Pharmacodynamics and Relative Bioavailability of Cabergoline Tablets vs Solution in Healthy Volunteers

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Abstract □ The effect of formulation on the urinary pharmacokinetics, pharmacodynamics, and relative bioavailability of cabergoline was investigated. Twelve healthy female volunteers, aged 23–35 years, were treated, according to an open, randomized, crossover design, with cabergoline (1-mg single oral dose) both as tablets and as a solution. The two administrations were separated by a 4-week wash-out period. Cabergoline and prolactin were measured in urine and plasma, respectively, by specific radioimmunoassays. Blood samples were collected before and up to 30 days after dosing. Urine was collected before and up to 8 days after dosing. Cabergoline elimination half-lives calculated from urinary data were 68 and 63 h after administration of the tablets and the solution, respectively. Urinary excretion of unchanged cabergoline accounted, on average, for 1.92% (range, 0.14–3.26) and 1.80% (range, 0.67–3.09) of the dose after administration of the tablets and the aqueous solution, respectively. Relative bioavailability of tablets vs solution was 99% (geometric mean with the 90% confidence intervals of 68–144%). Prolactin levels in 10 out of 12 subjects fell below the detection limit of the assay (1.5 μg/L) after both treatments. The mean maximum prolactin decrease (ca. 70%) was achieved by 2 or 3 h after dosing; the effect persisted up to 9 days, being completely exhausted 23–28 days after dosing. The analysis of variance performed on the pharmacodynamic effects of the two cabergoline formulations indicated that the percent decreases of plasma prolactin levels were not significantly different for tablets and solution. These results indicate that the pharmacodynamics and relative bioavailability of cabergoline are not influenced by formulation, as tablets or solution.

Introduction

Cabergoline (Figure 1), *N*-[3-(dimethylamino)propyl]-*N*-[(ethylamino)carbonyl]-6-(2-propenyl)ergoline-8β-carboxamide (FCE 21336) is a synthetic ergoline derivative with dopamine-agonist activity.[1] A major characteristic of cabergoline is the long duration of the prolactin-lowering effect upon oral administration. Previous studies have shown that this compound is well tolerated and highly effective in suppressing prolactin levels in healthy volunteers.[2] puerperal women,[3,4] and hyperprolactinemic patients[5,6] with a duration of action of up to 21 days after a single dose of 0.3–1 mg. Clinical experience indicates that cabergoline is highly effective in preventing puerperal lactation when administered as a single 1-mg dose[3,4] and in the treatment of hyperprolactinemia when administered once or twice weekly at doses ranging from 0.5 to 2 mg/week.[7–9]

Preliminary pharmacokinetic data were obtained in healthy volunteers after administration of a single dose of 0.6 mg of labeled cabergoline. Within 24 h after administration, the radioactivity was excreted mainly by the fecal route (about 76% of the dose), with biotransformation of the drug into several metabolites in urine.[10] In another preliminary study, using an HPLC method for the determination of cabergoline, the urinary elimination half-life in hyperprolactinemic patients treated with 0.5, 0.75, or 1 mg of cabergoline was found to be in the range 79–115 h (unpublished results). The great variability of the rates for each subject suggested the need for further investigation to confirm these results. The aim of the present study was to evaluate the relative bioavailability of a single 1-mg oral dose of cabergoline administered as tablets in comparison to solution and provide further information on the urinary elimination half-life. A radioimmunoassay for the determination of cabergoline was developed. The sensitivity of this assay made it suitable for the evaluation of cabergoline pharmacokinetics in urine but not in plasma. Therefore, we evaluated the relative bioavailability of cabergoline tablets vs solution from urinary data even though cabergoline urinary elimination accounts for only 3% of the administered dose.[10] Cabergoline pharmacodynamics were also evaluated for further assessment of the relative bioavailability of the two formulations tested.

