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Effect of medroxyprogesterone acetate on peritoneal adhesion formation*

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In 1980 Eddy et al.[1] reported reduced adhesion formation following ovarian wedge resection if the ovary operated upon contained a corpus luteum. They hypothesized that increased progesterone (P) production from this structure impeded adhesion formation. More recently, intraperitoneal and intramuscular aqueous P regimens have been reported to significantly reduce adhesion formation following peritoneal injury in a guinea pig model.[2] The suppression of adhesion formation by P is not inexplicable. Progestins have established immunosuppressive and antiinflammatory actions.[3, 4] Other agents with similar activity have been reported to inhibit adhesion induction.

This study was designed to assess the effectiveness of a more potent progestin, medroxyprogesterone acetate (MPA; Depo-provera, The Upjohn Company, Kalamazoo, MI) for adhesion prophylaxis. Additionally, it was anticipated that tissue damage might induce the development of autoantibodies to endometrial and peritoneal/myometrial tissue antigens. Their development and possible suppression by MPA was also evaluated.

MATERIALS AND METHODS

Eight adult, nonpregnant, female New Zealand White rabbits weighing 3 to 5 kg were used. The animals were individually housed and received uniform care. Prior to surgery they were assigned to control or treatment groups according to a predetermined randomization sequence. Animals in the treated group received intramuscular injections of MPA, 15 mg/kg body weight, beginning 2 days prior to surgery and continued daily for a total of six doses. Intramuscular ketamine and xylazine were used for anesthesia; no prophylactic antibiotics were employed. All animals underwent laparotomy through a lower midline incision with the use of sterile technique. Adhesions were induced by abrading the distal antimesenteric uterine horns with a scalpel until macroscopic bleeding occurred and then crushing them with a hemostat for 30 seconds in four locations.[5] The abdominal incisions were closed in two layers with 3-0 chromic suture. All surgery was performed by the same individual, who was without knowledge of the animals' treatment status.

Two weeks later the animals were killed, and the extent of pelvic adhesion formation was assessed by an individual who was without knowledge of the animals' prior therapy. Adhesions to each uterine horn were scored separately accord-

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Table 1. *Adhesion Scores and Reciprocal Titers of Antibodies to Human Red Cell Antigens (Heterophilic Antibodies), Rabbit Peritoneum/Myometrium, and Rabbit Endometrium in Nonoperated Animals, Surgical Control Animals, and MPA-Treated Animals*

Group	Adhesion score	Antibody titers to		
		Red cells	Peritoneum/myometrium	Endometrium
Nonoperated	—	11 ± 3	14 ± 4	15 ± 5
Control	2.5 ± 0.5	17 ± 5	128 ± 0	96 ± 19
Treated	4.0 ± 0	5 ± 1	65 ± 25	68 ± 23

Results are expressed as the mean ± standard error of the mean.

ing to the following classification: grade 0, no adhesions; grade 1, an easily separated filmy adhesion; grade 2, extensive filmy adhesions; grade 3, a single dense adhesion; and grade 4, widespread dense adhesions.

Additionally, blood was obtained from the study animals and from three rabbits that had never undergone surgery for determination of titers of antibodies to endometrium and peritoneum/myometrium as well as heterophilic antibodies to uncoated human O^+ red blood cells (RBCs). A passive hemagglutination assay was used.[6] Endometrial and peritoneal/myometrial tissues were obtained from surgical control animals, macerated, sonicated, and heat-solubilized. The crude antigenic extracts thus obtained were coated on human O^+ RBCs and titrated against serial dilutions of sera in microtiter plates (Fisher Scientific Company, Piscataway, NJ). The plates were incubated overnight at 4° C, centrifuged at 400 × *g* for 1 minute, and read at a 45-degree angle. A positive reaction was indicated by button formation, and a negative reaction, by a streaking pattern. The end-point was the dilution at which the button formation stopped.

The pooled *t*-test was employed for statistical analysis.

RESULTS

Adhesion scores and antibody titers are summarized in Table 1. There was no significant difference in antibody titers to uncoated RBCs in the three groups. Significantly greater titers were found to peritoneum/myometrium ($P < 0.0001$) and endometrium ($P < 0.025$) in surgical control animals than in nonoperated animals, confirming that intraoperative trauma was responsible for their development. The differences in titers to peritoneum/myometrium and endometrium between nonoperated and MPA-treated animals were insignificant. MPA-treated animals had significantly ($P < 0.05$) lower titer to peritoneum/myometrium than did surgical control animals, suggesting some reduction in immune reactivity in those that received MPA.

DISCUSSION

The results of this study are disappointing, particularly in light of the impressive reduction in adhesion formation reported with P by Maurer and Bonaventura.[2] There are, however, substantial differences between these studies. Most obvious is the employment of a synthetic progestin rather than the natural hormone used in their study. MPA has documented antiinflammatory and immunosuppressive activity, but it may be less effective in this application than P. The dosage employed is believed to be optimal, because previous studies have shown a biphasic dose response relationship for MPA when used for immunosuppression.[3] Pharmacodynamic studies have established that substantial tissue levels of MPA are achieved within a few hours of administration; thus, more prolonged preoperative therapy is not likely to be of greater benefit. The animal model employed is also different. It is possible that immunosuppressive regimens inhibit adhesion formation more effectively in the guinea pig than in the rabbit. Moreover, the degree of injury in our study was greater than that described in the P study.

The statistically significant increase in adhesion scores in the MPA group may represent a sampling error secondary to the small number of animals in the study. The significant reduction of titers of autoantibodies to peritoneum/myometrium suggests some degree of immune suppression by MPA, although not necessarily great enough to reduce adhesion formation. Alternately, the progestin may have actually increased adhesion formation, perhaps by blocking collagen breakdown.[4]

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