tumours of midgut type, i.e. positive Grimelius' argyrophil (14) and Masson argentaffin (15) reaction. The primary tumours had been resected in 12 patients and liver metastases were found in 22 of the 23 patients, 19 of the patients with advanced metastasing disease (more than five metastases seen on CT-scan).

Carcinoid symptoms such as flush and/or diarrhoea were found in 21 of 23 patients, whereas one patient also had bronchoconstriction. Thirteen of the 23 patients had previously been treated with interferon, which was withdrawn one month prior to start of treatment with the somatostatin analogue. Seven patients had been treated with a combination of streptozocin and 5-fluorouracil, which had been withdrawn three months prior to start of the treatment with the somatostatin analogue. Only seven of 23 patients were previously untreated.

All patients were started on a dose of SMS 201-995 (Sandoz, Basle) 50 μg twice daily, which was maintained for the first 6-month period. After that, the dose was gradually increased up to a median dose of 200 μg per day (range 100-600 μg per day), administered two or three times a day (Table 1). No other treatment was allowed except for loperamide for the diarrhoeas which was maintained at the same level throughout the study.

The treatment with the somatostatin analogue SMS 201-995 was maintained until tumour progression was established (median 12 months, range 1 to 30 months). Three patients were treated for 30 months, 9 patients for 12 months, 3 patients for 6 months and 3 patients for 3 months. Single patients were treated for 1, 9, 15, 18 and 24 months respectively (Table 1).

Methods. The response to treatment with the somatostatin analogue SMS 201-995 was monitored by measurements of urinary 5-HIAA in two 24-h collections at every visit, according to a method described earlier (16). The plasma level of neuropeptide K was taken after an overnight fast every third month and analyzed using a radioimmunoassay described earlier (17).

Routine haematology, liver function, blood glucose, albumin-modified serum calcium, renal function and blood lipids were followed every third month. Computerized tomography of liver metastases as well as ultrasound investigations were also performed every third month.

The patients showed an objective tumour response when urinary 5-HIAA or plasma neuropeptide K was decreased by more than 50% and/or tumour size measured as the product of two perpendicular diameters on CT-scan. Stable disease denoted a less than 50% reduction of tumour markers or tumour size without any signs of new metastases, whereas progressive disease was defined as more than 25% increase of tumour markers and/or size and observation of new metastases on CT-scan.

Student's t-test for paired samples was performed.

Results

Twenty-two of 23 included patients were evaluable for an effect of treatment. One patient was withdrawn after four weeks because of severe side-effects. Six of 22 patients (28%) showed objective tumour response with duration of 6, 12, 24, 27 and 30 months respectively (Fig. 1) (Table 1). Stable disease was observed in 8 of 22 patients (36%) and progressive disease was noted in a further 8 patients (36%). No patient demonstrated complete remission. Subjective response with less diarrhoea and/or flushing, was noticed in 11 out of 22 patients (50%). In order to maintain the clinical response, the dose had to be increased in all six responders (Fig. 1). When the dose of SMS 201-995 was increased after the first 6-month period, no further objective responders were encountered. There was no difference in the urinary 5-HIAA levels from start of treatment between patients with objective response versus those with progressive disease. The same was true for plasma neuropeptide K. Nor was there any difference between earlier treated and untreated patients or tumour mass. Two patients demonstrated a significant decrease of tumour size lasting for 6 months (Fig. 2) and 30 months respectively.

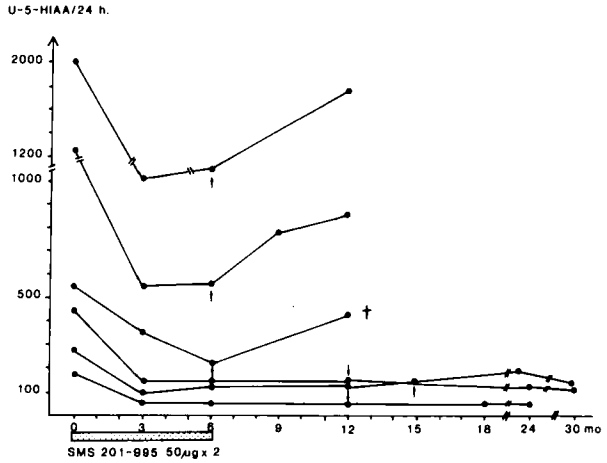
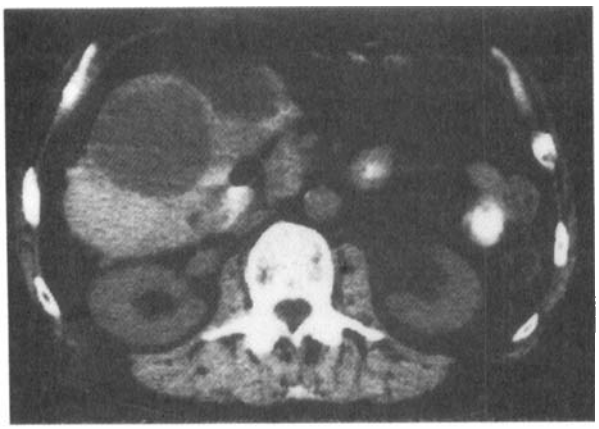
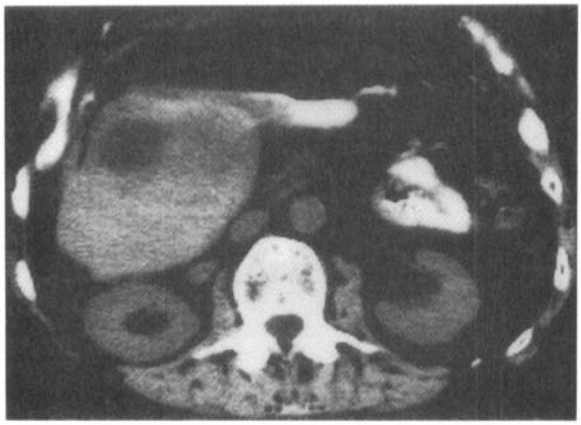


Fig. 1. Urinary 5-HIAA levels in 6 patients with objective tumour response during treatment with SMS 201-995, the upper reference limit is 80 μmol/24 h. Arrows indicate dose escalation. (†) denotes patient death.



