Br J clin Pharmac 1994; **38**: 213–219

Pharmacokinetic and pharmacodynamic properties of a long-acting formulation of the new somatostatin analogue, lanreotide, in normal healthy volunteers

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1 The aims of the study were to assess the pharmacokinetic parameters and the hormonal effects of the slow-release formulation of the somatostatin analogue (SR-L) in normal male volunteers.

2 Eight healthy males were studied. For the determination of basal values blood was sampled before the injection of vehicle and then every other hour for 8 h in order to measure plasma GH, prolactin (PRL), TSH, free thyroxin (fT4), insulin and glucagon levels. Plasma insulin-like growth factor 1 (IGF-1) levels were measured on a single sample. On day 1 of the study, 30 mg SR-L was administered intramuscularly. Blood was drawn just before injection and then every other hour for a period of 8 h. Thereafter, blood was sampled three times a week for 3 weeks in order to measure lanreotide, IGF-1, TSH, fT4 and PRL concentrations. Plasma GH was determined on days 6 and 11 of the study.

3 Plasma lanreotide concentrations rose to 38.3 ± 4.1 ng ml^{-1} 2 h following injection. The levels then progressively decreased, remaining above 1.5 ng ml^{-1} until day 11 and reaching 0.92 ± 0.28 ng ml^{-1} 2 weeks after injection. The apparent plasma half-life and mean residence time were 4.52 ± 0.50 and 5.48 ± 0.51 days respectively.

4 By comparison with the control day, plasma insulin concentrations only decreased 2 h following injection, whereas plasma glucagon did not change at any time.

5 Plasma TSH concentrations were significantly ($P < 0.01$) reduced from 2 h to day 4 following SR-L injection. fT4 concentrations dropped significantly ($P < 0.01$) from day 2 to day 4 but always remained within the normal adult range.

6 Plasma GH concentrations were constantly below 0.2 ng ml^{-1} whereas plasma IGF-1 concentrations were significantly ($P < 0.05$) reduced from day 4 to day 14 following SR-L injection. No significant changes in plasma PRL levels were observed.

7 These results show that lanreotide administered in slow-release formulation to normal healthy males decreases transiently plasma insulin and TSH, and consecutively fT4 levels, without affecting either PRL or glucagon secretion. In contrast, SR-L reduces IGF-1 levels (likely through a decrease in GH secretion) for at least 14 days. This indicates that SR-L could be injected every 14 days to decrease IGF-1 levels.

8 This slow-release formulation may be very convenient for the treatment of diseases for which a lowering of IGF-1 levels is essential, without side effects on glucose homeostasis and thyroid function.

Keywords lanreotide somatostatin analogue slow-release formulation pharmacokinetics pharmacodynamics normal men

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Introduction

Somatostatin and its analogues inhibit the secretion of both pituitary (i.e. growth hormone [GH] and thyrotrophin [TSH]), and pancreatic (i.e. insulin and glucagon) hormones [1–3] and have been used in patients with acromegaly [4–6], thyrotropinomas [7–8] and/or endocrine gut tumours [9, 10]. *In vitro* studies suggest that somatostatin analogues could be proposed for the treatment of some non endocrine tumours in which a pathophysiological role of growth factors has been implicated [11, 12]. Their use could then lead to endocrine side effects in patients with normal hormone secretion. The available somatostatin analogues have different potencies and pharmacological properties. Such differences are linked to their respective affinities for somatostatin [13–15] and opioid receptor subtypes [16, 17] which were also implicated in the regulation of hormone secretion [18]. Five somatostatin receptor subtypes (SSTR) have been cloned [19–21], and their respective activation could lead to specific effects. For example the *in vitro* inhibition of GH secretion appears linked to the activation of SSTR-2 receptor [14]. Lanreotide preferentially binds to SSTR2 and SSTR4 [14] and exhibits lower affinity for opiate receptors than other somatostatin analogues [22]. This could be responsible for either different activity or tolerance. On the other hand, it has been shown that continuous infusions of somatostatin analogues are more potent in reducing plasma GH and insulin-like growth factor 1 (IGF-1) levels than the same dose given as several subcutaneous (sc) injections daily [23, 24]. Effective treatment with the available analogues requires continuous infusions using pumps, or several subcutaneous injections a day. The long-acting formulation of lanreotide (SR-L), prepared to be active for 2 consecutive weeks could avoid such drawbacks [25]. The aim of the present study was to investigate the pharmacokinetics of SR-L and to evaluate its tolerance and its effects on hormonal parameters, when administered as a single intramuscular injection to healthy volunteers.

