AA-2414, an Antioxidant and Thromboxane Receptor Blocker, Completely Inhibits Peroxide-Induced Vasoconstriction in the Human Placenta

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ABSTRACT

We hypothesized that AA-2414, a novel thromboxane receptor blocker with antioxidant properties, would inhibit peroxide-induced vasoconstriction in the isolated perfused human placental cotyledon. In study 1, placental cotyledons (n = 5) were perfused serially for 20-min intervals with control Krebs-Ringer-bicarbonate (KRB) buffer, t-butyl hydroperoxide (Px; 100 μM), KRB buffer, and KRB buffer containing Px to which progressively increasing concentrations of AA-2414 were added (1 × 10^{-8} to 1 × 10^{-4} mol/l). In study 2, placental cotyledons (n = 6) were perfused with control KRB buffer, Px alone, KRB buffer, 1 × 10^{-5} mol/l AA-2414 alone, Px plus AA-2414, and Px alone. Compared with control perfusion with Px significantly increased perfusion pressure, vascular resistance, and the maternal and fetal secretion rates of lipid peroxides, thromboxane B_2 (TXB_2) and 6-keto prostaglandin F_1α.

In study 1, AA-2414 + Px produced a dose-response inhibition of Px-induced increases in perfusion pressure, vascular resistance, and maternal secretion of lipid peroxides and TXB_2. In study 2, perfusing AA-2414 at a dose of 1 × 10^{-5} mol/l completely inhibited Px-induced vasoconstriction and increases in lipid peroxide and TXB_2 secretion rates, but only partially inhibited the increase in 6-keto prostaglandin F_1α secretion. We conclude that AA-2414 inhibited peroxide-induced vasoconstriction in the human placenta, as well as peroxide-induced increases in the placental secretion rates of lipid peroxides and thromboxane, but only partially inhibited peroxide-induced increases in the placental secretion rate of prostacyclin.

Preeclampsia is one of the most significant health problems of human pregnancy. It is a leading cause of fetal growth retardation, premature birth, and low birth weight babies. Preeclampsia is characterized by maternal hypertension, reduced uteroplacental blood flow, increased platelet aggregation, endothelial cell dysfunction, proteinuria, and edema. Biochemically preeclampsia is associated with two significant imbalances: 1) an imbalance of increased thromboxane and decreased prostacyclin (Walsh, 1985; Friedman, 1988), and 2) an imbalance of increased lipid peroxides and decreased antioxidants (Walsh, 1994).

These imbalances may be significant because many of the physiologic and biochemical actions of lipid peroxides pertain to the abnormalities that are seen with preeclampsia, as recently reviewed in Walsh (1994). Some of the effects of lipid peroxides include the following. 1) Stimulation of prostaglandin endoperoxide synthase to increase production of thromboxane, but inhibition of prostacyclin synthase to decrease production of prostacyclin. This imbalance is believed to contribute to the increased platelet aggregation, maternal hypertension, and reduced uteroplacental blood flow that occur in preeclampsia because thromboxane is a potent vasoconstrictor and a stimulator of platelet aggregation, whereas prostacyclin is a potent vasodilator and an inhibitor of platelet aggregation. 2) Increased cell membrane permeability to proteins and increased incorporation of fatty acids into endothelial cell membranes. Alteration of endothelial cell membranes in the renal and systemic vasculatures with increased permeability to proteins could explain proteinuria and edema. 3) Increased thrombin generation and decreased antithrombin III levels to trigger thrombus formation. This, along with increased thromboxane synthesis, could explain coagulation abnormalities, such as disseminated intravascular coagulation and platelet consumption.

AA-2414 [(±)-7-(3,5,6-trimethyl 1-1,1,4-benzoquinon-2-yl)-7-phenylethanoic acid] is a novel, long-acting, potent stereospecific thromboxane A_2/prostaglandin endoperoxide type 2 receptor antagonist (Hussein et al., 1994). AA-2414 inhibits the contractile response of aortic and saphenous vein

ABBREVIATIONS: ET, endothelin; F, fetal; 6-keto PGF_1α, 6-keto prostaglandin F_1α; KRB, Krebs Ringer bicarbonate; M, maternal; Px, t-butyl hydroperoxide; TXB_2, thromboxane B_2.
preparations to the thromboxane analog, U-46619, and it is a potent inhibitor of platelet aggregation. Its effects are thought to be primarily by blocking thromboxane receptors rather than by affecting the synthesis of thromboxane, because AA-2414 has been shown to have only weak inhibitory effects on the activity of the cyclooxygenase enzyme. In addition to its thromboxane receptor blocking effects, AA-2414 also has antioxidant properties. AA-2414 inhibits the generation of reactive oxygen species by alveolar macrophages and polymorphonuclear leukocytes (Matsumoto and Ashida, 1996). These properties of AA-2414 might make it a potentially useful drug to consider for the treatment of women with preeclampsia.