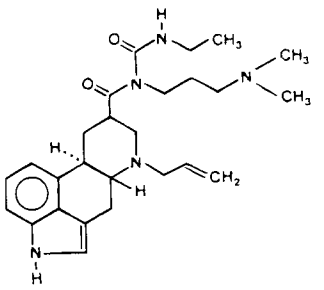

Figure 1—Structural formula of cabergoline (FCE 21336).

Experimental Section

Subjects and Study Design—This was an open, randomized, crossover study, balanced for sequence of administration. Twelve healthy female volunteers participated in the study, which was carried out at the Centre de Médecine Nucléaire, Hôpital Neuro-Cardiologique Lyon, France. The volunteers' demographic data are listed in Table 1. The study was approved by the institutional Ethics Committee (Université Claude Bernard et Hospices Civils de Lyon), and written informed consent was obtained from each volunteer. Subjects were judged to be in good health on the basis of medical history, physical examination, ECG, and routine laboratory data. Volunteers received cabergoline (1-mg single oral dose) both as tablets and solution, according to the sequence of a randomization list. All subjects received the first treatment on the same day and the second treatment after a 4-week wash-out period. The volunteers took cabergoline in the morning, under fasting conditions, according to the following scheme: (A) For tablets, two 0.5-mg cabergoline tablets were swallowed with about 150 mL of tap water. (B) For solution (obtained by reconstitution, with 5 mL of tap water, of a powder obtained by lyophilization of a solution with the following composition: cabergoline base (1 mg) and polyvinylpyrrolidone (20 mg) brought to pH 3 with phosphoric acid), the powder was reconstituted directly in a vial and

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Table 1—Mean Demographic Data ± SD of the 12 Volunteers Participating in the Study

Age (years)	Weight (kg)	Height (cm)
29.3 ± 4.8	56.4 ± 4.7	163.7 ± 7.4

immediately consumed. The empty vial was rinsed with an additional 5 mL of tap water and this solution was also consumed. Then a glass of water (about 150 mL) was drunk by each volunteer.

The volunteers were kept in the hospital during the 12 h following administration to evaluate adverse events and to monitor cardiovascular parameters.

Plasma prolactin levels were monitored immediately before each treatment (time 0), after treatment at 1, 2, 3, 5, 6, 12, 24, 48, 72, 96, 120, 144, 168, 192, and 216 h, and then at weekly intervals for 4 weeks after the first treatment and 5 weeks after the second. Blood samples were collected in heparinized tubes and immediately centrifuged at 1200*g*; the plasma was separated and stored at −20 °C until analysis.

Urine was also collected from each volunteer over the intervals 0–4, 4–8, 8–12, and 12–24 h and then every 24 h up to 192 h after dosing. At the end of each collection interval, urine volume was measured and recorded, and 50-mL fractions were immediately frozen and kept at −20 °C until the cabergoline assay was performed.

Analysis of Plasma and Urine Samples—Prolactin determination in plasma was performed by radioimmunoassay[11] with a limit of quantitation of 1.5 μg/L and with intra- and inter-assay coefficients of variation (measured at a concentration of 15 μg/L) of 6% and 10%, respectively. Cabergoline concentrations in urine samples were measured using a radioimmunoassay[12] with a limit of quantitation of 150 pg/mL and with intra- and inter-assay coefficients of variation (measured at a concentration of 1.5 ng/mL) of 4% and 8.1%, respectively.

