JPP Journal of Pharmacy and Pharmacology

JPP 2004, 56: 471–476
© 2004 The Authors
Received October 24, 2003
Accepted January 7, 2004
DOI 10.1211/0022357023123
ISSN 0022-3573

Pharmacokinetics of a new Autogel formulation of the somatostatin analogue lanreotide after a single subcutaneous dose in healthy volunteers

R. M. Antonijoan, M. J. Barbanoj, J. A. Cordero, C. Peraire, R. Obach, J. Vallès, R. Chérif-Cheikh, M.-L. Torres, F. Bismuth and M. Montes

Centre d'Investigació de Medicaments, Institute of Research, Servei de Farmacologia Clínica, Hospital of Santa Creu and Sant Pau, Departament de Farmacologia i Terapèutica, UAB Barcelona, Spain

R. M. Antonijoan, M. J. Barbanoj

Department of Pharmacokinetics, Ipsen Pharma SA, Barcelona, Spain

J. A. Cordero, C. Peraire, R. Obach

Medical Department, Ipsen Pharma SA, Barcelona, Spain

J. Vallès

Ipsen Pharma SA, Sant Feliu de Llobregat, Barcelona, Spain

R. Chérif-Cheikh, M.-L. Torres, F. Bismuth, M. Montes

Correspondence: R. Obach, Department of Pharmacokinetics, Ipsen Pharma SA, Barcelona, Spain. E-mail: rosendo.obach@beaufour-ipsen.com

Funding and acknowledgements: This study was supported by a grant from Ipsen Pharma SA, Barcelona, Spain. The authors acknowledge the assistance of J. Llauger, J. Palmer, E. Montserrat and J. Ruscalleda from the Diagnostic Radiology Service at the Hospital de la Santa Creu i Sant Pau, Barcelona. The authors would like to thank the staff of the Centre d'Investigació de Medicaments of the l'Hospital de la Santa Creu i Sant Pau, in particular D. Amirall and I. Padrol for their assistance during the trial.

Abstract

The pharmacokinetics/tolerability of lanreotide Autogel have been evaluated. Healthy volunteers (n = 24) first received immediate-release lanreotide as a single subcutaneous (s.c.) injection. After two days, 40 or 60 mg lanreotide Autogel was injected subcutaneously. Blood was sampled at various intervals for 56 days. Systemic/local adverse events and changes in biological profile/vital signs were recorded. Lanreotide Autogel produced a prolonged-release pharmacokinetic profile: mean area under the serum concentration–time curve from time 0 to infinity (AUC) was 53.73 ± 8.99 and 79.48 ± 13.06 ng mL^{-1} day for 40 and 60 mg, respectively, mean peak serum concentration (C_{max}) was 4.38 ± 2.91 and 5.71 ± 3.52 ng mL^{-1}, respectively, median time to reach C_{max} (minimum–maximum) was 0.50 (0.083–18.0) and 0.38 (0.083–9.01) days, respectively, mean apparent elimination half-life was 21.63 ± 9.42 and 22.01 ± 9.87 days, respectively, and relative bioavailability was 0.93 ± 0.12 and 0.82 ± 0.15, respectively. Thus, lanreotide Autogel exhibited linear pharmacokinetics for the doses studied. Pharmacokinetic profiles were similar in both genders, apart from statistically significant differences in C_{max} and C_{max}/AUC. The Autogel formulation of lanreotide was well tolerated, with systemic adverse events being mild/moderate. Erythema and a painless subcutaneous induration were the most common local adverse events. Lanreotide Autogel provided a prolonged dosing interval and good tolerability for treating acromegaly and carcinoid syndrome.

Introduction

Acromegaly is a condition in adults caused by the excessive secretion of growth hormone (GH), usually from a non-cancerous pituitary adenoma (Melmed et al 1983). The increased levels of GH lead to the excessive growth of skeletal and soft tissue. As a result, patients show broadening of the facial features, particularly the nose, enlargement of the feet and hands, a protruding lower jaw, thickening and wrinkling of the skin, excessive perspiration, tiredness, deepening of the voice, muscle weakness and joint pains. Diabetes mellitus and arterial hypertension are also common complications. Patients with acromegaly have a high risk of mortality related to cardiovascular and respiratory diseases. Indeed, the risk of death in untreated patients is twice that of people of the same age and gender without the disease (Alexander et al 1980).

