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Nanoemulsions of Nestorone®: How Good Medicine it Could Be !!

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Abstract

Nestorone (IUPAC name:16-methylene-17α-acetoxy-19-norpregn-4-ene-3, 20-dione; Molar mass: 370.482 g/mol) is a synthetic progestin. Nestorone being a derivative of Progesterone, it behaves as a 'pure progestational molecule'. However, in certain aspects it performs better than natural Progesterone. It's versatile roles in female contraception, hormone replacement therapy (HRT), male contraception and neuroprotection are well documented. Therefore, in the era of Nanomedicine, studying and reviewing the physiological performance of nanoemulsions of Nestorone would be a productive approach. Thus, the present review envisages the utilities of nanoemulsions of Nestorone as a medicine in coming decades.

Keywords: Nanoemulsion; Topical delivery of Nestorone; Nanoemulsion of Nestorone

Introduction

Nestorone is a fourth-generation progestin [1]. Progestin is a synthetic form of progesterone. Nestorone is an acetate ester and derivative of 19-norprogesterone. The 19-nor derivatives of progesterone bind almost exclusively to the progesterone receptors (without interfering with receptors of other steroids), therefore, they are referred to as 'pure progestational molecules'. Its role in female contraception is well investigated because of its strong progestational activity, high antiovulatory potency with non-androgenic or non-estrogenic effects [2,3]. It has a good safety profile. Therefore, it is recommended for hormonal contraception in breastfeeding women [2,3]. It is also found to be suitable for use in hormone replacement therapy (HRT) [2,3]. Moreover, Nestorone has been reported to have remarkable role in neuroprotection and male contraception [4-8].

Bioavailability of Nestorone is only 10% upon oral ingestion, a most common route of drug delivery [2]. However, the main problem associated with the oral delivery of drugs is the occurrence of peaks in serum levels of the drugs, which is followed by a drop in serum levels of the drugs due to its possible metabolism and elimination. Thus, the serum concentrations of orally administered drugs have peaks and valleys after ingestion. These highs and lows in serum concentrations of drugs often lead to undesirable side effects. In contrast, topical or transdermal delivery of drugs provides a relatively slow and steady delivery of the drugs. Accordingly, unlike orally administered drugs, the serum concentrations of topically or transdermally delivered drugs are substantially sustained and do not have the peaks and valleys associated with oral delivery [9]. The sustained serum concentrations associated with topical drug delivery avoids the systemic side effects of oral administration of drugs. Specifically, first pass metabolism of drugs by the liver is circumvented by utilizing topical delivery vehicles for the administration of drugs. Thus, nanoemulsions have been designed to address some of the problems associated with conventional drug delivery systems such as low bioavailability and noncompliance. In 2009, Vishwanathan et al. [10] have reported that nanoemulsions of lutein (a lipid soluble, oxygenated carotenoid) have significantly greater bioavailability than the supplement-pill forms. Moreover, they have also elucidated that nanoformulations are kinetically stable, and when adequately prepared can have a long shelf life [10]. In 2015, Sinha et al. have successfully evaluated the contraceptive performance of a highly biocompatible oil/water nanoemulsion of papaya seed oil [11]. In addition, nanoemulsions are reported to be best suited for topical delivery of drugs as it enhances the pharmacokinetic (PK) properties of drugs than the oral route of drug delivery [12,13]. Therefore, considering very poor bioavailability of Nestorone upon oral ingestion, it is not advisable to be taken orally. It is reported that the nanoemulsion of Nestorone is quickly absorbed into the skin upon topical administration. Nestorone is released into the blood stream on a sustained basis over a period of 24 hours, providing a practical and convenient once-a-day dosing regimen. The nanoemulsions of Nestorone have been reported to be fast-drying, non-irritating, and invisible upon transdermal application [14]. Therefore, the present review sheds light on the physiological performance of nanoemulsions of Nestorone (either alone or in combination with other steroids) through topical delivery and foresees it's role as a nanomedicine.

As a Hormonal Contraceptive for Females

Nestorone only gel

An original idea of Nestorone transdermal gel was proposed by a Chilean Scientist Dr. Horacio Croxatto. 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). This gel is basically prepared in the form of a nanoemulsion of Nestorone.

Various phases of clinical trials of nanoemulsion of Nestorone have shown its ability to safely and effectively suppress ovulation at low doses. It has shown its contraceptive activity in the similar way by which estrogen and progesterone do. Nanoemulsion of 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 etc. [15-17]. Successful prevention of pregnancy was reported in the women administering 3.0 mg Nestorone gel daily for a period of 7 months. The clinical studies in few women have provided real insight into the true potential of nanoemulsions 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 apply it on skin but so far the lack of unpleasant side effects appears very promising and renders it safe for breastfeeding women.

