INTERIM ANALYSIS OF POST-MARKETING MULTICENTRIC TRIAL ON USE-EFFECTIVENESS OF CENTRON : A ONCE-A WEEK, NON-STEROIDAL ORAL CONTRACEPTIVE

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SUMMARY

For the establishement of use-effectiveness and acceptability of CENTRON - the world's first once-a-week non-steroidal oral contraceptive - a post-marketing multicentric trial in varied demographic spectum is presently being carried out across the country. This interim report covers the study on 367 women over 2811.5 women-months of use. In line with previously reported clinical trial findings, the contraceptive has been found to exhibit accepted pregnancy protection with a significantly low incidence of side-effects. The study indicates the need for educating, counseeling and motivating women and for generating awareness for a wider acceptance of the contraceptive.

INTRODUCTION

CENTRON^R (Centchroman) administered once-a-week, is the first non-steroidal contraceptive pill in clinical use today. CENTRON^R is a potent antioestrogen with partial agonist activity and manifests its contraceptive activity primarily by producing asynchrony between ovum transport and endometrium development and by preventing implantation of fertilised ovum. CETRON^R administered at 2.5 times the contraceptive dose to female Rhesus monkey for one year does not affect the basal and peak levels of FSH, LH, estradiol and progesterone, and therefore implies that it does not disturb the hypothalamic-pi-

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tuitary-ovarian axis (Trivedi et al, 1985). CENTRON^R at weekly doses of upto 120 mg does not inhibit ovulation and shows characteristic cycle pattern (Ray S, Dhavan BN, 1992). The antifertility effect is readily reversible and subsequent pregnancy is normal (Kamboj et al, 1971; Kamboj et al, 1992).

In various clinical trials for establishing the efficacy of the contraceptive, a total of 1957 parous women of reproductive age group have been covered over 21,000 months of use. Excellent pregnancy protection with a pearl index of 1.83 and a cumulative pregnancy rate by llife table analysis at 12 months of 1.83 + 0.74 was reported with no major side-effects (Nityanand et al 1994).

This contraceptive is being marketed by Torrent Pharmaceuticals for over three and a half years. The experience gained over these years helped identifying factors involved in acceptance and use of contraceptives across varied demographic, ethnic and socio-economic population.

The use-effectiveness of a contraceptive is established only after its extensive use in varied population spectrum. It is reasonable to expect differences in contraceptive usage in clinical trial and in the actual field conditions. To document safety, efficacy and acceptability data on CENTRON^R in the post-marketing set-up, a multicentric contrceptive efficacy, safety and acceptability trial was planned and has been initiated at five medical institutions and two centers of Family Planning Association of India. The trial at FPAI has now been expanded and a total of six centers are presently on rolls. For the purpose of this report, which presents an interim analysis of the trial with the insights that have so far emerged out of the study, only the data from the initial two centers of FPAI has been treated. While presenting the final report of this trial, we shall document a detailed treatment of data from all the six centers.

MATERIAL AND METHODS

User Selection

Healthy women in the reproductive age group have been enrolled in the study. Women have been admitted to the study only if they have had normal gynaecological and clinical history. Women who have not used steroidal contraceptives for at least three months and women willing to use CENTRON^R have been enrolled. No pregnant or lactating woman has been selected for the trial. And no woman with a history of recent jaundice, severe anaemia, any abnormal Gynaecological finding or any other major disease has been enrolled in the trial.

Schedule of use

The users have been enrolled in the trial with due explanation about the drug. The dosage schedule and other particulars of the contraceptive have been explained to the users and they have been instructed to take the first tablet on the first day of menstrual bleeding and the second tablet on the following Thursday or Sunday whichever comes first. In the initial three months, they have been instructed to take one tablet of Thursdays and Sundays every week. Subsequently, they have been instructed to take a tablet every Sunday for the remaining nine months. In the initial two months the users have been advised to use a barrier contraceptive also.

