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Medicinal Chemistry In The Framework Of Hormonal And Non-Hormonal Contraception

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Abstract

The paper investigates the relevance of medicinal chemistry for family planning and birth control by means of contraception. It discusses hormonal and non-hormonal methods and draws attention to the two central aspects of contraception, namely efficacy and safety of contraceptive methods.

Introduction

Day after day, millions of women worldwide engage in contraceptive pursuits to aim for birth control or family planning. For this purpose, a considerable number of contraceptive options are available, including hormonal and non-hormonal methods. Whether it is hormonal contraception in the form of Long Acting Reversible Contraception (LARC) or non-hormonal contraception in the form of natural methods, it is medicinal chemistry that lays the foundation for efficacy and safety, the two main concerns of prospective users of contraceptive methods.

Discussion

Hormonal contraception

Hormonal contraception, and in particular Long Acting Reversible Contraception (LARC) has been discussed in numerous studies, and one of the most recent ones has focused on implants and intrauterine devices as "the most highly effective" methods of contraception [1].

Implants are available in the form of one or more sub-dermally placed rods which release progestin at a slow rate. This system of sustained release relies on diffusion of steroid hormones through semipermeable pieces of plastics. The synthetic progestin passes from the plastic into the surrounding tissues and enters the circulatory system through absorption by the local capillary network. The release rate of the progestin depends on the surface area and the density of the plastic (silastic or ethylene vinyl acetate) in which the progestin is contained [2].

Jadelle and Norplant

Among the most frequently chosen implants are Jadelle and Norplant. Each one of the two Jadelle rods contains 75 mg of levonorgestrel, for a total of 150 mg. This is 66 mg less than the amount in the six Norplant capsules. While the levonorgestrel in Norplant is packed into the capsules in crystal form, the core of the Jadelle rod is a mixture of levonorgestrel and an elastic polymer (dimethylsiloxane/methylvinylsiloxane).

The daily release rate of Jadelle and Norplant has been studied for the first month, for an entire year, and for 2 years [3]. During the first 6-12 months of use, Norplant and Jadelle release a total of about 80 µg (microgram) of levonorgestrel every 24 hours, which results in a plasma concentration of 0.35 ng/mL. At the end of the first year, the release rate gradually declines to a relatively constant rate of 30-35 microgram per day. At 5 years, the overall release rate is 25 microgram per day, with corresponding levonorgestrel plasma levels of 0.25-0.35 ng/mL. For comparison, progestin-only oral contraceptive pills also deliver about 80 µg of levonorgestrel per day, while combined oral contraceptives with levonorgestrel as the active progestin deliver 50-125 µg. Peak serum levels after ingestion of 75 µg of levonorgestrel reach 1.5-2.0 ng/mL; after ingestion of 150 µg of levonorgestrel, serum peaks reach 2.7-4.2 ng/mL. These serum peaks are reached within 30 minutes up to 2 hours after ingestion and are followed by a rapid decline, with an average half-life of 10-12 hours. The rapid changes are in contrast to the

stable, low serum concentrations of progestin accomplished by means of the sustained-release systems.

Nexplanon

The Nexplanon implant measures 40 mm X 2.0 mm and consists of one non-biodegradable rod of 40% ethylene vinyl acetate and 60% etonogestrel (the 3-keto derivative of desogestrel), covered with a rate-controlling ethylene vinyl acetate membrane of 0.06 mm thickness. The rod contains 68 mg etonogestrel which is released at a slow rate: initially at 60-70 μg/day, decreasing to 35-45 μg/day at the end of the first year, to 30–40 μg/day at the end of the second year, and further to 25 to 30 μg/day at the end of the third year. The high initial rate of absorption is probably due to a significant amount of etonogestrel released from the uncovered ends of the implant. Peak serum concentrations (266 pg/mL) of etonogestrel are achieved within 1 day after insertion, with the effect of suppressing ovulation, for which only 90 or more pg/mL are required.

"Serum concentrations of etonogestrel are adequate to provide contraception for 5 years and WHO data suggest efficacy for that long" [2].

As concerns mechanisms of action, progestin-containing implants have two principal mechanisms of action, ie, inhibition of ovulation and restriction of sperm penetration through cervical mucus. Anti-estrogenic actions of the progestins affect the cervical mucus by making it viscous, scanty, and impenetrable to sperm, inhibiting in this fashion fertilization. At high doses, progestins also inhibit gonadotropin secretion, preventing in this fashion follicular maturation and ovulation. This dual effect allows contraceptive efficacy to be sustained even though ovulation is not consistently inhibited in etonogestrel implant users toward the end of the 3-year period of use."Even if follicles grow during use of progestin implants, oocytes are not fertilized. If the follicle ruptures, the abnormalities of the ovulatory process prevent release of a viable egg. Although progestins suppress endometrial activity, which makes the endometrium unreceptive to implantation, this is not a contraceptively important effect since the major mechanisms of action prevent fertilization" [2].

