

Thursday, July 16, 1981

Poster Presentations

Prostaglandins - I

11:00-12:30 h

Kenora Room Boards 113-123

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EFFECT OF NOVEL PGE₁ ANALOGUE (OP-1206) ON THE PLATELET FUNCTIONS. T. Kitani, M. Nakagawa, Y. Maeda, T. Kawamura, M. Watada, H. Yoshikawa, Y. Hino and H. Ijichi. Second Department of Medicine, Kyoto Prefectural University of Medicine, Kyoto, Japan.

PGE₁ is one of prostaglandins which inhibit platelet functions and has vasodilating activity similar to PGI₂. Newly developed PGE₁ analogue (OP-1206) was supplied for the clinical evaluations on oral administration. This research was performed to analyze the effect of orally administrated PGE₁ analogue on platelet functions and to evaluate the usefulness on the thromboembolic disorders. Comparing with PGI₂, this analogue demonstrated the similar inhibitory activity on the platelet aggregation in vitro study. Oral administration of OP-1206 on the patients with thromboembolic disorders showed the dose-dependent inhibition on platelet aggregation and adhesiveness. This activity continued for 180 min (max at 120 min). Daily oral administration (20µg and 30µg t.i.d.) was continued for two weeks and its effect on blood pressure, heart rate, ADP induced platelet aggregation, platelet adhesiveness and platelet c-AMP level were evaluated. Both of administration doses caused remarkable depression of platelet aggregation, increment of c-AMP level in the platelet and mild suppression on the platelet adhesiveness. Blood pressure was decreased, but heart rate remained unchanged. Clinical improvement of symptoms were observed in the patients with deep vein thrombosis or angina pectoris. These results emphasize the effectiveness and usefulness of this orally administrated PGE₁ analogue against the prevention and treatment of thromboembolic disorders.

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THE CYCLIC-AMP-LOWERING EFFECT OF PGE₂ AND OF THE PGH₂ ANALOG, U46619. B. Martin and C. Bonne. Centre de Recherche sur les Maladies de la Rétine INSERM FRA N°45, Paris.

We have recently reported that PGE₂ counteracted the anti-aggregating action of PGE₁ and of other PG by inhibiting the adenylate cyclase system. But this effect is not due to the interference with anti-aggregating PG receptors. In this study, the mechanism of action of the c AMP-lowering effect of PGE₂ has been further investigated.

Suspensions of aspirin-washed human platelets were incubated for 1 min at 37°C in the presence of papaverine (0.5mM) with PGE₁, PGE₂, U46619, a chemical analog of PGH₂, 13-azaprostanic acid, a specific antagonist of TxA₂, either alone or in various associations. The c AMP concentration was determined by protein binding assays in platelet extracts. PGE₂ (150nM) and U46619 (1µM) inhibited the rise in c AMP induced by PGE₁ (30nM). On the other hand, when 13-azaprostanic acid (50µM) was added to the incubate, the inhibitory effects of these compounds were suppressed.

These results support the conclusion that TxA₂ and U46619 act on a unique receptor which triggers the c AMP-lowering effect and suggest that PGE₂ antagonizes the anti-aggregating PG through interaction with this receptor.

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BINDING AND METABOLISATION OF PGI₂ BY ERYTHROCYTES. Ch. Willems, J.A. van Mourik, H.V. Stel and W.G. van Aken. Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Amsterdam.

Prostacyclin (PGI₂) is rapidly hydrolysed in aqueous solution at neutral pH. Previously we have reported that PGI₂ is stabilized by plasma components; yet PGI₂ is rapidly metabolized in vivo. These findings prompted us to study the fate of PGI₂ upon incubation in whole blood. The data on the distribution of PGI₂ between blood cells and plasma indicate that PGI₂ not only binds to platelets but also to erythrocytes. The kinetics of binding were studied in more detail by incubating [³H] PGI₂ at 37°C with washed erythrocytes resuspended in autologous plasma. Binding of [³H] PGI₂ plateaued within 2 min. and was concentration dependant. The binding of [³H] PGI₂ was not influenced by PGE₁ or 6 keto PGF_{1α}. [³H] 6 keto PGF_{1α} showed no substantial binding to erythrocytes when compared with [³H] PGI₂. Upon repeated incubation of [³H] PGI₂ with erythrocytes less binding occurred than would have been expected from time and concentration dependency. The latter finding is explained by the demonstration of breakdown of [³H] PGI₂ - most likely into [³H] 6 keto-PGF_{1α} - and by measurements of the biological activity of PGI₂. Although metabolisation of PGI₂ complicates the evaluation of binding kinetics it could be shown, by using inhibition of platelet serotonin release, that erythrocytes and platelets compete for PGI₂. Binding of PGI₂ to erythrocytes and subsequent metabolisation explains the apparent lability of PGI₂ in whole blood. It is to be expected that under physiological conditions erythrocytes suppress the effectiveness of PGI₂ to act as a circulating platelet inhibitor.