Sandostatin® LAR® (microencapsulated octreotide acetate) in Acromegaly: Pharmacokinetic and Pharmacodynamic Relationships

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Double-blind, single-dose studies of 120 acromegalic patients given 10, 20, and 30 mg Sandostatin® LAR® (Sandoz Pharma Ltd, Basel, Switzerland) established the drug's pharmacokinetic profile. Patients then entered open-labeled extension phases, with Sandostatin® LAR® intramuscular (IM) injections every 4 weeks. These produced broadly constant octreotide concentrations with dose proportionality. Area fluctuations were minimal. Steady-state conditions were generally reached after the second to third injection. There was no evidence of downregulation with Sandostatin® LAR® over 1 year of study. Based on the pharmacokinetic/pharmacodynamic relationship of octreotide, a starting dose of 20 mg Sandostatin® LAR® and administrations every 4 weeks provide growth hormone (GH) control comparable to the thrice-daily subcutaneous (SC) injection regimen, which is commonly 0.3 to 0.6 mg/d. The reduction from the burden of two to three SC injections per day is a particular advantage of Sandostatin® LAR®, which is an attractive alternative to the approved Sandostatin® injection.

SANDOSTATIN® LAR® (Sandoz Pharma Ltd, Basel Switzerland) is designed to provide long-term controlled release of octreotide from an intramuscular (IM) (intragluteal) depot injection, reducing the frequency of injections from two to three per day with the standard subcutaneous (SC) administered Sandostatin®, to once every 4 weeks with Sandostatin® LAR®. To this end, experimental studies have been performed in animals, and human and clinical studies have been completed in acromegalic patients, using Sandostatin® LAR® to establish pharmacokinetic behavior and pharmacokinetic/pharmacodynamic relationships in comparison with Sandostatin® SC; to determine the optimal dose and dosing regimen with regard to injection intervals; and to obtain data on tolerability and long-term safety. These studies have served to confirm that Sandostatin® LAR® is a slow-release formulation that assures stable and consistent drug release with low fluctuations in octreotide serum concentrations, provides therapeutic octreotide concentrations without significant accumulation during long-term application, and assures reproducible and stable suppression of growth hormone (GH) secretion.

The studies reported in this overview were performed in a total of 120 acromegalic patients who were switched from SC treatment with Sandostatin®.

METHOD

After a washout phase, patients received in double-blind fashion either 10, 20, or 30 mg Sandostatin® LAR®. GH serum concentrations were assessed hourly from 8 AM to 8 PM during the screening phase, at the end of the washout phase (baseline), and on days 1, 7, 14, 21, 28, 35, 42, and 60 after the injection of Sandostatin® LAR®. Serum octreotide concentrations were determined on the same days and time points to define the pharmacokinetic profile of Sandostatin® LAR®.

Following these double-blind, single-dose studies, patients were entered into open-labeled extension phases, where the first injection was again followed for 60 days, and all the following injections were given in intervals of 4 weeks. GH and octreotide serum concentrations were assessed over 8 hours on days 1 and 28 after each injection administered in the first 6-month extension studies and thereafter on day 28 after each injection. For pharmacokinetic/pharmacodynamic considerations, data from all 13 injections per patient are considered together.

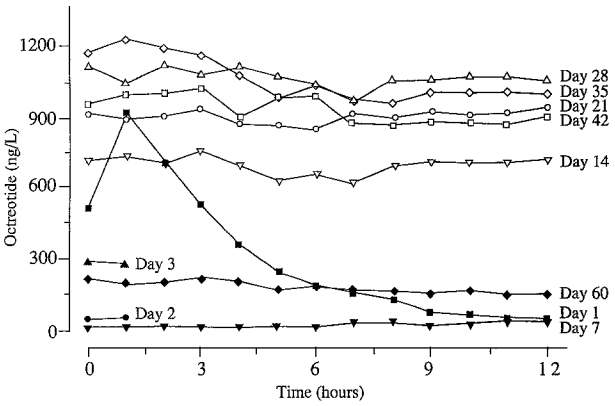

Fig 1. Twelve-hour octreotide concentration-*v*-time profiles on different days after a single IM injection of 30 mg Sandostatin® LAR® to 1 patient (no. 5107).

