Bioavailability of Leuprolide Acetate Following Nasal and Inhalation Delivery to Rats and Healthy Humans

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Systemic delivery of leuprolide acetate, a luteinizing hormone releasing hormone (LHRH) agonist, was compared after inhalation (i.h.) and intranasal (i.n.) administration. The i.n. bioavailability in rats was significantly increased by α-cyclodextrin (CD), EDTA, and solution volume. Intraanimal variability was 30–60%, and absorption ranged from 8 to 46% compared to i.v. controls. Studies in healthy human males were conducted with leuprolide acetate i.n. by spray, or inhalation aerosol (i.h.), and subcutaneous (s.c.) and intravenous (i.v.) injection. The s.c. injection was 94% bioavailable compared with i.v. The i.n. bioavailability averaged 2.4%, with significant subject-to-subject variability. Plasma peak concentrations (C_{max}) with 1- and 3-mg dosages ranged between 0.24–1.6 and 0.10–11.0 ng/ml, respectively. The low human bioavailability may be due to physical loss of drug down the oral cavity and differences between human and rat nasal mucosa. Inhalation delivery gave a slightly lower intersubject variability. Mean C_{max} with a 1-mg dose of solution aerosol was 0.97 ng/ml, compared with 4.4 and 11.4 ng/ml for suspension aerosols given at 1- and 2-mg bolus dosages, respectively. The mean bioavailability of the suspension aerosols (28% relative to s.c. administration) was fourfold greater than that of the solution aerosol (6.6%), suggesting that LHRH analogues may be delivered systemically via the lung as aerosol dispersions.

KEY WORDS: peptide delivery; nasal and lung delivery of leuprolide acetate; lung delivery of luteinizing hormone-releasing hormone (LHRH) analogues.

INTRODUCTION

Leuprolide acetate is a synthetic nonapeptide and analogue of naturally occurring luteinizing hormone releasing hormone (LHRH). It possesses greater biologic potency than the natural hormone, which when introduced to the systemic circulation induces the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the anterior pituitary (1). These factors exert trophic and steroidogenic effects on gonadal tissues. It has been demonstrated that pulsatile administration of GnRH analogues maintains pituitary function in GnRH-deficient animals (2). These compounds also possess long biologic half-lives in plasma, so that contrary to their effects when given in pulsatile fashion, long-term administration paradoxically desensitizes the pituitary resulting in a reversible biochemical castration. For this reason, chronic administration of these compounds is effective therapy for hormonally sensitive conditions such as prostatic cancer (3) and endometriosis (4,5).

Leuprolide acetate is a potent LHRH agonist and is often designated by the sequence of the component amino acids, namely, (D-Leu^6, des-Gly-NH$_2$^{10}, Pro-ethylamide^9)-GnRH or pGlu-His-Trp-Ser-Tyr-D-Leu-Leu-Arg-Pro-NHEt. Following an initial stimulation, the chronic administration of leuprolide acetate results in the inhibition of gonadotropin release (6–8). Consequently, ovarian and testicular function is suppressed. Leuprolide acetate is not orally active (9) and is available for daily s.c. administration (1 mg) or monthly single intramuscular (7.5-mg) depot injection in the palliative treatment for advanced cancer of the prostate. A monthly 3.75-mg depot injection is also available in the United States for use in treating endometriosis.

Animal model studies were conducted to evaluate the nasopharyngeal route (10) as an alternative to injection. Formulation variables influencing i.n. and i.h. (by intratracheal instillation) absorption of the drug in Sprague-Dawley rats were identified and used to conduct Phase I studies in healthy male volunteers.

EXPERIMENTAL METHODS

Formulations for Animal Studies

Formulations for animal studies (Table I) were prepared in double-distilled deionized water at drug concentrations ranging from 0.1 to 30 mg/ml. All solutions were adjusted to pH 5.2 with acetic acid and made isotonic with sodium chloride. Absorption promoting agents, including α-CD (Austin Chemical, Park Ridge, IL), EDTA (Mallinchrodt), and Azone (Nelson Research), where used, were added to the aqueous solutions prior to pH adjustment.