Nestorone-Estradiol gel

Ethinyl Estradiol currently used in oral contraceptives and contraceptive vaginal rings (CVR) [3,18,19] exert some adverse side effects like acne, breast tenderness and/or maybe enlargement, bloating (stomach cramps), vaginal spotting and maybe breakthrough bleeding etc., [15-17]. Previous research findings have indicated that the transdermal use of a natural estrogen (i.e, Estradiol or 17β -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, few progestins and estrogens have been investigated for their contraceptive roles. All of them differ in their qualities and performance. Being a pioneer in contraceptive development, Population Council scientists are developing jointly with antares Pharma, a novel combination contraceptive consists of nanoemulsions of Nestorone/Estradiol formulated in the form of a transdermal gel that is absorbed through the skin and may result in fewer side effects than currently available hormonal contraceptives. This gel is being developed for non-oral transdermal administration as specific daily doses.

This method seems to be advantageous in women of fertile age by providing contraception and additional health benefits. As well, it seems to offer hormonal therapy and lowers risk of thrombosis in postmenopausal women. This method relies using woman's abdominal skin as a preferred site of drug administration. By using the skin as a site of topical drug delivery, nanoemulsions of Nestorone combined with Estradiol in the form of a gel may help bypass the liver. Thus, it helps prevent toxicity of drugs. This nanoemulsions of Nestorone combined with Estradiol was found to suppress ovulation, efficiently. 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. This gel seems to be appealing to the women who prefer a method that can be used inconspicuously because the gel becomes invisible after application on the skin.

Previous findings have indicated that the Nestorone/Estradiol nanoemulsive 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. We 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 [20,21].

As a Hormonal Contraceptive for Males

Nestorone-Testosterone contraceptive gel

Recently, in the Endocrine Society meeting [7] an interesting finding related to the use of a nanoemulsions of testosterone and Nestorone was presented. This combination was found to suppress spermatogenesis hence lowering the sperm count. Fertilization of an ovum becomes nearly impossible when the sperm count lessen than 1.0 million per millimeter. 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 nanoemulsions 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 less 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 nanoemulsions of Nestorone-Testosterone in the form of gel formulation.

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 ceasation of spermatogenesis. The study showed the gel to be reversible, allowing a man to return to his normal fertility within three months following ceasation of treatment.

This was the first study to test nanoemulsion of Nestorone as a male contraceptive, in combination with testosterone. The side effects of this drug have yet to be studied. 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 [7,22].

Nestorone-Testosterone undecanoate contraceptive gel

Successful inhibition of spermatogenesis in men using various combinations of oral progestagens (progestins) and percutaneous or oral androgens have been reported. Effective hormonal contraception in males using Testosterone Undecanoate (TU) with oral or injectable Norethisterone (a progestin) preparations have been also documented. 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 [23-25].

A recent clinical trial by Mahabadi and colleagues [8] showed that transdermal Nestorone and a relatively high dose of testosterone gel (10 g Testim) had a summative 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 [7,22]. 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 nanoemulsions of Nestorone-TU gel formulation. Soon results are anticipated.

As a Neuroprotective Entity

Progesterone and Nestorone have been found to promote the remyelination of axons. The intracellular progesterone receptors (PR) are reported 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 [4].

Brain tissue damage and the impairment of nervous system can be protected by PR-dependent signaling of endogenous brain progesterone, within initial hours. However, for longer-term improvement, additional treatments with exogenous progesterone are required. In such cases, potent and selective PR agonist Nestorone has been investigated to be very effective. As PRs 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 [5]. Based on a patent [6] and recent reports [4,5], 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.

Application of nanoemulsions in the prevention and treatment of neurological and neurodegenerative diseases are well documented [26-28]. Sood and his colleagues have reported the use of curcumin–donepezil nanoemulsion for brain targeting in Alzheimer's disease [27]; whereas, nanoemulsions of Pomegranate seed oil have been used by Mizrahi and coworkers [28] for the prevention and treatment of neurodegenerative diseases. Considering these and other information reported elsewhere regarding the utility of nanoemulsion in treating neurological and neurodegenerative diseases, there is every feasibility of the nanoemulsions of Nestorone being potentially effective in preventing and treating such disorders. The preclinical and clinical studies using nanoemulsions of Nestorone in treating neurological and neurodegenerative diseases are being planned. Therefore, Nestorone seems to emerge as a neuroprotective entity, as well.

Conclusion

The poor bioavailability of Nestorone upon oral ingestion is well taken care off by topical administration of drug. Moreover, nanoemulsions of Nestorone seem to further enhance delivery of drug through topical administration and protect the human from systemic side effects arising from oral delivery of drug. Therefore, the coming decades are likely to witness an efficient usage of nanoemulsions of Nestorone as a medicine for better therapeutic outcomes in female contraception, HRT, male contraception, and treating neurological and neurodegenerative diseases. Nevertheless, the potential health risks/bio-hazards, if any, associated with topical administration of nanoemulsions of Nestorone are yet to be warranted.

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Conflicts of Interest

The author declares that there is no conflict of interest.

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