Pharmacokinetics and efficacy of the long-acting somatostatin analogue somatuline in acromegaly

MR Johnson, HS Chowdrey, F Thomas¹, C Grint and SL Lightman

Department of Medicine, Bristol Royal Infirmary, Bristol, UK; Ipsen Biotech¹, Paris, France


The aim of this work was to assess the use of a sustained-release formulation of somatuline, a long-acting analogue of somatostatin, in the treatment of acromegaly. Fifteen patients with active acromegaly, as defined by random growth hormone (GH) levels greater than 10 mU/l, which fail to be suppressed to less than 5 mU/l following an oral glucose load, were studied. Somatuline was administered as an intramuscular injection in two regimens: eight patients were given a single injection of the sustained-release formulation and blood samples taken over the next month for the measurement of both basal levels of GH and the GH response to thyrotrophin-releasing hormone; and eight patients were given injections of the sustained-release formulation at 2-week intervals over a 6-month period and basal plasma GH levels and the GH response to both an oral glucose load and to thyrotrophin-releasing hormone was assessed. Following a single intramuscular dose of the sustained-release preparation, random GH levels were reduced to below 10 mU/l in five patients and by greater than 50% of basal levels in the remainder. The insulin-like growth factor I (IGF-I) levels fell to within the normal range in three patients. In the long-term efficacy study, GH levels were reduced to < 10 mU/l in 7/8 patients. The IGF-I levels were normalized in four patients. Five of the eight patients experienced diarrhoea, two of mild and three of moderate severity; none of the patients withdrew from the study. Somatuline has been shown to be effective in the treatment of acromegaly. In its sustained-release formulation it clearly represents a useful therapeutic advance, although at the dosage and frequency of injection used in the current protocols it did not provide optimum GH suppression in all patients.

MR Johnson, Department of Medicine, Bristol Royal Infirmary, Upper Maudlin Road, Bristol BS2 8HW, UK

Recent advances in the diagnosis and management of acromegaly have allowed patients to be treated earlier, more effectively and with fewer side-effects. Previously, the diabetic and cardiovascular complications of acromegaly have resulted in a doubling of expected mortality (1). This, and the considerable morbidity associated with acromegaly, has driven the search for a more effective management for those patients who are unsuitable for surgery, or who require treatment while waiting for radiotherapy to take effect. Bromocriptine controls 19% of these cases (2), but the remainder are either unable to tolerate bromocriptine or resistant to it. For these patients the advent of the long-acting analogues of somatostatin has provided a viable alternative (3, 4). At present the only available agent, octreotide has to be given either as a continuous infusion or in three divided doses subcutaneously (5, 6). The mode of administration of octreotide and its expense have been the limiting factors in its use.

Recently, an alternative to octreotide, somatuline, has become available. Circulating GH levels are reduced by somatuline administered either as an infusion in normal men or as a slow-release intramuscular depot in acromegalic patients (7, 8). We have been using the long-acting sustained release preparation of somatuline in the management of acromegaly and report here the pharmacokinetics and its effects on the random and dynamic circulating levels of GH and IGF-I of the sustained-release formulation.

Methods

Somatuline (structure: Nα-[2]β-Nal-Cys-Tyr-[3]-Trp-Lys-Val-Cys- Thr-NH₂) has been used in the present study. The compound is synthesized chemically by Ipsen Biotech. The sustained-release formulation of somatuline is dispersed in polylactide glycolide acid-biocompatible biodegradable polymer. The preparation was administered as an intramuscular injection containing 30 mg of somatuline with local anaesthetic either as a single injection (N = 8) or repeatedly at intervals of 2 weeks for 6 months (N = 8). After the single injection, blood samples were obtained for GH, IGF-I and somatuline levels on days 0, 2, 4, 7, 9, 11, 14, 17, 21 and 24. Thyrotrophin-releasing hormone (TRH) tests were
performed on days 0, 7, 14 and 21. In the 6-month study period, blood samples were obtained at weekly intervals for the first 2 months and thereafter at 2-week intervals immediately prior to the next injection of somatuline. The oral glucose tolerance test (OGTT) and TRH test were performed at monthly intervals throughout. Gall bladder ultrasound examinations were performed before entrance into the study and at 3-month intervals thereafter.

All samples were analysed in batches at intervals during the study period.

**Growth hormone assay**

Normal levels of GH are considered to be less than 10 mU/l, or, following an oral glucose load, less than 5 mU/l. Growth hormone was measured using the Omnia radioimmunometric assay (IDS Ltd., Tyne and Wear, UK). The interassay imprecision \( cv \) was 6.4% (1.6 mU/l) and 8.0% (24.2 mU/l).

**Insulin-like growth factor I assay**

The IGF-I level was measured by an in-house radioimmunoassay following an acid ethanol extraction. The interassay imprecision \( cv \) was 19.1% (6.7 nmol/l) and 8.7% (21.7 nmol/l). The normal ranges of IGF-I for individuals of less than 60 years is 30–60 nmol/l and for those greater than 60 years it is 10–30 nmol/l.