Formulations for Human Studies

Intranasal Formulations

Nasal formulations of leuprolide acetate were packaged in 1-oz amber glass bottles, each closed with a metered mechanical spray pump (Valois, Inc., Greenwich, CT). All solutions were adjusted to pH 5.2 with acetic acid and made isotonic with sodium chloride. The enhancer system used in Formulations B and C included 5% α-CD and 25 m*M* EDTA. Generic compositions of the formulations are given in Table II.

Inhalation Aerosol Formulations

Three MDI (metered-dose inhaler) formulations were prepared and packaged in 20-ml Cebal aluminum cans with DF10/50-μl valves (Valois, Inc., Greenwich, CT). Tonicity and pH were not adjusted since the vehicles were nonaqueous. Generic compositions of the formulations are given in Table III.

Parenteral Formulation

A sterile aqueous solution of leuprolide acetate, 5 mg/ml, marketed under the trade name Lupron was administered either intravenously or subcutaneously.

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Table I. Bioavailability of Leuprolide Acetate Formulations Following Intranasal Administration to Sprague-Dawley Rats (Effect of Formula Absorption Promoters)[a]

Formulation components	Dose volume (ml/kg)	AUC (hr · ng/ml)	Bioavailability (%)
Saline[b]	1.0	84.2 ± 4.7	100.0
Saline	0.1	10.6 ± 2.1	12.6
NaCl + 5% α-CD	0.1	30.8 ± 2.2	36.6
NaCl + 5% α-CD + EDTA[c]	0.1	39.7 ± 8.8	47.1
NaCl + 1% Azone	0.1	13.4 ± 1.6	15.9
NaCl + 2% Azone	0.1	12.6 ± 0.4	15.0
NaCl + 4% Azone	0.1	16.2 ± 4.1	19.2

[a] Dose administered: 100 μg/kg. α-CD, α-cyclodextrin. *N*, number of rats per group = 9. Mean data are reported with standard deviations.
[b] Administered by i.v. All other formulations were administered i.n.
[c] Concentration in formulation was 25 m*M*.

ANALYTICAL METHODS

In vitro chemical assays for leuprolide acetate were done using a previously described HPLC assay method (11). Plasma circulating drug levels were determined using a modified radioimmunoassay (RIA) procedure (12). Leuprolide was iodinated, ^{125}I-[Tyr^5]leuprolide, and an antibody capable of recognizing the tripeptide antigenic determinant x-Leu-Arg-Pro-NHEt, was utilized. The EC_{50} and limit of detection for the assay were approximately 1.5 and 0.1 ng/ml (200 μl plasma per sample), respectively. Assay coefficient of variation (CV) was 10.5%; intraassay CV was 6.6%. Plasma samples obtained by centrifuging at 5000 rpm for 15 min were randomized and assayed in triplicate in one single run. The areas under the blood level-versus-time curves (AUC) were calculated and used to estimate the percentage bioavailability, *F*, according to the following equation:

$$F = \frac{AUC_{[BD]}}{AUC_{[SC]}} \times \frac{Dose_{[SC]}}{Dose_{[BD]}} \times 100 \qquad (1)$$

where [SC] represents the subcutaneous control formulation, and [BD] represents the respective bolus dosages of either the nasal or the inhalation dosage form.

PROTOCOL FOR HUMAN STUDIES

Three studies were conducted under single-dose, randomized, statistical designs with normal adult male volunteers, ages 19 to 39. Subject selection was based on medical histories, blood chemistry, chest X-ray, and electrocardiogram results. Study I evaluated three aqueous i.n. formulations of the drug in 15 subjects. Studies II and III evaluated three nonaqueous i.h. formulations and one sterile injectable (i.v. and s.c.) solution of the drug in 23 and 6 subjects, respectively.