Criteria for contraceptive evaluation

The users have been asked to follow the dosage schedule and return for follow-up every quarter. Both subjective and objective evaluation are recorded in each of the follow-up visits. The contraceptive efficacy has been determined from the number of method failure pregnancies reported during the trial period. Any pregnancy occurring due to tablet omission or non-schedule use has been classified as patient failure. All side effects have been documented to understand the safety profile of the contraceptive.

Besides, documentation is maintained for all cases of drug-related and drug-unrelated discontinuation. Any discontinuation due to irregularities in menstrual cycles or other side-effects has been treated as drug-related discontinuation while those due to lack of compliance or family objections or personal reasons have been treated as drug-unrelated discontinuation. Those cases who have failed to report to follow-up have been treated as lost-to-follow-up and for purposes of analysis have been treated in the larger category of drug-unrelated discontinuation.

RESULTS

Among five medical institutions and

Table I

STATUS OF THE ENROLLED CASES AS ON 30TH APRIL, 1996

Centre Code	Cases enrolled (n) Total cases	Comp-lete	Failure	Lost to followup	Discont-inued	Active	Mean age of use (years)	Women months
SND	30	17	0	0	3	10	24.58 +4.40	359.5
SP	48	7	2	4	6	29	26.92 +4.36	226
VKR	50	50	0	0	0	-	28.80 +3.85	600
NAK*	37	-	1	9	9	18	27.19 +4.40	126
IRR*	13	-	1	1	5	6	27.15 +4.10	36
FPAI	189	45	10	21	96	17	23.96 +3.99	1464
Total	367	119	14	35	119	80		2811.5

* Data from these centres have been tabulated as on 30th June, 1995.

two centres of Family Planning Association of India a total of 367 cases have been enrolled till date in this post-marketing multicentric trial (Table I). These cases have been followed unto 2811.5 women-month or 234.29 women-years of use. As many as 119 of these 367 cases (32.43%) have been in the trial for 12 months and more and have therefore been treated to have completed the trial. Excluding cases of drug related discontinuation (37 cases), drug-unrelated discontinuation (82 cases), loss to follow-up (35 cases) and failures (14 cases); a total of 80 cases (21.80%) are currently in active follow-up.

With the objective of evaluating use-effectiveness in varied demographic and socio-economic population spectrum, the enrollments have been spread across urban, semi-urban and rural areas. The users have also been spread across various age segments (Table II). 312 out of 367 cases (85.01%) belong to the age group of 21-35. This age bracket is predominantly reproductively active and needs contraceptive protection. 55 cases (14.99%) fall outside this age bracket. As many as 47 cases (12.81%) have been found to be in the age bracket of 15-20 years.

The effectiveness of a contraceptive is inversely related to the incidence of pregnancy during treatment. The determination of true effectiveness, i.e. the pregnancy protection rate when medication is taken as directed, is often entirely subjective, since it introduces the element of dependence on an individual's assertion. Nevertheless, attempts have been made to differentiate between failures that are drug-related (method failures) and those that are drug-unrelated (patient failures).

There have been 5 method (1.36%) and 9 patient failurees (2.45%) accounting for a total of 14 failures over 2811.5 cycles of use (3.81%), yielding a gross pregnancy

Table II
AGE PROFILE OF USER POPULATION IN POST-MARKETING MULTICENTRIC CONTRACEPTIVE EFFICACY TRIAL ON CENTRON

Sr. No	Age in years	Number if cases (n) SND	SP	VKR	NAK	IRR	FPAI	TOTAL
1	15-20	0	3	0	0	0	44	47
2	21-25	11	24	7	18	5	90	155
3	26-30	10	13	23	12	5	45	108
4	31-35	6	5	20	6	3	9	49
5	36-40	3	3	0	1	0	1	8

rate of 5.97/100 women-years of use (Table III).