The isolated perfused human placental cotyledon presents a useful model to study the potential effects of this drug in pregnancy. This model offers the advantage of studying the effects in a tissue unique to pregnancy, and one in which a physiological event, such as vasoconstriction, can be correlated to a biochemical event, such as secretion of vasoactive compounds. The following study was done to evaluate the ability of AA-2414 to block peroxide-induced vasoconstriction in the isolated perfused human placental cotyledon. Maternal and fetal effluent samples were also collected and analyzed for lipid peroxides, thromboxane, and prostacyclin to determine whether AA-2414 affects their secretion rates by the placenta.

**Materials and Methods**

Placentas were obtained immediately after term delivery from normally pregnant women delivering at the Medical College of Virginia main hospital. Institutional approval to conduct this study was granted by the Committee on the Conduct of Human Research at the Medical College of Virginia.

**Isolated Perfused Placental Cotyledon Methodology.** This methodology was used as previously described (Walsh et al., 1993). Briefly, a chorionic plate artery leading to a single placental cotyledon and a chorionic plate vein draining the cotyledon were catheterized and perfusion was begun immediately. Krebs-Ringer-bicarbonate (KRB) buffer gassed with 95% O₂, 5% CO₂ and warmed to 37°C was used for perfusion. The composition of the KRB buffer was 125...
mM CaCl₂, 1.0 mM MgSO₄, 4.4 mM glucose (80 mg/100 ml), and 29.8 mEq/l NaHCO₃. The placenta was placed in a water-jacketed perfusion chamber warmed to 37°C by a Haake constant-temperature circulating water bath (Haake model D1L, Fisher Scientific Co., Pittsburgh, PA). To continuously monitor the perfusion pressure, the molecular weight molecule that is evaporated by vacuum centrifugation (SpeedVac Concentrator, Savant Instruments, Holbrook, NY) and then reconstituted with ultrapure water to 0.5 ml. Px is a low molecular weight molecule that is evaporated by vacuum centrifugation (Walsh and Wang, 1993). Therefore, the Px perfused in the experiment was not a contaminant of the concentrated samples and did not influence the measurement of the lipid peroxides.

**Study 2: Single Dose of AA-2414.** A second study was done using a dose of AA-2414 of $1 \times 10^{-5}$ mol/l that is equivalent to plasma levels achieved in clinical studies after oral administration of AA-2414 (Hussein et al., 1994). In this study we evaluated the effects of AA-2414 on fetal, as well as maternal, secretion rates of lipid peroxides, thromboxane, and prostacyclin, and we evaluated whether its inhibitory effects persisted after its perfusion is discontinued.

Maternal effluent samples were collected during the last 10 min of each perfusion period, and the effluent flow rates were recorded. Five milliliters of each sample were evaporated under vacuum centrifugation (SpeedVac Concentrator, Savant Instruments, Holbrook, NY) and then reconstituted with ultrapure water to 0.5 ml. Px is a low molecular weight molecule that is evaporated by vacuum centrifugation (Walsh and Wang, 1993). Therefore, the Px perfused in the experiment was not a contaminant of the concentrated samples and did not influence the measurement of the lipid peroxides.

**Study 1: Dose Response of AA-2414.** The first study evaluated whether the effects of AA-2414 were dose dependent. Placental cotyledons ($n = 5$) were perfused serially for 20-min intervals with control KRB buffer, Px (100 μM), KRB buffer, and KRB buffer containing Px (100 μM) to which progressively increasing concentrations of AA-2414 were added ($1 \times 10^{-8}$, $1 \times 10^{-7}$, $1 \times 10^{-6}$, $1 \times 10^{-5}$, and $1 \times 10^{-4}$ mol/l). To validate the specificity of any inhibitory effects observed for AA-2414, four additional term placentas were studied in which the Px (100 μM) perfusions were repeated without AA-2414.