Table II. Generic Compositions of the Intranasal Formulations

Formula	Composition	Drug concentration (mg/ml)	Dose (mg)
A	Saline solution	5	1
B	5% α-CD	5	1
C	5% α-CD	15	3
Injection	0.9% sodium chloride	5	1

Table III. Generic Compositions of the Inhalation Aerosol Formulations

Formula composition	Amount per 100 vials (A) Solution	(B) Suspension	(C) Suspension
Water, purified, USP	1.7%	—	—
Decanesulfonic acid	0.7%	—	—
Alcohol, dehydrated, USP	20.0%	—	—
Leuprolide acetate	10 mg/ml	15 mg/ml	30 mg/ml
Sorbitan monooleate, NF	5.0%	—	—
Span 85 (sorbitan trioleate)	—	0.5%	0.5%
Trichlorofluoromethane	—	25.0%	25.0%
Dichlorodifluoromethane	q.s.	q.s.	q.s.

Plasma Sampling for Human Bioavailability Studies

Approximately 5 ml of blood were drawn from the arm vein of each subject via a heparin lock at 0, 5, 10, 15, 20, 30, and 45 min and at 1, 1.5, 2, 2.5, 3, 4.5, 6, 8, 12, and 24 hr after administration of each dose. In the i.v. and s.c. studies, the heparin lock for collection of blood samples was placed in the arm opposite that used for injection of the drug. After centrifuging, the plasma samples were immediately separated and frozen until assayed.

Drug Administration

All subjects were fasted for a minimum of 8 hr prior to dosing. Water was allowed ad libitum. Nasal formulations were administered with a mechanical spray pump (100 μl/spray; mean particle size, 80 μm; range, 55–95 μm) so that the total dosages administered were 1, 1, and 3 mg of leuprolide acetate for Formulations A, B, and C, respectively. Subjects were maintained in a reclining position for at least 5 min or until it was felt the spray would not drip out of the nostrils.

Inhalation delivery by MDI yielded mean particle diameters of 6 and 3 μm, for the solution and suspension aerosol formulations, respectively. Two sprays (2 × 50 μl) each of the aerosols were administered so that a total of 1, 1, and 2 mg of leuprolide acetate was administered for Formulations A, B, and C, respectively. Drug administration was carried out during inspiration with the head tilted back at an angle of approximately 45°. A breath hold of approximately 10 sec was requested before subjects were allowed to exhale through the nose.

Statistical Analyses

Mean plasma leuprolide concentration-versus-time profiles following administration of all formulations were

Table IV. Bioavailability of Leuprolide Acetate Formulations Following Intranasal Administration to Sprague-Dawley Rats (Effect of Administered Volume)[a]

Formulation components	Dose volume (ml/kg)	AUC (hr · ng/ml)	Bioavailability (%)
Saline[b]	1.0	117.7 ± 5.1	100.0
NaCl + 5% α-CD	0.4	18.1 ± 9.2	15.4
NaCl + 5% α-CD	0.2	26.9 ± 8.0	24.1
NaCl + 5% α-CD	0.1	39.7 ± 8.8	35.5
NaCl + 5% α-CD	0.05	23.7 ± 7.3	21.2
NaCl + 5% α-CD	0.025	19.8 ± 4.2	7.7

[a] Dose administered: 100 μg/kg. α-CD, α-cyclodextrin. *N*, number of rats per group = 9. Mean data are reported with standard deviations.
[b] Administered by i.v. All other formulations were administered i.n.

treated by the trapezoidal approximation to generate values for AUC. Differences in results for AUC, together with plasma C_{max} and T_{max}, were analyzed using ANOVA.

RESULTS

Nasopharyngeal Studies in Sprague-Dawley Rats

Summaries of bioavailability data generated with several formulations of leuprolide following i.n. administration of 100-μg/kg bolus dosages to male Sprague-Dawley rats are presented in Tables I, IV, and V. Results in Table I show the effect of α-CD and Azone on i.n. absorption of the drug. The presence of α-CD significantly improved the i.n. bioavailability of leuprolide ($P < 0.05$) to 36.6% versus the saline control formulation, i.e., AUC = 12.6. Addition of 25 m*M* EDTA further improved the bioavailability to 47.1%. Azone did not have any beneficial effect ($P > 0.05$) on i.n. absorption of leuprolide.