The pearl index has been calculated using the formula:

$$\text{Pearl Index} = \frac{\text{No. of failures} \times 12 \times 100}{\text{Total cycle of use or total months of exposure}}$$

Using this formula, the pearl index (method failure) has been 2.13 which is close to the reported pearl index of 1.83 reported in clinical trials. The pearl index (patient failure) has been 3.84. The overall pearl index has been 5.97. 10 out of the 14 cases (71.43%) of failures have been reported from the centers that were first to be initiated and the women enrolled in which are essentially from the low income, barely literate and exceedingly conservative social population. Besides, the control exercised on this user population is essentially quite different from those exercised at the other institutions. Significantly, 7 out of these 10 failures (70.0%) have been the result of either forgetfulness or non-compliance of instuctions on the part of the user. Another significant observation is that 9 out of a total of 10 failures from FPAI were reported prior to the initiaton of centrewise review of the trial. These failures were further reported out of 1012 women - months of use. Subsequent to our visits at the centre and interation with field personal and users, obly 1 failure has been reported out of 452 women months of use.

The objective of the study has been not only to establish use-effectiveness of the contraceptive but also to understand the safety of the contraceptive in the field usage conditions. As in earlier other clinical

Table III
METHOD AND PATIENT FAILURE DATA RECORDED AMONG USERS

Center Code	Total Cases	Women months of Use	Failure Recorded Method Failure	Failure Recorded Patient Failure	Total Failure enrolled	% of cases
SND	30	359.5	-	-	-	-
SP	48	226	1	1	2	4.17
VKR	50	600	-	-	-	-
NAK	37	126	1	-	1	2.70
IRR	13	36	-	1	1	7.69
FPAI	189	1464	3	7	10	5.29
TOTAL	367	2811.5	5	9	14	3.81

trials menstrual irregularities have accounted for the single highest incidence of side effects (16.62%), while other minor side effects have together accounted for 19.62% incidence.

Among menstrual irregularities, delayed periods have accounted for 19 cases (5.18%), scanty periods have been reported in 15 cases (4.09%). 9 cases (2.45%) reported shortened periods. Other menstrual abnormalities like irregular periods, heavy menstrual flow, midcycle pain, lactating ammenorhoea, cryptomenorrhoea and no periods account for a total of 18 cases (4.90%).

As in earlier clinical trials, except for menstrual irregularities accounting for an incidence of 16.62%, the contraceptive has been found to have a favourable safety profile.

Minor side effects observed in the present trial include pain in legs, abdomen and headache (11.84%); vomiting, nausea and dizziness (5.41%); itching and vaginal discharge (0.86%); abdominal discomfort and weight loss (0.65%); weight gain (0.53%) and general weakness (0.33%).

An interesting insight that has come up in the present trial is that discontinuations due to menstrual irregularities and other side effects together have been reported at an incidence of just 10.08%. Implying therefore that major discontinuations in the trial have come out of drug-unrelated factors rather than drug-related ones. We have regarded discontinuation due to irregularities in menstrual cycles (3.27%) and side-effects (6.81%) as drug-related. On the other hand, we have regarded discontinuation due to lack of compliance (1.36%), family objections (4.63%) desiring pregnancy (4.90%), desiring permanent contraception (5.45%) spouse away (1.09%), no reasons (3.27%) unrecorded cases (1.64%) or cases lost-to-follow-up as drug-unrelated.

The interim analysis of the trial has brought out variance in the rate of discontinuation among centers. To understand possible reasond for such disparity, a center-wise review was initiated. Among centers which accounted for high incidence of discontinuation, the observation that emerged was that the users were essentially multiparous, barely literate and most often from a mobile population who had been enrolled in the trial without having taken their family into confidence. Besides, we also came up with the observation that proper counselling, close monitoring and stringent control over the users can largely contribute in keeping discontinuation low. At centers where either such facilities have not been readily available or where family has not been taken into confidence over contraceptive decision, such discontinuation has been found to be significantly higher.

These observations led us to reinforce the importance of counseling and follow-up in the trial. Implementation of such criteria at the recently recruited centers of F.P.A.I. has resulted in discontinuation being as low as just 7.80% among 141 cases covering 180 women-months of use. Drug-related discontinuation, besides, has been reported at just 4.26%.