To validate the specificity of any inhibitory effects observed for AA-2414, four additional term placentas were studied in which the Px (100 μM) perfusions were repeated without AA-2414. Maternal effluent samples were collected during the last 10 min of each perfusion period, and the effluent flow rates were recorded. Five milliliters of each sample were evaporated under vacuum centrifugation (SpeedVac Concentrator, Savant Instruments, Holbrook, NY) and then reconstituted with ultrapure water to 0.5 ml. Px is a low molecular weight molecule that is evaporated by vacuum centrifugation (Walsh and Wang, 1993). Therefore, the Px perfused in the experiment was not a contaminant of the concentrated samples and did not influence the measurement of the lipid peroxides.

**Experimental Design.** The experimental designs were based on a previous study demonstrating that α-t-butyl hydroperoxide (Px) induces vasoconstriction in the human placenta specifically by stimulating thromboxane (Walsh et al., 1993). Peroxides stimulate the synthesis of thromboxane by stimulating the activity of the cyclooxygenase enzyme (Hemler et al., 1979; Kulmaez and Lands, 1983). A vasoconstrictive state can therefore be simulated by perfusing the human placental cotyledon with Px. Px was obtained from Sigma Chemical Co. (St. Louis, MO) and AA-2414 was obtained from TAP Holdings, Inc. (Deerfield, IL). AA-2414 was synthesized at Takeda Chemical Industries, Ltd., Osaka, Japan.

To evaluate whether attenuation in perfusion pressure was a specific effect of AA-2414 and not due to vascular fatigue or some other nonspecific factor, we conducted additional experiments ($n = 4$) in which we repeatedly challenged placental cotyledons with Px without AA-2414. The repeated challenges without AA-2414 resulted in increases in perfusion pressure and vascular resistance comparable with the first challenge demonstrating that the inhibitory effect observed for AA-2414 was specific. a significantly higher than controls; $P < .05$. Reprinted from Holles SM et al. (1997) courtesy of Marcel Dekker, Inc.
(100 μM), control KRB buffer, AA-2414 (1 × 10⁻⁵ mol/l), AA-2414 plus Px, and Px alone. Both maternal and fetal effluent samples were collected and processed as described above for study 1.

**Sample Analysis.** The samples were analyzed for thromboxane and prostacyclin by radioimmunoassay of their stable metabolites, thromboxane B₂ (TXB₂) and 6-keto prostaglandin F₁α (6-keto PGF₁α). Both assays were validated for placental perfusion samples as previously described (Walsh et al., 1993). TXB₂ and 6-keto PGF₁α standards and antibodies were purchased from PerSeptive Diagnostics, Inc. (Cambridge, MA). Titrated TXB₂ and 6-keto PGF₁α were purchased from New England Nuclear (Dupont Research, Wilmington, DE). Analysis of various volumes of perfusate samples resulted in parallelism with the standard curve for both assays. Recovery of exogenously added known amounts of TXB₂ or 6-keto PGF₁α, to 5 ml of KRB buffer followed by the concentration procedure was 83 to 98%. KRB buffer blanks resulted in zero dose responses. Within- and between-assay variations were <10% for both assays.

Lipid peroxides were analyzed by a spectrophotometric method specific for peroxides (Frew et al., 1983). Hydrogen peroxide (H₂O₂) was used to generate the standard curve so the data are expressed as peroxide equivalents. We previously described this procedure and its validation for placental secretion of lipid peroxides (Walsh and Wang, 1993). The results obtained after concentrating different volumes of placental perfusates resulted in parallelism with the standard curve. Analysis of a concentration of 200 μM Px in KRB buffer processed by the concentrating procedure resulted in a zero dose response verifying that Px is evaporated by the vacuum centrifugation process. KRB buffer blanks also resulted in zero dose responses. Within- and between-assay variations were <10%.

**Calculations.** Placental secretion rates were calculated by multiplying the concentrations in either the fetal or maternal effluents by their respective effluent perfusion flow rates. Placental vascular resistance was calculated by dividing the chorionic plate arteriovenous pressure difference by the fetal effluent flow rate.

**Statistical Analysis.** Data were analyzed by ANOVA using the randomized complete block design to account for variation between placentas. Duncan’s multiple range post hoc test was used to determine statistical differences between treatment means. A statistical computer software program was used (SuperANOVA, Abacus Concepts, Inc., Berkeley, CA). Log (X + 1) transformation was used when the variances were not equal. A probability level of P < .05 was considered significant. Data are presented as the mean ± S.E.

