Pharmacokinetics of triptorelin after intravenous bolus administration in healthy males and in males with renal or hepatic insufficiency

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Aims Triptorelin is a gonadotropin-releasing hormone (GnRH) analogue with enhanced affinity for GnRH receptors and a prolonged half-life due to its resistance to enzymatic degradation. The sustained-release formulation of this molecule is advantageous in conditions requiring chronic hormone suppression.

Methods This was an open study to determine the pharmacokinetics of a single i.v. bolus dose of 0.5 mg triptorelin acetate in four groups of six male subjects; namely in healthy subjects (Group I), in patients with varying degrees of renal insufficiency (Groups II and III), and in patients with hepatic insufficiency (Group IV).

Results The maximum concentrations of triptorelin were found to be similar for all four study groups (geometric mean C_{max} between 41.6 mg ml^{-1} and 53.9 mg ml^{-1}). The total clearance of triptorelin decreased with increasing renal impairment, and was even lower in patients with hepatic insufficiency (geometric mean CL_{tot}: 210 ml min^{-1}, 113 ml min^{-1}, 86.8 ml min^{-1} and 57.3 ml min^{-1} for Groups I, II, III and IV, respectively). Serum triptorelin concentrations in all four groups were adequately described by a three-compartment model. The elimination half-life for patients with hepatic impairment was similar to that of patients with renal impairment (geometric mean $t_{1/2,z}$: 6.6 h, 7.7 h and 7.6 h for Groups II, III and IV, respectively), but significantly longer than in healthy volunteers (2.8 h for Group I). The first and second distribution half-lives were similar for the four groups studied, with geometric mean distribution half-lives of about 0.1 h (6 min) and 0.75 h (45 min), respectively.

Conclusions Although both renal and hepatic function are important for the clearance of triptorelin, the liver plays the predominant role in subjects suffering from some degree of renal impairment.

Keywords: triptorelin, Decapeptyl®, GnRH, pharmacokinetics, renal insufficiency, hepatic insufficiency

Introduction

Gonadotropin-releasing hormone (GnRH), also called luteinizing hormone-releasing hormone (LHRH), selectively stimulates the gonadotroph cells to synthesize and release luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which, in turn, stimulate the gonadal production of sex steroid hormones and gametogenesis. Hypothalamic release of GnRH and its action on the pituitary are controlled by bio-feedback mechanisms based on the amount of sex steroid hormones in the circulation [1]. The chronic and continuous stimulation of LH secretion by either repeated administration of GnRH or single administration of long-acting GnRH agonists results in the 'desensitization' of gonadotropin secretion and induces biochemical castration in man [2–5]. This has provided new approaches to the use of reversible medical castration for the treatment of hormone-dependent disorders such as advanced prostate cancer in men, endometriosis in women, and precocious puberty in children.

GnRH is rapidly degraded by peptidases in several organ tissues such as the liver, kidneys, anterior pituitary, posterior pituitary, hypothalamus and brain tissue [6]. After injection, GnRH agonists progressively accumulate in the anterior pituitary and in the main inactivating organs, the liver and kidneys. In the pituitary, agonists are inactivated by *N*-terminal cleavage via pyroglutamyl-peptidase and a neutral endopeptidase. In the liver and the kidneys, agonists are degraded to biologically inactive *C*-terminal metabolites[6].

Triptorelin is a synthetic decapeptide agonist analogue of GnRH with a prolonged half-life by virtue of its resistance to enzymatic degradation [7]. The sustained-release formulation of this peptide produces a continuous release of triptorelin over 1 month which is advantageous with regard to patient compliance in conditions requiring chronic hormone suppression with a GnRH analogue. Triptorelin acetate was developed for therapeutic use as Decapeptyl®.

