

SUPPRESSION OF HUMAN POLYMORPHONUCLEAR FUNCTION AFTER INTRAVENOUS INFUSION OF PROSTAGLANDIN E₁

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ABSTRACT

In two of three patients with peripheral vascular disease, systemic infusion of PGE₁ inhibited chemotactic factor induced secretion of glucosaminidase from neutrophils.

Abundant experimental evidence now supports a view that prostaglandins of the E series can help regulate inflammatory responses. Although PGs appear to be local mediators of inflammation, (reviewed, 1) systemic administration of PGE₁, E₂ and the stable E₁ analog, 15-(S)-15-methyl-PGE₁ suppress inflammation in several experimental animal models (2,3,4,5). In vitro studies suggest that the ability of these compounds to limit inflammation may result from inhibition of polymorphonuclear leukocyte (PMN) functions such as aggregation (6), enzyme release (7), and directed migration (chemotaxis) (8). In this report we describe neutrophil function in 3 patients who received systemic treatment with PGE₁ for peripheral vascular disease. Two of the patients exhibited significant inhibition of leukocyte function following PGE₁ treatment. This represents one of the first observations in humans of altered neutrophil function after in vivo treatment with PGE₁.

Three patients with peripheral vascular disease were treated with intravenous (I.V.) administration of PGE₁ (kindly provided by Dr. William Martin, Upjohn Co., Kalamazoo, Michigan). Each patient had peripheral total white blood cell counts and white blood cell differential counts within normal ranges. The patients received PGE₁ by continuous I.V. infusion of 3µg/hr for 6 hours followed by a 6 hours "rest" period and a second 6 hour infusion period. Peripheral blood neutrophils were isolated by Ficol gradient separation from three patients before PGE₁ treatment and 4 hours after the second 6 hour PGE₁ infusion period began. Secretion of the lysosomal enzyme N-acetyl-b-D-glucosaminidase from cytochalasin B (5µg/ml) treated neutrophils (5x10⁶) stimulated with N-formyl-methionyl-leucyl-phenylalanine (F-met-leu-phe) was determined (9). A range of F-met-leu-phe concentration was examined. This was compared to a similar dose response as determined in a healthy control individual. The

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response of the control individual's neutrophils to F-met-leu-phe was similar to the response of two other healthy individual's neutrophils. The percent maximum enzyme release (MER) was determined as follows: per cent MER = $\frac{\text{MER patient}}{\text{MER control}} \times 100$

The effects of systemic infusion of PGE₁ on chemotactic factor induced secretion of glucosaminidase from neutrophils is shown in Fig. 1A. Before PGE₁ infusion, enzyme secretion from PMNs from patients #1 and #2 was not significantly different from control values. However, during treatment a decrease of 15.3% (p < .01) and 33.4% (p < .01) in MER from pre-treatment values was seen in patients #1 and #2, respectively. MER was achieved with approximately 5x10⁻⁸ M F-met-leu-phe. Patient #3 showed a significant decrease in MER compared to the control individual even before treatment with PGE₁. Although the value of MER of patient #3 increased slightly during treatment it is not known why this patient's initial studies were significantly less than the control individual. Thus, it is difficult to interpret this patient's response to PGE₁ treatment.

After stimulation at various doses of F-met-leu-phe, Figures 1 (B) and 1 (C) show the variation in enzyme release of the neutrophils from patients #1 and #2. Significant inhibition of enzyme release (glucosaminidase activity) was seen throughout the F-met-leu-phe dose response range (Figs. 1B & 1C).

Addition of PGE₁ to PMNs in vitro inhibits neutrophil chemotaxis (8), aggregation (6), and endocytosis induced lysosomal enzyme release (7). In addition, systemic administration of PGE₁, or its analog 15-(S)-15-methyl-PGE₁ prolongs survival and retards progression of glomerulonephritis in NZB/NZW F₁ hybrid mice (3), inhibits the joint inflammation of chronic adjuvant arthritis in rats (4), suppresses the dermal Arthus reaction (5), and inhibits vascular permeability changes due to vasoactive mediators (6). However, there is a paucity of data in humans regarding the effects of systemic administration of PGE₁.