Further, reinforcing the importance of counseling and follow-up at centers recruited earlier, have led to the re-initiation of, at the time of compitation of this report, at least 7 cases who had earlier discontinued from the trial. These re-initiated cases are now being monitored and shall

Table IV
DISTRIBUTION OF DISCONTINUATION IN RELATION TO USE DURATION

Month of use	Number of cases (n)						
	SND	SP	VKR	NAK	IRR	FPAI	TOTAL
1 - 3	2	4	-	7	5	48	66
4 - 6	-	-	-	1	-	17	18
7 - 9	-	-	-	1	-	20	21
10 -12	-	1	-	-	-	11	12
Not recorded	1	1	-	-	-	-	2
Total	3	6	-	9	5	96	119

be treated in-depth in our subsequent report.

It is worth also looking into the data relating to distribution of discontinuation of users (Table IV). The rate of discontinuation is significantly higher in the initial months of use. 17.98% discontinuation rate has been reported in the first three months of contraceptive use. In the initial six months of use the rate of discontinuation stands at 22.89% as opposed to just 9.54% of discontinuation beyond six months of use. This is again in reaffirmation that a more detailed counseling is essential for establishing a new drug concept and that the initial months of contraceptive use is extremely crucial.

DISCUSSION

The objectives underlining post-marketing multicentric trials on CENTRON[R] have been to generate data on use-effectiveness in population of varied demographical, psychographical and socio-economic spectrum. Such extensive use is intended to throw up valuable data regarding efficacy, acceptability and side-effect profile of the contraceptive.

In a study reported in Population, May 1985, failure in the first year of contraceptive use has been as high as 21% for diaphragms, 20% for abstinence, 15% for spermicidals, 12% for condoms, 7% for oral pills and 4% for IUCDs. CENTRON[R] compares at 6%. Patient failure, as with other contraceptives, in the initial months of use in this trial, occured out of non-compliance and / or failure to understand user instructions. The users need to be counseled and helped in shedding her inhibitions for seeking clarification. In the latter months, when the contraceptive schedule got accepted and understood, patient failures occurred largely due to complacence on the part of the user. When a woman skips a few tablets for any reason and does not get pregnant, it is likely that she continues with this pattern of incorrect use with misplaced confidence leading to

pregnancy. Also, when assured of abstinence over a period of time, intermittent discontinuation of contraceptive protection and consequent failure cannot be ruled out. These are major reasons that have accounted for patient failures when users were randomly interviewed in their own homes.

Earlier reports in other controlled trials had brought out the fact that except for some incidence of menstrual irregularities, CENTRON[R] exhhibits an extremely favourable safety profile. With menstrual irregularities as the only significant side-effect reported, our present trial has endorsed this observation.

We have, out of this study, identified the need to educate the user and to make them feel comfortable with the idea that there may be some menstrual cycle delays if CENTRON[R] is to be acceptable. The anxiety generated by delayed periods often led the user to seek help and where this was available readily there were less dropouts. At centers when such help was not readily sought or available, the drop-out rate was higher. Another finding that emerged out of this study was that if the husband is also involved and educated, the acceptability of the method is much higher as it is for any other method.

Besides, the populace of some of the centres often do not like to or will not involve the male while initially deciding about contraceptives. Most of the "family objections" were from the husband or other significant elders in the family. The role of social workers in such situations is invaluable. The method to inform and educate these workers at centres taken up in the recent past have been modified. This procedure has improved the acceptability of the contraceptive as the informed worker is able to address any anxiety of the user or spouse more effectively.

It needs emphasis that no contraceptive is without failures. More importantly no contraceptive enjoys complete acceptance across all social segments. While it has taken sustained efforts through decades to establish virtually every alternative in the contraceptive armamentarium, it is reasonable to expect the concept of a safe and effective non-steroidal oral contraceptive also to get eventually accepted. The present study is a part of larger endeavor to generate confidence in our populace for what clearly appears to be safe, effective and a viable contraceptive.

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