The pharmacokinetics of triptorelin in subjects suffering from renal or liver insufficiency are not well established. As

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one of the main indications for triptorelin administration is the treatment of prostatic carcinoma, and as such patients could develop some degree of renal or hepatic insufficiency, it is important to assess the pharmacokinetics of triptorelin in patients with impaired renal or liver functions, relative to healthy individuals. An increase in the half-life from 4.2 to 12 h for the GnRH analogue goserelin is reported in patients suffering from renal insufficiency [8, 9]. No data are available, however, on the role of the liver in determining the pharmacokinetics of GnRH.

The present study compares the pharmacokinetics of the GnRH analogue triptorelin, administered as a single intravenous bolus dose of 0.5 mg triptorelin acetate in healthy male subjects and patients with varying degrees of renal or hepatic insufficiency.

Methods

Subjects

Twenty-four male subjects ($n=6$ per group) who gave written informed consent entered the study. The criteria for allocation to a specific group were as follows:

Group I: Healthy subjects with a creatinine clearance of 100 ml min^{-1} or higher and normal liver function.

Group II: Patients with mild to moderate renal insufficiency (creatinine clearance of 20–60 ml min^{-1}), and normal liver function.

Group III: Patients with severe renal insufficiency (creatinine clearance of less than 20 ml min^{-1}), and normal liver function.

Group IV: Patients with impaired liver function (Child A or Child B) [10] and normal renal function (creatinine clearance 80 ml min^{-1} or higher).

The inclusion criteria made provision for the inclusion of patients on dialysis. The study was approved by the Ethics Committees for Medical Research of the University of the Orange Free State and the University of Cape Town, and was conducted in accordance with Good Clinical Practice guidelines [11].

Study drug

Decapeptyl® 0.5 mg (manufactured by Ferring Arzneimittel GmbH, Kiel, Germany) was supplied in pre-filled syringes containing 0.5 mg of triptorelin acetate. Each pre-filled syringe contained 0.5 mg triptorelin acetate, 9 mg sodium chloride, acetic acid at pH 4–5 and 1 ml water for injection. The study drug was protected from light and stored at a temperature below 8° C but not frozen.

Study design and procedure

This was an open, single-dose, non-randomized study in four groups of six male subjects. Due to logistical constraints, the clinical trial for Group IV was conducted after completion of the Group I, II and III trials. No significance was attached to this difference in completion dates since the protocol procedure, as described in the sections below, was identical for all four groups.

The study consisted of one pharmacokinetic profile period of 24 h. Subjects had breakfast at 06.00 h after an overnight fast of 10 h. The study drug was administered between 07.00 h and 07.30 h. Subjects received 0.5 mg triptorelin acetate as an i.v. bolus injection after a pre-dose blood sample had been taken. Meals were served at 5, 10 and 24 h after drug administration and a snack at 13 h after drug administration. Subjects received 200 ml tap water at 2 and 4 h after drug administration, 200 ml orange juice with each meal and 200 ml of a caffeine-free warm beverage at 8 and 13 h after drug administration. Subjects were allowed to leave the clinic 24 h after drug administration.

Safety assessments

Pre-study examinations and investigations included a medical history, physical examination, demographic data, vital signs, haematology, clinical chemistry and urinalysis. The post-study safety evaluation consisted of haematological and clinical chemistry analyses.

Sample collection protocol

Blood Venous blood samples of 5 ml each were collected into glass tubes according to the following time schedule: 5, 10, 15, 30 min, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 h after drug administration. Blood samples were allowed to clot for 30 to 60 min at 10° C and centrifuged immediately afterwards. Blood samples were centrifuged at 950 to 1240 *g* for 10 min. Two aliquots of serum (1 ml per aliquot) were stored at −80° C until triptorelin was assayed.

Urine Subjects were instructed to empty their bladders before drug administration. Urine collections were made during the following intervals after drug administration: 0–4, 4–8, 8–12 and 12–24 h after drug administration. Urine volumes were recorded and samples stored at −80° C until triptorelin was assayed.