Currently, the first choice of treatment for acromegaly is surgery (transsphenoidal adenomectomy), sometimes accompanied by pituitary radiation. The aim of surgery is to debulk the tumour, removing as much as possible, while minimizing damage to surrounding structures such as the adjacent normal pituitary. Despite this, patients usually require additional pharmacological treatments to control the refractory disease. The inhibitory effects of the hormone somatostatin on GH secretion have been known since 1968 (Krulich et al 1968), and several clinical studies have shown that somatostatin analogues are effective in controlling de-novo or refractory acromegaly (Thomas 1983; Ho et al 1990; Sassolas et al 1990; Ezzat et al 1992; Heron et al 1993; Johnson et al 1994; Morange et al 1994). The principal reason why somatostatin analogues may prove to be such a boon in acromegaly is that they leave the rest of the pituitary pretty well

undisturbed so that spontaneous fertility in a young acromegalic woman, for example, is more likely to be preserved. This is also the reason why there is a major discussion at the moment about whether such drugs should be used first line, rather than reserved for failed surgery.

Neuroendocrine tumours arise from enterochromaffin cells, which are widely distributed throughout the small intestine, including the appendix, and are also present in the lungs, stomach, pancreas, colon, rectum and gonads. In functioning tumours, the hormones released often lead to the onset of symptoms such as severe diarrhoea and flushing. The first line of treatment is surgery, where the aim is to remove the whole tumour and metastases, but this is not always possible. The majority of neuroendocrine tumours express somatostatin receptors, providing the rationale to treat symptoms associated with the hormone release from the tumours with somatostatin analogues, which respond to the inhibitory action of these analogues (Kulke & Mayer 1999).

Lanreotide is an octapeptide analogue of somatostatin. Clinical trials with the compound have shown that it is both effective and well tolerated in the treatment of acromegaly (Colao et al 1999; Chanson et al 2000) and neuroendocrine tumours (Wymenga et al 1999; O'Toole et al 2000). Lanreotide is available as a prolonged-release microparticle formulation (Somatuline PR), which enables treatment (a single intramuscular injection) to be given only once every 7–14 days, depending on the severity of the disease (Heron et al 1993; Johnson et al 1994; Morange et al 1994). Recently, a new formulation of lanreotide has been licensed. The aqueous semisolid formulation of lanreotide in Autogel has a prolonged-release pharmacokinetic profile, providing sustained serum lanreotide levels and enabling optimal suppression of GH secretion to be achieved. It is hoped that the increased convenience of a dose interval of at least one month with Autogel should further facilitate and improve the medical control of acromegaly and carcinoid symptoms arising from neuroendocrine tumours.

In this study, the pharmacokinetic profile and systemic and local tolerability of the Autogel formulation of lanreotide acetate has been determined in healthy volunteers.

Materials and Methods

Patients and study design

A total of 24 healthy volunteers (12 men, 12 women; six of each in each dose group) aged 18–40 years were recruited into this open-label, parallel-group, phase I study.

Written informed consent was obtained from each participant before enrolment into the study. The study was conducted in compliance with the globally accepted standard of Good Clinical Practice, the latest revision of the Declaration of Helsinki, the Ethics Committee of the Hospital of Santa Creu and Sant Pau, and the General Directorate of Pharmacy and Health Care Products of the Spanish Ministry of Health.

Subjects underwent a physical examination, standard biochemical and haematological tests, and a 12-h overnight fast before drug administration. Their baseline characteristics are summarized in Table 1; there were no clinically significant abnormalities between dose groups at baseline.

Table 1 Demographic characteristics of the study sample.

Characteristic	Dose of lanreotide (Autogel formulation)	
	40 mg (n = 12)	60 mg (n = 12)
Age (years)	24.3 ± 2.2	25.0 ± 5.2
Weight (kg)	62.1 ± 5.3	63.7 ± 7.2
Height (cm)	170.1 ± 8.2	167.9 ± 10.9

Data are expressed as mean ± s.d.

On the morning of drug administration, a full medical history was taken and subjects underwent a further physical examination.