Methods

Product

Lanreotide (D-NAL-CYS-TYR-D-TRP-LYS-VAL-CYS-THR-NH2) was provided by Ipsen-Biotech (Paris, France). SR-L comprises microspheres containing the peptide. The somatostatin analogue is encapsulated in a polyactide-polyglycolide copolymer. Previous studies showed that the daily lanreotide dose required to reduce plasma GH levels ranges from 1000 to 2000 mg day^{-1} [26] in acromegalic patients. On this basis vials containing 30 mg SR-L were designed for twice a month administration.

Volunteers

The study was performed in eight healthy males who gave their informed consent. The volunteers (24–28 years), were selected on the basis of normal clinical data and hormone parameters (i.e. free T4 [fT4], TSH, Prolactin [PRL], fasting GH and insulin, IGF-1).

Study design

The study protocol was submitted to and approved by the Institutional Review Committee of the Centre Hospitalier Universitaire de Rouen, France.

On day 1 of the study, a blood sample was drawn at 08.00 h. A subcutaneous injection of 1 ml NaCl 150 mmol l^{-1} was performed, and the blood was then sampled every other hour for a period of 8 h. On each blood sample plasma fT4, TSH, PRL, insulin and glucagon levels were measured. Plasma GH and IGF-1 levels were only determined on the basal sample.

On the second day of the study, a blood sample was drawn at 08.00 h before SR-L injection. Each volunteer then received SR-L. Thereafter, blood was drawn every other hour for 8 h and then, as a single sample (at 08.00 h) on the following days: 1, 2, 4, 6, 8, 11, 14, 17, 21 and 24 after SR-L injection. The same hormone measurements as those investigated on control day were performed except for plasma GH levels which were measured on days 6 and 11 and for plasma IGF-1 levels which were not determined on days 1 and 24 of the study. In contrast, plasma lanreotide levels were measured on each plasma sample.

Blood samples were immediately centrifuged (10 min, 4500 rev min^{-1}, 4° C), plasma separated and kept frozen (−80° C) until assayed.

Pharmacokinetic analysis

The pharmacokinetic analysis of lanreotide plasma levels was carried out by a non-compartmental approach using the MKmodel. The following parameters were calculated: $t_{1/2}$ = the apparent plasma half life, C_{max} = highest plasma concentration, t_{max} = time where C_{max} was reached, AUC0–∞ = area under the curve from 0 to infinity, MRT = mean residence time, C_{14} = plasma lanreotide concentration on day 14. The AUC0–*t* (area under the curve from 0 to the last experimental point) was estimated by linear/log trapezoidal method using the Unicue program.

Hormone measurements

Plasma hormone levels were measured by either immunoluminometric-assay (ILA) or radioimmunoassay (RIA) using techniques established in our laboratory: fT4 (fT4-ILA, Behring, Germany), TSH (TSH-ILA, Behring, Germany), PRL (PRL-ILA, Behring, Germany), insulin (Phadeseph, Pharmacia, France), glucagon (Biodata, Serono, Italy), GH (hGH

coat RIA, Biomérieux, France), plasma IGF-1 (IGF-1 RIA, Baxter-Sorin, USA) with plasma acidification with HCl 0.5 N and separation on C18 columns using methanol in acetic acid as elution system.

Plasma lanreotide levels were measured by radioimmunoassay as previously described [25].

Statistical analysis

Analysis of variance (ANOVA) was carried out by using a two way analysis for the statistical comparisons. Then, statistical differences for quantitative variables were evaluated by applying Student's *t*-test for paired data. The chosen level of significance was $P < 0.05$.