Drug assay

Blood A heterogeneous, liquid phase, competitive double antibody radioimmunoassay was used to determine D-Trp^6-GnRH levels in unextracted human serum samples. Samples were incubated with the primary antibody (rabbit D-Trp^6-GnRH antiserum) and tracer molecule (radioiodinated D-Trp^6-GnRH; lot nos. 1168, 1186b 1199, 2016, 2029, 2040 and 2050) at 6–8° C for 20 h. This was followed by a second incubation with a secondary antibody [goat anti rabbit gamma globulins and normal reference serum (NRS)] at 6–8° C for 4 h, followed by separation by means of centrifugation for 15 min at 4–6° C. Accuracy of recovery of the D-Trp^6-GnRH, added at four different concentrations was 85 to 117%. Intra-assay precision ranged from 4.2 to 9.7%, with inter-assay precision ranging between 2.4 and 6.8%. The limit of quantification was <15.2 pg/tube or 0.76 ng ml^{-1} if 20 μl are analysed.

Urine The methods employed to quantify D-Trp^6-GnRH levels in urine samples were the same as those described for quantification of serum D-Trp^6-GnRH levels. Accuracy of

recovery of the D-Trp^6-GnRH, added at five different concentrations was 90–130%. Intra-assay precision ranged from 9.0 to 11.8%, with inter-assay precision ranging between 7.12 and 10.2%. The limit of quantification was <5.2 pg/tube or 0.26 ng ml^{-1} if 20 μl are analysed.

Pharmacokinetic variables

The serum pharmacokinetics of triptorelin were assessed by calculating the following variables:

— maximum concentration (C_{max})
— first distribution half-life ($t_{1/2,\,x}$)
— second distribution half-life ($t_{1/2,\,y}$)
— apparent elimination half-life ($t_{1/2,\,z}$)
— area under the serum concentration *vs* time curve [AUC(0, t_{last})]
— area under the serum concentration *vs* time curve, with extrapolation to infinity [AUC(0, ∞)]
— mean residence time (MRT)
— total clearance (CL_{tot})
— volume of distribution (V_{ss}).

The total clearance (CL_{tot}) and volume of distribution (V_{ss}) were normalized for body mass.

Urine triptorelin concentrations and urine volumes were used to calculate the following variables for each subject:

— total cumulated amount of excreted triptorelin after 4 [Ae_{ur}(0–4 h)], 8 [Ae_{ur}(0–8 h)], 12 [Ae_{ur}(0–12 h)] and 24 h [Ae_{ur}(0–24 h)]
— renal clearance over 24 h (CL_{renal}). The renal clearance for the total collection interval (0–24 h) was calculated as Ae_{ur}(0–24 h)/AUC, where Ae_{ur} is the cumulative urinary excretion and AUC is the area under the curve from 0 h to infinity.

The first and second distribution half-lives, and the elimination half-life were calculated from the adjustment of a triple exponential function to the serum concentration *vs* time profile. Regressions were obtained using the method of weighted non-linear least squares, weighting being inversely proportional to the measured concentration. Non-linear regression analyses to determine the terminal half-lives were performed using HOEREP-PC (Version 1.05.00) (Brockmeier and Lückel, 1991) [12]. Standard non-compartmental methods were used to determine the other pharmacokinetic variables.

Statistical analyses

The three groups of patients with renal or hepatic insufficiencies were compared to Group I (healthy subjects) with respect to the pharmacokinetic variables using an analysis of variance (ANOVA) with group effect after a logarithmic transformation of the data. Point estimates and 90% confidence intervals (CI) for the inter-group mean ratios of the pharmacokinetic variables were calculated [13]. A linear regression analysis between triptorelin clearance and creatinine clearance was performed in the following way: First, two different regression lines were fitted for the data of Groups I, II and III and for Group IV. The two regression lines were then restricted to have a common slope. Finally, the intercept for the regression line for Group IV was forced through the origin.