**Somatuline assay**

Antiserum that does not cross-react with endogenous somatostatin was raised against somatuline conjugated to bovine thyroglobulin with carbodiimide and injected into New Zealand white rabbits. Tracer was prepared by incubating somatuline (5 \( \mu g \) in 10 \( \mu l \) of 0.1 mol/l phosphate buffer) with \( ^{125}I \) for 10 min in a tube coated with Iodo-Gen (Pierce and Wassiner, Chester, UK) eluted in assay buffer (0.1 mol/l TRIS·HCl, containing 0.2% BSA and 0.1% Triton X-100; pH 7.4). Plasma (20 \( \mu l \)) was diluted 1:5 in buffer and 100 \( \mu l \) of antiserum added (final dilution 1:5000). Tracer (100 \( \mu l \)) was added and these tubes incubated for 24 h at 40°C. Bound peptide was precipitated by the addition of second antibody and normal rabbit serum, assisted by a 4% solution of polyethylene glycol. Supernatants were decanted and pellets counted for gamma radioactivity. The antiserum did not cross-react with native somatostatin (SS 1–14). The intra-assay and interassay coefficients of variation were assessed by the addition of synthetic somatuline to human plasma at concentrations of 1 and 5 \( \mu g/l \), and were 8% and 16%, respectively (mean of 10 assays).

The study had the approval of the East Riverside Ethics Committee and all patients gave their fully informed written consent.

**Patients**

**Pharmacokinetics and efficacy of a single injection of somatuline**

Four males and four females with active acromegaly and an age range of 31–73 years (median 44) were recruited to this part of the study. Six had been treated by surgery (＞6 months previously) and radiotherapy (＞24 months previously; one of whom had had a partial response to bromocriptine and was maintained on this medication throughout) and two had received no treatment.

Patients were assessed prior to the injection and each week after the injection with a TRH test (200-\( \mu g \) bolus injection) and with random GH levels (measured in samples obtained prior to each injection of somatuline). Initially, all patients demonstrated a paradoxical rise in GH following TRH. The peak response in the first TRH test was used as a baseline against which the later peak GH responses to TRH were compared.

**Efficacy of repeated injections of somatuline**

Three males and five females with active acromegaly and an age range of 31–73 years (median 43) were recruited to this part of the study. Four had been treated by surgery (＞6 months previously) and radiotherapy (＞24 months previously; one of whom had a partial response to bromocriptine and was maintained on this medication throughout), three had received no treatment and one had been treated with surgery alone.

Patients were assessed prior to the first injection and each month after the initiation of treatment with an OGTT (75 g) followed by a TRH test (200-\( \mu g \) bolus injection) and with random GH measurements before each injection. Initially, all patients failed to suppress in response to oral glucose (normal response is a suppression of circulating GH levels to less than 4 mU/l) and six demonstrated a paradoxical rise. The peak response following the first TRH test was used as the baseline response against which later peak GH responses to TRH were compared.

**Results**

**Pharmacokinetics and efficacy of a single injection of somatuline**

The IGF-I (Fig. 1a and b) and random GH levels (Fig. 1c) were reduced in all cases. The IGF-I levels fell to within
The circulating levels of IGF-I (a, b) and GH (c) measured in the peripheral plasma of eight patients with acromegaly over 24 days following a single intramuscular injection of the sustained-release formulation of somatuline: (a) patients less than 60 years of age, (b) patients greater than 60 years.

The circulating levels of somatuline measured in the peripheral plasma of eight patients with acromegaly on days 2, 4, 7, 9, 11, 14, 17, 22 and 24 following a single intramuscular injection of the sustained-release formulation of somatuline.

Random GH levels were reduced to less than 10 mU/l in 5/8 patients (Fig. 1c) and increased in two patients towards the end of the study period. The reduction of GH and IGF-I from their initial values (for GH: range 20.4–174, median 28 mU/l; for IGF-I: 56.1–230, median 98 nmol/l) to their nadir (for GH: range 4.4–116, median 28 mU/l; for IGF-I: range 32–84, median 60 nmol/l) was significant (p = 0.024 for GH and p = 0.004 for IGF-I). The GH response to TRH was reduced in four cases, but the response persisted in all cases. Plasma levels of somatuline remained greater than 1 µg/l in all patients until 14 days after the injection. Levels were detectable in all but two patients for the duration of the study (Fig. 1d). Five of these patients elected to continue on the drug. Of the three patients who did not continue with treatment, one chose not to and two returned to their own country.

