

Nestorone®: A new hope for Gynecologists, Andrologists and Neurologists

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Introduction

Nestorone (C₂₃H₃₀O₄, 16-methylene-17 α -acetoxy-19-norpregn-4-ene-3, 20-dione) is a synthetic progestin, an steroidal compound, created by the Population Council Inc., New York, USA. Progestin is a synthetic form of progesterone. Chemically, Nestorone is an acetate ester and derivative of 19-norprogesterone. The 19-nor derivatives of progesterone are referred to as "pure progestational molecules" as they bind almost exclusively to the progesterone receptors without interfering with receptors of other steroids. Nestorone is also named as Elcometrine, ST-1435, SureCN1261001, AC-6844, CS-0411 [1-3].

Considering its strong progestational activity and antioviulatory potency with no androgenic or estrogenic effects in vivo, it was hypothesized to be highly suitable for use in contraception and hormone replacement therapy (HRT) [3,4]. Therefore, rigorous preclinical researches and clinical trials have primarily established it as one of the hormonal contraceptives for females. However, recent studies have also found its role as a male contraceptive due to its spermatogenic suppressive effects. Moreover, its neurogenic and neuroprotective roles have also come to the light, recently [5]. These versatile roles of a single progestin 'Nestorone' have attracted basic scientists, gynecologists, andrologists and neurologists all over the world to investigate some of its unrevealed physiological capabilities. Forthcoming sections retrospect some of its recently investigated physiological roles either alone or in combination with other steroids:

Nestorone only Gel as a Birth Control Contraceptive for Females

Dr. Horacio Croxatto, a Chilean Scientist and member of the Population Council's International Committee for Contraception Research (ICCR), originally proposed an idea of a Nestorone transdermal gel. He demonstrated that Nestorone, a non-androgenic progestin, could be readily absorbed through the skin. The Nestorone gel was initially created at the Population Council's Center for Biomedical Research, and the Council is collaborating with Antares Pharma, USA to continue developing and testing this gel formulation using Advanced Transdermal Delivery (ATD).

In Phase 1 and 2 Clinical trials, Nestorone has shown its ability to safely and effectively suppress ovulation at low doses. It has shown its contraceptive action in the similar way by which estrogen and progesterone do. Nestorone seems to be unique in the sense that it can be applied daily in the form of a gel by rubbing it onto the skin. It is slowly absorbed into the bloodstream. But unlike other forms of birth control pills or ring, it does not seem to have the adverse side effects such as cramps, acne, weight gain or other issues. Clinical testings by administering 3.0 mg Nestorone gel for a period of 7 months have successfully prevented pregnancy.

Studies on small group of woman, have provided real insight into the true potential of Nestorone. It also seems to be an attractive alternative to existing methods of birth control. Not only does Nestorone have a quick and easy way to take it but so far the lack of unpleasant side effects appears very promising. Moreover, research and testing has indicated that Nestorone is safe for breastfeeding women. Therefore, being a creator of Nestorone – Scientists at the Population Council strongly hope that this gel will obviously be approved by the FDA, United States for use. As these were early stage studies, so the investigators have planned for long-term studies and the results are awaited.

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Nestorone-Ethinyl Estradiol Combination Contraceptive for Females

The contraceptive vaginal rings (CVR) are made up of silicone rubber. They are designed to release both 150 microg of Nestorone and 15 microg of Ethinyl Estradiol (an estrogen used in oral contraceptives) per day for a period of an year (13 menstrual cycles) in women. Then CVR can be replaced in them depending on their contraceptive needs. By using these CVR, reports of effective suppression of ovulation for 13 consecutive cycles in women are available [4,6]. Therefore, multicentric, open-label, Phase 3 clinical trial (Duration 1-year study) have been performed to evaluate the efficacy and safety of a new CVR delivering low doses of Nestorone and Ethinyl Estradiol [7]. Its promising results are likely to open new avenues for further developments.

Nestorone-Estradiol Contraceptive Gel for Females

Ethinyl Estradiol currently used in oral contraceptives exert some side effects like acne, breast tenderness and / or maybe enlargement, bloating (stomach cramps), vaginal spotting and maybe breakthrough bleeding etc. Previous research findings have indicated that the transdermal use of a natural estrogen (e.g. Estradiol or 17 beta - Estradiol) may result in fewer side effects than experienced with Ethinyl Estradiol. Therefore, with a continuing quest for developing a safe, noninvasive, reversible, cost effective contraceptive, several progestins and estrogens have been studied for their contraceptive roles. All of them differ in their qualities and performance. In this attempt, Population Council is developing in collaboration with Antares Pharma, a novel combination contraceptive comprised of Nestorone/Estradiol (an estrogen made by a woman's body) transdermal gel that is absorbed through the skin and may result in fewer side effects than currently available hormonal contraceptives. This gel is developed for non-oral transdermal administration as specific daily doses.

This method seems to be beneficial in both women of fertile age where it ensures contraception with additional health benefits and in postmenopausal women where it offers a hormonal therapy with additional medical benefits such as the potential for lower risk of thrombosis. In this method, woman's abdominal skin was chosen as a preferred site of drug administration. By using the skin as a site of drug delivery, Nestorone combined with Estradiol in a gel may help bypass the liver. This method was found to suppress ovulation, efficiently. Thus, it helps prevent toxicity of drugs. Moreover, use of estradiol through non-oral delivery system may have the potential to minimize safety factors related to oral hormonal contraceptives that use ethinyl estradiol. In addition to this, as the gel becomes invisible after application on the skin, so this gel may be appealing to the women who prefer a method that can be used inconspicuously.