Subjects then received a single dose of the immediate-release formulation of lanreotide (Beaufour-Ipsen Industrie, Dreux, France), 7 $\mu g\,kg^{-1}$, administered subcutaneously (s.c.) into the upper quadrant of the buttock. The pharmaceutical form consisted of lanreotide acetate (1 mg) and mannitol (10 mg), with water (1 mL) as the vehicle. A blood sample (5 mL) was taken immediately before dosing and at 2, 5, 15, 30, 60 and 90 min, and 2, 4, 6, 8, 12 and 24 h after administration.

After a wash-out period of two days, the volunteers received a single dose of 0.246 $mg\,mg^{-1}$ of the Autogel formulation of lanreotide (Ipsen Pharma SA, Sant Feliu de Llobregat, Spain), either 40 or 60 mg subcutaneously (12 subjects in each dose group). The pharmaceutical form for both doses consisted of lanreotide acetate (30%), with water (70%) as the vehicle. As before, a blood sample was taken immediately before dosing and at 15 and 30 min, 1, 2, 4, 6, 8, 12 and 24 h, and 2, 4, 7, 9, 14, 18, 23, 28, 32, 35, 39, 42, 46, 49, 53 and 56 days after administration.

All subjects remained at the hospital until 24 h after lanreotide administration. At the end of follow-up (56 days), subjects underwent a final physical examination and standard biochemical and haematological tests.

Analytical method

The concentration of lanreotide in the serum samples was measured using a validated radioimmunoassay (Barbanoj et al 1999) previously developed at Institut Pasteur. The limit of quantitation of the assay was 0.078 $ng\,mL^{-1}$ and the overall precision (as % coefficient of variation) ranged from 2.3% to 13.6%, with no more than 6.9% deviation from the nominal value for accuracy.

Pharmacokinetic assessments

The pharmacokinetic parameters were derived by non-compartmental analysis using WinNonlin Version 2.1. The following parameters were derived, where appropriate, from the individual plasma concentration–time profiles: the maximum observed serum concentration (C_{max}), the time of occurrence of C_{max} (t_{max}), the apparent elim-

ination rate constant (λ_z), estimated by linear regression of the terminal linear phase of the semi-logarithmic plasma concentration–time curve, and the apparent elimination half-life ($t½_{\lambda z}$), calculated using equation 1:

$$t½ = (\ln 2)/\lambda_z \quad (1)$$

The area under the serum concentration–time curve from time 0 to the last experimental point (AUC_t) was calculated by the linear trapezoidal rule, the area under the serum concentration–time curve from time 0 to infinity (AUC) was calculated according to equation 2:

$$AUC = AUC_t + C_t/\lambda_z \quad (2)$$

The mean residence time from time 0 to infinity (MRT) was calculated according to equation 3:

$$MRT_{s.c.} = AUMC/AUC \quad (3)$$

where AUMC is the area under the first moment curve from time 0 to infinity. Also the ratio C_{max}/AUC as an absorption index was calculated.

The relative bioavailability (F_{rel}) of lanreotide prolonged-release formulation compared with the immediate-release formulation (i.r.f.) was calculated using equation 4:

$$F_{rel} = (AUC_{Autogel\ s.c.}/D_{Autogel\ s.c.})/(AUC_{i.r.f.\ s.c.}/D_{i.r.f.\ s.c.}) \quad (4)$$

In addition to the pharmacokinetic parameters mentioned above, in-vivo dissolution time curves (mean cumulated dissolved amounts vs time) were determined and produced from the raw data using the technique of deconvolution solved numerically using the mid-point method (Linz 1985) by means of the PCDCON program (Deconvolution for pharmacokinetic applications version 1.1 written by Gillespie http://anesthesia.stanford.edu/pkpd/).

Safety assessments

General tolerability

Adverse events were monitored throughout the study. Other safety assessments were performed at baseline and 56 days after administration of the Autogel formulation. These included a physical examination, measurement of weight, vital signs and standard biochemical and haematological parameters in the blood samples.

Local tolerability

Pain and local inflammation at the injection site were assessed at the same time as blood samples were collected. Pain at the injection site was assessed by the volunteers with the aid of a visual analogue scale, while signs of local inflammation (erythema, haematoma or eczema) were quantified by the investigator.

