CLINICAL RESEARCH

Glucose tolerance during long term treatment with a somatostatin analogue

LOUIS VERSCHOOR, STEVEN W J LAMBERTS, PIET UITTERLINDEN, EMILIO DEL POZO

Abstract

Seven patients with active acromegaly were treated with SMS 201-995, an analogue of somatostatin, for one year, the maximum dose being 100 μg three times a day. Three patients had impaired glucose tolerance before treatment, due to insulin resistance in two and insulin deficiency in one. In all patients treatment with the analogue slightly increased postprandial glucose concentrations and suppressed insulin concentrations for two to two and a half hours after each injection; growth hormone concentrations decreased progressively with treatment. The patient with impaired glucose tolerance due to insulin deficiency developed diabetes mellitus after four months' treatment; concomitant treatment with glibenclamide resulted in a decreased glucose concentration and increased insulin concentration.

This analogue of somatostatin had only minor side effects on glucose tolerance in patients with acromegaly and may be used in patients with impaired glucose tolerance provided that glucose concentrations are monitored closely.

Introduction

Several reports on the use of somatostatin analogues in endocrine and gastrointestinal diseases have been published recently.[1-4] The analogues used have varying inhibitory effects on several hormones. As more than one hormone is affected by each drug undesirable side effects may occur. We treated seven patients with acromegaly with SMS 201-995 for one year. This preparation is a synthetic octapeptide analogue of somatostatin whose inhibitory activity against growth hormone is greater than that against insulin.[5] We report the effects of this treatment on glucose tolerance in these patients.

Patients and methods

Seven patients with acromegaly, of whom six had undergone surgery or radiotherapy in the past, participated in the study, which was approved by the local ethical committee; all gave their informed consent. All patients were studied twice before long term treatment was started: on one day they did not receive any treatment (control day), and on the other day they received a single test dose of 50 μg SMS 201-995 subcutaneously at 0815.

Long term treatment was started with two or three daily subcutaneous injections of 50 μg of the analogue, the number of injections being based on the patients' reactions to the test dose. Depending on the clinical and biochemical response, the dose was increased to 100 μg three times a day. The first injection was always given at 0815. Patients were admitted to hospital and placed on diets of three meals, which were served at exactly 0830, 1230, and 1800 on the days when blood was drawn through an indwelling venous catheter at various intervals. The blood samples were centrifuged, and plasma was frozen at −20°C until assayed. In all samples glucose, insulin, and growth hormone concentrations were determined. Glucose concentrations were measured with a glucose oxidase method. Insulin and growth hormone concentrations were determined by specific radioimmunoassays using commercially available kits (INC, Stillwater, Minnesota; Sorin, Milan, Italy). Significance was calculated with the paired *t* test.

Results

Three of the seven patients had impaired glucose tolerance before treatment. In two this was primarily due to insulin resistance, as they had substantially increased insulin concentrations. The third patient had low insulin concentrations, which suggested insulin deficiency as the primary cause. The results obtained during treatment were analysed separately for the subgroups with normal (n=4) and impaired (n=3) glucose tolerance to start with.

Figure 1 shows glucose concentrations in both groups before and after breakfast. In both groups treatment with the somatostatin analogue slightly

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increased glucose concentrations after breakfast. Long term treatment did not aggravate this effect. Fasting glucose concentrations did not change during treatment. The patient with impaired glucose tolerance and low insulin concentrations developed frank diabetes mellitus after four months of treatment: glucose concentrations were between 14·8 mmol/l (256 mg/100 ml) and 17·3 mmol/l (311 mg/100 ml) without ketonuria. To see whether sulphonylureas might overcome the inhibition of insulin by the somatostatin analogue we treated this patient with glibenclamide 5 mg thrice daily. Within days the glucose concentration had returned to the values seen at the beginning of treatment with the somatostatin analogue, and at the end of the study the concentration was even lower.

In all patients the analogue suppressed insulin concentrations for two to two and a half hours after each injection, and this effect was seen during the whole year of treatment (fig 2). As a group the patients with impaired glucose tolerance had hyperinsulinaemia. Only the patient who became diabetic showed a progressive decrease in insulin concentration, which was near the limit of detection (2-4 mU/l) at the time that hyperglycaemia developed. Treatment with sulphonylureas increased the insulin concentration to values even greater than those seen at the start of the trial—that is, fasting concentrations of around 30 mU/l with a 50% decrease after each injection of the analogue.

Growth hormone concentrations decreased progressively during treatment: fasting concentrations fell from 41·0 (SE 6·5) μg/l to 31·6 (7·1) μg/l at six months and 21·2 (3·2) μg/l at one year.