(a)



(b)

Fig. 2. Effects of the somatostatin analogue SMS 201-995 on the size of liver metastases in a patient with midgut carcinoid tumours and metastases. a: Before treatment. b: Six months after treatment.

Adverse reactions (Table 2). The fasting blood glucose was significantly ($p = 0.0016$) increased during treatment with SMS 201-995 and 8 out of 22 (36%) tested patients developed diabetic blood glucose levels (upper ref. limit > 5.7 mmol/l). No one needed insulin treatment, only food restriction. Albumin-modified serum calcium was significantly decreased during SMS treatment ($p = 0.0023$) and one patient developed symptoms of hypocalcemia (serum calcium 1.89 mmol/l). The patient needed supplementation with calcium and D-vitamin. Subjective adversed reactions were borborygmia and diarrhoea in 10 out of 23 patients, bradycardia in one (46 beats/min), and yet another developed cholangitis. The patient who developed slow heart rate had to stop the treatment already after one month due to vertigo. This adverse reaction disappeared after cessation of the SMS treatment.

Table 2

Adverse effects of SMS 201-995

	n	(%)
Diabetic blood glucose	8/22	(36)
Severe hypocalcemia	1/22	(5)
Diarrhoea	10/22	(43)
Bradycardia	1/23	(4)
Cholangitis	1/23	(4)

Discussion

Kvols et al. (13) in 1986 reported on the beneficial value of octreotide with an objective response rate of 72% in patients with malignant carcinoid syndrome. However, in a similar material we could not confirm these high objective response rates in our study only reaching an objective response rate of 28%. The major difference between the two studies is that we started on a low-dose treatment with 50 μg two times per day for 6 months, and thereafter increased the dose up to a median of 100 μg two times a day, which is well in the dose range suggested by the manufacturers and other investigators (11, 13). Since there was no relation of treatment response to tumour burden, evaluated as urinary 5-HIAA levels or number of liver metastases, it might depend on the 'sensitivity' of different carcinoid tumours to the drug. It might be possible that starting with low doses of SMS 201-995 for 6 months continuously downregulates the number of receptors or receptor sensitivity for the drug, and increases of the dose will not give any further effect (18). This is supported by the observation in our six patients with objective responses since in three of them, after increasing the dose, no further objective responses were obtained (Fig. 1). Furthermore, no additional responders were encountered when the dose of SMS 201-995 was increased. Instead, tachyphylaxis developed in all responders necessitating an increase of the dose after 6 to 12 months' treatment. However, this cannot be the sole explanation since there have been demonstrated in vivo effects of the analogue on tumours lacking somatostatin receptors (19, 20). The question whether the somatostatin analogue SMS 201-995 could really cause a shrinkage of the tumour size has been much debated. Single cases with responses in tumour size have been reported (10, 13). In the present study we could clearly demonstrate a significant reduction of tumour size in two of our six responders, but in one of these patients the reduction of tumour size was short-lasting (only 6 months) and in parallel with increasing hormone levels, the tumours started to grow in size. It is not known whether the antineoplastic action of somatostatin is a direct effect or whether it is exerted indirectly by inhibition of growth factors which are still unknown for this type of tumour. Effects on the blood supply to the tumour cells might also be a mechanism of action (21).

The adverse reactions to the analogue were few, but our observation of significantly elevated blood glucose and

decreased albumin modified serum calcium after octreotide treatment must be taken into consideration. A high proportion of the patients actually developed diabetic glucose levels, which might in the long run be of significant clinical importance. Our observation of decreasing serum calcium levels during SMS treatment has also been found in patients with malignant pancreatic tumours and especially in patients with the MEN-1 syndrome previously subjected to parathyrectomy (12). Since somatostatin and its analogues induce a slight steatorrhoea and malabsorption, the hypocalcemia might depend on malabsorption of calcium and D-vitamins from the gut. In the patient with severe hypocalcemia these adverse reactions could be reversed by addition of calcium and D-vitamins. One patient developed cholangitis and it is important to keep in mind that patients with gall stones might not tolerate the drug.

We believe that the role of the somatostatin analogue in long-term treatment of carcinoid tumours has to be studied further. Alternative treatment such as interferons with a response rate of about 50% is now introduced (22, 23). Adverse reactions of α-interferons are somewhat more severe than with the somatostatin analogue, but the administration of interferon, once a day to every second day, is easier to manage than the analogue which has to be administered two or three times per day. The development of tachyphylaxis to the analogue might indicate that this drug is more useful in the acute situation, whereas α-interferon might be more suitable for long-term treatment (24). An important study for the future could be a combined treatment with the analogue and α-interferons to see whether additive or even synergistic effects could be obtained.

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