Results in Table IV with 100 μg/kg dosages as a function of volume showed a parabolic effect on i.n. absorption of leuprolide. Maximal bioavailability occurred at a dose volume of 0.1 mL/kg and intergroup CV ranged from 21 to 51%. Increasing levels of EDTA also had a parabolic effect on i.n. bioavailability of leuprolide (Table V). Maximal bioavailability was obtained with 25 m*M* EDTA. Intergroup CV ranged from approximately 12 to 30%. Unlike results from the i.n. studies, i.h. leuprolide by instillation to rats showed that there was no benefit of absorption promoters on lung bioavailability of the drug. Rather, there was quantitative absorption of leuprolide by this route of administration using i.v. as a control (Table V).

Intranasal Studies in Human Males

Plasma leuprolide concentration–time profiles for the three i.n. formulations are presented in Fig. 1. Analysis of circulating plasma levels for individual subjects revealed aberrant absorption of the drug. Plasma C_{max} for the 1-mg dosages ranged from 0.24 to 1.55 ng/ml, with many subjects showing levels of drug near the limit of the assay. Plasma C_{max} for the 3-mg dosage ranged from 0.10 to 11.05 ng/ml, with one subject showing measurable levels only between 1.5 and 3 hr after drug administration. There were no meaningful differences in the extent of absorption of leuprolide acetate based on period effects when adjusted for dose of drug administered ($P > 0.05$).

Table VI summarizes bioavailability results for the three formulations. Plasma AUCs revealed that the extent of drug absorption was generally low, with substantial subject-to-subject variability. Bioavailability for each of the 1-mg dosages (i.e., Formulations A and B) averaged 2.3% relative to the i.v. (2.5% based on s.c.; see Table VIII). Bioavailability of the 3-mg dose (Formulation C) was approximately 10.2% by i.v. (or 11.1% relative to s.c.), which when adjusted for dose (3.5% by i.v. or 3.7% relative to s.c.), was slightly higher than but not statistically different ($P > 0.05$) from results for Formulations A and B. Although not statistically significant ($P > 0.05$), the AUC for formulation A (without α-CD) was higher than that for formulation C (with α-CD).

Inhalation Studies in Human Males with MDI

Table VII summarizes plasma leuprolide levels following administration of the three aerosol formulations to male subjects. The results suggested that onset of absorption from

Table V. Bioavailability of Leuprolide Acetate Formulations Following Nasopharyngeal Administration to Sprague-Dawley Rats (Effect of Varying Levels of EDTA as Absorption Promoter)[a]

Formula composition	Route of delivery	EDTA level (m*M*)	No. of rats	AUC (hr · ng/ml)	Bioavailability (%)
Saline[b]	i.v.	0	9	68.5 ± 5.7	100.0
NaCl + 5% CD	i.n.	0	9	23.5 ± 6.0	34.2
NaCl + 5% CD	i.n.	25	9	32.0 ± 9.7	46.5
NaCl + 5% CD	i.n.	50	9	25.0 ± 2.5	36.3
NaCl + 5% CD	i.n.	100	9	19.0 ± 3.5	27.6
NaCl + 5% CD	i.n.	200	9	12.1 ± 1.5	17.6
Saline[b]	i.v.	0	3	102.5 ± 5.8	100.0
Saline	i.h.	0	3	107.0 ± 7.2	104.4
NaCl + 5% α-CD	i.h.	0	3	110.1 ± 8.1	107.4
NaCl + 5% α-CD	i.h.	25	3	99.0 ± 3.2	96.6
NaCl + 5% α-CD	i.h.	50	3	105.6 ± 6.5	103.0

[a] Dose administered, 100 μg/kg; dose volume, 0.1 ml/kg. α-CD, α-cyclodextrin. Mean data are reported with standard deviations.
[b] Administered by i.v.

