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Optimization of contraceptive dosage regimen of Centchroman☆

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Abstract

Centchroman (Ormeloxifene), a non-steroidal oral contraceptive, is used at a dose of 30 mg once a week. To prevent failures in the beginning of the therapy, it is recommended that a dose of 30 mg twice a week for 12 weeks be administered to build up adequate blood levels. The present study was undertaken to simplify the dosing schedule without sacrificing the purpose of twice a week dosing regimen, using modeling and measurement approaches. The drug was given to 60 female volunteers who were divided into seven groups: group I, 30 mg weekly; group II, 30 mg twice a week; group III, 30 mg twice a week for 12 weeks followed by 30 mg weekly; group IV, 30 mg twice a week for 6 weeks followed by 30 mg weekly; group V, 60 mg weekly; and groups VI and VII, single 60 mg loading dose followed by 30 mg weekly doses. The blood samples were collected and analyzed by HPLC. In group I, mean trough concentrations of centchroman and its active metabolite, 7-desmethyl centchroman, were comparable to the steady-state trough concentrations in groups III, IV, VI, and VII. The metabolite to parent drug ratio remained constant in all the groups. The pharmacokinetic parameters in group VII were comparable to those reported after a single 30 mg dose. Dosage regimen VI was more convenient and provided better pregnancy protection (Pearl index 1.18; unpublished report) than regimen III, which is currently on the market and, thus, could be effectively used for contraception. © 2001 Elsevier Science Inc. All rights reserved.

Keywords: Contraceptive; Centchroman; Dosage regimen; Pharmacokinetics

1. Introduction

Centchroman (INN: Ormeloxifene), *trans*-1-[2-{4-(7-methoxy-2,2-dimethyl-3-phenyl]-phenoxy}-ethyl]-pyrrolidine, a non-steroidal oral contraceptive, has been developed at the Central Drug Research Institute, Lucknow, India [1–3] and is currently marketed. It is also undergoing clinical evaluation for the treatment of advanced breast cancer, and for prevention of osteoporosis due to its potent antiestrogenic and weak estrogenic activities [4–5].

Centchroman is effective for contraception in a 30 mg and 60 mg once a week post-coital dose regimen [6]. But the regimen (30 mg once a week) suffered from some early failures (pregnancies, most of which happened during the initial period of its use) possibly due to inadequate levels before attaining steady-state. To reduce the failure rates, centchroman is, at present, recommended to be used with an initial twice a week 30 mg dose for 12 weeks followed by a 30 mg once a week regimen [6,7]. The dependency of the steady-state concentrations of dose and time to achieve these levels on the frequency of dosing regimen is well known [8]. The steady-state concentrations (>99%) are achieved after 6 to 8 doses when a drug is given once every half-life (7 days), and the same levels can be attained more quickly when dosed twice every half-life. With the currently practiced dosing schedule of centchroman, the higher levels achieved after the 24th dose (twice a week for 12 weeks) will eventually decline to the steady-state levels expected to be attained after 30 mg weekly doses. Moreover, twice a week for 12 weeks followed by a once a week dosing schedule (currently used regimen) is inconvenient and creates some logistic problems to determine on which 2 days of the week to take the drug. The long elimination half-life of centchroman (7 days) [9,10] provides a basis to be able to devise a suitable weekly dosing schedule beginning with a loading dose. A simulation study for centchroman was carried out to generate an alternate dosing schedule without

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sacrificing its contraceptive efficacy, using pharmacokinetic data from 30 mg single dosing. Out of several dosage regimens, the regimen consisting of a 60 mg loading dose, followed by 30 mg weekly doses, exhibited steady-state concentrations of centchroman with the first maintenance dose of 30 mg itself and this regimen also was user friendly. These factors prompted the present study to assess the pharmacokinetics of centchroman during alternate dosing schedules and their suitability in effective contraception, in an attempt to economize and reduce the unnecessary exposure of the body to centchroman. In the present study, the steady-state minimum concentrations of centchroman were assessed after 6 different 30 mg dosing schedules. In addition, the pharmacokinetic parameters were assessed with the dosing schedule consisting of a single 60 mg loading dose followed by 30 mg weekly doses.

2. Materials and methods

Following approval of the protocol by the Ethics Committee, which was in accordance with the regulations of the Drug Controller of India, healthy women of reproductive age were recruited for the study. The women were judged healthy, based on medical history, a physical examination, and standard laboratory tests. In addition, all the participants were nonsmokers and refrained from alcohol intake. The women were not exposed to any other medication for at least 2 weeks before and during the study. The nature and purpose of the study were fully explained to them, and an informed written consent was obtained from each participant before the study.

