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DESIGN OF PHASE I STUDIES FOR DEPOT CONTRACEPTIVES

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SUMMARY

Phase I clinical studies for depot contraceptives should provide information about clinical pharmacology. By necessity, these studies need to last longer than 10 days and therefore require prior completion of one year animal toxicology studies. The clinical studies should include 10–20 motivated healthy women aged 19–39 with normal menstrual cycles. In addition to determining the effect of the depot preparation upon the endocrine system, studies should be undertaken to evaluate renal and hepatic functions as well as carbohydrate and lipid metabolism. If the mechanism of action is other than ovulation inhibition, weekly examination of cervical mucus should be performed. Endometrial biopsies should be obtained at less frequent intervals. In addition, duration of action of the depot preparation and time to return to normal function should also be determined. Assays should be developed to measure circulating levels of the pharmacologic agent at frequent intervals to determine its rate of release from the depot preparation. Ideally, release rates should be relatively constant to lower incidence of side effects.

Clinical trials of pharmaceutical agents have been classified into 3 phases of investigation by the United States Food and Drug Administration [1]. Phase I clinical studies for oral contraceptives are required for new drugs in which clinical safety is not known, as well as for drugs already given to humans at lower dosage or for shorter duration of action. Thus, most new depot contraceptives have to be initially studied under Phase I guidelines. The purpose of these studies is to determine human toxicity, metabolism and pharmacology, including the effective dosage and formulation of the drug. These studies are usually limited to 10 to 20 subjects, and for oral agents are limited to 10 days of administration. Initially clinical studies of injectable contraceptives pose special problems in comparison with those of oral formulation. The United States Food and Drug Administration has developed guidelines for animal studies for oral contraceptives. Prior to Phase I studies of all contraceptives, the FDA requires that the drug be tested for 90 days in rats, dogs and monkeys. However, before starting Phase II studies, which for contraceptives involves about 50 subjects for about 3 menstrual cycles, one year animal studies are required in rats, dogs and monkeys. Phase I clinical studies for depo-contraceptives, by necessity, last longer than 10 days and therefore require prior completion of one year animal toxicologic studies. Therefore, new drugs designed specifically for long activity require the completion of one year animal studies before clinical testing can be initiated. On the other hand, different formulations of gestogens already in use as contraceptive agents have had these toxicologic studies performed previously and therefore, Phase I clinical studies can usually be initiated without additional animal toxicology. Furthermore, the duration of action proposed, which may vary from 1 to 12 months, affects the nature of the Phase I studies. Most of the oral formulations have a duration of action of only a few days and thus Phase I studies can be completed in less than 10 days. Because of the long duration of action of the injectable formulations, Phase I studies of these agents by necessity have to last for a prolonged time period, of one or more months duration. Therefore, it seems advisable that, prior to the initial administration to humans of any long acting contraceptive agent, the same drug be first administered in a short acting, rapidly metabolized form to prevent prolonged action of a possible toxic effect.

The selection of volunteers to act as subjects in Phase I studies with injectables, should be similar to the selection of volunteers for other Phase I oral contraceptive studies. The proper selection of patients is extremely important in order to obtain the information desired from the Phase I clinical trials. One very important criterion for selection is being certain that the subjects are motivated well enough to remain in the trial until its scheduled conclusion, which in the case of injectables will last for several months. Monitary or other types of rewards are usually necessary to motivate subjects to take part in these Phase I clinical trials. Candidate selection and motivation should be sufficiently rigid so that all or nearly all of the subjects enrolled in Phase I trials will complete the scheduled series of tests. In order to achieve this high continuation rate, careful screening of potential candidates is an important prerequisite prior to enrollment in clinical trials. For careful screening, it is best to use experienced clinical personnel especially those who have operated previous clinical trials. The best candidates for Phase I clinical trials are those who reside near or work in the institution in

which the clinical trial will be taking place. Hospital or clinic employees are ideal subjects for Phase I clinical trials while patients are usually not the best candidates. Suitable subjects are those individuals who anatomically and physiologically have normal reproductive systems. In an attempt to exclude patients with abnormal reproductive function, it is best to restrict clinical trials in female subjects to those (a) between the ages of 19 and 39, (b) who for the past year have had regular menstrual cycles between 26 and 30 days in length with less than 7 days menstrual flow and absence of intermenstrual bleeding, (c) have had at least two consecutive menstrual periods since terminating their last pregnancy or discontinuing oral contraceptives, (d) no previous injectable contraceptives, (e) no cardiovascular, hepatic renal, endocrine or gynecologic disease and (f) normal breast and pelvic examination. Because very little is known about contraceptive efficacy prior to the Phase I studies, the most suitable female subjects are those who have had tubal ligation or whose husbands have had vasectomy. If subjects who are not sterilized are utilized, they should be willing to have a therapeutic abortion if they become pregnant during the trial, as it is likely that inadequate teratologic studies will have been previously performed. For trials of male subjects, the same criteria of age and health apply. Prior to administering the therapeutic agent, two semen analyses performed at intervals of two weeks should both be entirely normal in respect to count, morphology and motility.