Efficacy of repeated injections of somatuline

The IGF-I (Fig. 2a and b) and random GH levels (Fig. 2c) and the GH response to TRH and to glucose were reduced in all cases. The IGF-I levels remained suppressed in 4/8 patients (Fig. 2a and b). Random GH levels were reduced to below 10 mU/l in seven patients, but one patient (patient 5) showed no response to treatment. In two patients (patients 1 and 3), following a good initial response, GH levels rose towards the end of the study (Fig. 2c). The reduction of GH and IGF-I from their initial values (for GH: range
Fig. 2. The circulating levels of IGF-I (a,b) and GH (c) measured in the peripheral plasma of eight patients with acromegaly receiving intramuscular injections of the sustained-release formulation of somatuline at 2-week intervals over a 6-month period: (a) patients less than 60 years; (b) patients greater than 60 years. (d) The circulating levels of somatuline measured in the peripheral plasma of eight patients with acromegaly taken prior to each intramuscular injection of the sustained-release formulation of somatuline, which was given at 2-week intervals over a 6-month period.

20.4–174, median 48 mU/l; for IGF-I: range 56.1–230.4, median 43 nmol/l) to the nadir (for GH: range 2.2–13, median 5.5 mU/l; for IGF; range 9.5–86, median 60 nmol/l) was significant (p = 0.017 for GH and p = 0.0001 for IGF-I). The paradoxical increase of GH to oral glucose was reduced in all patients, but while GH levels were reduced by oral glucose in four patients, GH levels were not suppressed to < 4 mU/l in any. Prior to treatment, GH levels rose in all but one case in response to TRH; following treatment with somatuline, the GH response to TRH was reduced in all seven cases (10–89% of first response). Plasma levels of somatuline measured before the next injection remained stable in all but one case (Fig. 2d). There were no correlations between the circulating levels of somatuline and those of either IGF-I or GH.

**Symptomatic relief**

Two patients had marked symptomatic improvement, which included an improvement of their facial signs and reduction in the volume of hands and feet. The remainder, all with long-standing acromegaly, showed little objective change.

**Side effects**

Five patients had diarrhoea, two of mild (one occasion, for less than 48 h) and three of moderate severity (after each injection, for less than 48 h). Four had abdominal cramps. No patients withdrew from the study. One patient developed biliary sludge over the period of study.
Table 1. The characteristics of the patients who took part in the pharmacokinetic and efficacy study of the long-acting formulation of somatuline.

<table>
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<tr>
<th>Patient no.</th>
<th>Age</th>
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<th>Previous treatment</th>
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<th>Initial IGF-I (nmol/l)</th>
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<tr>
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</tbody>
</table>

*Study 1: single injection of somatuline. Study 2: reported injections of somatuline.

**TSH: transphenoidal hypophysectomy; DXY: radiotherapy.

Discussion

Somatuline, a long-acting analogue of somatostatin, binds preferentially to pituitary somatostatin receptors (9) and has previously been shown in inhibit GH secretion in normal men (10). In the present study we show that, like octreotide, somatuline is active in the treatment of acromegaly. Using the sustained-release preparation resulted in GH reductions to < 10 mU/l in 7/8 (87.5%) and by greater than 50% overall in seven (87.5%), both figures being comparable to the 46% and 87% reported for octreotide by Harris et al. (11). The normalization in IGF-I in 4 cases is again similar to that reported with octreotide (11). Furthermore, the present study almost certainly underestimates the overall control of GH secretion achieved, because random and dynamic estimations of the circulating levels of GH were taken 2 weeks after each injection (prior to the next injection) and therefore at the time of the lowest circulating level of somatuline. In addition, in this study, patients were treated on a fixed regimen of 2-week injections. It is now important to extend this study by altering the time interval between injections in order to achieve both optimum control in the circulating levels of GH and IGF-I and maximum relief from the symptoms of acromegaly. Undoubtedly, resistant subjects will be encountered, such as patient 5. The basis of this resistance is most likely to be the reduced expression of somatostatin receptors, as has been reported previously (12). In such patients, alteration of the treatment regimen is unlikely to be of benefit.

During the dynamic tests of GH release all but one patient responded with a paradoxical increase to TRH, while in five patients the GH levels increased in response to glucose. In none was the response to TRH normalized, although in all the patients the magnitude of the response was diminished. Whereas following a glucose load, although the suppression of GH levels to less than 4 mU/l was not achieved, the magnitude of the paradoxical increase was reduced. These data confirm that somatuline reduces GH release but that, like octreotide (13), it does not normalize the GH response to either glucose or TRH.

Somatuline impairs glucose tolerance in normal men (7). However, one patient in this series, who was taking oral hypoglycaemic agents, was able to stop all medication while on treatment with somatuline. This is similar to the experience with octreotide (14).

The advantage of this long-acting analogue of somatuline lies in its availability as a sustained-release formulation, allowing a markedly reduced frequency of administration. The side-effects of octreotide and somatuline relate to their somatostatinergic activity, and the incidence of the side-effects seems to be similar with both agents (15). In conclusion, we find that somatuline is an effective drug in the treatment of acromegaly, and that the sustained-release preparation represents a technical advance in the pharmacological treatment of the disease. Further studies are needed to ascertain the optimum dose and frequency of administration of this new formulation.

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References


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