RESULTS

Pharmacokinetic Data

The area fluctuation after SC thrice-daily administration (screening phase) was between 35% and 41% and the peak-to-trough fluctuation varied on average between 175% and 211%. Both fluctuation parameters point to a relatively high variation of the serum concentrations of Sandostatin® after SC administration.

Figure 1 shows, in a representative patient, 12-hour octreotide concentration-versus-time profiles on different days after a single IM injection of 30 mg Sandostatin® LAR®. The pharmacokinetic profile on the day of injection was similar to that after a single SC injection of Sandostatin®. After this initial peak, octreotide concentration remained at a low level, reflecting a biphasic profile with negligible release of drug for up to 7 days. At day 14 after the injection of Sandostatin® LAR®, the octreotide concentration increased again to 700 pg/mL. From day 21 until day

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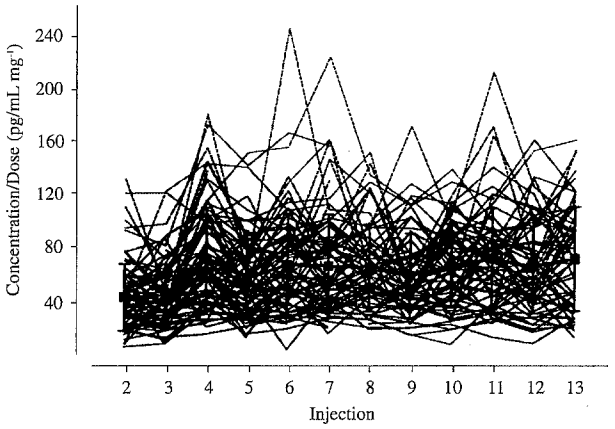

Fig 2. Individual dose-normalized mean serum octreotide concentrations (pre-dose or trough concentration) for day 28 of each of 13 administrations.

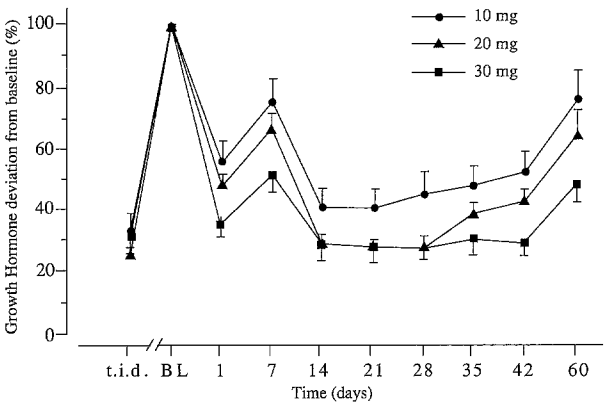

Fig 4. Representation of the mean daily average GH concentrations in acromegalic patients after single injections of 10 (n = 13), 20 (n = 36) and 30 (n = 34) mg Sandostatin® LAR®, followed for 60 days.

42, concentrations were quite stable in the range 900 pg/mL to 1,200 pg/mL. After day 42, the octreotide concentration decreased slowly; however, even on day 60 after the injection it was still at 200 pg/mL. There was low variation of the octreotide release during all 12-hour profiles, except on day 1. During the plateau phase, day 21 to day 42, peak-to-trough fluctuation was 25% compared with approximately 200% after SC injection of Sandostatin®. Area fluctuation was between 5% and 10% compared with approximately 40% after SC treatment.