Previous findings have indicated that the Nestorone/Estradiol gel is well tolerated with no serious adverse events, which may increase a woman's ability and desire to continue using the method. By enrolling approximately 2,500 women, Phase 3 clinical trials for the safety and efficacy of the gel in preventing pregnancy have been planned. Investigators are anticipating promising results, which may help this method to get approval by

the FDA, USA. Upon approval by the FDA, Nestorone/Estradiol gel would be the first-of-its-kind transdermal contraceptive gel using the natural estrogen Estradiol [8,9].

Nestorone-Testosterone Contraceptive Gel for Males

Recently, the National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH) and The Population Council, United States presented the Endocrine Society [10] with their findings related to the use of a combination of testosterone and Nestorone to suppress spermatogenesis hence lowering sperm count. A count of less than 1 million per millimeter makes fertilization nearly impossible. In the most recent clinical trial, Dr. Christina Wang, the study's Principal Investigator, tested the sperm count of men who used the combination therapy of testosterone and Nestorone in comparison to those who solely used testosterone and a placebo. She reported that approximately 88% of the men who used the combination of the two hormones had sperm levels lower than 1 million sperm per millimeter, compared with only 23% of men who took the placebo. This preliminary study has clearly exhibited the contraceptive efficacy of Nestorone-Testosterone gel preparation.

Nestorone gel when applied to the arm or the abdomen in combination with testosterone gel, worked by feedback inhibition of Testosterone in the testes resulting in cessation of spermatogenesis. The study showed the gel to be reversible, allowing a man to return to his normal fertility within three months following cessation of treatment.

This was the first study to test Nestorone as a male contraceptive, in combination with testosterone. The side effects of this drug have yet to be investigated. However, during the study, none of the participants reported major side effects, except moderate acne. We are now planning to combine Nestorone and testosterone into one gel and assessing it for easier application, continued and prolonged use. This promising gel seems to have the potential to prevent unwanted pregnancy and lower the risk of sexually-transmitted infections and HIV transmission by lowering sperm counts. So this can work not only as a hormonal male contraceptive but also as an important preventive technology [10,11].

Nestorone-Testosterone Undecanoate Contraceptive Gel for Males

Previous studies have shown successful inhibition of spermatogenesis in men using various combinations of oral progestagens (progestins) and percutaneous or oral androgens. Effective hormonal male contraception using Testosterone Undecanoate (TU) with oral or injectable Norethisterone (a progestin) preparations have been reported. Clinical studies have shown its high efficiency in Caucasian males with either oral or i.m. norethisterone and TU. Treatment at the intervals of 8-week had a higher azoospermic rate than 12-week treatment. This combination was found to be very promising for a depot, as the 8-week injection of both testosterone and norethisterone exhibited high efficiency in a potentially single injection [12-14].

A recent clinical trial by Mahabadi and colleagues [15] showed that transdermal Nestorone and a relatively high dose of testosterone gel (10 g Testim) had an additive effect

on gonadotropin suppression. This randomized, multicenter, unmasked trial showed that the gel applications were well tolerated with few short-term adverse effects. The effects on cholesterol were mixed with a small drop in low-density lipoprotein and high-density lipoprotein. Because Nestorone is a progestin without estrogenic or androgenic activity, it represents a noteworthy candidate to augment the effectiveness of testosterone alone [10,11]. Based on these findings and Nestorone's ability to augment the effectiveness of Testosterone in sperm suppression, a new sperm suppression study with this regimen has been planned using Nestorone-TU gel preparation. Soon results are anticipated.

Nestorone as Neuroprotective Medicine

There are reports that progesterone and Nestorone promote the remyelination of axons. The intracellular progesterone receptors (PR) have been found to mediate the proremyelinating actions of Nestorone. Moreover, like progesterone, Nestorone has been also found to strongly increase the reappearance of cells of the oligodendroglial lineage in the demyelinated slices. The increase in oligodendroglial cells by Nestorone resulted from enhanced NG2⁺ and Olig2⁺ oligodendrocyte progenitor cell (OPC) recruitment. Nestorone stimulated the migration of OPC towards demyelinated axons. Nestorone indeed markedly increased the number of EGFP⁺ cells migrating into the demyelinated cerebellar slices. Moreover, it was also observed that Nestorone helps in myelin repair efficiently by stimulating the recruitment and maturation of OPCs. Thus, they may open new perspectives for the use of progestins, which selectively target PR, to promote the endogenous regeneration of myelin. As a promising proremyelinating agent, Nestorone has potential for neuroprotective interventions.

Brain tissue damage and the impairment of nervous system can be protected by PR-dependent signaling of endogenous brain progesterone, within an initial hours. However, for longer-term improvement, additional treatment with exogenous progesterone dependent on PR are required. In such cases, potent and selective PR agonist Nestorone has been investigated to be very effective. As PR are direct key targets for both endogenous neuroprotection and for therapeutic strategies after stroke, so they have suggested a novel indication for synthetic progestins already validated for contraception. Therefore, it appears that Nestorone could have great roles in neuroprotection after stroke [16]. Based on a patent [17] and recent reports [5,16], Nestorone seems to have tremendous potential to prevent and/ or treat demyelinating or degenerative diseases such as Multiple Sclerosis, Alzheimer's Disease, Parkinson's Disease, and stroke. Thus, Nestorone appears to enhance the endogenous capacity of myelin repair which is a major therapeutic challenge in degenerative diseases.

Therefore, considering its potential roles in female and male contraception and neuroprotection, it will not be an exaggeration to say that Nestorone would certainly make its mark among the future medicine.

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