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13. Sustained Release Preparations for the Delivery of Fertility Regulating Agents

IMPROVED LONG-ACTING FERTILITY REGULATING AGENTS: WHAT ARE THE PROBLEMS?

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SUMMARY

Why is it so difficult, costly and time-consuming to develop improved long-acting agents for fertility regulation? What are the attributes of a "perfect" long-acting agent? What are the major limitations and unsolved problems at present?

This review addresses itself to the above questions, with special emphasis on the problems of long-term safety, efficacy and adverse reactions.

The past is never dead; it is not even past... WILLIAM FAULKNER

INTRODUCTION

Many of the contemporary readers of *Henle and Pflüger's "Zeitschrift"*, felt, and rightly so, that an article entitled "Beiträge zur Lehre von der Menstruation und Befruchtung" and published in 1853 by Professor Th. L. W. Bischoff from Giessen [1] was of more than cursory interest. Bischoff observed that the bloody vaginal discharge in bitches contained freshly shed ova and concluded that ovulation in the bitch, and hence also in the human species, takes place at the time of menstruation. Since simplistic concepts always had an almost irresistible appeal to the human mind, the thesis of Professor Bischoff became a very popular one among European gynaecologists, and during the rest of the 19th century, infertile couples were frequently advised to "improve" their chances for conception by concentrating intercourse around the period of menstruation.

The attributes of the "perfect" long-acting steroid contraceptive as indicated in Fig. 1 might perhaps also be viewed as another great classic in the field of simplistic concepts; however, by stating the problem in a somewhat exaggerated way, it may become easier to analyze the present limitations and to single out the major factors interfering with the development of significantly improved long-acting agents.

Let us first see what the available agents and the problems related to their use are. Figure 2 shows the two preparations available for the time being: depomedroxyprogesterone acetate* (DMPA), given every third month in the form of a crystalline aqueous microsuspension of 150 mg, and norethisterone oenanthate (NET-EN), an oily solution (200 mg) with several dose schedules recommended between 60 and 84 day injection intervals.

What are then the problems with these preparations? The problems are the classical ones: safety, efficacy and adverse reactions.

Safety

There are two major problems related to the preclinical safety testing in animals: the relevance of the animal models used and the empirical judgement: how much is too much when the animals are grossly overdosed in chronic toxicological studies? [2, 3]. In the case of long-acting steroidal contraceptives the problem is compounded by possible species differences in the half-life time of the steroid administered, and the temptation becomes great to base the dose to be administered to the animals on certain assumptions (like in the good old times), rather than on solid pharmacokinetic data obtained previously in the

THE IDEAL LONG-ACTING STEROID CONTRACEPTIVE; DREAM, OR REALITY?		
SAFETY	:	100 %
EFFICACY	:	100 %
SIDE EFFECTS	:	NONE
STEROID LOAD	:	MINIMAL
OTHER PROBLEMS	:	NONE

Fig. 1. Attributes of the "perfect" long-acting steroidal contraceptive.

* The following trivial names are used: Dihydroxyprogesterone acetophenide: 16α,17α-dihydroxy-4-pregnene-3,20-dione 16,17-acetophenide, estradiol oenanthate: 3,17β-dihydroxy-1,3,5(10)-estratrien-17β-yl-heptanoate, ethinyl oestradiol: 17α-ethinyl-3,17β-dihydroxy-1,3,5(10)-estratriene, medroxyprogesterone acetate: 6α-methyl-17α-acetoxy-4-pregnene-3,20-dione, norethisterone: 17α-ethinyl-17β-hydroxy-4-estren-3-one, norethisterone oenanthate: 17α-ethinyl-17β-hydroxy-4-estren-3-one-17β-yl-heptanoate, laevo-norgestrel: (−)-13β-ethyl-17α-ethinyl-17β-hydroxy-4-gonen-3-one.