Pharmacokinetic Analysis—For each urinary collection interval, the average excretion rate (nanograms per hour) was calculated and the data plotted against the midpoint of the collection interval on a semilogarithmic scale. Cabergoline elimination half-life ($t_{1/2}$) was estimated by least-squares fitting of data judged to be on the terminal linear part of the curve. The analysis was carried out with the aid of the SIPHAR software package (Simed Créteil, France). Relative bioavailability ($F_{T/S}$) of cabergoline tablets (T) vs the solution (S) was estimated from the total amount of unchanged cabergoline excreted in urine (Ae) as the ratio $F_{T/S} = Ae_T/Ae_S$. A 90% confidence interval for the geometric mean relative bioavailability was calculated by applying a *t*-distribution to the difference of log Ae values, with $p < 0.05$ cutoffs from each tail. The standard error for this difference was obtained as $(2MSE/n)^{1/2}$, where MSE is the mean square error of an analysis of variance (ANOVA) for a two-way crossover design, with sequence, subject nested in sequence, period, and treatment as factors; $n = 12$ subjects. ANOVA was carried out using SAS release 6.04 (SAS Inst., Cary, IL) and confidence limits were calculated explicitly on a Lotus 1-2-3 worksheet (Lotus Co., Cambridge, MA).

Pharmacodynamics—The plasma concentrations of prolactin at each time were transformed to a percent decrease from baseline (0 h) to improve the precision of the treatment comparison. The percent decrease at 1 h was subjected to ANOVA as described above for Ae (but without log transformation) and used as a measure of the rate of onset of the pharmacodynamic effect. A 90% confidence interval for the difference between treatment effects (tablet−solution) is also presented for 1-h levels. ANOVA was not performed for subsequent sampling times since the concentration in many samples was below the quantitation limit of the assay. For calculation of means, concentrations below this limit were set at 1.5 μg/L, giving a conservative estimate of decrease from baseline.

Results and Discussion

The collection of urine samples was cumulative and complete after administration of both the tablets and solution. In Figure 2 the mean cabergoline urinary excretion rates vs time are reported for the 12 volunteers after administration of the tablet and solution dosage forms. The individual and mean data of urinary cumulative excretion, also expressed as percentage of the administered dose, and the elimination half-life of cabergoline administered as tablets and aqueous solution are reported in Table 2. The same table shows the individual relative bioavailability data, with the geometric mean and corresponding 90% confidence intervals. After administration of 1 mg of cabergoline as tablets, the cumulative urinary excretion of unchanged drug was on average 1.92% of the dose (range, 0.14–3.26); after the same dose as an aqueous solution, mean cumulative urinary excretion was 1.80% (range, 0.67–3.02). The mean elimination half-life of cabergoline was 68 and 63 h after administration of the tablets and the solution, respectively (Table 2). In one subject (no. 1) the $t_{1/2}$ was not evaluable, as cabergoline urinary concentrations after both treatments were often below the quantitation limit of the radioimmunoassay. The results of relative bioavailability evaluation indicated that, on average, the extent of cabergoline absorption after administration of the tablets and the solution was comparable (geometric mean relative bioavailability $F_{T/S}$ equal to 99% with 90% confidence interval; range, 68–144%). As indicated in Table 3, no significant differential carry-over effect (sequence) or effect of administration period (sequence × treatment interaction) was detected.

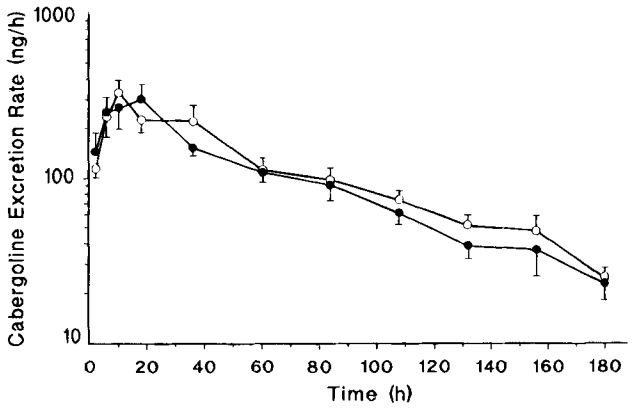

Figure 2—Mean excretion rates (nanograms per hour) of cabergoline in the 12 volunteers participating in the study after administration of a single dose of 1 mg of the drug as tablets (○) or solution (●); standard error of the mean is shown by vertical bars.