Considering the population mean octreotide serum concentration-versus-time profiles after administration of 10, 20, and 30 mg to acromegalic patients, the initial peak of octreotide concentration at the day of injection was usually lower than the plateau concentration, and the day 1 area under the curve (AUC) represented less than 0.5% with respect to the total AUC. The highest average octreotide concentration was reached between day 26 and day 34 after injection. However, plateau concentration (defined as 80% of maximum concentration [C_{max}]) was reached at day 14 and stayed stable for approximately 19 days. Linear regression and analysis of variance, applied for C_{max} and AUC (directly and after normalization by dose) after 10-, 20-, and 30-mg doses, revealed a statistically significant linear relationship between the pharmacokinetic parameters and the dose administered. For both parameters, the intercepts of the regression model were not different from zero, suggesting that there was a dose-proportional relation in the dose range between 10 and 30 mg.

Mean serum octreotide concentrations (Fig 2) at day 28 did not accumulate beyond those expected from addition of residual concentrations from the previous injections. Linearity of the pharmacokinetics was maintained. The ratios of average octreotide concentrations assessed at day 28 of the third injection versus the average concentration at day 28 of the first injection indicated an accumulation factor of 1.6. Thereafter, no further accumulation was noted. The variability of drug release from Sandostatin® LAR® was low for all consecutive injections; area fluctuation indices (ie, release profiles) did not change over time.

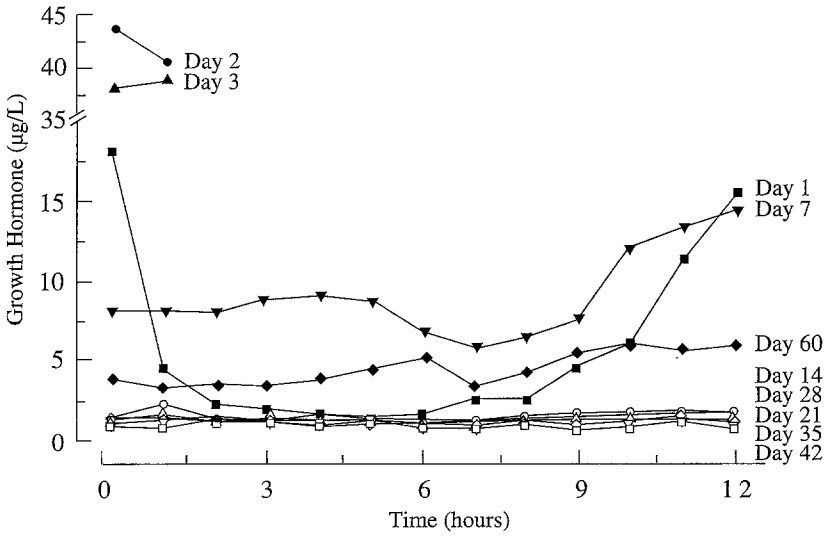

Fig 3. Typical time course of effect of octreotide administered as Sandostatin® LAR® on GH inhibition in a single acromegalic patient (no. 5107).

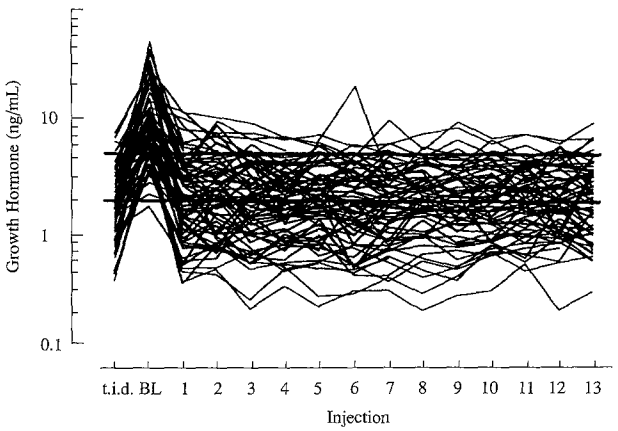

Fig 5. Average serum concentrations of GH after SC injections of Sandostatin® (screening day), at baseline after washout (day 0), and at day 28 after each of the 13 injections of Sandostatin® LAR® in 120 patients.