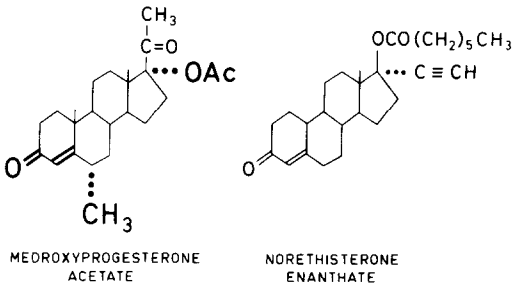

Fig. 2. Medroxyprogesterone acetate and norethisterone oenanthate.

same species. This may sound cynical, but the outcome of such studies might be a true disaster in case the dosage schedule results in a major, gradual accumulation, "build-up", of the long-acting steroid administered at too frequent intervals during a period of several years. Indeed, the risk that a valuable and much needed drug disappears because of the simplistic schedule employed in its toxicological evaluation is far from theoretical. Hence, the concept of 100% safety in animal toxicology may be a dream, more than reality, depending on the desirable—and by necessity arbitrary—safety factor (e.g. 25 times or 100 times the proposed human dose).

Efficacy

The only safe way of assessing contraceptive efficacy of a long-acting agent is in properly randomized comparative studies, carried out in the same clinics by the same personnel during the same time [4, 5]. It goes without saying that the results must be analyzed by proper statistical methods, using life table analysis.

Table 1 indicates the results of such comparative studies with the two presently available injectable preparations.

The results of the studies reviewed [6–9] indicate that, using a 3-monthly injection regimen, the efficacy of DMPA is significantly higher than that of NET-EN (administered every 84 ± 3 days). Preliminary evidence suggests that the efficacy of NET-EN can be improved by more frequent (e.g. 2-monthly) administration [10]. It is clear from the data, however, that none of the presently available injectables fulfill the attributes of the "perfect" method, as shown in Fig. 1, i.e. 100% efficacy. Is it possible at all to achieve such an efficacy? The answer is yes, provided one is willing to pay the price. And the price may be high indeed. Table 2, which has been condensed from a more extensive one published by Benagiano [11], indicates in a few representative studies [12–17], the efficacy of a previously used combined monthly injectable contraceptive, consisting of 150 mg of dihydroprogesterone acetophenide (DHPA) and 10 mg of oestradiol oenanthate (EEn).

It should be noted that not a single pregnancy was reported in these studies, nor in those summarized in detail by Benagiano in an in-depth review of the field [11].

Question: What is the price to be paid? Answer: A significant accumulation of both steroid esters in the organism. Figure 3, taken from a paper published by Gual *et al.* [18], indicates the presence of considerable quantities of the administered esters and/or their

Table 1. Comparative studies with two 3-monthly injectables: Depot medroxyprogesterone acetate (DMPA) and norethisterone oenanthate (NET-EN)

Author	Year	Preparation	No. of subjects	Total woman-months	Pregnancy rate
Chinnatamby	1971	DMPA	515	5770	0.4
		NET-EN	520	4391	2.3
Rice-Wray *et al.*	1972	DMPA	110	2446	0.0
		NET-EN	112	1377	4.3
Zanartu and Onetto	1972	DMPA	561	22,000	0.2
		NET-EN	130	2300	5.2
WHO*	1977	DMPA	832	50,484	$\underline{0.7} \pm 0.4$
		NET-EN	846	47,820	$\underline{3.6} \pm 0.7$

* Randomized 10-centre study.

Table 2. Clinical experience with the monthly injectable contraceptive consisting of dihydroxyprogesterone acetophenide (150 mg) and oestradiol oenanthate (10 mg)

Author	Year	No. of subjects	Total woman-months	Pregnancy rate	Discontinuation rate (%) for cycle irregularities
Swartz *et al.*	1967	279	1921	0	—
Herzog and Soule	1968	189	1255	0	—
Ragab *et al.*	1969	120	1736	0	—
Keifer *et al.*	1970	170	2585	0	25.7
Tyler *et al.*	1970	615	6197	0	11.4
Wallach and Garcia	1970	385	4512	0	7.5
Total		1758	18,206	0	