Discussion

Long term treatment with SMS 201-995 in patients with acromegaly not only results in a progressive decline in growth hormone concentrations but also suppresses insulin concentrations. The suppression of insulin concentrations was progressive in only one patient, in whom it led to diabetes mellitus. In the six other patients administration of the analogue resulted in slightly higher post-prandial glucose concentrations, which did not deteriorate further with long term treatment. The fact that no further deterioration occurred may partially be explained by decreased insulin resistance during the study, given the lower ambient growth hormone concentrations.

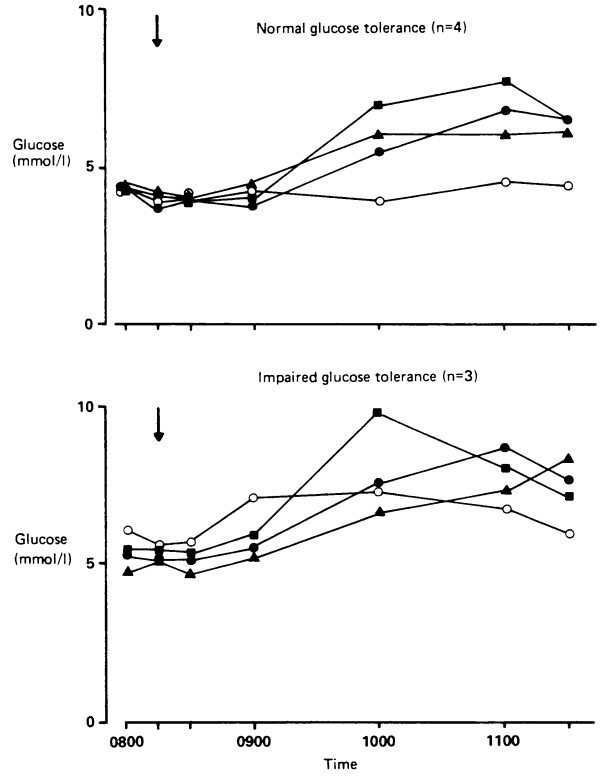

FIG 1—Mean glucose concentrations before treatment (○), after a 50 μg test dose (●), and after continuous treatment for six months (■) and one year (▲) in seven patients with acromegaly according to whether they had normal or impaired glucose tolerance before treatment. SMS 201-995 was given at 0815 (arrow); breakfast was served at 0830.

Conversion: SI to traditional units—Glucose: 1 mmol/l≈18 mg/100 ml.

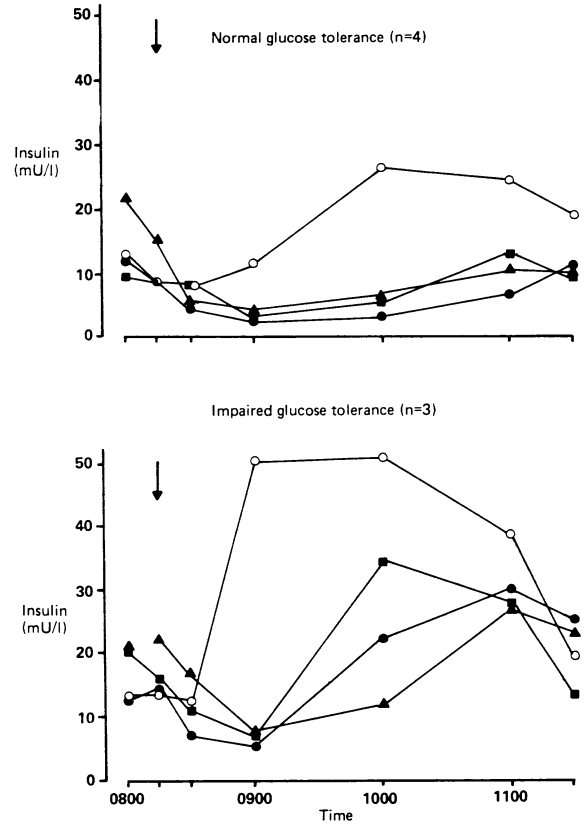

FIG 2—Mean insulin concentrations before treatment (○), after a 50 μg test dose (●), and after continuous treatment for six months (■) and one year (▲) in seven patients with acromegaly according to whether they had normal or impaired glucose tolerance before treatment. SMS 201-995 was given at 0815 (arrow); breakfast was served at 0830.

This study shows that patients with active acromegaly despite surgical and radiotherapeutic management may be offered a medical treatment that is highly effective[1 2] and has only minor side effects on glucose tolerance. The one patient who developed diabetes mellitus during treatment had impaired glucose tolerance that was not due to increased insulin resistance. As in this patient treatment with sulphonylureas increased the insulin concentration and rendered glucose tolerance almost normal even such patients can benefit from treatment with somatostatin analogues as long as their glucose tolerance is closely monitored.

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