Selection of dosage for the depo-contraceptive poses problems dependent upon the desired duration of action. There are little conclusive data concerning optimum duration of action. However, it probably varies in different populations. For example, an injection administered once a month has been found to be most acceptable in Mexico, while administration once every three months is more accepted in the United States. Intervals of 6 or more months are believed optimal in other countries. If gestagens alone are going to be tested, then the duration of action can be lengthened to more than 1 month, dependent upon dosage and vehicle. However, if a combination gestagen and estrogen is going to be used, then the proposed duration of action usually will not last more then one month. Generally, the longer the duration of action, the greater the necessary dosage of gestagen to be utilized in any given formulation. However, by utilizing different vehicles having lower rates of release of steroid, a lower amount of drug can be made to act for a longer time period. It is probably best to use three different dosages for each proposed duration of action and from 3 to 5 subjects at each dosage. If the drug has been previously utilized as a contraceptive in humans, but administered by a different route, a narrower range of proposed dosages can be studied than if prior human experience is not available. In the latter case, a wide range of dosages should be tested and it may be best to use a logarithmic progression of doses, such as 1, 10 and 100 mg or 10, 100 and 1,000 mg. To act as a completely effective contraceptive in women, the dosage chosen in the formulation should inhibit ovulation for the entire proposed duration of action. If ovulation occurs prior to the desired duration of action, then the formulation may still have contraceptive action, but its effectiveness will be diminished. To be completely effective in men, persistent azospermia should be produced. The development of oligospermia is not always associated with an inability to conceive. To determine the duration of action in the Phase I studies of agents administered to women, progesterone should be measured in serum or plasma at least once and preferably twice a week for the duration of the study. In this manner, information about duration of inhibition of ovulation for various dosages will be obtained. For gestagens, duration of elevation of basal temperature will aid in determining duration of action. To determine duration of action in men, semen analyses need to be performed every two weeks. Because of the longer duration of spermatogenesis from ovulation, Phase I studies in men usually will be of longer duration than similar studies in women.

Specific assays are now available for many of the steroids and ideally a pure antigen (steroid bound to protein) and antiserum should be made available prior to the initiation of Phase I studies in order that blood levels of the drug can be measured by radioimmunoassay in the same samples obtained for the measurement of progesterone. The pharmacodynamics of the injectable materials in humans can thus be studied. With most of the injectable steroids tested thus far, there appears to be an initial rapid increase in blood levels of the drugs soon after the injection of the depo-preparation, followed by a fairly rapid decline within a few days [2]. A plateau is then reached after which there is a further gradual decline. Hopefully, preparations will be made with different delivery systems so that this initial burst effect will be diminished and the drug will be released at a more constant level.

In order to study the effects of the agent on other primary target organs, in women, in addition to measuring progesterone, estradiol should be measured in the same serum samples. These steroids should be measured twice per week during the pre-treatment control cycle and for at least one month after the expected duration of action is reached to determine the return of ovulation. Samples of cervical mucus should be obtained for measurement of spinnbarkeit at weekly intervals during the control cycle, for the expected duration of treatment, as well as one month thereafter. Two endometrial biopsies, one during the time period when the drug is expected to be active and one during the estimated recovery phase are also of value in determining drug activity. The timing of the first endometrial biopsy may be varied among the 3 to 5 subjects studied for each dosage. In men, study of the drug on other primary targets can be provided by measuring FSH, LH and testosterone

every two weeks in addition to performing a semen analysis at the same time intervals. Fractose and glucose concentrations should be measured in the semen as well as the number, motility and morphology of the spermatozoa.

In an attempt to provide information about short term safety of the agent in humans, effects on other organs should be monitored by a relatively large number of clinical and laboratory examinations. These parameters should be studied 3 times; pretreatment, during the time of expected maximum blood levels of the drug and during the recovery phase. For practical purposes, the parameters can be measured during the second part of the control cycle, two weeks after administration of the drug and once during the month after expected termination of action.

The effects on other organs can generally be divided into three groups, as follows: (a) effect on endocrine systems, (b) effect on other organs and (c) general effects. In the first category, effects of thyroid function can be determined by measuring T3 and T4. Effect on the adrenal can be determined by serum cortisol measurement, while effect on the pancreas can be analysed by a glucose tolerance test and insulin measurement. In women, it is probably not necessary to determine the effects on the pituitary at this stage of clinical testing, but in later studies FSH, LH, HGH and human prolactin can be measured. The second category, hepatic effects can be determined by measuring SGOT, SGPT, alkaline phosphatase and bilirubin. Renal effects can be determined by creatine and bilirubin measurements and hematologic effects by performing a complete blood count. In the final category of general effects, the effects on lipids can be monitored by measuring cholesterol and triglycerides. Total serum proteins and electrolytes, including sodium potassium, and calcium should also be measured. Finally, a urinalysis completes the list of laboratory determinations. Clinically it is wise to measure body weight and blood pressure at monthly intervals and in men to attempt to detect the development of gynecomastia. Although the FDA has suggested that EKG and eye examinations should be included in Phase I clinical testing, the necessity of these last two examinations is not clearly defined.

Finally, prior to treatment and following the completion of treatment a complete physical examination should be performed. In women, in addition to careful breast and pelvic examinations, cervical cytologic examination should be obtained at both times. In men, testicular size should be measured before and after therapy.

These Phase I studies as outlined above, involve a large number of tests that will entail considerable expense. Nevertheless, these studies will provide a considerable amount of information regarding safety, metabolism and clinical pharmacology, including optimal dosage and duration of action within a relatively short time period.

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