Pharmacodynamic Data

In a single acromegalic patient (patient no. 5107, see previous data for octreotide levels), in response to the initial octreotide peak concentration, GH secretion was rapidly suppressed and the GH concentration decreased within 2 to 3 hours from a baseline value of approximately 16 ng/mL to 2 ng/mL (Fig 3). GH secretion was inhibited for 8 hours and the GH concentration returned to baseline value 12 hours after the injection and remained at that level for the next 7 days. From day 14 onwards, GH concentration was consistently reduced to less than 2 ng/mL and remained at this level for the following 34 days. Noteworthy are the stable GH concentrations over the 12-hour profiles on each of the profile days (except day 1). On day 60, GH concentration increased, but remained below baseline values.

Considering mean daily average GH concentrations in the acromegalic patients after single injections (Fig 4), the dose-dependency of the effect of octreotide was most prominent, and reached statistical significance in the baseline-corrected parameters, Effect-AUC and plateau duration, defined as the duration of greater than 80% inhibition. However, maximum inhibition (E_{max}) was already reached with 20 mg Sandostatin® LAR®. Increasing the dose to 30 mg did not further decrease GH levels relative to baseline, but contributed to the duration of the effect. The time of maximum effect (t_{max}) was independent of dose and was on average 20 days after administration of Sandostatin® LAR®. The minimum achievable GH concentration showed a dose-dependent trend with 2.7 ng/mL for the 10-mg dose

