ISSN 0975-6299 Vol 2/Issue 1/ Jan-Mar 2011

International Journal of Pharma and Bio Sciences

RESEARCH ARTICLE

PHARMACOLOGY

CENTCHROMAN A BETTER ALTERNATIVE FOR HORMONAL ORAL CONTRACEPTIVE PILLS.

Corresponding Author

MAJOR(DR) V K YADAVMD

Assistant Professor Dept of pharmacology.
Peoples college of medical sceinces& Research center Bhanpur
Bhopal (MP) 462010.

Co Authors

DR.PARAG SHARMA.MD*,DR. RAJ SHARMA.PHD* AND DR.JAYANTHI YADAV.MD,**

***Assistant Professor Dept of pharmacology Peoples college of medical sciences& Research center Bhanpur Bhopal (MP) 462010**
****Associate Professor Dept of Forensic Medicine & Toxicology Gandhi Medical College Bhopal (MP) – 462001**

ABSTRACT

Centchroman (Ormeloxifene) is a non steroidal Oral Contraceptive Pill (OCP), popular in India as once weekly pill being issued free of cost through Primary Health Centers as an initiative from the government and also commercially available. It has several advantages over steroidal OCPs and thus it is logical to offer this OCP to women all over the world. This commentary tries to highlight on this issue.

KEY WORDS

Centchroman, Hormonal OCPs, Beneficial effect of Centchroman.

INTRODUCTION

Centchroman (ormeloxifene) is a non steroidal Selective Estrogen Receptor Modifier with strong anti estrogen and weak estrogenic and anti progestin properties. The drug is marketed in India since last 20 years as an alternative to steroidal Oral Contraceptive Pills (OCPs) and it is provided free of cost through Government sponsored Family Welfare Program. Though data in terms of multicentric trials are limited, the drug has proved to be a highly effective and safe in various studies (Chandra H, Srimal RC, Kamboj VP, Dhawan BN, and Gupta NN.1977) and is devoid of side effects of steroidal OCPs.
It is the other beneficial effects of Centchroman apart from antifertility effect which makes it a perfect candidate for world wide use.

ROLE AS ORAL CONTRACEPTIVE

Centchroman is an effective oral contraceptive. At a weekly dose of 30mg it does not alter basal or peak gonadotrophin (FSH/LH) levels and also no effect on the production of estrogen or progesterone. The effects which are seen at these dose levels are slight increase in transport of zygote through oviducts, acceleration of Blastocyst formation and suppression of endometrial proliferation and decidualization (Anand and Ray 1977, Kamboj et al 1977, Kamboj V P, Ray S and Dhawan B N 1992). The plausible mechanism of contraception is thus appears to be asynchrony between developing zygote and endometrial maturation leading to prevention of implantation (Singh MM, Bhalla V, Wadhwa V, Kamboj VP. 1986).
Limited data is available on the effectiveness of the Centchroman as oral contraceptive. One trial in PhaseIII studied the effectiveness of weekly single dose of 30mg Centchroman for a total pregnancy exposure of 13483 months in 898 women. The pregnancy rate as indicated by Pearl Index (PI) was found to be 2.84. The main adverse effect seen during the drug administration was delayed menstruation of >45days, which was seen in 8% of subjects (puri et al 1988).
Another phase III trial including 11 centers and 376 women with a changed dosage schedule of 30mg twice weekly for 3 months followed by 30mg weekly dose showed an improved PI of 1.83 on total pregnancy exposure of 3959 months (3397 actual menstrual cycle). The efficacy of this dosage schedule was proven better with the adjusted PI of 1.63 at 12 months which is comparable to the PI of Hormonal OCP with PI of 0.1-8.0 (Trussel et al 1990). The only major adverse effect noted in this level was delayed menstruation which occurred in 6% of participants (Nityanand et al. 1994). Current recommendation is 60mg loading dose followed by 30mg weekly dose (Lal J, Nityanand S, Asthana OP, Nagaraja NV, and Gupta RC.2001). Return of fertility on stopping the drug is prompt. Centchroman has also not shown teratogenicity in animals and also no untoward effect of the drug was seen in infants born to mothers with contraceptive failure (puri et al 1988).