Table 2—Individual and Mean Values of Urinary Excretion, Elimination Half-Life, and Relative Bioavailability of Free Cabergoline, ($F_{T/S}$) Grouped by Treatment (T, Tablets; S, Solution)[a]

	Amount Excreted (ng)		% Dose		$t_{1/2}$ (h)		
Subject	T	S	T	S	T	S	$F_{T/S}$
1	1 427	6 694	0.14	0.67	ne	ne	0.21
2	13 951	30 360	1.40	3.04	62.57	42.53	0.46
3	23 396	16 945	2.34	1.69	60.43	62.36	1.38
4	22 487	13 896	2.25	1.39	26.07	160.82	1.62
5	12 106	28 603	1.21	2.86	47.05	41.63	0.42
6	32 354	30 868	3.24	3.09	62.53	58.11	1.05
7	18 253	11 641	1.83	1.16	57.15	52.07	1.58
8	32 560	13 875	3.26	1.39	61.77	42.35	2.35
9	18 012	24 032	1.80	2.40	97.86	68.39	0.75
10	15 722	10 985	1.57	1.10	147.45	52.84	1.43
11	22 003	19 764	2.20	1.98	79.81	49.56	1.11
12	18 530	8 573	1.85	0.86	51.31	63.78	2.15
Mean	19 233	18 020	1.92	1.80	68.54	63.13	1.21 0.99[b]
SD	8 509	8 590	0.85	0.86	31.76	33.66	0.67

[a] ne = not evaluable. [b] Geometric mean: the corresponding 90% confidence interval of relative bioavailability ($F_{T/S}$) is 0.68–1.44.

Table 3—Significance (p Value) for Sources of Variations in Cabergoline Urinary Excretion and Prolactin Plasma Decrease (ANOVA Results)

Source of Variation	Cabergoline Amount Excreted (Ae)	% Decrease in Plasma Prolactin Levels at 1 h
Sequence	0.13	0.51
Subject (sequence)	0.08	0.30
Period	0.28	0.0003[b]
Treatment	0.97	0.36[a]

[a] 90% confidence interval for tablet–solution treatment difference: −5 to 15% of baseline. [b] Statistically significant.

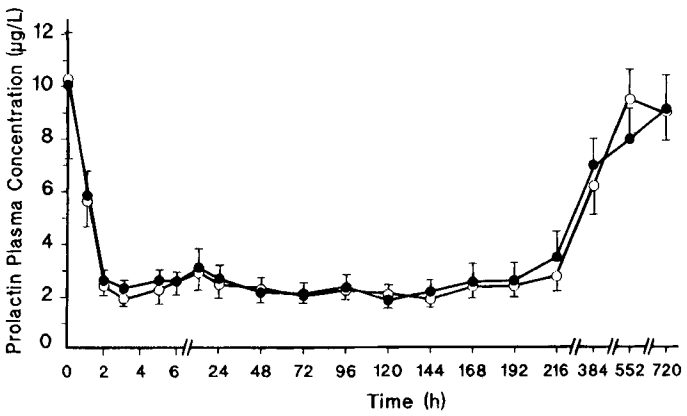

Figure 3—Mean plasma prolactin concentration (nanograms per milliliter) in the 12 volunteers participating in the study (n = 6 for the 720-h time point) after administration of a single dose of 1 mg of the drug as tablets (○) or solution (●); standard error of the mean is shown by vertical bars.