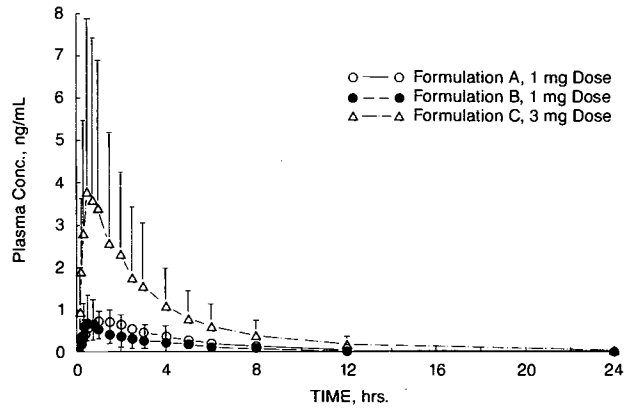

Fig. 1. Bioavailability of leuprolide acetate in humans following nasal delivery to male volunteers.

the solution aerosol formulation was slower than from the suspension formulations. Plasma levels for the solution aerosol were below 1 ng/ml but were generally higher than the limit of the assay. Mean plasma T_{max} for the solution aerosol occurred at 2.3 hr, compared with 1.4 hr for the suspension aerosols. Mean plasma C_{max} for the suspension aerosols was significantly higher than for the solution aerosol ($P \leq 0.01$) at the same dose. The mean C_{max} was 0.97, 4.38, and 11.37 ng/ml for the 1-mg solution aerosol and the 1- and 2-mg suspension aerosol formulations, respectively. Plasma concentrations of at least 0.3 ng/ml were maintained through 8 hr for the 1-mg solution, compared with 24 hr for the 1- and 2-mg inhalation suspension aerosols. These data indicated a longer plasma duration of drug with the suspension compared with the solution aerosols. Of the 23 subjects participating in the study, 8 subjects on the solution, 22 subjects on the 1-mg suspension, and all 23 subjects on the 2-mg suspension had detectable plasma drug levels at 24 hr. The mean AUC for the 1- and 2-mg dose suspension aerosols were approximately three- to fourfold that of the 1-mg solution aerosol formulation. These apparent AUC differences were significant ($P \leq 0.05$) and followed the general order B,C > A.

Parenteral Formulations

Pharmacokinetic analyses of the plasma results for leuprolide following s.c. and i.v. administration are summarized in Table VIII. The mean plasma $T_{1/2}$ from the terminal linear phase was 2.9 hr (range, 2.6 to 3.8 hr) for i.v. delivery, compared with 3.6 hr (range, 2.7 to 6.8 hr) for s.c. administration. These differences were significant ($P \leq 0.05$).

DISCUSSION

Effect of Carriers on i.n. and i.h. Absorption of Leuprolide

The data reported in Table VI reveal that the pharmacokinetics of nasally administered leuprolide acetate in humans were not significantly affected by coadministration with EDTA and α-CD. Contrary to the rat data, although not statistically significant, there was a slight decrease in bioavailability of leuprolide with vs without α-CD/EDTA, suggesting a negative effect of this enhancer system on nasal absorption of this peptide in humans (Fig. 2). The lower bioavailability upon administration of leuprolide with this enhancer system was unexpected. This nonapeptide analogue of LHRH exists as a highly hydrophilic acetate ion pair, $-NH3^+ \cdot {}^-00CCH3$ with high aqueous solubility. Therefore, adjuvants intended to promote *in vivo* solubilization of leuprolide should have little or not benefit. The lack of any beneficial effect of the EDTA/α-CD system on i.n. absorption of leuprolide acetate in humans compared with rats suggests that the absorption mechanism for this drug is significantly different in the two species. Further, the optimal i.n. dose volume of 0.1 μl/kg from the rat screening studies was not used for subjects in this investigation. Such a dose volume relative to body weight would have been impractical (i.e., approximately 7 ml per person). Thus, drug administration at a suboptimal dose volume could have been responsible in part for the lower i.n. bioavailability in man.