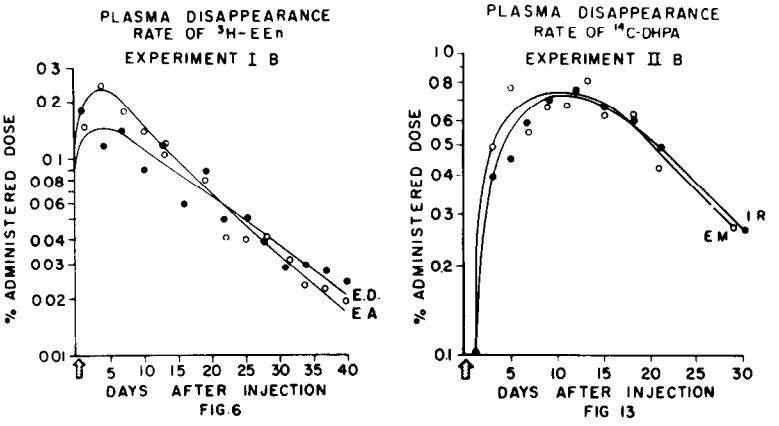

Fig. 3. Plasma levels of radioactive material following the administration of labelled oestradiol oenanthate (EEn) and dihydroxyprogesterone acetophenide (DHPA). From Gual *et al.* [18]. With permission of the authors and editor.

metabolites in the circulating blood of volunteers immediately prior to the time of the next injection (scheduled at 28 ± 3 days). And even if information is admittedly scarce and incomplete, simple pedestrian logic would seem to be sufficient to caution against the use of contraceptive steroid formulations leading to a gradual "build-up" of hormonally active long-acting compounds in the organism. In other words, it does not seem justifiable to pay the price of steroid accumulation in order to achieve a 100% efficacy, and it is likely that we shall have to settle for somewhat less. This raises immediately the next problem: how much is "somewhat" less? What is the definition of an "acceptable" pregnancy rate: 0.5, 1.0 or 2.0%, or more? The answer is only in part scientific and will vary from country to country, depending on the availability of adequate facilities for abortion and for the proper follow-up of the progeny, together with solid data on the relative frequency of adverse reactions compared to those seen with other long-acting formulations. Since it is likely that at least a few pregnancies will be observed with all long-acting formulations, the proper evaluation of the teratogenic potential of all long-acting preparations is and remains a very important task.

Adverse effects

In theory, any adverse reaction attributed to oral contraceptive preparations could be a potential candidate for careful assessment in relation to long-acting formulations. In practice, however—perhaps mainly because of the established association between several adverse reactions and the oestrogenic component of the "pill"—the problem with long-acting steroidal contraceptives boils down to a single, but major, adverse effect: bleeding irregularities [9, 19]. There is hardly any doubt that this is the main reason for discontinuation of use of long-acting formulations. The data of Table 3, based on the results of a recent WHO-sponsored study [19], are self-explanatory and indicate the true magnitude of the problem.

Were it possible to eliminate or reduce the occurrence of prolonged bleeding or amenorrhoea, significantly improved long-acting fertility regulating agents could be developed. However, a prerequisite for this is a better understanding of the factors regulating endometrial development and desquamation in women exposed to various types of long-acting steroidal contraceptives.

What is the problem? George Corner, in his book published more than 30 years ago, gives a beautiful description of the ovary as a timepiece [20]. For the discussion of our problem, let us recall that the ovary has two major, highly interrelated functions, the periodic production of a fertilizable ovum and the secretion of various steroids. The steroids secreted act upon a number of important target tissues, including the endometrium, as shown schematically in Fig. 4. The problem in a nutshell is that it does not seem possible—at least not with steroidal contraceptives—to inhibit ovulation without inhibiting or grossly altering the secretion of ovarian steroids. The extraordinary usefulness of the so-called "Pincus Pill", the combined oestrogen–progestogen oral contraceptive, is based on the fact that during the 21 days of its administration it both inhibits ovulation and replaces the effect of the suppressed ovarian steroids by producing an endometrium resembling to a certain extent the normal one. When, subsequently, the administration of the pill is discontinued for a week

Table 3. Percentage of women with one or more "normal" cycles* during all injection intervals

No. of normal cycles	NET-EN $n = 740$	DMPA $n = 748$
0	47.0	70.6
1	27.2	20.9
2	15.0	5.3
3	6.2	2.4
4 or more	4.6	0.8