Results

Demographic data

Twenty-four volunteers in four groups of six individuals were enrolled. The demographic characteristics of the study population are summarized in Table 1. The creatinine clearance of Subject 8 (60.9 ml min^{-1}) was deemed to be acceptable for inclusion in Group II and he was entered into the study at the investigator's discretion. The age distribution of the study population suggests an increase in renal impairment with age. There were no significant differences between the study groups with respect to weight or height. None of the subjects withdrew or was withdrawn from the study.

Serum pharmacokinetics

The serum pharmacokinetic variables for triptorelin are tabulated in Table 2. Table 3 summarizes the point estimates and 90% confidence intervals for the between group mean ratios of the pharmacokinetic variables C_{max}, $t_{1/2,\,x}$, $t_{1/2,\,y}$, $t_{1/2,\,z}$, AUC(0, t_{last}) and AUC(0, ∞). The geometric mean serum concentrations of triptorelin in the four study groups are shown in Figure 1.

Urine pharmacokinetics

Subject 14 was on dialysis and produced no urine. The analysis of urine pharmacokinetic data was therefore limited to the analysis of five subjects for Group III. The urine pharmacokinetic variables are tabulated in Table 4. The inter-group mean ratios and 90% confidence intervals for total cumulated amount of excreted triptorelin over 24 h was 44% (90% CI: 29%—67%), 13% (90% CI: 9%—21%) and 156% (90% CI: 119%—204%) for Groups II *vs* I, III *vs* I and IV *vs* I, respectively. The inter-group mean ratios and 90% confidence intervals for renal clearance over 24 h was 24% (90% CI: 14%–40%), 6% (90% CI: 3%–10%) and 43% (90% CI: 30%–62%) for Groups II *vs* I, III *vs* I and IV *vs* I, respectively. Figure 2 depicts the cumulative urinary triptorelin excretion over time. Figure 3 shows the regression lines of triptorelin clearance against creatinine clearance for Groups I, II and III (combined) and Group IV.

Discussion

Serum triptorelin concentrations for all four groups of subjects are adequately described by a three-compartment model after single i.v. injection of 0.5 mg triptorelin acetate. The maximum concentrations of triptorelin were similar for all four groups. The concentrations follow a triphasic decline, with the first and second distribution half-lives being similar for the four groups studied [the geometric mean distribution half-lives are about 0.1 h (6 min) and 0.75 h (45 min)]. The elimination half-life in patients with liver impairment is similar to that observed in patients with renal impairment (geometric mean half-life of 6.6 h for

Table 1 Demographic characteristics of the study population. Data are represented as arithmetic mean, s.d. and range.

Variable	*Group I*	*Group II*	*Group III*	*Group IV*
Age (years)	20.5	34.7	42.2	51.5
	0.8	10.7	4.8	13.0
	20–22	23–46	34–49	26–63
Mass (kg)	78.7	80.3	69.7	72.7
	7.0	19.1	8.7	16.4
	71.2–88.5	54.5–104	59.5–82.3	53–93
Height (cm)	183.8	177.3	175.8	175.2
	2.5	14.0	8.7	9.3
	181–188	165–201	166–186	165–189
Creatinine clearance at inclusion (ml min^{-1})	165.8	34.5	8.1	94.6
	31.1	16.4	6.4	12.9
	123.7–202.4	20.0–60.9	$0^{\#}$–19.4	82.5–115.3

#: Dialysis patient.

Table 2 Serum pharmacokinetic data for triptorelin after i.v. injection of 0.5 mg triptorelin acetate. Data are represented as geometric mean, geometric s.d. and range.