Formulation Effects on i.n. and i.h. Bioavailability of Leuprolide

Plasma Levels

The recommended daily dosage to prostatic cancer patients is 1 mg s.c. of leuprolide acetate. Analysis of variance of plasma concentration–time profiles for 1-mg dosages of this drug following i.n., i.h., and s.c. administration revealed that mean plasma leuprolide levels for the suspension aerosols were significantly higher ($P < 0.01$) than either the solution aerosol or the three i.n. formulations. Plasma $T_{1/2}$ following i.n. and i.h. administration of leuprolide acetate (average, 3.0 and 4.0 hr, respectively) were also significantly different ($P \leq 0.05$), which may account partially for the higher AUCs obtained for the 1-mg i.h. aerosol compared to the 1-mg i.n. formulations. Since the elimination rates for the three routes of administration were not different (Tables VI–VIII; $P < 0.05$), the noted AUC and plasma level differences among the formulations might be attributed in part to undefined differences at the absorption site.

Table VI. Pharmacokinetic Parameters for Leuprolide Acetate Intranasal Spray Formulations in Humans[a]

Formula dose	T_{max} (hr)	C_{max} (ng/ml)	K_{el} (hr^{-1})	$T_{1/2}$ (hr)	AUC (hr · ng/ml)	CV (%)
A (1 mg)	1.1 ± 0.4	0.72 ± 0.4	0.24 ± 0.1	2.9	3.41 ± 1.8	53
B (1 mg)	0.8 ± 0.4	0.56 ± 0.4	0.22 ± 0.1	3.2	2.32 ± 1.9	60
C (3 mg)	1.7 ± 2.6	3.42 ± 3.5	0.21 ± 0.1	3.2	13.12 ± 12.1	92

[a] AUC unadjusted for dose. Number of subjects used in the study, $n = 15$. Mean $T_{1/2}$ values (approx. 3.0 hr) were not statistically significant ($P > 0.05$) between these intranasal formulations. Mean data are reported with standard deviations.

Table VII. Pharmacokinetic Parameters for Leuprolide Acetate Aerosol Formulations[a]

Formula dose	T_{max} (hr)	C_{max} (ng/ml)	K_{el} (hr^{-1})	$T_{1/2}$ (hr)	AUC (hr · ng/ml)	CV (%)
A (1 mg)	2.3 ± 2.2	0.97 ± 0.4	0.24 ± 0.06	3.5	7.80 ± 3.9	51
B (1 mg)	1.6 ± 0.8	4.38 ± 1.7	0.20 ± 0.04	4.4	33.14 ± 10.1	30
C (2 mg)	1.1 ± 0.8	11.37 ± 16.6	0.20 ± 0.06	4.2	25.95 ± 10.4	40

[a] AUC unadjusted for dose. Mean data are reported with standard deviations. Number of subjects started in the study, $n = 24$. One subject dropped out before the end of the study. Mean $T_{1/2}$ values (approx. 3.5 hr) were not statistically significant ($P > 0.05$) between these aerosol formulations. *Note:* These data were previously reported in the work of Adjei and Garren (15).

Extent of Absorption

Bioavailability for the i.h. formulations (Table VIII) ranged from 6.6 to 28% based on s.c. and 6.2 to 26% based on i.v. administration. These results were significantly higher ($P < 0.01$) than those obtained with i.n. administration of the drug (i.e., 1.8 to 2.9%). The noted increase in i.h. bioavailability may be attributed to morphological differences of the drug via the two routes of administration, namely: (i) the nasal membrane has a lower drug permeability than the lung, where leuprolide transport into the systemic circulation should span across only a few cells (13); (ii) enzymatic deactivation and absorption barrier effects may be greater for leuprolide acetate when given by i.n. compared to the i.h. route; and (iii) physical loss of drug from the nasal turbinates into the oral cavity may be significant via the i.n. route. The aerosol formulations evaluated in this study contained the hydrophobic surfactant sorbitan trioleate as a protective colloid. Thus, the aerosolized drug particles are relatively hydrophobic because of the surfactant system, which could have provided slowed drug dissolution at the site of absorption. This process might support a prolonged drug absorption phase by i.h. compared to i.n. administration. In contrast, earlier studies showed no beneficial effect of surface active agents on nasal absorption of this drug (14).