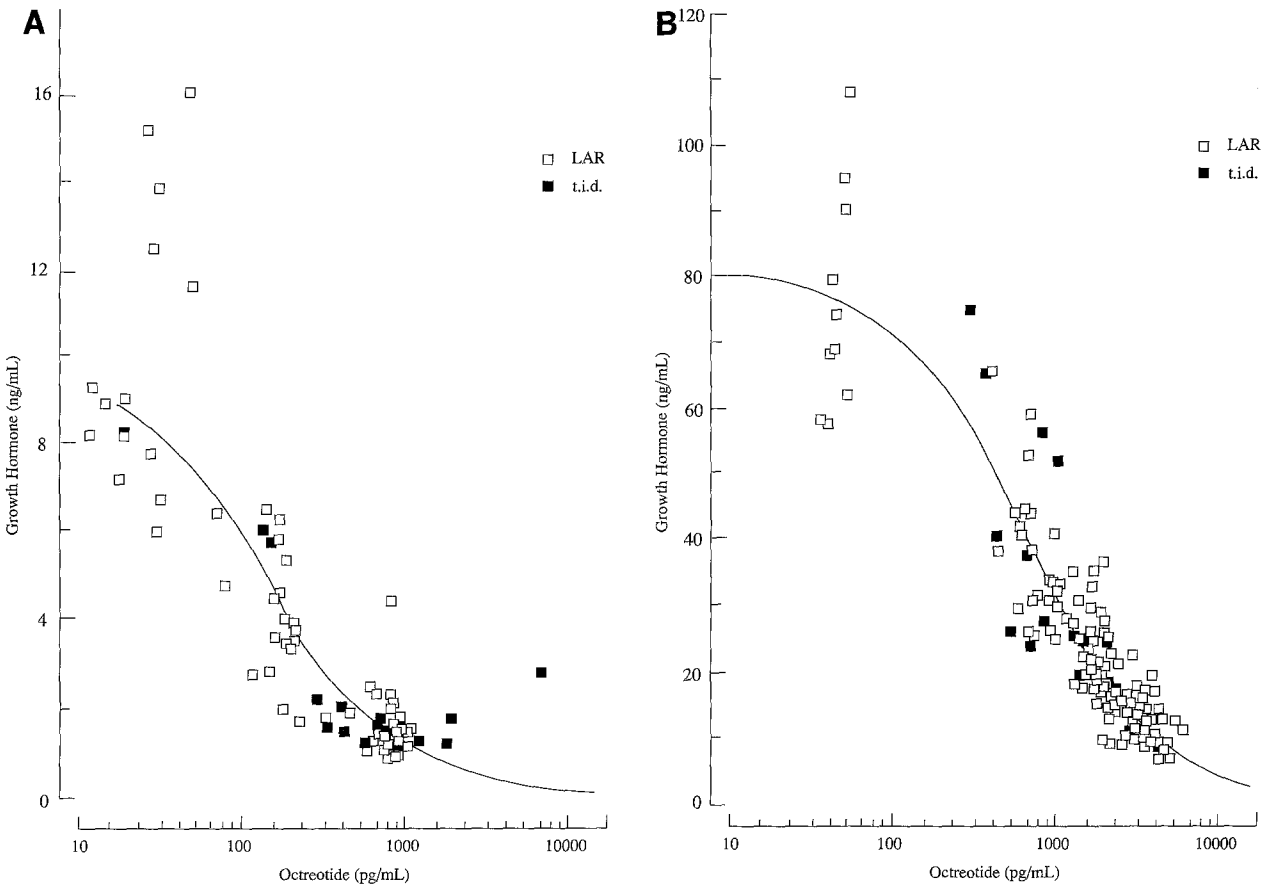

Fig 6. GH concentrations plotted against octreotide concentrations in all samples from 7 consecutive administrations of Sandostatin® LAR® in "high-responder" patient no. 5107 (A) and "low-responder" patient no. 5006 (B).

and 1.6 ng/mL for the 30-mg dose. The duration of GH suppression to less than 2 ng/mL increased significantly ($P = .02$) with dose, being 10 days for 10 mg Sandostatin® LAR® and 25.5 days for the 30-mg dose.

There was no indication of development of downregulation during long-term treatment with 4-weekly injections of Sandostatin® LAR® over a period of more than 1 year (Fig 5). Conversely, GH concentrations showed a clear tendency to decrease further under multiple injections.

Pharmacokinetic/Pharmacodynamic Relationships

The close relationship between octreotide and GH concentrations is apparent from Fig 6. An integrated pharmacokinetic/pharmacodynamic analysis of the data in patient no. 5107 yielded a sigmoid relationship between GH and octreotide concentrations, with an EC_{50} for octreotide of 153 ± 26 ng/L and an approximated EC_{90} of 800 ng/L, respectively. In this "good-responder" patient, the basal GH level of 9.8 ng/mL was consistently suppressed to 1 ng/mL, with plasma octreotide concentrations in the range of 1,000 pg/mL. Also included in Fig 6 are the respective GH and octreotide data from the SC screening phase. These data show that the concentration-effect relationship is similar for Sandostatin® SC and Sandostatin® LAR®.

The same analysis, applied to a less sensitive "partial-responder" patient (patient No. 5006), revealed a similar sigmoidal relationship with an EC_{50} for octreotide of 784 ± 54 ng/L. In this patient, the basal GH level was 81 ng/mL and could be suppressed only to 10 ng/mL, even with plasma octreotide concentrations in the range of 4,000 pg/mL.

These data are in good agreement with calculations based on an "effect compartment" model using data from multiple SC injections in acromegalic patients.[1] The model revealed optimal curve-fitting consistent with an EC_{50} in the effect compartment of 241 ng/L. This demonstrates that treatment of acromegalic patients with Sandostatin® follows a consistent, concentration-effect relationship, and that the biochemical response parameters are therefore independent of the route of administration.

CONCLUSION

Sandostatin® LAR® offers an attractive alternative to the approved Sandostatin® injection with substantial benefits to the patient. The reduction of the burden of two to three SC injections per day to only one IM injection every 4 weeks is a particular advantage.

REFERENCE

1. Mazer NA: Pharmacokinetic and pharmacodynamic aspects of polypeptide delivery. J Contr Release 11:343-356, 1990