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## Relief of Premenstrual Symptoms, Dysmenorrhea, and Contraceptive Tablet Intolerance

A Preliminary Report

By

Joseph B. Miller, M.D.

Mobile, Alabama 36609

A new method of providing rapid relief of progesterone-related symptoms is based on the administration of progesterone injections in a dosage far smaller than in conventional usage. A hundredth, a thousandth, or a ten thousandth of a milligram of progesterone may give far superior, more rapid, and more dependable relief than 100-200 mgm. The exact dose is usually dramatically effective within 20 minutes; a dose slightly stronger or weaker than this is often ineffective, and may even aggravate symptoms. The proper dose can be determined precisely for each patient by a simple intradermal test.

Two types of progesterone-related symptoms can be relieved: (1) untoward reactions or unwanted side effects of the administration of exogenous progesterone, e. g. progesterone injections, and oral preparations containing progesterone, such as contraceptive tablets; and (2) symptoms occurring at a time of declining endogenous progesterone blood levels, such as premenstrual symptoms, dysmenorrhea, abnormal menstrual flows, and premenstrual and menstrual exacerbations of allergic syndromes such as asthma, perennial allergic rhinitis, urticaria, headache, vertigo, etc.

### Materials

The primary material used has been Progesterone Aqueous Suspension, 50 mgm/ml (obtained from Elkins-Sinn Incorporated, Cherry Hill, New Jersey 08034). The commercial material is used as the stock bottle or "concentrate." Nine or more vials of diluted progesterone are prepared by the 1:5 serial dilution method. To do this, 4 ml of diluent (sterile saline containing 0.4 per cent phenol preservative) is added to each of the vials, and the vials are labelled Progesterone No. 1, Progesterone No. 2, etc. Then 1 ml of the progesterone concentrate is added to the No. 1 vial, obtaining thorough mixing by 5 to 6 push-pulls of the syringe plunger. With the hypodermic needle still in the No. 1 vial, 1 ml of this mixture is then withdrawn. This is added to the No. 2 vial, and the process is repeated until all vials are similarly mixed.

### Technique of Testing

Testing is scheduled for a time when the patient is experiencing her premenstrual or menstrual symptoms, or on days that she is having symptoms from her contraceptive tablets, etc. The therapeutic dose is 0.05 ml of that dilution which clears these symptoms

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completely within 20 minutes of administration as an intradermal test.

The usual starting dose is 0.05 ml of Dilution No. 1, administered intradermally. If this clears the symptoms within 20 minutes, as it often does, it is the treatment dose. If it does not, 0.05 ml of Dilution No. 2 is used next. If the symptoms remain unchanged or improve only partially, 0.05 ml of Dilution No. 3 is used, followed by consecutively weaker dilutions at 20 minute intervals as long as the symptoms become progressively better or at least do not worsen. In other words, if symptoms improve or remain unchanged while going consecutively weaker, one should continue going weaker until the symptoms either clear completely or become worse. Worsening while going weaker indicates moving consecutively stronger again.

The rule is: while moving in a given direction, if symptoms are improving with each dilution, continue in the same direction; if symptoms are worsening, change to the opposite direction. If worsening occurs after moving from Dilution No. 1 to Dilution No. 2, then 0.05 ml of the Concentrate is used next, and may produce relief. If this still does not give relief, Dilution No. 1 should be given again; it may give relief on the second try. If it does not, then Dilutions No. 2, No. 3, No. 4, No. 5, etc. are used until relief occurs.

### Testing Hyper-reactive Patients

About 3 per cent of patients are too hyper-reactive to start with 0.05 ml/No. 1. If a patient is unusually sensitive in general, or has unusually severe symptoms with menses, particularly exacerbations of asthma, vertigo, or syncope, she should be started with 0.01 ml of Dilution No. 4, No. 8, No. 12 or weaker. Then any symptoms or changes that occur will probably be mild.

The idea is to start in a zone of little or no reaction, i. e. a dilution so weak that it stimulates mild or no symptom response. The "0.01 ml volume" is too small to read by the syringe markings, so is defined as

that volume of fluid required to produce a 4 mm wheal. It is recognized that this volume is not always precisely 0.01 ml, but the term is used for convenience.

For example, if the first test injection is 0.01 ml/No. 4 and this makes the symptoms worse, or better but not clear, the next dose administered should be 0.01 ml/No. 5. If 0.01 ml/No. 5 produces no change or only partial clearing, it should be followed by consecutively weaker dilutions until symptoms clear. If 0.01 ml/No. 5 or any subsequent weaker dose produces worsening, this indicates moving consecutively in the opposite direction, i. e. stronger, until relief occurs. In either case, once clearing of symptoms occurs on the 0.01 ml dose, 0.05 ml of the same dilution should be administered as the definitive treatment dose.

On the other hand, if the first test injection (0.01 ml/No. 4) clears the symptoms completely, 0.05 ml of No. 4 is given to verify that this is the definitive treatment dose. If symptoms return on the 0.05 ml dose, then 0.05 ml of the next weaker dilution is given, followed by 0.05 ml of consecutively weaker dilutions until either clearing or worsening occurs. Clearing indicates the definitive treatment dose; worsening indicates moving consecutively stronger until relief is obtained.