BENEFICIAL EFFECTS OF CENTCHROMAN OTHER THAN CONTRACEPTION

1. ***Prevention of breast cancer:*** There are reports of prevention of breast cancer by Centchroman (Mishra NC, Nigam PK,

Gupta R, Agarwal AK, Kamboj VP. 1989). Centchroman has shown regression of breast cancer lesion as well as anti mutagenic properties in bacterial mutagenicity assay and mutation assays in female mice (Giri AK, Mukhopadhya A, Sun J, Hsie AW, and Ray S.1999). In one study Centchroman has shown anti neoplastic activity similar to Tamoxifen irrespective of estrogen receptor status in breast cancer cell lines (Nigam M, Ranjan V, Srivastava S, Sharma R, Balapure AK.2008). The mechanism cited is the caspase dependent apoptosis. Centchroman has also shown its worth in treatment of mastalgia and fibroadenoma of breast. In a study group of 60 patients Centchroman was proved as a safe drug in comparison to Danazol and Bromocriptine which are the currently used drugs for the above conditions (Dhar A, Srivastava A.2007).

2. ***Role in immunity:*** One study has shown the positive effect of Centchroman on the humoral immunity, but failed to show any effect on the cellular immunity (Thomas L, Asad M, Hrishikeshavan HJ, Chandrakala GK.2007). These results can be extended in humans as immunity boosting effect of Centchroman. Boost in humoral immunity could provide protection against bacterial infections.

3. ***Prevention of Osteoporosis:*** Centchroman has some anti resorptive activity as it inhibits the osteoclastic bone resorption evident by some in vitro studies. When compared with Raloxifene and 17 beta estradiol Centchroman inhibited osteoclast cytoplasmic spreading, a measure of osteoclastic activity by 32% at the therapeutic concentration (Paliwal JK, Gupta RC.1996). Another study on the anti resorptive activity and osteoporosis preventive effect in ovarectomized female rats shown that Centchroman not only inhibited Parathyroid hormone induced resorption of 45Ca from pre labeled chick and rat fetal limb bones in chase cultures but also prevented osteoporotic changes in female rats (28.3% P< 0.01 for femur neck and 23.7% P< 0.01 for mid shaft) (Arshad M, Sengupta S, Sharma S, Ghosh R, Sawlani V, Singh MM.2004). These findings could be extended in humans with a positive effect on Bone Mineral Density.

4. ***Anti oxidant effect of Centchroman*****:** In experiments on female rats for the antioxidant effect Centchroman has shown strong antioxidant activity in terms of increased Superoxide Desmutase (SOD) and Reduced Glutathione (GSH) activity in Liver, heart and kidneys apart from total inhibition of pregnancy.(Jatwa R, Kar A.2007)

5. ***Other beneficial effects*****:** Their use has been shown to be associated with decrease in the incidence of epithelial ovarian cancer, endometrial cancer, pelvic inflammatory disease, ectopic pregnancy, benign breast disease, iron deficiency anemia and formation of functional ovarian cysts.(Centers for Disease Control.1983)

PHARMACOKINETIC STUDIES IN HUMANS

The maximum serum concentration of 55.53mcg/lit was achieved with 30mg single oral dose in 11 healthy female volunteers. The mean terminal half life was 165hrs (SD -49hrs) with clearance of 6.17 lit/hr (SD 1.67) and Volume of distribution of 1420 Lit (SD 478). (Lal J, Asthana OP, Nityanand S, Gupta RC.1995). Centchroman is also found secreted in Human milk with strong correlation with the serum concentration (n 13 r=0.64 P<0.01) without any significant physiological effect on infants (Gupta RC, Paliwal JK,

Nityanand S, Asthana OP, Lal J.1995). Centchroman has shown some drug interactions with Amoxicillin and Tetracyclines in animal studies, both of which interfere with the contraceptive efficacy. Otherwise drug appeared to be safe for co administration with commonly used drugs (Kumar V, Lal J, Singh MM, Gupta RC.2006, Khurana M, Lal J, Singh MM, Paliwal JK, Kamboj VP, and Gupta RC.2006).