Figure 3 shows the mean prolactin plasma concentrations at each time point after treatment with tablets and solution. No evident difference in the pharmacodynamic effect of the two cabergoline formulations was observed. Plasma prolactin levels showed a mean decrease of about 40% 1 h after drug intake (43% for tablets, 38% for solution), the nadir (mean percent decrease of the order of 70%) being achieved by 2 or 3 h. Plasma prolactin levels remained constantly low up to 9 days after drug administration. The mean percent decrease averaged over 2–192 h was 75% for tablets and 72% for the solution. Prolactin levels below the limit of quantitation occurred comparably in the two treatment groups. In subjects 1, 2, 4–6, and 8–11 (i.e. 10/12), some of the prolactin plasma levels were below the limit of quantitation in both treatment periods; in the remaining subjects the prolactin levels remained detectable for the whole time-course in both treatment periods. Starting from day 16 a clear increase in plasma prolactin levels was observed with a return to pretreatment values between days 23 and 27 (Figure 3).

ANOVA on 1-h prolactin data confirmed that the difference between treatments was not significant (Table 3): the 90% confidence interval for this difference (tablet–solution) was calculated to be −5 to 15% of baseline. No differential carryover was detected. However, the effect of period was significant: in the first period a 26% depression (averaged over both treatments) was found versus 55% in period 2. This finding might be due to the fact that the absolute baseline prolactin levels of the second treatment were lower than those of the first (9.1 vs 11.2 µg/L, respectively) and this can influence the percentage decrease observed. In fact, when the first hour is excluded from analysis, this significant period effect is no longer present, and the results shows comparable prolactin values between the two formulations up to 192 h (data not shown).

In this study a single 1-mg oral dose of cabergoline significantly decreased plasma prolactin levels for up to 9 days (Figure 3).

These results confirmed the potent and long-lasting prolactin-lowering activity of cabergoline already demonstrated in previous clinical trials.[1]

After administration of cabergoline as tablets and as aqueous solution, similar percentages of administered dose were excreted in urine (1.92% and 1.80%, respectively) whereas the mean elimination half-life was quite long, being approximately 68 and 63 h, on average, after administration of tablets and solution, respectively. The low percentages of administered dose recovered in the urine are in agreement with the results of previous studies in which it was found that cabergoline undergoes extensive metabolic degradation and is mainly eliminated by the fecal route, whereas urinary excretion is a minor route of elimination.[10] The study protocol required the collection of urine samples up to 8 days after dosing. Since cabergoline urinary elimination half-life is about 2.5 days, approximately 88% of the amount of unchanged drug excreted in urine up to infinite time is eliminated within 8 days. Therefore, even though cabergoline was still detectable in the urine samples collected 8 days after dosing (indicating that the urinary elimination of the drug was not complete), the majority of the unchanged cabergoline can be considered to have been eliminated by that time. In addition, it has to be taken into consideration that the collection of further samples of urine would have given rise to compliance problems.

The stability of cabergoline in urine samples stored under more drastic conditions than those encountered in the present study was investigated. The drug proved stable in urine when stored at room temperature or at 4 °C for 24 h and up to 1 year when stored at −20 °C (data not shown). These results indicated that no errors in the measurements of urinary cabergoline concentrations should have occurred during the study due to drug instability.

The present study showed that the extent of absorption, assessed from urinary data, was comparable for the two formulations. The pharmacodynamic results obtained in the study provide further evidence that the two formulations are equivalent. In other studies the bioavailability of another dopamine agonist, bromocriptine, as tablets or solution was evaluated by comparison of the area under the plasma concentrations/time curves obtained with the two formulations.[13] It was found that, even though the bioavailability of the two formulations was identical, the rate of absorption of the drug administered as tablets was lower than that of the solution. The authors indicated that this finding was due to the fact that administration of the tablets with a meal resulted in delayed peak levels compared to the solution, which was administered under fasting conditions. In the present study both formulations were administered under fasting conditions and the absorption rate, reflected by the onset of the plasma prolactin lowering effect, was identical for the two formulations (Figure 2). Other studies have failed to show any effect of food on the pharmacokinetics and pharmacodynamics of cabergoline tablets (S. Persiani, et al., unpublished results).

In conclusion, when cabergoline is administered as tablets or solution, its efficacy is not influenced by the formulation.

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