Variable	*Group I*	*Group II*	*Group III*	*Group IV*
C_{max} (ng ml^{-1})	46.6	41.6	44.3	53.9
	1.35	1.61	1.44	1.10
	26.2–60.1	20.8–76.7	22.5–64.9	47.1–61.8
AUC(0, t_{last}) (ng ml^{-1} h)	35.6	62.8	78.2	117
	1.17	1.43	1.21	1.13
	30.1–45.6	38.9–93.4	56.3–99.3	99.1–134
AUC(0, ∞) (ng ml^{-1} h)	35.6	66.2	86.4	131
	1.17	1.45	1.24	1.15
	30.4–45.5	41.4–103.0	61.2–116	109–156
$t_{1/2,\,z}$ (h)	2.81	6.56	7.65	7.58
	1.21	1.25	1.25	1.17
	2.25–3.69	5.23–9.13	5.92–10.3	6.00–9.14
$t_{1/2,\,y}$ (h)	0.62	0.82	0.79	0.56
	1.51	1.44	1.36	1.96
	0.39–1.16	0.44–1.12	0.58–1.33	0.16–1.08
$t_{1/2,\,x}$ (h)	0.11	0.07	0.10	0.06
	1.87	1.96	1.36	1.88
	0.07–0.37	0.03–0.20	0.05–0.14	0.02–0.12
CL_{tot} (ml min^{-1})	210	113	86.8	57.3
	1.17	1.45	1.24	1.15
	165–247	72.7–181.0	64.8–123.0	48.2–69.1
MRT (h)	2.48	6.65	9.04	10.1
	1.23	1.20	1.15	1.17
	1.72–3.05	5.10–8.90	7.8–11.6	7.82–12.10
V_{ss} (l)	31.2	45.2	47.1	34.7
	1.16	1.28	1.17	1.17
	25.5–39.8	34.9–70.1	40.8–63.9	25.8–39.7
$CL^{\#}_{tot}$ (ml min^{-1} kg^{-1})	2.67	1.45	1.25	0.81
	1.22	1.25	1.32	1.17
	2.03–3.47	1.05–1.89	0.91–1.98	0.69–1.04
$V^{\#}_{ss}$ (l kg^{-1})	0.40	0.58	0.68	0.49
	1.14	1.18	1.26	1.14
	0.35–0.47	0.47–0.73	0.53–1.03	0.41–0.61

#: Normalized for body mass.

Group II, 7.7 h for Group III and 7.6 h for Group IV), but significantly longer than that observed in healthy subjects (geometric mean half-life of 2.8 h for Group I).

There is an apparent correlation between total clearance of triptorelin and creatinine clearance as assessed by linear regression. The following regression model fits the data

Table 3 Inter-group mean ratios and 90% confidence intervals for selected serum pharmacokinetic variables.

	Group II vs *Group I*		*Group III* vs *Group I*		*Group IV* vs *Group I*	
Variable	*Mean ratio (%)*⋆	*90% C.I. (%)*⋆⋆	*Mean ratio (%)*⋆	*90% C.I. (%)*⋆⋆	*Mean ratio (%)*⋆	*90% C.I. (%)*⋆⋆
C_{max} (ng ml^{-1})	89	60–132	95	64–140	116	92–146
AUC(0, t_{last}) (ng ml^{-1} h)	176	137–227	220	170–283	328	283–381
AUC(0, ∞) (ng ml^{-1} h)	185	142–242	242	185–315	366	314–427
$t_{1/2,\,z}$ (h)	234	189–289	273	220–337	270	226–323
$t_{1/2,\,y}$ (h)	132	91–190	127	88–184	90	50–161
$t_{1/2,\,x}$ (h)	64	36–113	89	50–157	53	27–102

⋆: Estimate of 'test/reference' mean ratio from analysis of variance of log-transformed data. ⋆⋆: 90% Conventional confidence interval for the 'test/reference' mean ratio analysis of variance of log-transformed data.