Statistical methods

Pharmacokinetic parameters were compared for the two doses of the Autogel formulation and by gender using a general linear model analysis of variance after log-transformation of data (except for t_{max} values, which were rank transformed from the lowest to the highest value after considering all the estimated values). The occurrence of adverse events was compared between groups using the Fisher exact test. The level of significance was considered to be $P < 0.05$.

Results

Pharmacokinetic parameters

Serum levels of lanreotide could not be correctly quantified in one volunteer after administration of the Autogel formulation due to the presence of an analytical interference in his blood samples. This subject was therefore excluded from the pharmacokinetic analysis for this formulation. This gave 11 subjects for evaluation for the 40 mg dose and 12 subjects for the 60 mg dose.

The pharmacokinetic parameters obtained after administration of the immediate-release formulation of lanreotide are summarized in Table 2. The concentration–time curve for this formulation over the first 12 h after administration is shown in Figure 1.

After administration of the Autogel formulation of lanreotide, the pharmacokinetic parameters obtained after the administration of 40 and 60 mg are summarized in Table 3. Serum levels of lanreotide were measurable for up to 56 days post-injection in most volunteers. The pharmacokinetic profile for the Autogel formulation is summarized in Figure 2. No statistically significant differences between the two doses of this formulation were observed for any pharmacokinetic parameter.

Similar pharmacokinetic profiles were obtained with the Autogel formulation of lanreotide for men and women, apart from a statistically significant difference in C_{max} and C_{max}/AUC, these parameters being significantly lower in women than in men ($P < 0.05$ and $P < 0.01$, respectively).

Table 2 Pharmacokinetic parameters after a single subcutaneous dose of the immediate-release formulation of lanreotide (7 $\mu g\,kg^{-1}$) in 24 healthy volunteers.

Parameter	Mean	s.d.
t_{max} (h)[a]	0.25	(0.25–0.5)
C_{max} ($ng\,mL^{-1}$)	7.98	2.15
λ_z (h^{-1})	0.43	0.12
$t½_{\lambda z}$ (h)	1.74	0.55
AUC ($ng\,mL^{-1}\,h$)	16.51	3.64
MRT (h)	1.95	0.45
C_{max}/AUC (h^{-1})	0.49	0.10

AUC is the area under the serum concentration–time curve from time 0 to infinity, C_{max} is the peak serum concentration, MRT is the mean residence time from time 0 to infinity, t_{max} is the time to reach C_{max}, $t½_{\lambda z}$ is the apparent elimination half-life, λ_z is the apparent elimination rate constant. [a]Median with range values.

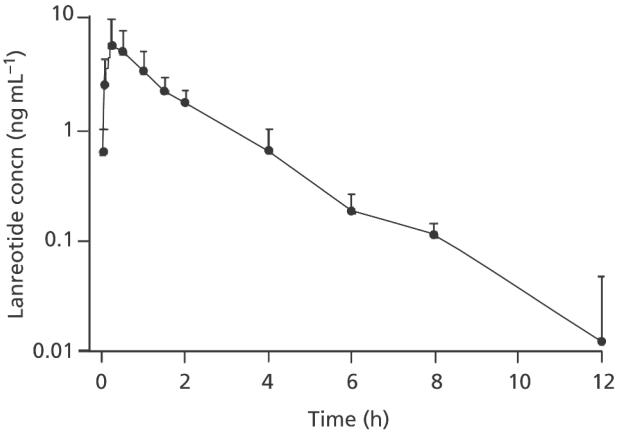

Figure 1 Concentration–time curve for the immediate-release formulation of lanreotide after a single subcutaneous injection of 7 μg kg^{-1} in 24 healthy volunteers.