In a study of 330 women with over 2 years of weekly or Biweekly use of Centchroman , the various organ functions were shown with in normal limits (vaidya et al 1977) and in another small study involving 161 women found no abnormality of genital tract and ovaries during USG monitoring upon continuous use of Centchroman (Nityanand et al 1994).

CONCLUSION

Thus to conclude Centchroman is an effective and safe contraceptive which can prove to be a better alternative to Hormonal OCPs. This drug which is widely used in Indian family welfare program should be offered to all women opting for this form of contraception. The newer combined pills available in the market (e.g. YASMIN etc) claim to have low incidence of side effects, still they are not completely devoid of it. In women who are above 35years of age the continued use of hormonal OCP pose special risk which is multiplied many folds if the woman smokes. It is also not clear how long a woman can continue with combined OCP, which is not a case with Centchroman.

Centchroman do not pose cardiovascular risk in older women as well and it can be continued as long as the contraception is required. In all probability it will further give protection against Breast cancer, Osteoporosis and other disorder such as fibroadenoma of breast.

The key points which argue in favor of use of Centchroman are summarized:

- High efficacy.
- Prompt return of fertility upon discontinuation.
- Devoid of side effects of Hormonal OCPs.
- Lack of teratogenic evidence.
- Lack of effect on Hypothalamic Pituitary Ovary axis.
- Delayed menstruation being the only major side effect which occurred in less than 8% of women.

The only probable shortcoming of Centchroman is the dosage schedule. The once weekly dose can be easily forgotten. This problem can be overcome by proper counseling and follow up. In a way this dosage schedule might be preferred by the women who are not comfortable with daily dosing of Hormonal OCPs. Another option could be the use of blank pills in between to maintain daily pill cycle.

Although the drug is in use for well over 2 decades in India, it is still advisable to conduct large scale clinical trials over various geographical regions to permanently establish the role of Centchroman as an alternative to Hormonal OCPs.

REFERENCE

1. Chandra H, Srimal RC, Kamboj VP, Dhawan BN, Gupta NN. Clinical Pharmacology studies with Centchroman. Indian J Exp Biol 1977 Dec; 15(12): 1170-1172.
2. Anand N, Ray S. Centchroman-a postcoital contraceptive agent. Indian J Exp Biol 1977 Dec;15(12):1142-30.
3. Kamboj VP et al .Biological profile of Cenchroman- a new post coital

