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The progesterone receptor antagonist mifepristone does not lower serum progesterone induced blocking factor (PIBF) in the presence of progesterone

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Summary

Purpose: To determine if mifepristone can lower serum levels of a progesterone (P) induced immunomodulatory protein believed to be needed for the fetus to escape immune surveillance. *Materials and Methods:* A female volunteer had her serum P induced blocking factor (PIBF) increased by ingestion of oral micronized P. While remaining on P mifepristone, 200 mg/day was given for six days when another serum PIBF level was obtained. *Results:* The serum PIBF was 273 ng/ml after five days of oral micronized P. It increased further to 737 ng/ml despite taking six days of 200 mg mifepristone. *Conclusions:* The mechanism for inducing abortion by mifepristone does not seem to be related to decreasing serum levels of PIBF. This does not eliminate the possibility that the mechanism involves reducing the intracytoplasmic PIBF levels.

Key words: Selective progesterone receptor antagonists; Mifepristone; Serum immunomodulatory protein; Progesterone induced blocking factor; Therapeutic abortion.

Introduction

It is common knowledge that a certain minimal level of progesterone (P) must be maintained from ovulation until delivery to allow a full-term baby to be born. P acting in conjunction with the P receptor causes the production of various molecules needed for appropriate development of a secretory endometrium to allow proper implantation [1].

The maintenance of P secretion throughout pregnancy is needed, at least in part, for inhibiting myometrial contraction and for immune suppression of the fetal semi-allograft [1]. One of the mechanisms by which the interaction of P and P receptors may inhibit immune suppression is by the secretion of the immunomodulatory protein, the progesterone induced blocking factor (PIBF) [1-4]. One of the main functions of PIBF is to inhibit degranulation of perforin granules in natural killer (NK) cells thus inhibiting their cytotoxicity [5].

The PIBF is a protein which when detected in serum measures 34 kDa and is a splice variant of the parent compound which resides in the nucleus at a centrosomal position and measures 90 kDa [6]. The full length protein consists of 757 amino acid residues and the 48 kDa N terminal part is biologically active [7]. PIBF seems to be unique in that it shows no significant amino acid sequence homology with any known protein [7].

RNA expression analysis has demonstrated that centrosomal PIBF is overexpressed in rapidly proliferating cells irrespective of whether they have been found to be positive or not for P receptors [1,6]. Serum levels of PIBF are mainly produced by the interaction of P with P receptors on gamma delta T cells [8]. Whereas addition of P to the media of certain leukemia cell lines caused an upregulation of the 34 kDa intracytoplasmic splice variant of PIBF, in contrast, adding the P receptor antagonist mifepristone caused downregulation of PIBF expression [9].

Interestingly mifepristone was found to reduce NK cell activity in pregnant women [10]. The assumption was made, but not proven, that the mechanism of action probably was related to the P receptor antagonist interfering with the reaction of P with P receptors on gamma/delta T cells, and thus reduction of secretion by these cells of the circulating 34 kDa protein, and thus failure to stabilize perforin granules in circulating NK cells. Recently, with purification of the PIBF protein, a sensitive ELISA assay to PIBF has been developed [11-13]. The objective of the present study was to determine if mifepristone can suppress circulating levels of serum PIBF.

Materials and Methods

A 23-year-old young lady volunteer on continuous oral contraceptives had a baseline serum PIBF level obtained. On day 5 of taking oral micronized P 200 mg daily, a serum PIBF level

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was obtained. The 200-mg oral micronized P was maintained, and she was also given 200 mg mifepristone orally concomitantly. On the 6th day of combined oral P and mifepristone, another serum PIBF was obtained. The PIBF was measured by a non-commercial research ELISA assay using a monoclonal anti-PIBF antibody [12,13].

Results

The baseline serum PIBF was 62 ng/ml. The PIBF levels increased to 273 ng/ml after five days of oral P therapy. The level was over 737 ng/ml six days later, despite taking a dosage of mifepristone that will usually terminate a live fetus.

Discussion

Mifepristone is a known abortifacient. As mentioned, in view of the inhibiting effect of mifepristone on NK cell activity, and since NK cell activity is suppressed by PIBF (which is induced by P), logically, it seemed likely that the mechanism of causing abortion was by immune rejection probably by inhibiting PIBF production by circulating gamma/delta T cells [10]. However, mifepristone has been hypothesized to have other actions abrogating immune suppression other than via a PIBF mechanism [14,15]. Thus, based on the present data, failing to demonstrate any suppression of PIBF by mifepristone in a patient taking exogenous P, one hypothetical conclusion is that the mechanism of action does not involve PIBF. However, the study by Ivanova-Todorova *et al.* did not evaluate serum PIBF levels and thus reduced NK cell activity may not have been through suppression of circulating PIBF secreted by gamma/delta T cells [10].

The study of the effect of mifepristone on reducing the intracytoplasmic 34-36 kDa splice variant of PIBF secretion by certain leukemia cell lines allow an alternative hypothesis [9]. Mifepristone may cause immune rejection of the fetus by suppressing intracytoplasmic PIBF of the rapidly growing cells of the placenta or the fetus itself thus abrogating immune tolerance to the fetal semi-allograft leading to abortion.

Mifepristone has been demonstrated to have a palliative effect on a variety of human and murine cancers, not only not known to be P receptor positive, but where there has been demonstration of normal serum PIBF levels [16-24]. Though there are many mechanisms of how P and P receptors may allow cancer cells to grow even without effects on tumor immunology, suppressing intracellular conversion of the parent 90 kDa parent PIBF compound to the 34-36 kDa intracytoplasmic splice variant is one of the possibilities. Thus, mifepristone suppressing intracytoplasmic PIBF could be one, if not the major mechanism, as to how mifepristone ingestion leads to pregnancy termination.

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