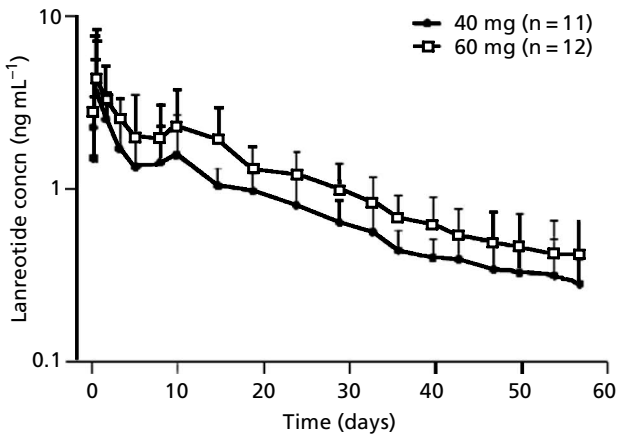

Figure 2 Concentration–time curve for the prolonged-release Autogel formulation of lanreotide after a single subcutaneous injection of 40 or 60 mg.

The in-vivo release curves for the two administered doses (produced using the technique of deconvolution) are shown in Figure 3.

Safety results

Adverse events

All adverse events reported during the study were either mild or moderate in nature. The most common adverse events were of gastrointestinal origin and included diarrhoea, intestinal and gastric discomfort, and nausea. One episode of moderate headache was reported in a volunteer after administration of the immediate-release formulation of lanreotide. Table 4 shows the incidence of adverse events after administration of the Autogel formulation. The incidence of adverse events for the 40 and 60 mg doses was similar.

Vital signs, and biochemical and haematological parameters

No clinically significant changes in vital signs or biochemical and haematological parameters were observed with either lanreotide formulation.

Local tolerability

Erythema was recorded in 17/24 volunteers following administration of the immediate-release formulation of lanreotide. Following administration of the Autogel formulation, transient erythema and a painless subcutaneous induration appeared promptly at the injection site in all

Table 3 Pharmacokinetic parameters after a single subcutaneous dose of the prolonged-release Autogel formulation of lanreotide, 40 (n = 11) or 60 (n = 12) mg.

Parameter	Dose of lanreotide				*P* value
	40 mg		60 mg		
	Mean	s.d.	Mean	s.d.	
t_{max} (days)[a]	0.50	(0.083–18.0)	0.38	(0.083–9.01)	NS
C_{max} (ng mL^{-1})[b]	4.38	2.91	5.71	3.52	NS
λ_z (per day)	0.04	0.01	0.04	0.03	NS
$t_{½\lambda z}$ (days)	21.63	9.42	22.01	9.87	NS
AUC (ng mL^{-1} day)[c]	53.73	8.99	79.48	13.06	NS
MRT (days)[c]	30.47	12.90	31.97	13.56	NS
C_{max}/AUC (per day)[c]	0.08	0.05	0.07	0.05	NS
F_{rel}[c]	0.93	0.12	0.82	0.15	NS

AUC is the area under the serum concentration–time curve from time 0 to infinity, C_{max} is the peak serum concentration, F_{rel} is the relative bioavailability, MRT is the mean residence time from time 0 to infinity, t_{max} is the time to reach C_{max}, $t_{½\lambda z}$ is the apparent elimination half-life, λ_z is the apparent elimination rate constant. NS is a non-significant difference between doses (two-way general linear model analysis of variance). [a]Median with range values. [b]The values were normalized by dose for statistical comparisons. [c]Values were determined with more than 20% of extrapolated AUC in some subjects.