Lung deposition of pharmaceutical aerosols is generally less than 100% of the nominal dose due to complex biophysical factors associated with filtration mechanisms of the respiratory system (15). Incomplete delivery of pharmaceutical aerosols to the lung is also due to nonabsorptive loss of drug on the mouth adapter (actuator) and on the throat as a result of inertial impaction (13,16). Particle size distribution studies by cascade impaction were used to generate the respirable fraction (RF; the amount of medication delivered to subjects based on impaction losses on actuator and throat) and mass median aerodynamic diameter (MMAD) of the i.h. formulations. Corrections of leuprolide bioavailability based on medication delivery showed no significant differences ($P < 0.05$) between the i.h. solution and suspension formulations.

Okada *et al.* (17) reported that LHRH analogues are poorly absorbed when administered orally. Maximal absorption after i.n. administration of Nafarelin was found to be 3.6% (SEM = ±1.0%, CV = 68%) compared to a s.c. control (18). Further, the delivery of Nafarelin via the vaginal and sublingual routes was poor, with essentially no detectable drug serum levels in all blood samples drawn after drug administration (18). The current study indicated lung delivery of leuprolide acetate was more effective than nasal delivery, suggesting that LHRH analogues may be systemically delivered by this route.

Table VIII. Pharmacokinetic Parameters for Formulations of Leuprolide Acetate[a]

Formula dose	T_{max} (hr)	C_{max} (ng/ml)	AUC (hr · ng/ml)	CV (%)	K_{el} (hr^{-1})	$T_{1/2}$ (hr)
1 mg s.c.	0.6 ± 0.1	32.3 ± 11.1	118.6 ± 32.3	27	0.19 ± 0.06	3.6
1 mg i.v.	—	121.3 ± 41.3	125.8 ± 32.9	26	0.24 ± 0.04	2.9

Summary of bioavailability of leuprolide acetate following nasal and inhalation delivery[b]

Formulation dose	RF · MD	Mean AUC (ng · hr/ml)	Bioavailability (%)		
			F(sc)	F(sc-md)	F(iv)
1 mg i.n. solution	—	3.41 ± 1.82	2.9	—	2.7
1 mg i.n. solution + AP	—	2.32 ± 1.39	2.0	—	1.8
1 mg i.h. solution	10	7.80 ± 3.94	6.6	66	6.2
1 mg i.h. suspension	38	33.14 ± 10.10	27.9	73	26.3
1 mg subcutaneous	—	118.6 ± 32.3	100.0	—	94.3

[a] Number of subjects used in the study, $n = 15$.

[b] RF, respirable fraction; MD, medication delivery; F(sc), bioavailability relative to s.c.; F(sc-md), bioavailability corrected for medication delivery; F(iv), bioavailability relative to i.v.; AP, α-CD + 25 m*M* EDTA.

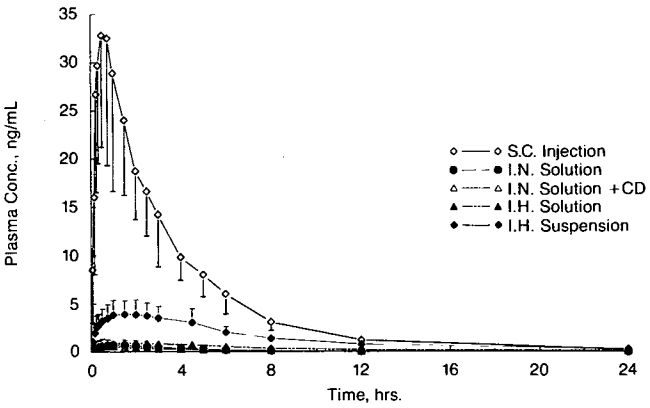

Fig. 2. Bioavailability of leuprolide in humans via various routes of administration of 1-mg bolus dosages.

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