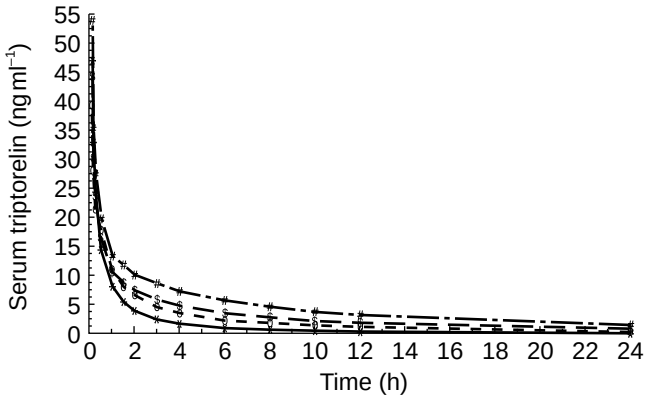

Figure 1 Geometric mean serum triptorelin concentrations in Groups I (—⋆—), II (—○--), III (—$—) and IV (−·−#−·−).

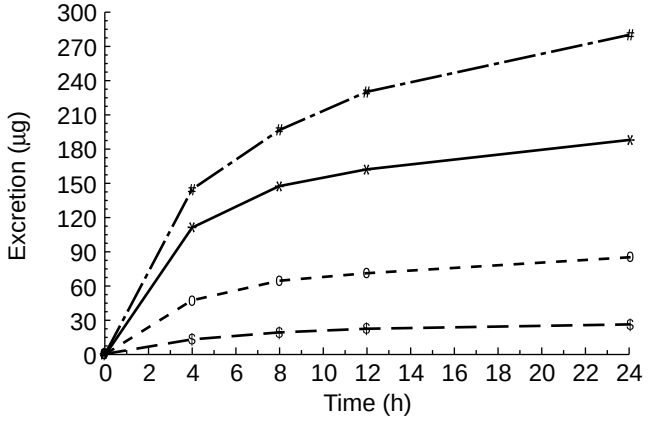

Figure 2 Cumulative urinary triptorelin excretion in Groups I (—⋆—), II (--○--), III (—$—) and IV (−·−#−·−).

Table 4 Summary of urine pharmacokinetic data for triptorelin after i.v. injection of 0.5 mg triptorelin acetate. Data are represented as geometric mean, geometric s.d. and range.

Variable	*Group I (n = 6)*	*Group II (n = 6)*	*Group III (n = 5)*⋆	*Group IV (n = 6)*
Ae_{ur}(0–4 h) (µg)	85.8	44.0	11.7	144
	2.63	1.51	1.79	1.12
	13.8–173.0	30.4–87.9	5.82–25.6	124–173
Ae_{ur}(0–8 h) (µg)	132	60.1	17.0	197
	1.77	1.51	1.74	1.08
	46.5–208.0	38–115	9.68–33.3	182–219
Ae_{ur}(0–12 h) (µg)	151	65.2	20.2	229
	1.55	153	1.67	1.12
	69.6–228	38–125	12.0–37.6	193–256
Ae_{ur}(0–24 h) (µg)	179	78.4	23.8	280
	1.43	1.54	1.6	1.08
	92.6–244	45.6–145	14.5–40.1	252–303
Ae_{ur}(0–24 h)$^{\#\,(\%)}$	39.8	17.4	5.29	62.1
	1.43	1.54	1.6	1.08
	20.6–54.2	10.1–32.2	3.22–8.92	56.1–67.2
CL_{renal}(0–24 h) (ml min^{-1})	83.5	19.8	4.72	35.6
	1.61	1.78	1.58	1.15
	38.2–130	12.5–58.4	2.79–7.86	29.2–41.6
CL_{creat}(0–24 h)$^{\#\#\,(ml\,min^{-1})}$	150	35.5	9.8	88.9
	1.05	1.65	1.6	1.18
	137–157	21.1–81.5	6.0–16.4	72–117

⋆: Excluding subject 14. #: Normalized for body mass. ##: Creatinine clearance on profile day.