Concerning abortogenicity, it has been claimed that no signs of embryonic development were found in implant users, indicating that progestin implants have no abortifacient properties. Regarding abortifacient properties, it must be remembered that in the past, women were sometimes given large doses of estrogens for 4-6 days to prevent contraception after coitus during the fertile period (postcoital or "morning-after" contraception). "However, in this instance pregnancy is probably prevented by interference with implantation of the fertilized ovum rather than changes in gonadotropin secretion" [4].

For contemporary prospective users of emergency contraception Ella, Plan B One-Step, and Next Choice are available and various aspects of emergency contraception have been discussed exhaustively in a recent publication [5].

Non-hormonal methods

The mechanisms of action described above have hardly any relevance for non-hormonal contraception. However, considerations of biochemical processes are pivotal also in natural methods, ie, changes in basal body temperature due to progesterone and changes in cervical mucus structure due progesterone and estrogen. Hormonal contraception in the form of LARCs is based on progestins and in the form of oral contraceptives on estrogens and gestagens. In non-hormonal contraception, on the other hand, it is the naturally occurring hormones estrogen and progesterone that are fundamental, especially their changes in plasma concentration during the menstrual cycle.

Naturally occurring estrogens are 17 beta- estradiol, estrone, and estriol, all of which are C18 steroids. It is in the liver that estrogens are oxidized or converted to glucuronide and sulfate conjugates. Considerable amounts are secreted in the bile and absorbed into the bloodstream (enterohepatic circulation). In the urine, at least 10 different metabolites of estradiol can be found. Estrogens foster the growth of the ovarian follicles and increase the motility of the uterine tubes. In addition, they are responsible for cyclic changes in the endometrium, cervix, and vagina. As systemic effects increased secretion of angiotensinogen and thyroid-binding globuline are of importance.

Progesterone is a C21 steroid secreted by the corpus luteum, the placenta, and (in small amounts) the follicle. 17alpha-Hydroxyprogesterone is obviously secreted along with estrogens from the ovarian follicle, and its secretion corresponds to that of 17 beta-estradiol. Progesterone has a brief half-life, and it is converted in the liver to pregnanediol, which is conjugated to glucuronic acid and excreted in the urine.

In women the plasma progesterone level is approximately 0.9 ng/mL during the follicular phase of the menstrual cycle. Late in the follicular phase, progesterone secretion begins to increase, and during the luteal phase, the corpus luteum produces large quantities of progesterone so that ovarian secretion increases about 20-fold. "The result is an increase in plasma progesterone to a peak value of approximately 18ng/mL (60 nmol/L)" [4].

For non-hormonal contraception, especially for the basal body temperature (BBT), it is important to note that progesterone is thermogenic "and is probably responsible for the rise in basal body temperature at the time of ovulation" [4]. The effects of progesterone, like those of other steroids, are brought about by an action on DNA to initiate synthesis of new mRNA. Substances that mimic the action of progesterone are at times called progestational agents, gestagens, or progestins. Along with synthetic estrogens they are used as oral contraceptive agents.

The effects of estrogens and progesterone described above

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are the basis for the so-called fertility awareness-based methods, also called natural family planning or periodic abstinence. They have been described extensively as early as 2000 by German research [6]. The most effective among them, the so-called symptothermal method (Pearl index of 0.8) combines the principles of two other methods, namely basal body temperature and Billings Ovulation method (or Zervixschleimstruktur-Methode nach Billings) [7].

Concerning the basal body temperature method physiologists emphasize the easy practicability and argue that a convenient and reasonably reliable indicator of the time of ovulation is a change - usually a rise - in the basal body temperature. "Women interested in obtaining an accurate temperature chart should use a thermometer with wide gradations and take their temperatures (oral or rectal) in the morning before getting out of bed. The cause of the temperature change at the time of ovulation is probably the increase in progesterone secretion, since progesterone is thermogenic" [4].

With respect to the ovulation method physiological research emphasizes the importance of the cervical mucus. "Estrogen makes the mucus thinner and more alkaline, changes that promote the survival and transport of sperm. Progesterone makes it thick, tenacious, and cellular. The mucus is thinnest at the time of ovulation, and its elasticity, or spinnbarkeit, increases so that by mid-cycle, a drop can be stretched into a long, thin thread that may be 8-12 cm or more in length"[4].

Conclusion and Implications

As can be seen from the foregoing discussion, medicinal chemistry is at the heart of any form of contraception, clarifying not only efficacy but also safety of contraceptive methods. Whether a woman opts for a hormonal or non-hormonal method, safety is a primary concern. When safety is understood as protection against sexually transmitted diseases, the recommendations of the FDA should be heeded: "Except for abstinence, latex condoms are the best protection against HIV/AIDS and other STIs"[8]. When safety is understood as protection against harm, ie, adverse events, one of the non-hormonal methods will be the first choice. When safety is understood as not causing death or any serious complication, one of the hormonal methods will suffice, although bleedings, amenorrhea, perforations, expulsions, and pelvic inflammatory disease -- associated with the most efficacious methods -- might be considered by some women as sufficiently serious to discontinue a particular method, albeit it is hailed by some authors as "safe" [1].

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