The women participants were divided into seven groups. Each of the participants received centchroman according to the following schedule: group I, 30 mg once a week for 13 weeks (n = 19); group II, 30 mg twice a week for 13 weeks (n = 16); group III, 30 mg twice a week for 12 weeks, followed by 30 mg once a week for 13 weeks (n = 5); group IV, 30 mg twice a week for 6 weeks followed by 30 mg once a week for 6 weeks (n = 3); group V, 60 mg once a week for 7 weeks (n = 10); group VI, single 60 mg loading dose in the first week followed by weekly 30 mg doses for 13 weeks (n = 7); and group VII, single 60 mg loading dose in the first week followed by weekly 30 mg doses for 4 weeks (n = 6). Each participant fasted overnight before dosing. However, in group VII, the subjects fasted overnight before the loading dose and after the last maintenance dose. In groups I–VI, blood samples (5 mL) were collected immediately before 6 to 7 and 12 to 13 weeks of drug administration to determine trough concentrations (C_{min}). In group VII, blood samples were collected at 0, 1, 2, 4, 6, 8, 10, 24, 48, 72, 96, and 168 h after the loading 60 mg dose. Additional blood samples were collected immediately before and after 6 h of the 1st, 2nd, 3rd, and 4th maintenance 30-mg doses, and serial blood samples were obtained up to 672 h after the last maintenance dose. Blood samples were centrifuged and the serum samples were stored at −30°C until analysis.

Serum centchroman and 7-desmethyl centchroman concentrations were determined by a validated HPLC assay [11]. In brief, sample processing involved liquid-liquid extraction using diethyl ether. Chromatographic separation was carried out on a nitrile column (100 × 4.6 mm, 5 μm) coupled with a guard column (30 × 4.6 mm), utilizing 60% acetonitrile in 20 M phosphate buffer (pH 3) as mobile phase. Detection was performed with a fluorescence detector (Shimadzu, Kyoto, Japan) set at an excitation wavelength of 285 and emission wavelength of 310 nm. The lowest limit of quantitation (LLOQ) of centchroman was 1 ng/mL. Sets of spiked serum standards (1 to 250 ng/mL) were assayed with the study samples in every assay batch. In each analytical run, quality control samples in serum were analyzed to ensure precision and accuracy of the assay. The observed concentrations of the quality control samples deviated less than 10% from their nominal values, and the between- and within-batch variability was also less than 10%.

2.1. Pharmacokinetic analysis

Peak serum concentration (C_{max}) and time to reach peak concentration (t_{max}) were derived directly from the raw data. The nonlinear, least-squares regression computer program PCNONLIN (SCI Software Inc., Lexington, KY, USA) was used to fit the following equation

$$C_t = A.e^{-\propto(t-t_{lag})} + B.e^{-\beta\,(t-t_{lag})} - (A+B).e^{-k_a(t-t_{lag})}$$

[12] to individual centchroman serum concentration (C) versus time (t) curves in which A and B are intercepts, k_a, α, and β are the rate constant for absorption, distribution, and elimination phases, respectively, and t_{lag} is the lag time.

The terminal half-life was calculated from the ratio of $0.693/\beta$. The clearance (CL/F) and the volume of distribution (Vd/F) were calculated from CL/F = Dose/AUC and Vd/F = Cl/β, where F is the fraction of the administered dose absorbed. Area under the concentration-time curve (AUC) was calculated by the trapezoidal method, with extrapolation from the last observed concentration using the relationship C(last)/β [13].

Statistical analysis was carried out by analysis of variance (ANOVA) to determine if C_{max} and C_{min} values varied over time. For statistical analysis of the parameters between this and earlier studies [9], Student's *t* test for independent samples was used. Statistically significant differences were assessed at a $p \pm 0.05$ level.

3. Results

None of the women reported any adverse events such as nausea, vomiting, dizziness or breakthrough bleeding. The

Table 1
Mean ± S.D. trough concentrations of centchroman and 7-desmethyl centchroman following various dosage regimens

	Dosing schedule	Duration (week)	No. of subject N[a]	Concentration (ng/mL) D	M	Ratio M/D
I	30 mg Weekly	7	19	16.1 ± 5.0	6.5 ± 2.8	0.43 ± 0.14
		12.6	4	15.1 ± 4.0	7.4 ± 1.6	0.50 ± 0.07
II	30 mg Twice a week	7.0	16	28.2 ± 5.6	12.5 ± 4.7	0.45 ± 0.17
		12.5	8	31.5 ± 5.6	13.3 ± 4.9	0.43 ± 0.13
III	30 mg Twice a week for twelve weeks followed by 30 mg weekly	12.9[b]	5	18.8 ± 4.1	6.5[a]	0.29
IV	30 mg Twice a week for six weeks followed by 30 mg weekly	5.9	3	13.9 ± 7.9	4.2[a]	0.18
V	60 mg Weekly	6.4	10	41.5 ± 10.5	13.7 ± 6.5	0.32 ± 0.20
VI	60 mg A week loading dose followed by 30 mg weekly	13.1	7	23.7 ± 4.6	9.4 ± 2.1	0.39 ± 0.03