* A normal cycle was defined as the one with 26–35 days' duration

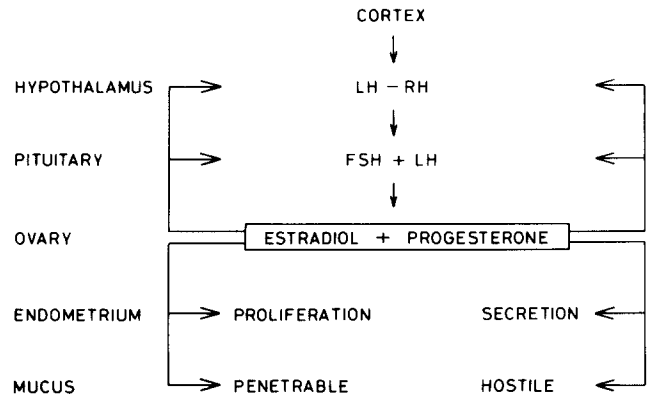

Fig. 4. The ovary as timepiece. Simplified scheme of the regulatory effects of the principal ovarian steroids at the hypothalamic, pituitary, endometrial and cervical levels. Modified from Diczfalusy [24].

(for instance by giving placebo tablets), this results in a "classical" oestrogen–progestogen withdrawal, with a more or less normal menstrual-like bleeding as a consequence.

What happens now to these endometrial functions, when long-acting steroidal contraceptives of different type are administered? The expected mechanisms are indicated in Table 4, and the problem is that "true life" does not seem to produce the expected mechanisms.

One would expect that the administration of monthly injectables is accompanied by regular bleeding patterns, but bleeding irregularities were reported fairly frequently (e.g. Table 2). Furthermore, the expectation that the administration of relatively large doses of progestagens (such as DMPA and NET–EN) should result in a progressive atrophy and hence amenorrhoea, is contradicted by the high incidence of bleeding anomalies [19], perhaps because follicle maturation is not invariably suppressed. Finally, the near zero order release of small, "minipill"-like quantities of progestogens would not be expected to alter the normal menstrual mechanisms regulated by the rhythmic secretion of endogenous steroids, since, in the majority of such cycles, ovulation is not inhibited, but the available evidence indicates an increase in bleeding irregularities and a rather unexpected correlation between bleeding irregularities and predecidual and atrophic changes in the endometrium [21].

Our inability to predict the bleeding pattern with various long-acting formulations points to our ignorance of the factors responsible for the bleeding (or no bleeding) from an endometrium exposed to various types and quantities of progestogens with or without oestrogens. This strongly suggests that without a better understanding of these factors it will be hardly possible to improve the performance of long-acting steroidal contraceptives.

Hence, for the time being, a long-acting agent exhibiting no adverse reactions is a dream more than a reality, and it will be necessary to re-define the question in different societies by asking more specifically, what types of bleeding irregularities are women willing to accept in that particular setting (for instance, amenorrhoea versus prolonged bleeding versus frequent spotting)?

Metabolic steroid load

Let us forget for a moment the many problems concerning the specificity of current radioimmunoassay techniques for DMPA and NET-EN, and let us make the fairly reasonable assumption that these methods measure the steroid in question together with a number of more or less well defined metabolites. We can state then that the plasma levels of these agents a few days after their administration are at least 10–20 times higher than immediately before the next injection [22, 23]. Plasma levels around

Table 4. Expected mechanisms of action of long-acting steroidal contraceptives based on different principles

Principle	Duration of effect	Ovulation	Endometrium	Menstruation
Oestrogen–progestagen combination	1 month	Inhibited	Normal	Regularly induced by exogenous steroids
Large dose of progestagen	3–6 months	Inhibited	Progressive atrophy	Amenorrhoea
Small dose of progestagen	Up to several years	Not inhibited	Normal	Regularly induced by endogenous steroids