contraceptive. Indian J Exp Biol. 1977 Dec; 15(12):1144-50.
4. Kamboj V P, Ray S and Dhawan B N. Centchroman. Drugs Today 1992; (28) 227–232
5. Singh MM, Bhalla V, Wadhwa V, Kamboj VP. Effect of centchroman on tubal transport and preimplantation embryonic development in rats. J Reprod Fertil. 1986 Jan; 76(1):317-24.
6. Puri V et al. Results of multicentric trial of Centchroman, in Pharmacology for Health in Asia. Dhawn BN editor 1988. Allied Publishers: New Delhi, India. p 432.
7. Trussel et al. A guide to interpreting contraceptive efficacy studies. Obstet Gynecol. 1990 Sep; 76(3 Pt 2):558-67.
8. Nityanand, S., Kamboj, V.P., Chandravati, K.D., Gupta K., Rohtagi, P., Baveja, R., Jina, R., Mitra, R. and Sharma, U. Contraceptive efficacy and safety of centchroman with biweekly-cum-weekly schedule. In: *Current Concepts in Fertility Regulation and Reproduction.* Eds. C.P. Puri and P.F.A. Van Look,. Wiley Eastern Ltd, New Delhi, p. 61, 1994.
9. Lal J, Nityanand S, Asthana OP, Nagaraja NV, Gupta RC. Optimization of contraceptive dosage regimen of Centchroman. Contraception.2001 Jan; 63(1): 47-51.
10. Mishra NC, Nigam PK, Gupta R, Agarwal AK, Kamboj VP. Centchroman- a non steroidal anti cancer agent for advanced breast cancer; phase II study. Int J Cancer 1989. 43 : 781-783.
11. Giri AK, Mukhopadhya A, Sun J, Hsie AW, Ray S. Antimutagenic Effect of Centchroman – a contraceptive and candidate drug for Breast cancer in multiple mutational assays. Mutagenesis 1999 Nov; 14(6): 613-620.
12. Nigam M, Ranjan V, Srivastava S, Sharma R, Balapure AK. Centchroman induces G0/G1 arrest and caspase dependent apoptosis involving mitochondrial membrane depolarization in MCF7 and MBA231 human breast cancer cells. Life Sci 2008 Mar12; 82(11-12) 577-590.
13. Dhar A, Srivastava A. Role of Centchroman in regression of mastalgia and fibroadenoma. World J Surg. 2007 Jun; 31(6): 1178-1184.
14. Thomas L, Asad M, Hrishikeshavan HJ, Chandrakala GK. Effect of Centchroman on cellular and humoral immunity. Indian J Physiol Pharmacol. 2007 Oct-Dec; 51(4): 387-394.
15. Paliwal JK, Gupta RC. Tissue distribution and pharmacokinetics of Centchroman. A new nonsteroidal post coital contraceptive agent and its 7 des methyl metabolite in female rats after single oral dose. Drug Metab Dispos. 1996 Feb; 24(2): 148-155.
16. Arshad M, Sengupta S, Sharma S, Ghosh R, Sawlani V, Singh MM. In vitro anti resorptive activity and prevention of ovariectomy induced osteoporosis in female Sprague-Dawley rats by ormeloxifene, a selective estrogen receptor modulator. J Steroid Biochem Mol Biol. 2004 Jun; 91(1-2):67-78.
17. Jatwa R, Kar A. Positive influence of Centchroman on cardiovascular system and tissue lipid peroxidation in rats. Contraception. 2007 Nov; 76(5):408-412.
18. Centres for Disease Control, Cancer and Steroid Hormone Study. Oral contraceptive use and the risk of ovarian cancer. *J Am Med Assoc 249*: 1596, 1983.
19. Centers for Disease Control, Cancer and Steroid Hormone Study. Oral contraceptive use and the risk of endometrial cancer. *J Am Med Assoc 249*: 1600, 1983.
20. Lal J, Asthana OP, Nityanand S, Gupta RC. Pharmacokinetics of Centchroman in healthy female subjects after oral administration. Contraception. 1995 Nov; 52(5): 297-300.
21. Gupta RC, Paliwal JK, Nityanand S, Asthana OP, Lal J. Centchroman: a new

non steroidal oral contraceptive in human milk. Contraception. 1995 Nov; 52(5): 301-305.

22. Kumar V, Lal J, Singh MM, Gupta RC. Effect of concurrently co-administered drugs on the pharmacokinetic/pharmacodynamic profile of Centchroman, a nonsteroidal oral contraceptive in rats. Contraception 2006 Aug; 74(2): 165-173.
23. Khurana M, Lal J, Singh MM, Paliwal JK, Kamboj VP, Gupta RC. Evaluation of interaction potential of certain concurrently administered drugs. Contraception. 2006 Aug; 74(2): 165-173.
24. Vaidya R et al. Activity profile of Centchroman in healthy female volunteers. Indian J Exp Biol. 1977 Dec; 15(12):1173-1176.