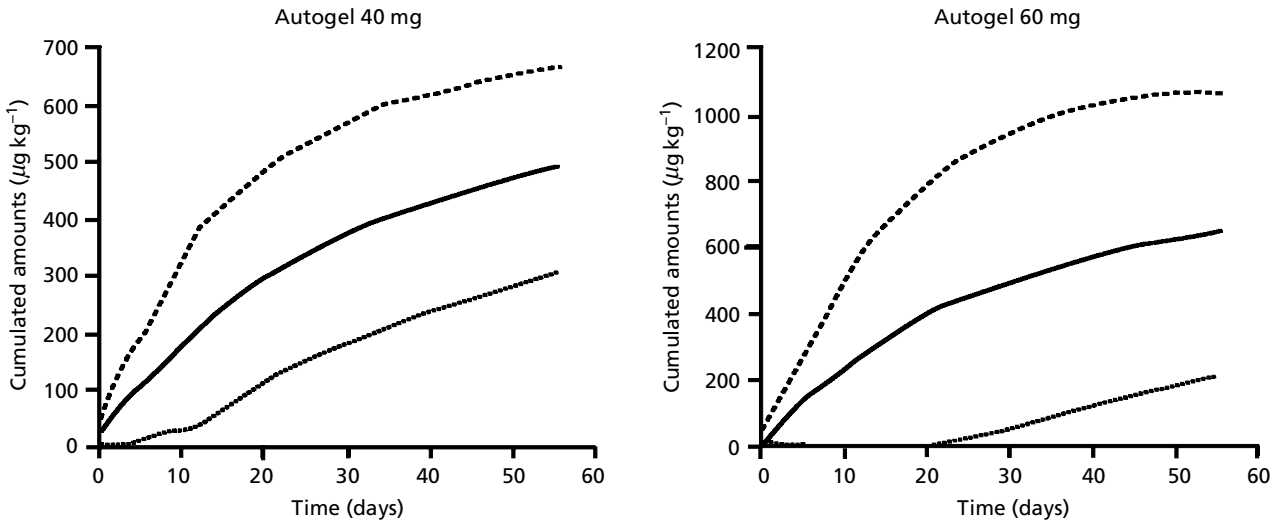

Figure 3 In-vivo release of lanreotide from the Autogel formulation (both doses) in 12 men and 11 women, measured as the mean cumulated amounts. Mean values and 95% confidence interval are shown.

Table 4 Incidence of adverse events after the administration of a single subcutaneous dose of the prolonged-release Autogel formulation of lanreotide, 40 or 60 mg, to 24 healthy volunteers.

Adverse event	Dose of lanreotide		
	40 mg	60 mg	*P* value
Diarrhoea	11/12 (92%)	12/12 (100%)	NS
Acholia	10/12 (83%)	11/12 (92%)	NS
Gastric discomfort	5/12 (42%)	2/12 (17%)	NS
Stomach cramps	4/12 (33%)	9/12 (75%)	NS
Abdominal pain	4/12 (33%)	4/12 (33%)	NS
Headache	2/12 (17%)	3/12 (25%)	NS
Nausea	2/12 (17%)	1/12 (8%)	NS
Vomiting	0/12 (0%)	2/12 (17%)	NS

NS, not significant.

volunteers. The intensity of erythema was higher with the 60 mg dose compared with the lower dose of 40 mg. The surface area of this local event decreased with time, and by day 56 the subcutaneous induration was no longer noted in 19/24 volunteers and was small (0.25–1.00 cm^2) in the remaining five volunteers.

Discussion

This study showed that both doses of the Autogel formulation of lanreotide produced prolonged-release pharmacokinetic profiles, and the profiles were similar for the two doses and for men and women. Lanreotide was detected in the serum of almost all subjects 15 min after administration, and levels of the drug increased rapidly to a mean (± s.d.) peak of $4.38 \pm 2.91\ ng\,mL^{-1}$ for the 40 mg dose and $5.71 \pm 3.52\ ng\,mL^{-1}$ for the 60 mg dose. Concentrations then decreased until four to seven days after administration, giving mean serum lanreotide levels of approximately 1.5 and $2.0\ ng\,mL^{-1}$ for the 40 and 60 mg doses, respectively, during this time. After this time, some subjects showed a slight increase in serum lanreotide levels and a 'pseudo-plateau', while others showed a slow decrease in levels. Lanreotide was still detected at the end of the study (day 56) in most volunteers (22/24), and the mean remaining serum concentrations were above the minimum concentration associated with therapeutic effect (the previously determined EC50 of $0.206\ ng\,mL^{-1}$ for lanreotide to reduce GH levels in acromegaly (Cendros et al 2003)), thus serum concentrations were $0.27\ ng\,mL^{-1}$ for the 40 mg dose and $0.40\ ng\,mL^{-1}$ for the 60 mg dose at day 56. The mean terminal half-life was approximately 22 days for both doses of lanreotide.

The prolonged-release Autogel formulation of lanreotide was associated with a much higher $t½_{\lambda z}$ value (21.63 and 22.01 days for the 40 and 60 mg doses, respectively) than the immediate-release formulation (1.74 h), and also with a higher MRT value (30.47 and 31.97 days for the 40 and 60 mg doses, respectively, vs 1.95 h for the immediate-release formulation). This suggested that a 'flip-flop' phenomenon occurred, whereby absorption rather than elimination was the rate-limiting factor.