D = centchroman; M = 7-desmethyl centchroman.
[a] n = 1; [b] during 30 mg weekly dosing period.

trough concentrations (C_{min}) of centchroman were measured at steady-state after each of the regimens and the results are summarized in Table 1. The C_{min} after weekly 30 mg doses was about 16 ng/mL. The dosing schedule of 30 mg twice a week resulted in C_{min} values twice that obtained in group I. In group III, the C_{min} of centchroman 12–13 weeks after the start of weekly 30 mg doses was comparable to that obtained in group I. Similar C_{min} values were observed in group IV, also confirming that the C_{min} of centchroman will be similar to that obtained after weekly 30 mg doses. The single 60 mg regimen once a week (group V) resulted in C_{min} values higher than those obtained in groups I and II. In group VI, the trough concentrations were higher than those obtained after weekly 30 mg doses. The concentrations of 7-desmethyl centchroman during each of the 6 dosing regimens are also included in Table 1. It was observed that the relationship between the dosing schedules and concentrations of 7-desmethyl centchroman was similar to the parent drug, and the metabolite to parent drug ratios remained consistent with different dosage regimens except for groups III and IV participants (Table 1).

Pharmacokinetic parameters for centchroman were evaluated in 6 volunteers in group VII after the last maintenance dose. The mean serum centchroman concentration-time profile in the participants and the data simulated using the parameters of a single oral dose [9] are shown in Fig. 1. Both the simulated and observed data are superimposable. Following the 60 mg dose, C_{max} of 88.8 to 152.9 ng/mL was observed after 4 to 6 h of drug administration. To obtain the pharmacokinetic parameters, serum concentration-time data were analyzed by compartment modeling and the data were best described by a 2-compartment model, similar to earlier studies. The calculated pharmacokinetic parameters of the drug in serum are summarized in Table 2. The average steady-state concentration (C_{ss}) ranged from 17.0 to 35.6 ng/ml following the 4th maintenance dose. The clearance, volume of distribution and elimination half-life following the fourth maintenance dose of 30 mg (Table 2) were comparable with those obtained after a single 30 mg dose [9].

4. Discussion

The dosage schedule for centchroman is presently recommended as 30 mg twice a week for 12 weeks followed by 30 mg once weekly dose for effective contraception. Frequent initial doses are required to prevent possible failures in the early phase which might be due to inadequate steady-state centchroman concentrations. The present study attempted to modify the currently used dosing regimen by rationally applying pharmacokinetic principles, and correlating the results with contraceptive efficacy of centchroman derived from multicentric controlled clinical evaluations of 220 subjects (unpublished results). These results were com-

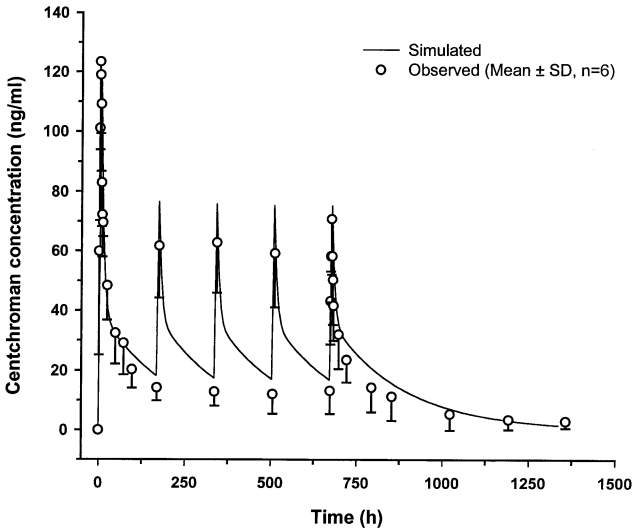

Fig. 1. Serum concentrations of centchroman after a single 60 mg loading followed by weekly 30 mg oral dose.

Table 2
Pharmacokinetic parameters of centchroman in serum of female volunteers

Parameter	Day	Mean ± SD
C_{max} (ng/mL)	1	125.2 ± 22.2
C_{max} (ng/mL)	28	74.7 ± 15.2
C_{min} (ng/mL)	7	14.3 ± 4.8
C_{min} (ng/mL)	28	13.2 ± 8.5
β (h^{-1})		0.006 ± 0.002
t_{lag} (h)		0.8 ± 0.6
C_{ss}(ng/mL)		24.1 ± 7.1
$t_{1/2}$ (h)		125 ± 69
Cl/F (L/h)		5.7 ± 2.5
Vd/F (L)		852 ± 140
$AUC_{672\text{-}840\ h}$ (ng · h/mL)		3828 ± 1438

β = elimination rate constant, C_{max} = peak concentration, C_{min} = trough concentration, C_{ss} = steady-state concentration, $t_{1/2}$ = elimination half-life, t_{lag} = lag time, Cl/F = clearance, Vd/F = volume of distribution.

pared with the clinical efficacy of the presently practiced centchroman dosage regimen (30 mg twice weekly for 12 weeks followed by 30 mg once weekly dose).