**Results**

**Study 1: Dose Response of AA-2414.** Figure 1 shows a representative tracing of the changes in perfusion pressure in response to peroxide perfusion and peroxide perfusion plus increasing concentrations of AA-2414. Perfusion pressure was substantially increased by the peroxide (Px) alone, but the increase in pressure was inhibited in a dose-response manner by AA-2414. Endothelin (ET; 40 nM), a compound that vasocostricts independent of thromboxane, was perfused at the end of the experiment to demonstrate that the tissue was viable and capable of vasoconstriction.

Figure 2 demonstrates that the increase in perfusion pressure and vascular resistance induced by peroxide is inhibited in a dose-response manner by AA-2414. Compared with the control perfusion, perfusion with t-butyl hydroperoxide significantly increased placental perfusion pressure (32.1 ± 0.8 versus 59.6 ± 3.9 mm Hg, P < .01) and vascular resistance (10.3 ± 1.0 versus 27.9 ± 8.6 mm Hg·mmHg·min/ml). Perfusion of the placenta with Px in combination with increasing doses of AA-2414 resulted in a significant dose-response inhibition of peroxide-induced vasoconstriction. Significant inhibition was achieved with a dose as low as 1 × 10⁻⁸ mol/l.

Attenuation of the peroxide-induced increases in perfusion pressure and vascular resistance observed with AA-2414 was a specific effect and not due to vascular fatigue or some other nonspecific factor, because when we repeatedly challenged the placental cotyledon with Px without AA-2414, Px increased perfusion pressure and vascular resistance comparable with the initial challenge (Fig. 3). Figure 4 shows a representative recording of a placenta that was repeatedly challenged with Px. Note that the subsequent challenges with Px result in faster rates of rise in pressure than what occurs with the initial challenge.

The changes in the pattern of perfusion pressure and vascular resistance were paralleled by changes in the maternal secretion rates of lipid peroxides and thromboxane (Fig. 5). Compared with control, Px significantly increased the maternal secretion rates of lipid peroxides (19.8 ± 7.0 versus 31.3 ± 5.5 nmol/min, P < .05) and thromboxane (1.6 ± 0.8 versus 3.4 ± 0.8 ng/min, P < .01). Significant inhibition of peroxide-induced increases in the maternal secretion of lipid peroxides was achieved with a dose of AA-2414 of 1 × 10⁻⁷ mol/l (14.6 ± 5.5 nmol/min) and of thromboxane with a dose of 1 × 10⁻⁸ mol/l (2.3 ± 0.5 ng/min).

**Study 2: Single Dose of AA-2414.** Consistent with the first study, compared with the control perfusion, perfusion...
with Px significantly increased perfusion pressure ($30.8 \pm 0.8$ versus $60.3 \pm 5.6$ mm Hg, $P < .01$) and vascular resistance ($11.5 \pm 1.3$ versus $23.4 \pm 1.9$ mm Hg · min/ml, respectively, Fig. 6). Perfusion with AA-2414 alone had no effect, but when the placenta was again challenged with Px, AA-2414 completely blocked the ability of peroxide to increase perfusion pressure ($25.7 \pm 1.1$ mm Hg) and vascular resistance ($9.4 \pm 0.8$ mm Hg · min/ml).

AA-2414 inhibited peroxide-induced increases in both the maternal and fetal secretion rates of lipid peroxides (Fig. 7). Compared with control, Px significantly increased the secretion rates of lipid peroxides on both the maternal (M) and fetal (F) sides of the placenta (M, $48.9 \pm 6.0$ versus $68.0 \pm 2.7$ nmol/min, $P < .01$; F, $4.1 \pm 1.6$ versus $7.1 \pm 1.9$ nmol/min, $P < .05$, respectively). Perfusion with AA-2414 alone for 20 min resulted in slight decreases in the maternal and fetal secretion rates of lipid peroxides, but the declines were not statistically significant. When AA-2414 was perfused along with Px, it completely inhibited the ability of peroxide to increase the maternal (23.2 $\pm 4.1$ nmol/min) and fetal (4.0 $\pm 0.7$ nmol/min) secretion rates of lipid peroxides. The maternal secretion rate of lipid peroxides was highly correlated with changes in perfusion pressure, $r = 0.750$, as was the fetal secretion rate, $r = 0.514$.