Results

Side effects

Moderate abdominal cramps and loose stools occurred in four men for 2–4 days after SR-L injection. Two other volunteers had more severe abdominal pain accompanied by diarrhoea. When necessary an adsorbant clay which greatly reduced the intensity of the side-effects (Smecta, Ipsen Laboratories, France) was used. Side effects led in no case to interruption of the study. Overall the side effects disappeared 1 week after SR-L injection.

Pharmacokinetic study

C_{max} of plasma lanreotide levels (38.3 ± 4.1 ng ml^{-1}) was reached about 2 h after lanreotide injection (t_{max} = 2.26 ± 0.25 h). Plasma lanreotide levels decreased during the next 6 h (Figure 1). Mean plasma lanreotide levels were 9.4 ± 0.9 and 5.0 ± 0.7 ng ml^{-1} 24 and 48 h after injection, respectively. Thereafter, plasma lanreotide levels progressively declined. It remained higher than 1.5 ng ml^{-1} until day 11 and was 0.75 ± 0.07 ng ml^{-1} (C_{14}) 2 weeks after the injection (Figure 3).

AUC was 65.98 ± 6.53 ng ml^{-1} day. Apparent plasma half-life and mean residence time were 4.52 ± 0.51 and 5.46 ± 0.51 days respectively.

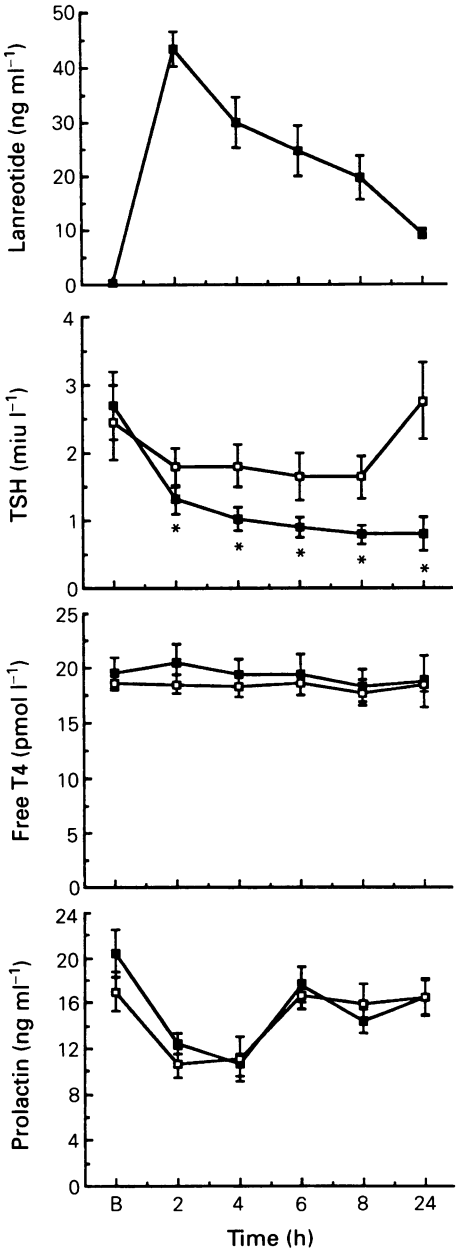

Figure 1 Plasma lanreotide, TSH, fT4 and prolactin concentrations after the administration of placebo (□) and during the first day following the administration of a slow-release formulation of lanreotide (■). B = basal value. *$P < 0.01$.

Plasma hormone concentrations

On day 1 of the study, plasma fT4 levels remained stable (mean ± s.e. mean: 18.4 ± 0.2 pmol l^{-1}), whereas, plasma TSH and PRL levels showed their physiological nycthemeral variation (Figure 1). Plasma insulin levels were modulated by meals and glucagon levels remained unchanged throughout the study (Figure 2).

Basal plasma GH (< 0.2 μg l^{-1}) and plasma IGF-1 levels were in the normal adult range (mean: 218 ± 7 ng ml^{-1}).