Using the immediate-release formulation of lanreotide as the reference form, the relative bioavailability of the Autogel formulation was 0.93 for the 40 mg dose and 0.82 for the 60 mg dose. The relative bioavailability of the 60 mg dose tended to be lower than that of the 40 mg dose, although the differences between the two doses were not statistically significant.

The pharmacokinetic parameters were similar for the two doses of the Autogel formulation of lanreotide, with no statistically significant differences being observed, suggesting that Autogel exhibited linear pharmacokinetics over the dose range studied. The pharmacokinetic profiles for this formulation were similar for the two genders, with

statistically significant differences only being observed for C_{max} (normalized by dose) and C_{max}/AUC. These parameters were dependent on the peak serum lanreotide levels. After the administration of either of the two doses of Autogel, the C_{max} values obtained in women were consistently lower compared with those obtained in men.

The Autogel formulation of lanreotide was well tolerated: the adverse events reported during the study were mainly of gastrointestinal origin, and were all mild or moderate in nature. Such events are well-known adverse effects of somatostatin analogues (Caron et al 1997; Colao et al 1999; Baldelli et al 2000; Chanson et al 2000). No clinically significant changes in vital signs or biochemical and haematological parameters were observed with either formulation. Erythema and painless subcutaneous induration at the injection site were noted after injection of the Autogel formulation. As erythema was observed with the immediate-release formulation, it was likely that this effect was directly related to the vasomotor activity of lanreotide. Indeed, the intensity of erythema was greater with the 60 mg dose than with the 40 mg dose of the Autogel formulation. In all volunteers, the subcutaneous induration decreased with time.

Conclusions

A single subcutaneous injection of the Autogel formulation of lanreotide, 40 or 60 mg, in healthy volunteers produced a prolonged-release pharmacokinetic profile that was similar for the two doses (see Table 3). Thus, Autogel exhibited linear pharmacokinetics over the dose range studied. The terminal half-life of the Autogel formulation was particularly long and measurable lanreotide levels above the minimum concentration associated with therapeutic effect were present for up to 56 days post-injection in most volunteers (EC50 of 0.206 ng mL^{-1} for GH reduction in acromegaly (Cendros et al 2003)). The lanreotide Autogel formulation was well tolerated both systemically and locally. All systemic adverse events were mild or moderate in nature and characteristic of a somatostatin analogue. It is concluded that Autogel offers advantages in the treatment of acromegaly and symptoms associated with neuroendocrine tumours by enabling a prolonged dosing interval, while maintaining therapeutic lanreotide levels.

References

Alexander, L., Appleton, D., Hall, R., Ross, W. M., Wilkinson, R. (1980) Epidemiology of acromegaly in the Newcastle region. *Clin. Endocrinol. (Oxf.)* **12**: 71–79

Baldelli, R., Colao, A., Razzore, P., Jaffrain-Rea, M.-L., Marzullo, P., Ciccarelli, E., Ferretti, E., Ferone, D., Gaia, D., Camanni, F., Lombardi, G., Tamburrano, G. (2000) Two-year follow-up of acromegalic patients treated with slow release lanreotide (30 mg). *J. Clin. Endocrinol. Metab.* **85**: 4099–4103

Barbanoj, M., Antonijoan, R., Morte, A., Grinyo, J. M., Sola, R., Valles, J., Peraire, C., Cordero, J. A., Munoz, A., Jane, F., Obach, R. (1999) Pharmacokinetics of the somatostatin analog lanreotide in patients with severe chronic renal insufficiency. *Clin. Pharmacol. Ther.* **66**: 485–491

Caron, P., Morange-Ramos, I., Cogne, M., Jaquet, P. (1997) Three-year follow-up of acromegalic patients treated with intramuscular slow-release lanreotide. *J. Clin. Endocrinol. Metab.* **82**: 18–22

Cendros, J. M., Peraire, C., Troconiz, I., Obach, R. (2003) Lanreotide Autogel in acromegaly: a pharmacokinetic and pharmacodynamic analysis. *Endocr. Abs.* **6**: P47

