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THE DESIGN AND EVALUATION OF FIELD TRIALS OF INJECTABLE CONTRACEPTIVES

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SUMMARY

The design of a field trial depends principally upon precise definitions of terms to be used with universal application in all centres conducting the study. This goes also for recording events that occurred during the trial such as pregnancy and bleeding, local and systemic side effects. Advantage should be taken of these trials to conduct metabolic studies on patients undergoing long term therapy, and those patients who discontinue with a wish to become pregnant should be closely followed for the timing of restoration of fertility and the outcome of the subsequent pregnancy.

1. INTRODUCTION

Generally speaking, the vast majority of clinical trials on injectable contraceptives have involved the administration to women. There are very few large scale studies on injectables which might affect male fertility. The principal reasons for this concentration upon women is that the methods so far tried in men have unacceptable side effects, the most important of which, at least for the men, is loss of libido.

Despite the lack of success in producing an acceptable method for men to date, I think we must assume that sooner or later a method will be developed. Therefore, I shall address my comments to both male and female studies but principally confine them to effects that one might anticipate from the administration of steroidal compounds.

2. DESIGN

It goes without saying, but needs to be stated, that, when designing a clinical trial on any method of fertility regulation or for that matter any scientific investigation, one needs to define precisely what one is going to measure. It is at this stage that the clinician in charge of the study should consult a biostatistician. The clinician will be able to tell the biostatistician the approximate frequency at which he would expect that event to occur in the study, and in turn the bio-statistician will be able to tell the clinician how many patients he will require and how often he should make the observations. The clinician should state quite precisely what, in his judgement, would or would not be an acceptable rate of events, for example, pregnancy rate. This of course is based upon his knowledge of what is acceptable for that population and what he could reasonably expect from his knowledge of the mode of action of the compound. For example, if a compound consistently inhibits ovulation one can expect a fairly low pregnancy rate. If however, the mode of action depends upon changes induced in the cervical mucus or endometrium, then, from past experience, one might anticipate a higher pregnancy rate. In any event, from the ethical point of view, it is essential that certain indices for terminating a study should be spelled out. For example, the lower 95% confidence limit for the pregnancy rate so that if and when the pregnancy rate of the trial exceeds that figure, then the trial is stopped, for to continue the trial would be exposing the patient to what might be considered an unnecessary risk of pregnancy. The same goes for the more serious side effects and for those side effects which can be considered as life threatening or adverse reactions.

3. INVOLUNTARY PREGNANCY

Monitoring the occurrence of pregnancy in female trial subjects is not particularly difficult but in male subjects monitoring the pregnancies in the female partners involves an additional subject to the one that is being treated and therefore leaves more opportunity for that subject, i.e. the wife, to be missed from follow-up. It may at first seem simple to monitor pregnancy but it does depend upon a number of factors such as how is the pregnancy diagnosed and by whom? When is the pregnancy diagnosed? This to some extent depends upon the intervals between follow-up and these are governed by the expected duration of action of the preparation. For example, if the preparation has an expected duration of action of one year and the patient is only seen at yearly intervals, she may well fail to report a pregnancy. Additional problems arise in the case of preparations which have a well recognized incidence of amenorrhoea as this may well be confused in the patient's mind as pregnancy. This serves to emphasize the necessity for laboratory diagnosis or histological confirmation of pregnancy. One cannot rely upon the patient nor in many instances upon clinical examination alone.

4. OUTCOME OF INVOLUNTARY PREGNANCY

In view of the wide spread concern about teratogenicity it is absolutely essential that all pregnancies are followed until concluded, either by abortion or

by delivery. Details should be collected as to the normality of the pregnancy, labour, off-spring and with steroidal compounds special attention should be paid to the possible masculinizing effects on the female foetus. In any event, the products of conception whether dead or alive should be subjected to very close scrutiny for possible teratogenic effects.

5. BLEEDING

Irregular vaginal bleeding has been one of the major draw-backs of all injectable contraception tested so far. It is not only an inconvenience for the patient and in rare cases a life threatening situation but in many of the communities in which injectable methods have been found to be acceptable, most patients can ill afford a continuous drain on their iron reserves from uterine blood loss. This irregular bleeding is not only confusing for the patient and clinician but also results in major problems in terms of analysis of results. Unfortunately most patients and many clinicians are obsessed with the term "menses", which by definition is not applicable in this sort of situation where steroidal compounds are being given. With the conventional oral preparations it can be termed a "withdrawal bleed" but when the steroid being administered is present in the body for a prolonged period of time, there may well be no bleeding at all or alternatively there may be irregular, or continuous, light or heavy or any combination of these bleeding episodes. I think it is reasonable to assume that most women are happy to tolerate one bleeding episode at approximately four week intervals with a certain amount of variation on either side. For this reason most of the results are looking for a periodicity, in the statistical sense, of the bleeding pattern. To look for this periodicity, it is necessary for the patient to record on a day-by-day basis her vaginal blood loss. In sophisticated communities where the women have access to sanitary towels and vaginal tampons, it is possible to arbitrarily distinguish between spotting and bleeding. Spotting is usually taken as vaginal blood loss not requiring sanitary protection and bleeding as vaginal blood loss that does necessitate protection. Even so, this definition is open to pitfalls as it does depend upon the patient's appreciation of how much blood loss requires protection and how much does not. In less sophisticated communities, it is usually not possible to distinguish between these two events, in which case any vaginal blood loss should be recorded as bleeding. This will result in a higher reported incidence of bleeding compared to centres that can differentiate between the two events.