After lanreotide injection plasma TSH levels were significantly ($P < 0.001$) reduced 2 h after SR-L injection. As shown on Figure 1 the mean plasma TSH levels were greatly reduced (lower than 30% of the control level) 24 h after lanreotide administration and remained significantly ($P < 0.01$) suppressed until day 4. Plasma TSH levels then rose on day 6 before dropping again up to the end of the study (Figure 3).

Plasma fT4 levels did not show any change during the first 24 h following lanreotide injection, but were significantly reduced ($P < 0.01$) on days 2 and 4 of the study. Thereafter, plasma fT4 returned to normal values until day 24 (Figure 3).

Plasma PRL levels were not modified by the treatment at any time.

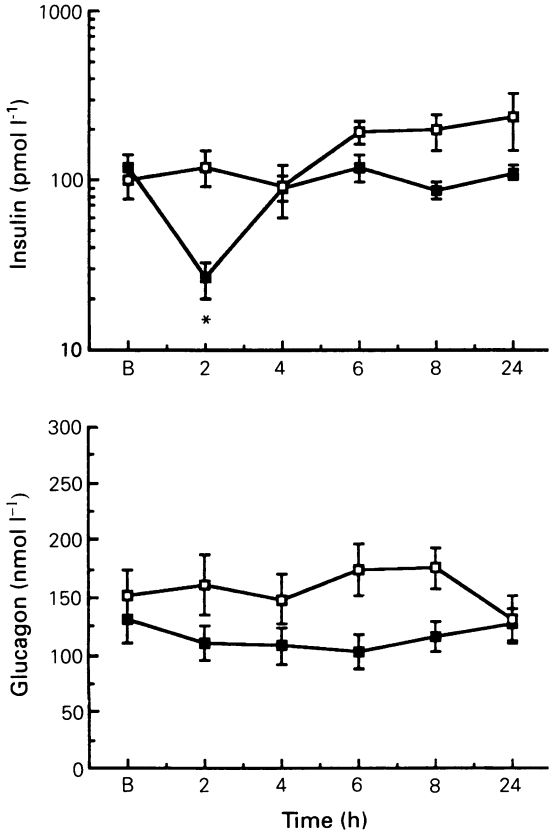

Figure 2 Plasma insulin and glucagon levels after the administration of placebo (□) and during the first day following the administration of a slow-release formulation of lanreotide (■). B = basal value. (08.00 h). *$P < 0.01$.