Chanson, P., Leselbaum, A., Blumberg, J., Schaison, G. (2000) Efficacy and tolerability of the long-acting somatostatin analog lanreotide in acromegaly. A 12-month multicenter study of 58 acromegalic patients. French Multicenter Study Group on Lanreotide in Acromegaly. *Pituitary* **2**: 269–276

Colao, A., Marzullo, P., Ferone, D., Marino, V., Pivonello, R., Di Somma, C., Di Sarno, A., Giaccio, A., Lombardi, G. (1999) Effectiveness and tolerability of slow release lanreotide treatment in active acromegaly. *J. Endocrinol. Invest.* **22**: 40–47

Ezzat, S., Snyder, P. J., Young, W. F., Boyajy, L. D., Newman, C., Klibanski, A., Molitch, M. E., Boyd, A. E., Sheeler, L., Cook, D. M., Malarkey, W. B., Jackson, I., Vance, M. L., Thorner, M. O., Barkan, A., Frohman, L. A., Melmed, S. (1992) Octreotide treatment of acromegaly. A randomized, multicenter study. *Ann. Intern. Med.* **117**: 711–718

Heron, I., Thomas, F., Dero, M., Poutrain, J. R., Henane, S., Catus, F., Kuhn, J. M. (1993) Traitement de l'acromégalie par une forme de libération prolongée du lanréotide. Un nouvel analogue de la somatostatine. *Presse Méd.* **22**: 526–531

Ho, K. Y., Weissberger, A. J., Marbach, P., Lazarus, L. (1990) Therapeutic efficacy of the somatostatin analog SMS 201-995 (octreotide) in acromegaly. Effects of dose and frequency and long-term safety. *Ann. Intern. Med.* **112**: 173–181

Johnson, M. R., Chowdrey, H. S., Thomas, F., Grint, C., Lightman, S. L. (1994) Pharmacokinetics and efficacy of the long-acting somatostatin analogue somatuline in acromegaly. *Eur. J. Endocrinol.* **130**: 229–234

Krulich, L., Dhariwal, A. P., McCann, S. M. (1968) Stimulatory and inhibitory effects of purified hypothalamic extracts on growth hormone release from rat pituitary in vitro. *Endocrinology* **83**: 783–790

Linz, P. (1985) *Analytical and numerical methods for Volterra equations*. SIAM, Philadelphia, Pennsylvania

Kulke, M., Mayer, R. J. (1999) Carcinoid tumors. *N. Engl. J. Med.* **340**: 858–868

Melmed, S., Braunstein, G. D., Horvath, E., Ezrin, C., Kovacs, K. (1983) Pathophysiology of acromegaly. *Endocr. Rev.* **4**: 271–290

Morange, I., De Boisvilliers, F., Chanson, P., Lucas, B., DeWailly, D., Catus, F., Thomas, F., Jaquet, P. (1994) Slow release lanreotide treatment in acromegalic patients previously normalized by octreotide. *J. Clin. Endocrinol. Metab.* **79**: 145–151

O'Toole, D., Ducreux, M., Bommelaer, G., Wemeau, J. L., Bouche, O., Catus, F., Blumberg, J., Ruszniewski, P. (2000) Treatment of carcinoid syndrome: a prospective crossover evaluation of lanreotide versus octreotide in terms of efficacy, patient acceptability, and tolerance. *Cancer* **88**: 770–776

Sassolas, G., Harris, A. G., James-Deidier, A. (1990) Long term effect of incremental doses of the somatostatin analog SMS 201-995 in 58 acromegalic patients. French SMS 201-995 approximately equal to Acromegaly Study Group. *J. Clin. Endocrinol. Metab.* **71**: 391–397

Thomas, J. P. (1983) Treatment of acromegaly. *Br. Med. J. (Clin. Res. Ed.)* **286**: 330–332

Wymenga, A. N., Eriksson, B., Salmela, P. I., Jacobsen, M. B., Van Cutsem, E. J., Fiasse, R. H., Valimaki, M. J., Renstrup, J., de Vries, E. G., Oberg, K. E. (1999) Efficacy and safety of prolonged-release lanreotide in patients with gastrointestinal neuroendocrine tumors and hormone-related symptoms. *J. Clin. Oncol.* **17**: 1111