The results for thromboxane (Fig. 8) were similar to those for lipid peroxides. Compared with control, Px significantly increased both maternal and fetal thromboxane secretion rates (M, $1.4 \pm 0.5$ versus $4.8 \pm 0.7$ ng/min; F, $0.02 \pm 0.01$ versus $0.97 \pm 0.18$ ng/min, respectively). Perfusion with AA-2414 alone for 20 min resulted in declines in both the maternal and fetal secretion rates of thromboxane from $1.6 \pm 0.4$ to $0.8 \pm 0.2$ ng/min and from $0.4 \pm 0.2$ to $0.05 \pm 0.04$ ng/min, respectively. The decline in the fetal secretion rate for thromboxane was statistically significant ($P < .05$). When the placenta was again challenged with Px in combination with AA-2414, AA-2414 inhibited the peroxide-induced increases in maternal and fetal thromboxane secretion in comparison with peroxide perfusion alone (Px-1) (M, $1.9 \pm 0.5$ ng/min, $P < .01$, F, $0.4 \pm 0.08$ ng/min, $P < .01$). The maternal secretion rate of thromboxane was highly correlated with changes in perfusion pressure, $r = 0.725$, as was the fetal secretion rate, $r = 0.493$.

The effect of AA-2414 on prostacyclin secretion (Fig. 9) was somewhat different than that on lipid peroxide and thromboxane secretion rates. As for lipid peroxides and thromboxane, Px increased the secretion rate of prostacyclin (M, $2.7 \pm 2.3$ versus $8.1 \pm 5.4$ pg/min; $P = \text{N.S.}$; F, $1.8 \pm 0.4$ versus $28.3 \pm 7.7$ pg/min, $P < .01$). AA-2414 alone did not affect prostacyclin secretion. Unlike the results for lipid peroxides and thromboxane, perfusion of AA-2414 in conjunction with Px did not block the ability of peroxide to increase prostacyclin secretion, although the increase was not as great as with peroxide alone (M, $6.0 \pm 2.9$ ng/min, $P = \text{N.S.}$; F, $15.9 \pm 4.2$ ng/min, $P < .05$). The maternal secretion rate of prostacyclin was not correlated with changes in perfusion pressure, $r = 0.130$, but the fetal secretion rate was correlated, $r = 0.442$. 
In the second study we also evaluated whether the antioxidant and thromboxane receptor blocking effects persisted after perfusion with AA-2414 was discontinued. At the end of each experiment, we challenged the placenta a second time with Px (100 μM) alone. As seen in Figs. 6–9, the second challenge with peroxide (Px-2) had no significant effect when it was given immediately following the AA-2414 perfusion. To see whether the inhibitory effects of AA-2414 were long lasting, we conducted two additional experiments in which we first perfused Px alone to demonstrate an increase in perfusion pressure and then peroxide plus AA-2414 (1 × 10⁻⁵ mol/l) to verify inhibition. The AA-2414 perfusion was then discontinued and the placental cotyledon was repeatedly challenged with 20-min peroxide perfusions alternated with 20-min KRB buffer control perfusions for 2 h and 20 min. The inhibitory effects of AA-2414 persisted during this time period as demonstrated by the inability of peroxide to induce an increase in perfusion pressure (data not shown). The antioxidant effect of AA-2414 also persisted because the peroxide challenges did not increase lipid peroxide or thromboxane secretion rates (data not shown). To demonstrate persistent antagonism of the thromboxane receptors, we gave a bolus injection of the thromboxane mimic, U46619, 5 μg, at the end of these experiments. In previous experiments, a 2.5-μg bolus injection of U46619 routinely increased perfusion pressure 100 to 140 mm Hg and the effect was long lasting, but after perfusion with AA-2414, a 5-μg bolus injection increased perfusion pressure by only 5 to 20 mm Hg and then only transiently.

Discussion

This study demonstrated that AA-2414, a compound that is both a potent antioxidant and thromboxane receptor antagonist, caused dose-response inhibition of peroxide-induced vasoconstriction in the isolated perfused human placental cotyledon. The inhibition was a specific effect of AA-2414 because the isolated placental cotyledon will repeatedly vasoconstrict to repeated challenges with Px.

AA-2414 also inhibited in a dose-response manner the maternal secretion rates of lipid peroxides and thromboxane. At a dose of AA-2414 of 1 × 10⁻⁵ mol/l that approximates plasma levels achieved in clinical studies (Hussein et al., 1994), there was essentially complete inhibition of peroxide-induced vasoconstriction, as well as inhibition of peroxide-stimulated increases in the maternal secretion rates of lipid peroxides and thromboxane. Interestingly, AA-2414 only partially inhibited peroxide-stimulated increases in the fetal secretion rate of prostacyclin. The inhibitory effects of AA-2414 persisted after perfusion of the drug was discontinued.