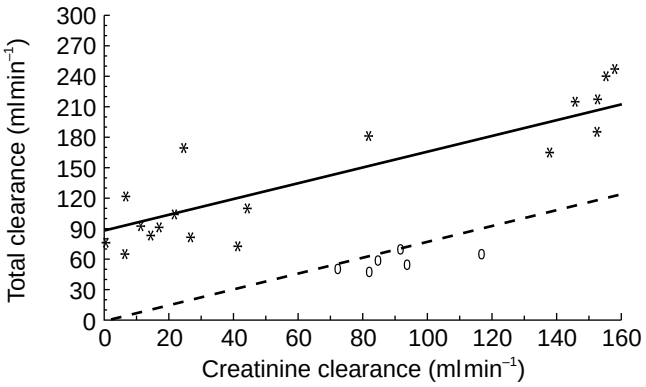

Figure 3 Regression lines of total triptorelin clearance *vs* creatinine clearance for Groups I, II and III combined (—⋆—) and Group IV (---○---). The two regression lines are y = 88.82 + 0.776x and y = 0.776x, respectively, where y is the total triptorelin clearance (ml min^{-1}) and x is the creatinine clearance (ml min^{-1}).

reasonably well: a linear regression between total clearance and creatinine clearance for the subjects in Groups I, II and III, and a parallel line through the origin for the patients in Group IV [Hypothesis of parallel regression lines for Groups I, II, III *vs* Group IV: $t = -0.70$; $P = 0.49$: Hypothesis of zero intercept for Group IV: $t = -1.50$; $P = 0.15$ (Figure 3)]. The total clearance of triptorelin decreased with increasing renal impairment, and was even lower in patients with hepatic insufficiency with geometric mean CL_{tot} of 210 ml min^{-1}, 113 ml min^{-1}, 86.8 ml min^{-1} and 57.3 ml min^{-1} for Groups I, II, III and IV, respectively (Table 2). The total clearance (non-renal clearance) of triptorelin in the anuric patient (patient on dialysis) was 76.2 ml min^{-1}, while for patients with liver impairment and a creatinine clearance of about 80 ml min^{-1}, the total triptorelin clearance was about 60 ml min^{-1} (Figure 3).

Urinary excretion of unchanged triptorelin was about 40% of the dose on average for healthy subjects, but decreased to an average of about 17% of the dose for Group II and to about 5% of the dose for Group III. For patients suffering from hepatic insufficiency (Group IV) the average urinary excretion of triptorelin was 62% of the dose.

A recent study on the pharmacokinetics of triptorelin in 19 female patients suffering from endometriosis or uterine myomas also found that the pharmacokinetics of triptorelin were well described by a three-compartment model with mean distribution and elimination half-lives of 3.2 min, 46.1 min and 5.1 h. The mean total clearance was 107 ml min^{-1}, and on average 16.7% of the dose was excreted unchanged in the urine [14]. These results correspond closely with results for Group II patients from the present study.

These results suggest that the dose of triptorelin may be halved in patients with liver or renal impairment as their triptorelin clearance is about half or less on average compared to that of healthy volunteers. It should be noted, however, that the group of healthy subjects included in this study presents a high creatinine clearance (149.9 ml min^{-1}) which is twice as high as the one generally observed in the target population of old patients suffering from prostate cancer in whom an effective and safe dose regimen of triptorelin has been determined. Also, the prolonged terminal half-lives observed in both populations have no real practical consequence, since the drug is administered as a slow release formulation whose release rate is much slower than the elimination rate of the drug. In view of these findings and of the large safety margin of triptorelin, no dose reduction is recommended in patients with liver disease or renal insufficiency.

In conclusion, the data from the present study suggest that the non-renal clearance of triptorelin (about 80 ml min^{-1}) is largely hepatic. Thus, whilst renal and hepatic function are both important for the clearance of triptorelin, the liver plays the predominant role in subjects with some degree of renal impairment.

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