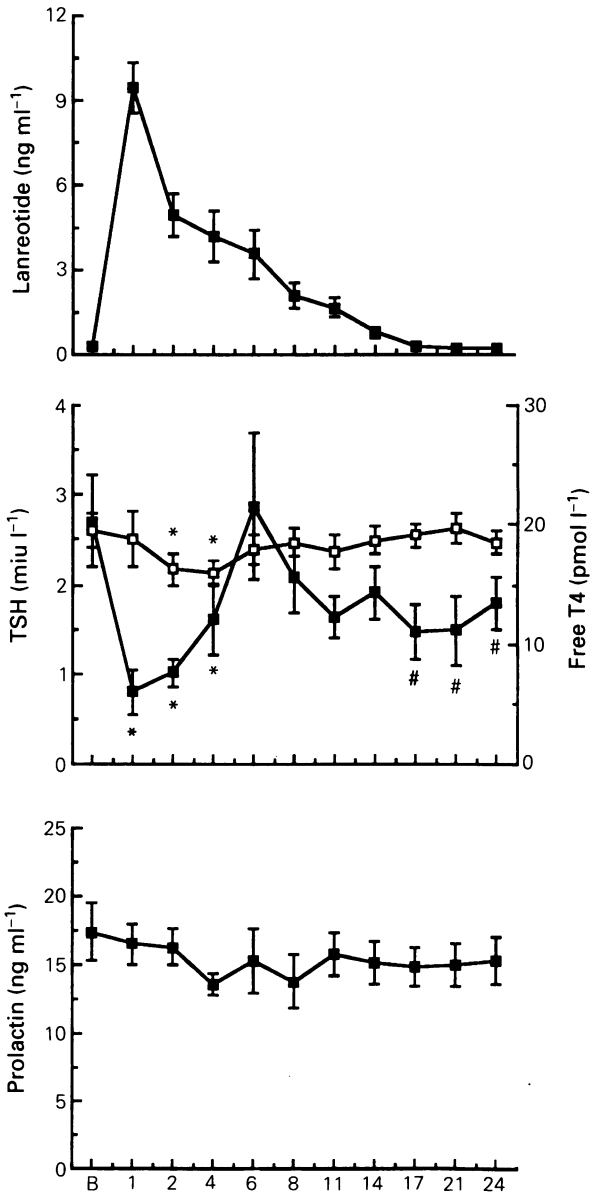

Figure 3 Plasma lanreotide, TSH, fT4 and prolactin levels after the administration of a slow-release formulation of lanreotide. B = basal value. *$P < 0.01$, #$P < 0.05$.

Fasting plasma GH levels, measured on days 6 and 11 of the treatment were < 0.2 μg l^{-1} at any time. Plasma IGF-1 levels unchanged on day 2, were significantly ($P < 0.01$) reduced from day 4 to day 14 following lanreotide injection. Thereafter, plasma IGF-1 levels reached control values (Figure 4).

Plasma insulin levels were significantly ($P < 0.01$) lower 2 h after SR-L injection (26.5 ± 6.5 pmol l^{-1}) than after placebo (119.8 ± 27.9 pmol l^{-1}). The levels did not differ after either placebo or lanreotide treatment at any other time point. Plasma glucagon levels were not modified by SR-L (Figure 2).

Discussion

Somatostatin analogues are able to improve clinical symptoms and to reduce both plasma GH and IGF-1 levels in a large number of acromegalic patients [4–6] not cured by treatment with radiotherapy and/or transsphenoidal surgery. Similar results are obtained in thyrotropinomas [7, 8]. The effectiveness of the analogue appears to be modulated by the number of somatostatin receptors on tumour cells [27, 28] and

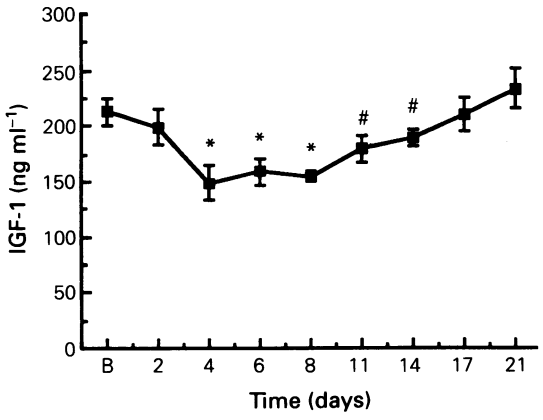

Figure 4 Plasma IGF-1 concentrations after the administration of a slow-release formulation of lanreotide. B = basal value. *$P < 0.01$, #$P < 0.05$.

by the mode of administration of the drug [23, 24]. Lanreotide, a cyclic octapeptidic analogue of somatostatin is able, as subcutaneous infusion, to suppress GH secretion either in normal males or in acromegalic patients [26, 29]. The use of slow-release formulations such as SR-L [25] could overcome the inconvenience associated with either repeated subcutaneous injections or continuous administration with pumps for the treatment of patients with acromegaly [23, 24]. Lanreotide has also been shown to be able to decrease gastrointestinal endocrine secretion [1] and to reduce the growth of experimental tumours [30] suggesting its potential usefulness for the treatment of some endocrine gut tumours. In these patients with normal pituitary function, undesirable side effects linked to the blockade of pituitary hormone secretion might occur. Thus, we studied the pharmacokinetic parameters and endocrine effects of SR-L in normal healthy male volunteers.