The document on which the patient records her vaginal blood loss has unfortunately come to be known as a menstrual diary card. From past experience, I think it is important that the patient should not have to complete more than six calendar months on any one card as it often becomes mutilated or lost. The information on the diary card should be transferred to the follow-up form for the clinical trial in the patient's presence so that she can help with the interpretation of any signs or symbols.

A number of definitions of irregular bleeding and amenorrhoea have been developed. Probably, within reason, any one definition is as good as the next so long as that definition is applied to all patients in that study and that it is not left to interpretation by one or more individuals by inspection of the diary cards.

6. LIBIDO

Libido is probably one of the most abused terms associated with the use of steroidal contraceptives. In the vast majority of reports of either diminished or increased libido, these have depended upon the patient's own recollection and understanding of the term. As there is no commonly accepted definition of libido, it makes interpretation of this observation very difficult. The same applies to men as to women.

Libido depends very largely on many extraneous, external factors such as opportunity, time of the day *or* night at which it is recorded, diet, e.g. alcohol, psychological profile of the person at that time, and so on. Basically in this type of study one is not interested in quantifying libido at any one point in time but studying the effects of the treatment longitudinally. This allows us a more liberal approach as one is looking at trends. So far this subject has been largely neglected but plays an important part in most people's lives. One possible approach to this is an adaptation of the Aitken personality self-rating scale [1–3], which has been used successfully for monitoring trends in depressive illness. It consists of a small piece of paper with a 10 cm long line on it. On one end it has the expression "the most unhappy I have ever been" and at the other end "the happiest I have ever been". Appropriate wording suitable to the study of libido could be substituted for these phrases. The precise words depend upon the phrase in current use in the population under study. The patient marks on the line how they feel in terms of sexual desire at that time. They then post the slip of paper into a box so that they cannot compare notes from day to day. However, obviously this method is not fool-proof because the patient can keep copies. When it comes to the analysis it is quite simple. The clerk handling the data simply measures on the 10 cm line the patient's mark and thus it is given a figure and by observing the change in these figures over a period of time, one should be able to make comments as to the trend. This approach is especially important in the male where all methods so far have resulted in an unacceptable loss of libido.

7. POTENTIA

The component of sexual function which is confined to the male which may be affected by therapy is potentia, the ability to obtain and maintain an

erection. This of course is more difficult to measure and depends upon the patient's recall of events but should not be ignored in the assessment of the treatment. Such instruments as penile plethysmographs do not have a practical application in a field trial.

8. SIDE-EFFECTS

With injectable contraceptives it should be remembered that there may well be local as well as systemic side effects and the site of the injection should be regularly inspected for any adverse signs. It should also be remembered that the excipients used as a vehicle for the preparation may not be entirely inocuous. The recording of side effects is a somewhat controversial subject. There are studies in which the patient is asked specific questions relating to specific expected side effects on a checklist basis. There are studies in which the patient is not asked specific questions but asked generalized questions such as "how have you been since your last visit?" If then they mention a side effect, it is recorded. A compromise between these two approaches, the first of which will over-record and the second of which will under-record the incidence of side effects, is to ask non-specific questions that are related to the anatomical systems, such as "have you had any trouble with your chest?". The draw back of this approach is, of course the difficulty of ensuring uniformity of questions in multi-centre trials involving different ethnic groups.

In general terms, side effects can be divided into objective and subjective. Objective side effects include alteration in weight, ankle swelling, vomiting, hair loss. Subjective side effects include nausea, headache, depression, fatigue, anxiety, and so on. In the female, particular attention should be paid to the genital organs including the breasts and regular examination of both the breasts and the pelvis are desirable together with cytological examination of the cervix. Examination in the male should include the tests for signs of atrophy, and for this purpose instruments such as the Prager orchidometer have been devised. The draw back of this method is that it requires between 30–50% reduction in volume before atrophy can be detected. In selected cases, testicular biopsy can be performed and the measurement of seminiferous tubular diameter can be calculated from a sample of 50 tubules.