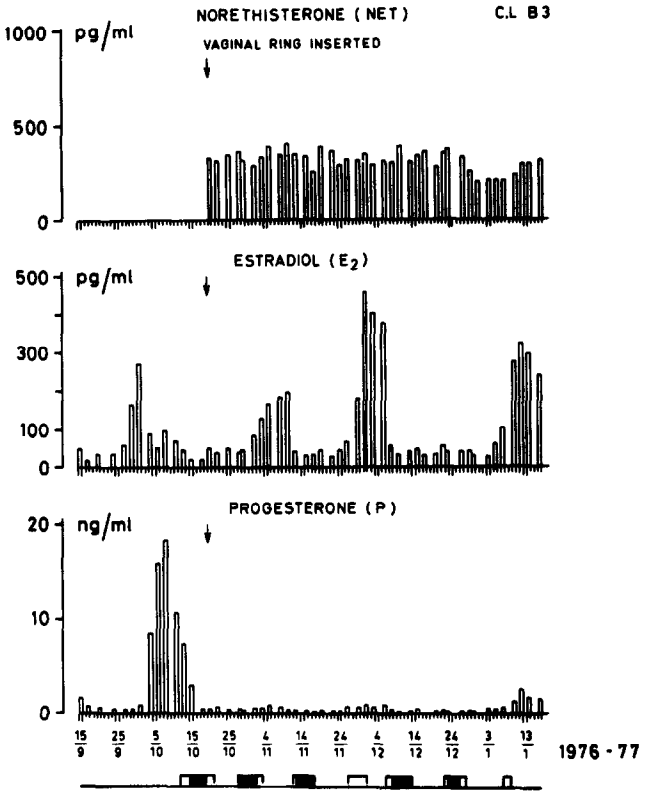

Fig. 5. Plasma levels of norethisterone, oestradiol and progesterone in a subject with a vaginal device releasing norethisterone at a rate of approx. 200 μg/24 h. From Landgren *et al.* [21].

15–20 ng/ml certainly reflect a big and rather unnecessary steroid load, since 5% or so of the above level might be sufficient to block ovulation, as indicated by the example shown in Fig. 5, where near constant low (<500 pg/ml) plasma levels of norethisterone are maintained for almost 100 days following the release of some 200 μg/24 h norethisterone from a vaginal device [21].

Furthermore, irrespective of the variation in plasma levels, the total steroid load to which the organism is exposed during 84 (NET-EN), or 90 (DMPA) days is at least 10 times higher than that represented by a "modern" oestrogen-progestogen oral contraceptive (for instance a dose of 150 μg of laevo-norgestrel +30 μg of ethinyl oestradiol given during 21 out of 28 days). An additional advantage of the latter is the periodic recurrence of 7 steroid-free ("dry"?) days, and although opinions may differ as to the patho-physiological significance of this steroid-free period, it is obvious that it cannot cause any harm. Since, as suggested by Fig. 6, it is likely that there is a correlation not only between dose and effect, but also between dose and adverse effects (although not necessarily of the same type, or order), sheer pragmatism dictates that a case can be made for the development of improved long-acting formulations representing a minimum of steroid load. This can be achieved by the development of various near zero order delivery systems, and the subsequent speakers will discuss the latest developments in the areas of subcutaneous implants, vaginal and intrauterine delivery systems.

NEW DEVELOPMENTS

What are then the new approaches to long-acting systemic agents? Theoretically speaking, the options at hand are: (a) new schedules of administration for "old" agents; (b) new compounds; (c) new formulations; and (d) new delivery systems. The methods of assessing the relative merits of the new products will remain the classical ones, preclinical safety evaluation, followed by the long term clinical and/or epidemiological assessment of safety, efficacy and adverse reac-

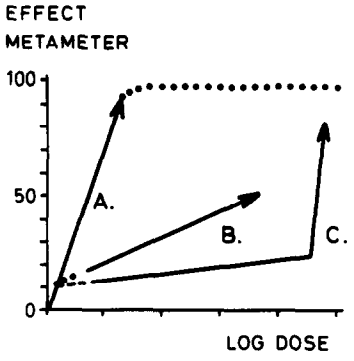

Fig. 6. Various types of dose–effect and dose–adverse effect relationships.

tions. The sad truth to remember in this, and in all other fields of fertility regulation, is that a major scientific "breakthrough" made to-day simply cannot be translated into a widely available improved fertility regulating agent in less than 12–15 years, and the "translation" will involve an average yearly cost of 2–3 million dollars.

To develop significantly improved long-acting injectables causing a minimum of bleeding irregularities will be a difficult, but most challenging, task, which will require a great deal of imagination and mission-oriented collaborative research into the fine details of endometrial, ovarian, pituitary and hypothalamic function in women. And the critics, who feel that the improved long-acting agent will remain a permanent dream for several generations to come, may wish to recall what Sir Francis Bacon said more than 370 years ago: "they are ill discoverers that think there is no land, when they can see nothing, but sea" [25].

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