OII-A-4

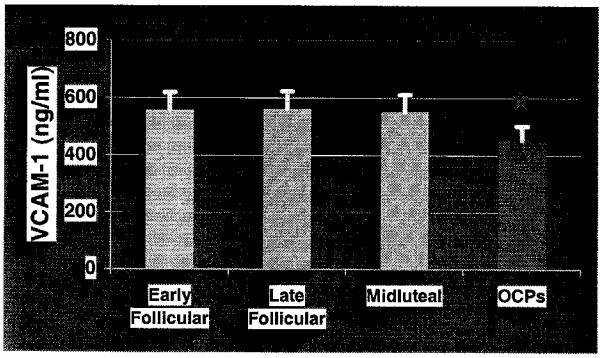
SOLUBLE VASCULAR CELL ADHESION MOLECULE-1 (SVCAM-1) LEVELS ARE SUPPRESSED BY ESTROGENS IN WOMEN ON ORAL CONTRACEPTIVES COMPARED TO NORMALLY MENSTRUATING WOMEN. C. Janzen, MD, I. Souter, MD, O. Martinez-Maza, PhD, F. Stanczyk, MD, G. Chaudhuri, MD, PhD, L. Nathan, MD, UCLA Center for Health Sciences, USC, Los Angeles, CA.

Objective: The purpose of this study is to assess the effect of estrogens on the expression of VCAM-1, an adhesion molecule that is responsible for the attachment of monocytes to the endothelial cell, leading to the formation of atherosclerotic plaque.

Methods: We measured the serum levels of 17β- estradiol (E_2) and sVCAM-1 (as this correlates with the expression of VCAM-1 on the endothelial cells) in early follicular phase, preovulatory period and midluteal phase in 14 menstruating women. Similar measurements were performed in serum samples obtained from 10 healthy premenopausal women receiving combined oral contraceptives. As cytokines, such as IL-6 and TNF-a stimulate the expression of sVCAM-1, serum levels of these cytokines were also measured by ELISA in all of the above patients. Serum levels of E_2 and sVCAM-1 were quantified by a highly specific RIA and ELISA respectively.

Results: Serum levels of soluble VCAM-1 demonstrated no significant change when correlated with serum E_2 levels assessed throughout various phases of the menstrual cycle (Fig 1). The mean VCAM-1 level was 490.36 ± 29.77 ng/mL).

However, in women receiving exogenous estrogens in the form of combined oral contraceptives, the mean sVCAM-1 level was significantly decreased when compared to normally menstruating women. (350.3± 19.50 ng/mL vs. 490.36 ± 29.77 ng/mL, p=0.0007). The circulating levels of TNF-a and IL-6 did not show any significant difference throughout the menstrual cycle and when compared to serum levels in women receiving exogenous estrogen.



Conclusions: Our data indicate that the levels of sVCAM-1 are significantly reduced in the serum of women receiving exogenous estrogen in the form of oral contraceptives, suggesting that long-term exposure to E_2 (and not short-term fluctuation) suppresses E_2 expression. This effect of long-term exogenous exposure to E_2 in inhibiting sVCAM-1 may help in the attenuation of early atherogenesis by preventing the adhesion of monocytes to the endothelial cells. This may be one potential explanation as to why women in their reproductive years have a lower incidence of cardiovascular morbidity when compared to men of similar age.

OII-B-1

INCREASED α_1 ADRENERGIC VASCULAR SENSITIVITY IN THE DORSAL HAND VEIN IN AFRICAN-AMERICANS. G. Sofowora, MD, M. Muszkat, MD, V. Dishy, MD, H.C. Prasad, MD PhD, A.J.J. Wood, MD and C.M. Stein, MD. Div of Clin. Pharm., Vanderbilt University, Nashville, TN.

The α_1 adrenergic receptor is highly expressed in human resistance arteries and veins and is the prime mediator of adrenergic smooth muscle contraction. We have previously shown that sensitivity to phenylephrine, an α_1 adrenergic agonist, is increased in forearm resistance vessels in African-Americans (AA) compared to Caucasians (CA). To determine if this finding was localized to one vascular bed or reflected a more generalized alteration in vascular sensitivity we compared dorsal hand vein responses to phenylephrine in AA and CA. Responses to incremental doses of phenylephrine (1- 12,000 ng/min) infused into a dorsal hand vein were measured using a linear variable differential transformer in 73 healthy non-smoking adults (53 CA and 20 AA). Dose response curves to phenylephrine were constructed for each subject and the dose that constricted the vein by 50% (ED50) expressed as geometric mean (95% CI) and maximum response (Emax ± SEM) calculated. AA were significantly more sensitive to phenylephrine (ED50 177.8 ng/min CI 93.3-338.8 ng/min), than CA (426.6 ng/min CI 288.4-645.7 ng/min) P= 0.02. The average Emax in CA (93.9 ± 2.0%) and AA (88.8 ± 2.6%) was not different (P = 0.2). These findings suggest that vascular α_1 adrenergic receptor sensitivity in AA is increased in several vascular beds and that the dorsal hand vein model can be used to study the mechanism underlying these differences.

OII-B-2

MEALTIME PRAMLINTIDE ADMINISTRATION REDUCES EARLY POSTPRANDIAL GLUCOSE EXCURSIONS WHEN ADDED TO REGULAR INSULIN OR INSULIN LISPRO IN PATIENTS WITH DIABETES: A DOSE-TIMING STUDY. M. S. Fineman, BS, S. B. Johnson, PharmD, Amylin Pharmaceuticals, FDA, San Diego, CA.

Previous studies have shown that administration of pramlintide (PRAM) modifies early (2hr) postprandial glucose excursions in patients with diabetes by regulating gastric emptying and suppressing postprandial glucagon secretion. The present single-blind, placebo-controlled, 5-way cross-over study assessed the optimal timing of PRAM administration in relation to a mixed meal in patients using regular (R) or lispro (L) insulin. Fifty-nine patients with diabetes (40 Type 1 & 19 Type 2) received subcutaneous injections of placebo (PBO) at -15 minutes, or PRAM (60 μg Type 1, 120 μg Type 2) at –15, 0, +15, and +30 minutes relative to a mixed meal. Patients also received either L at 0 min or R at –30 min, relative to the meal. Plasma glucose and PRAM were measured before and after the meal. PRAM Tmax occurred within 30 minutes, regardless of dose or dose timing. Plasma glucose in the PBO group increased from baseline within the first 15 minutes (59.6 mg/dL), and decreased in the –15 and 0 PRAM groups (2hr Cavg 4.0 and -9.4 mg/dL, respectively). PRAM administered post-meal was less effective at reducing the early glucose rise (2hr Cavg 8.6 and 21.7 mg/dL, respectively), compared to PRAM administered pre-meal (–15 or 0 min). Subcutaneous PRAM, administered at or just prior to the meal, improved early postprandial glucose excursions in insulin-treated diabetics, with the extent of the glucose lowering action depending on the duration of action of the short-acting insulin.