9. METABOLIC STUDIES

Most of the short term metabolic side effects of the injectable contraceptive will have been established from the early clinical studies. However, the field trial situation offers the opportunity of monitoring the metabolic effects of long term therapy and a small group of patients should be selected for examination. The most commonly studied effects include those on carbohydrate metabolism either by intravenous or oral glucose tolerance. The precise technique varies considerably from centre to centre and probably the best approach is to use the technique that your laboratory is most used to. These carbohydrate studies can be combined with serial insulin and growth hormone assays. With some compounds it may be worthwhile to study prolactin levels, especially if some patients develop galactorrhoea. Lipid studies, including cholesterol, and triglycerides should be carried out when using steroidal compounds. Liver function tests include the standard tests such as serum bilirubin, SGOT, SGPT. Recently more precise tests have been developed in kit form. These are for the enzymes γ-glutamyltranspeptidase (γGTP) and 5′ nucleotidase. γ-Glutamyltranspeptidase is very sensitive to liver cell damage but is not absolutely specific, for it is also raised in conditions such as renal carcinoma, coronary thrombosis, pancreatitis, diabetes mellitus and following radiotherapy for cervical carcinoma. 5-Nucleotidase is an isoenzyme in the alkaline phosphatase family and is sensitive to biliary tract damage [4].

10. REASONS FOR WITHDRAWAL FROM STUDY

These can be quite readily classified under the following headings:

(a) *Involuntary pregnancy.* In this instance it is important to determine that the patient was not pregnant prior to the start of the therapy.

(b) *Voluntary pregnancy.* In which case the patient withdraws of her own free will so as to become pregnant.

(c) *Side effects of the treatment.* It is sometimes quite helpful to try and distinguish between the patient wishing to withdraw from the study and the doctor advising her such course of action. When this information is available one can assess if there was any investigator bias in the conduct of the study.

(d) *Adverse reaction.* There is no universally accepted definition of adverse reaction. There are those that consider any "reaction of a drug that is noxious, is unintended and occurs at doses normally used in man" [5] is an adverse reaction. This definition includes side effects as well but from an ethical point of view it is probably better to distinguish between "life threatening side effects" which may be called adverse reactions from those side effects which are not so considered. However, this does depend upon the individual physician deciding whether the side effect is "life-threatening" and therefore an adverse reaction.

(e) *No further need.* Includes such circumstances as the patient no longer co-habiting or the husband or patient having been sterilized.

(f) *Adverse publicity.* This general title covers a number of relatively minor reasons for discontinuing, such as the husband disliking the method, adverse publicity the patient has come across either through the media or through contact with opinion leaders such as officials in religious communities, etc.

(g) *Loss to follow-up.* This is one of the major problems associated with field trials. When the loss to

follow-up rate exceeds 15–20%, it becomes exceptionally difficult to make any firm conclusions about the study for it is not known how many of the 15–20% of patients lost to follow-up have become pregnant or suffered side effects or adverse reactions. It is not necessarily reasonable to assume that these patients will behave in the same way as those who continue to be followed up. Therefore, each clinic should make every effort to find patients who fail to return by the use of correspondence, telephone calls, home visits by social workers and so on. To some extent this problem can be avoided by adequate selection of patients prior to entry to the study but this will introduce a bias.

(h) Finally, in the design of a field trial it is necessary to have a section indicating the natural termination of the study so that when it comes to analysis, the computer will recognize that the study for that patient is ended and will not register the patient as lost to follow-up.

11. RESTORATION OF FERTILITY

By definition, this means a successful outcome of a pregnancy within a reasonable length of time since stopping the treatment. Usually this is taken as one year but varies from study to study. There may be a background of infertility due to such things as pelvic inflammatory disease in this group of patients. Secondly it is known that fertility diminishes with increasing age which may be in part due to a decreased frequency of coitus. However, rather than wait a year there are certain presumptive indices of fertility that can be studied. One of these is ovulation. In the female following the first vaginal blood loss after discontinuation of treatment, weekly serum progesterones can be done. This first episode of bleeding is a convenient timing mechanism for the patient to return to the clinic. However, this technique does not exclude ovulation occurring prior to the first bleed and unless the study is continued will not exclude irregular ovulation.

In the male, fertility can be monitored indirectly by monthly sperm counts and directly by pregnancy in the female partners.

In this type of study however, conception that occurs should be closely monitored for the duration and outcome of the pregnancy with appropriate chromosomal studies where indicated and in particular in male trials where the mode of action is inhibition of spermatogenesis. Scrupulous avoidance of all drug therapy during the pregnancy should be observed so as not to confuse the issue if any abnormalities are seen.

REFERENCES

1. Aitken R. C. B.: *Proc. Roy. Soc. Med.* **62** (1969) 989–993.
2. Zealley A. K. and Aitken R. C. B.: *Proc. Roy. Soc. Med.* **62** (1969) 993–996.
3. Aitken R. C. B. and Zealley A. K.: *Brit. J. Hosp. Med.* **4** (1970) 215–224.
4. Briggs M. H. and Hus P.: *Med. J. Austral.* (1974) February 9th, 194–195.
5. Wld Hlth Org. techn. Rep. Ser. No. 498 (1972) 9.