The trough concentrations of centchroman in group I reached steady-state by the 6th dose of the 30 mg once weekly dosing and were maintained afterwards, as reflected by its C_{min} after 6 and 12 weeks (Table 1). In groups III and IV, the drug was given twice a week for 12 and 6 weeks, respectively, followed by 30 mg once weekly maintenance dose. The steady-state trough concentrations in groups I, III, and IV were not statistically different ($p > 0.05$). Twice a week dosing regimen of 30 mg centchroman (dosing schedule II) resulted in apparently higher trough levels after 6 weeks than with the 30 mg once weekly regimen. These results confirm the dependency of steady-state levels of centchroman on the frequency of dosing. However, these higher levels of centchroman eventually declined to the steady-state levels expected after 30 mg weekly dosing. As expected, weekly dosing with a single 60 mg dose (group V) also resulted in steady-state levels after the 6th dose, and the levels were about twice higher than group I. In group VI, it was as predicted by simulation, the steady-state levels were maintained throughout the dosing regimen which were reflected in the trough levels after the 13th weeks. These trough levels were not significantly different ($p > 0.05$) from those obtained after 6 weeks of the 30 mg weekly dosing regimen (group I).

The trough concentrations of 7-desmethy centchroman were also monitored during each of the dosage regimens. The metabolite to parent drug concentration ratio did not show dose and time dependency, similar to the parent drug (Table 1). This metabolite has been found to be pharmacologically active, showing a 20-fold increase in cytosol receptor binding affinity, without appreciable changes in antiimplantation activity [14].

Because of month long sampling protocol [$t_{1/2}$ (terminal elimination half-life) ~7 days] [9,10], volunteer compliance to blood sampling was poor. The retention of volunteers deteriorated and only 6 female volunteers completed the pharmacokinetic study.

Pharmacokinetic parameters of centchroman were assessed in 6 volunteers in group VII after the last 30 mg maintenance dose. Centchroman concentrations at steady-state and the concentration-time profile after the last maintenance dose were predicted by simulation on PCNONLIN software using pharmacokinetic parameters obtained in the earlier single 30 mg dose study [9] (Fig. 1). Average serum concentrations of centchroman in these 6 volunteers were compared with the simulated data. An excellent correlation was observed between the simulated and observed data throughout the period of 8 weeks. However, minor deviations were observed in the C_{max} levels during the maintenance doses. The participants showed apparently lower steady-state C_{min} values than those obtained in group VI participants. These variations could be due to the small sample size and the fact that simulation results were based on the single dose study carried out with overnight fasted subjects. In contrast, the study subjects were on a normal but variable diet during the present study and the effect of food and its type on the absorption behavior of a drug is well established [15]. The superimposable centchroman concentrations after the first and last doses at which time subjects fasted, support this point.

Because of the similarity in the steady-state levels between the regimen VI and the clinically effective steady-state levels [9], the dosing regimen VI was clinically evaluated in a multicentric study and was compared with the currently practiced dosing schedule. A total of 220 female subjects were recruited for clinical evaluation of schedule VI. These data were compared with the contraceptive efficacy in 377 subjects reported earlier [6]. The duration of the study was 2–27 months, covering a total number of 1912 menstrual cycles, as compared with 3471 cycles in the previous study. The results showed that the dosing regimen caused delayed cycles, a common user problem [6] as experienced in group II. Other evaluation parameters such as method failure, the number of cases with delayed cycles, and Pearl index [16] also proved that the loading dose regimen offers distinct advantages over the currently practiced dosing regimen (unpublished results).

In the present study, a combination of modeling and measurement approaches was used to address a dosing recommendation of centchroman, i.e., a single 60 mg loading dose followed by 30 mg once weekly doses. Both the pharmacokinetic and clinical evaluation studies have shown that clinically effective steady-state concentrations of 30 mg once weekly dosing were achieved immediately after a loading dose of a single 60 mg dose. Also, the distinct disadvantages encountered in the initial 30 mg twice a week schedule are minimized in this proposed schedule. Moreover, the new dosage regimen is devoid of unnecessary additional exposure to centchroman and was more convenient and provided better pregnancy protection (Pearl index 1.18; unpublished report) than the current regimen on the

market and, thus, could be effectively used for contraception.

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