It can be seen that the same principles of testing apply as in less reactive patients, particularly in regard to the direction signals. Giving doses in consecutive order is more informative of direction signals than skipping about. Whenever symptoms finally clear on the 0.01 ml dose, the 0.05 ml dose should be given for verification, for greater accuracy, and for more prolonged relief.

If a seemingly less reactive patient is started on the 0.05 ml/No. 1 dose, and symptoms are distressing and neutralization is difficult to achieve in the first few doses in the stronger range, it is sometimes well to re-categorize her as a hyper-reactive patient and start over again immediately in a weaker

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range, e. g. 0.01 ml/No. 8, and proceed as described above for hyper-reactive patients. If the patient is unable to tolerate continued testing, relief can almost always be provided by administering a small subcutaneous dose of epinephrine. The preferred dosage form is *Susphrine (R)\**, five-hundredths ml (0.05 ml), as it usually takes effect in 3 minutes and may provide up to 24 hours relief.

### Response

When the treatment dose is reached, there is complete or near-complete clearing of symptoms within 20 minutes. Symptoms tend to recur, and are best handled by administration of repeated treatment doses subcutaneously as needed. Usually the patient needs only one, two, or three treatment doses with each period, administered when symptoms recur. Some develop a lasting immunity within a few months, and then get along without any further injections. This often applies to patients on contraceptive tablets also, and some can continue taking their tablets without symptoms and without further progesterone injection therapy.

The symptoms which have responded to progesterone minidose therapy, in order of frequency of occurrence, are headache, tenderness, cramps, nausea, depression, vertigo, heavy flow, fatigue, backache, discharge, scant flow, breast soreness, ovulation pain, nasal congestion, asthma, and urticaria. It is interesting that heavy flows (flooding) are decreased toward normal, and scant painful flows are increased toward normal. It is also interesting that gross overusage of treatment doses usually manifests itself, if at all, by changes in flow, e. g. heavier flow, lighter flow, spotting, late period, skipped period, etc. This is prevented by simply using the treatment injections only when definite symptoms recur, and only if relief is obtained with each such injection, indicating correct dosage. If complete or near-complete relief does not occur, this signifies that the dosage need has changed, and the injections should be discontinued until retesting can be done.

At this writing, 53 cases have been studied. Favorable response occurred in 43 (80 per cent). Complete and dramatic relief occurred in 15 (28 per cent). Marked but not quite complete relief occurred in an additional 10 (19 per cent). Good relief occurred in an additional 18 (33 per cent), with only a moderate degree of residual symptoms. Those who obtained relief on testing also obtained relief by subcutaneous treatment when symptoms recurred.

### Treatment Options

Treatment can be managed with greater convenience and virtually perfect control of discomfort by having the treatment injections administered at home. The patient or a member of the family can be instructed in the technique of subcutaneous hypodermic injection so that they can give the injections at any hour of the day that symptoms recur. Printed forms can be issued to reinforce verbal instructions. In order to facilitate home administration, prevent errors, and make it easier to withdraw the proper dose from the vial, the patients can be issued 1 ml single-dose vials each containing one treatment dose (0.05 ml of the treatment dilution) mixed with 0.5 ml of phenolated saline diluent. As the entire contents of one vial equals one dose, dosage errors are virtually impossible. Five such vials can be issued, along with 5 disposable tuberculin syringes and 5 disposable alcohol sponges in aluminum foil.

Physicians who prefer office administration can simply repeat the treatment dose daily in the office, as needed, managing any interim symptoms pharmacologically if necessary.

### Instructions To The Patient

The patient should be instructed in advance that this is routinely a two-day test, that neutralizing doses can change at any time, that these changes can result in lessened effectiveness or even heightened symptoms when the obsolete treatment dose is administered, that retesting will restore effectiveness immediately, and that the long-

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term benefit is worth the temporary discomfort involved in undergoing office testing while suffering from headache or menstrual cramps. By retesting the second day, one can inquire about the effectiveness of the first days treatment dose, and verify by retesting that the treatment dose is unchanged, or find the new treatment dose if a change has occurred.

### Discussion

From the practical standpoint, progesterone minidose therapy is effective in a sufficient number of patients, 80 per cent, to make it a worth while clinical procedure. It is particularly appreciated by patients with severe prolonged progesterone-related symptomatology. Their relief is often great and at times dramatic, especially when considering their previous poor response to analgesics and other therapeutic modalities. Severe cases who could formerly obtain little relief with large doses of hormones and analgesics can often be given marked relief with progesterone minidoses alone or in conjunction with lesser doses of analgesics. There is no question but that other hormonal

and nonhormonal factors are involved in the symptomatology of the menstrual cycle, so progesterone treatment alone cannot be expected to prove 100 per cent effective in all cases.

### Conclusions and Summary

1. A treatment is described for obtaining marked and often dramatic relief of hormonally related symptoms within 20 minutes by administration of relatively tiny doses of progesterone.
2. A simple skin-test technique is described for finding the effective dose for each patient.
3. The method is effective in premenstrual and menstrual symptoms, premenstrual and menstrual exacerbation of allergic syndromes such as asthma, allergic rhinitis, urticaria, atopic dermatitis, headache, vertigo, etc., and intolerance or side effects from the administration of contraceptive tablets and other progesterone-containing preparations.

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\*Cooper Laboratories Inc., Mystic, Connecticut 06355.