Recent studies have demonstrated physiologic effects of prostacyclin in vivo. Following intravenous administration of prostacyclin in humans with peripheral vascular disease, Szczelik et al (10) reported improvement in peripheral vascular perfusion. Although we have examined only a small number of patients, our data with humans parallel observations in experimental animals; that is, in vivo treatment with PGE₁ induces significant functional defects in neutrophils. Thus, PGE₁ treatment in this manner has the potential to produce significant anti-inflammatory effects in vivo. It is important to underscore that induction of chemotactic defects in PGE₁ treated rats was of an order far greater than could be achieved by in vitro exposure of neutrophils to PGE₁ (5). Thus, administered PGE may influence the function of cells involved in the inflammatory response in ways that can be used to clinical advantage.

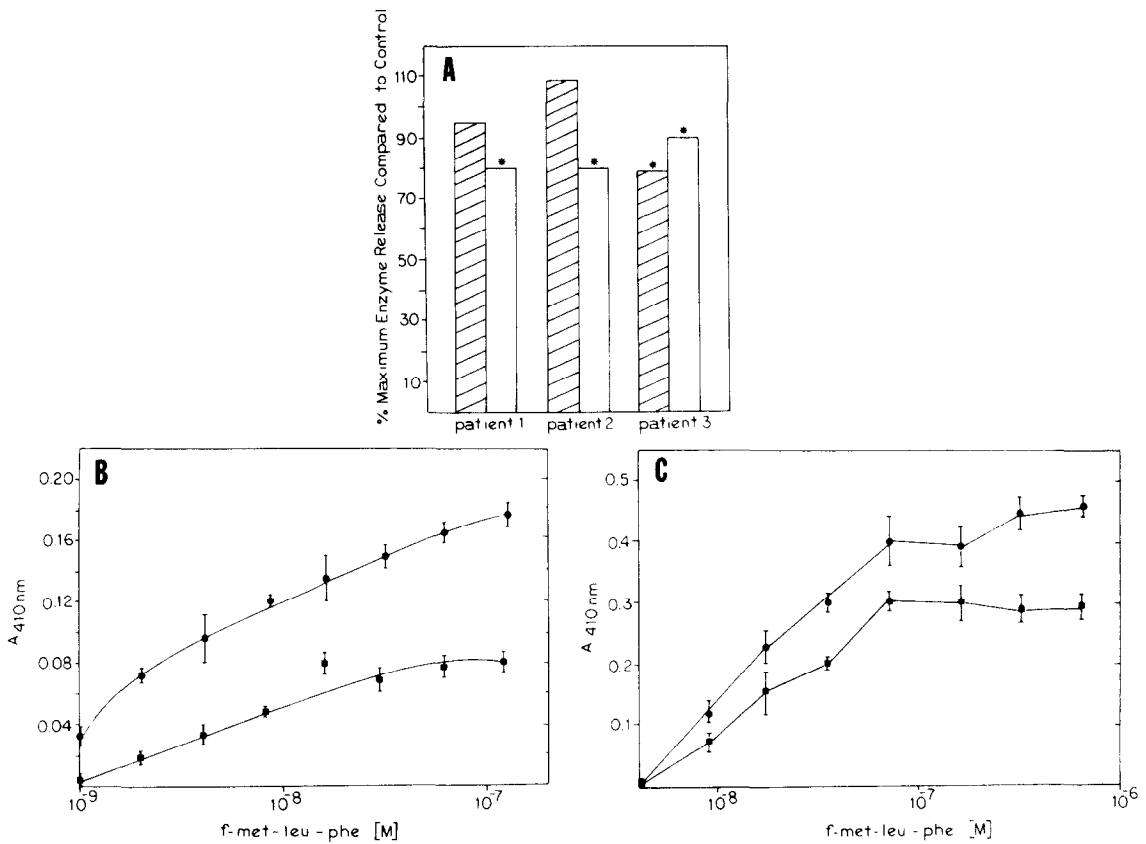


FIGURE 1:

(a) Percent maximum enzyme release (MER) in three patients compared to a control individual. ▨ = prior to PGE₁ treatment. □ = during PGE₁ treatment. * = p < .01. Student's T-test was used to compare the patient's MER to the control individual's MER.

(b) and (c)

Comparison of the effect of the concentration of F-met-leu-phe in the presence of cytochalasin B (5 μg/ml) on the secretion of glucosaminidase (expressed as the change in absorbance at 410 nm) from neutrophils isolated from patient #1 (b) and patient #2 (c) during PGE₁ treatment.

(●) = control individual, † SEM

(■) = patient #1 (b), patient #2 (c), † SEM.

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