The maternal and fetal secretion rates of both lipid peroxides and thromboxane were highly correlated with changes in perfusion pressure, suggesting that peroxide-induced changes in vascular tone were dependent on its ability to
stimulate both lipid peroxidation and synthesis of thromboxane. These data also suggest that the inhibitory effects of AA-2414 were manifest both through its antioxidant effect and its thromboxane receptor blocking effect.

When AA-2414 was perfused alone for 20 min, basal maternal and fetal secretion rates of lipid peroxides and thromboxane started to decline with the decline in fetal thromboxane reaching statistical significance. A 20-min perfusion period is a rather short time to test the effects of AA-2414 by itself, and was used primarily as a pretreatment for the combined perfusion of AA-2414 plus peroxide. It is impressive that within such a short time AA-2414 was able to significantly inhibit basal secretion of thromboxane on the fetal side of the placenta and it is possible that the declines in the secretion rates of lipid peroxides and maternal thromboxane would have reached statistical significance if the duration of the perfusion with AA-2414 would have been longer.

The ability of AA-2414 to block peroxide-induced secretion of thromboxane is a rather interesting finding with regard to the mechanism of action of AA-2414. In some other studies using cyclooxygenase purified from bovine vesicular glands, AA-2414 had only weak inhibitory effects on cyclooxygenase activity. In our study, it is likely that the inhibitory effects on thromboxane secretion were indirect and related to the inhibition of lipid peroxidation. The amount of peroxide tone in a tissue is an important factor in determining the activity of cyclooxygenase (Hemler et al., 1979; Kulmacz and Lands, 1983). When the level of peroxide tone increases, the activity of cyclooxygenase increases. When the level of peroxide tone decreases, the activity of cyclooxygenase decreases. In our study, AA-2414 completely inhibited the ability of exogenous peroxide to stimulate an increase in lipid peroxide secretion, indicating inhibition of endogenous lipid peroxide formation. Therefore, in the presence of AA-2414, the level of endogenous peroxide tone was not increased by exogenous peroxide and the secretion rates of thromboxane did not increase over control.

AA-2414 differentially affected the placental secretion rates of eicosanoids. AA-2414 completely blocked the ability of peroxide to increase the secretion of thromboxane above control, but it only partially inhibited the ability of peroxide to increase prostacyclin secretion. Although the fetal prostacyclin secretion rate for AA-2414 plus peroxide was significantly lower than for peroxide alone, it was significantly higher than control. A lesser blocking effect on the fetal side would be a favorable effect because the increase in prostacyclin would promote vasodilatation of the placental vasculature, whereas the vasoconstrictive effects of thromboxane would be blocked by the thromboxane receptor antagonistic properties of AA-2414.

The reason AA-2414 differentially affects placental eicosanoid secretion is not known, but it may relate to the compartmentalization of thromboxane and prostacyclin synthesis within the human placenta. Thromboxane is primarily synthesized by the trophoblast cells on the maternal side of the placenta, whereas prostacyclin is primarily synthesized by the endothelial cells on the fetal side of the placenta (Thorp et al., 1988; Nelson and Walsh, 1989; Shellhaas et al., 1997). Lipid peroxides are also primarily synthesized by trophoblast cells as opposed to the vasculature (Walsh and Wang, 1995), so inhibition of lipid peroxidation by AA-2414 would conceivably have a greater impact on thromboxane synthesis in the trophoblast cells than on prostacyclin synthesis in the endothelial cells because peroxide-induced activity of cyclooxygenase would be inhibited to a greater extent in the trophoblast cells than in the endothelial cells.

AA-2414 clearly prevents peroxide-induced vasoconstriction and placental secretion of lipid peroxides demonstrating both its antioxidant and thromboxane receptor blocking effects. It also inhibits peroxide-induced increases in thromboxane secretion. Given the abnormal increases of lipid peroxides and thromboxane in preeclampsia, AA-2414 has pharmacologic properties that would make it a candidate to consider for the treatment of women with preeclampsia. Its actions as a thromboxane receptor blocker should prevent thromboxane-induced vasoconstriction and platelet aggregation, and its action as an antioxidant should decrease lipid peroxide production.

References


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