Pharmacokinetic studies performed following SR-L injection showed a two-phase pattern. A rapid increase in plasma lanreotide levels is followed by a progressive decrease to a nadir 48 h later. After this period of time, plasma lanreotide levels rose again and remained ≥ 1 ng ml^{-1} for 2 weeks after the injection. A similar pharmacokinetic profile was observed for GnRH agonists using the same type of copolymers [31, 32]. This two phase pattern is due to the instant release of the peptide localized at the surface of the microspheres and subsequently to a slower and prolonged liberation of the peptide by enzymatic breakdown of the copolymer. The pattern of plasma lanreotide levels following the first day of the SR-L injection appears close to that obtained by continuous subcutaneous infusions [29]. The apparent plasma half-life was 4.52 ± 0.51 days demonstrating an important increase when compared with the half-life of about 1.5 h [29] observed for the non encapsulated peptide and proved the fact that the terminal logarithmic phase of the plama level curve is representative of the prolonged release of the peptide from the microspheres. The mean residence time was as high as 5.46 ± 0.50 days. These results demonstrate that SR-L is able to provide a prolonged release of lanreotide. Some volunteers complained of loose stools and moderate abdominal pains for a few days following the injection. When necessary, the intensity of these transient side effects was greatly reduced by the associated use of an adsorbant clay. Despite the changes in plasma lanreotide levels throughout the study, the overall clinical tolerance of the treatment was good, as previously observed in acromegalic patients treated with SR-L [25].

Plasma TSH levels showed a significant decrease during 4 days after the injection. A similar drop in plasma TSH levels was observed as in previous studies using somatostatin [2] or analogues as subcutaneous injections [1, 33]. The secondary TSH rise observed 6 days after injection does not exclude a transient desensitization of somatostatin receptors localized on normal TSH-secreting cells, as previously observed for some somatostatin receptor subtypes [34, 35]. In contrast such an event has not been observed in thyrotropinomas treated by SR-L [36], demonstrating that SR-L could be proposed as a treatment of such tumours. Plasma fT4 levels were significantly reduced for a shorter period of time extending from day 2 to day 4 after injection of SR-L. During this period of time fT4 remained in the normal range of adult men, showing that a single injection of SR-L does not lead to transient hypothyroidism in normal man.

According to the results reported with octreotide in prolactinomas [37], no significant changes in plasma prolactin levels were observed during the study. In contrast plasma IGF-1 levels were significantly reduced from day 4 to day 14, and then progressively reached basal values. Lanreotide use as subcutaneous infusion dramatically suppresses GH secretion in normal men [1, 26] and SR-L is able to inhibit GH and to normalize IGF-1 secretions in acromegalic patients [25]. These results show that SR-L is able to lower plasma IGF-1 levels (likely through inhibition of GH secretion) for a mean period of time of 14 days in normal males. Such formulations of lanreotide might be useful for the treatment of non pituitary tumours, such as breast cancer [11, 12], in which a physiopathological role of GH and/or IGF-1 has been suggested [38, 39]. SR-L might also be used without deleterious effects in children with tall stature for which treatment with somatostatin analogues has been proposed [40, 41].

Insulin secretion showed a decrease only 2 h following SR-L injection and then reached those noted during the control period. Glucagon showed no significant change after lanreotide administration. Thus, SR-L appears to induce slight and transient changes in endocrine pancreatic secretion of normal males. Such results further support the previous data obtained during continuous subcutaneous infusion of lanreotide in healthy volunteers which demonstrate a transient change in insulin and no effect on glucagon secretion [42]. The relative potencies of lanreotide on pituitary and pancreatic secretion could be linked to the respective affinity of lanreotide for the somatostatin receptors localized on the cells of both organs [13]. This in turn suggests that the use of SR-L will not induce prolonged glucose intolerance. The lack of significant changes in glucose homeostasis observed in acromegalics treated for one year with SR-L injected twice monthly [43] further supports such a conclusion.

Conclusion

The slow-release formulation of lanreotide selectively reduces IGF-1 and TSH secretion in normal males. Prolactin and glucagon are not modified after the administration of the analogue, whereas insulin and fT4 secretions are only transiently reduced. The side effects are moderate and transient. The use of the slow-release formulation of lanreotide could avoid the inconveniences of the modes of administration (i.e. 3 subcutanous injections a day) of the currently available somatostatin analogues.

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(Received 9 August 1993, accepted 12 May 1994)