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# COMMUNICATIONS

## Prostaglandin $E_1$ is more effective, when incorporated in lipid microspheres, for treatment of peripheral vascular diseases in man

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Prostaglandin $E_1$ ($PGE_1$) is a potent vasodilator as well as an inhibitor of platelet aggregation. Because of these properties, $PGE_1$ has been used clinically for the treatment of several vascular disorders such as Raynaud's and Buerger's diseases (Clifford et al 1980; Martin et al 1981). Since $PGE_1$ is rapidly inactivated in the lungs, $PGE_1$ must be administered into the obstructed artery or a large amount of it has to be given intravenously. The distribution of $PGE_1$ in-vivo induces the systemic effects of diarrhoea and hypotension. $PGE_1$ also causes irritation in blood vessels near the site of injection. To avoid these problems of $PGE_1$, we have incorporated $PGE_1$ in lipid microspheres (small lipid particles) with an average particle size of 0·2 μm, suspensions of which are in widespread use for parenteral nutrition in man, and we have compared the vasodilator property of the preparation in man with that of commercially available $PGE_1$.

$PGE_1$ was purchased from Fuji Chemical Co., Ltd, Toyama, Japan. $PGE_1$-CD (cyclodextrin clathrated $PGE_1$, Prostandin) was kindly supplied by Ono Pharm. Co., Ltd, Osaka, Japan. The method of preparing a suspension of lipid microspheres containing $PGE_1$ (lipo-$PGE_1$) and the content were those of Mizushima et al (1982, 1983). Briefly, $PGE_1$ was dissolved in soybean oil containing yolk phospholipids (10:1·2). The mixture was emulsified in water (1:9) with a Manton-Gaulin homogenizer. The resultant emulsion was put in 1 ml glass ampoules and sterilized at 121 °C for 10 min. The final concentration of $PGE_1$ in the lipo-$PGE_1$ preparation was approximately 3 μg $ml^{-1}$. The concentration was measured according to Terragno et al (1981).

Nine patients with peripheral vascular diseases, 5 with scleroderma (1 male and 4 female) and 4 with diabetes (2 male and 2 female) were treated with $PGE_1$. The age of patients with scleroderma was 19–68 years, average 50 years and that of diabetic patients was 41–75 years, average 62 years. All patients with scleroderma showed a Raynaud's phenomenon and all with diabetes suffered a numbness and a cold sensation in the feet. They were treated with 3 μg of lipo-$PGE_1$ and 40–60 μg (usual dose for Japanese) of $PGE_1$-CD in a cross-over test. Lipo-$PGE_1$ was given first in 6 cases and $PGE_1$-CD first in 3 cases. The intervals between the two treatments were at least 3 days. Lipo-$PGE_1$ was diluted by, and $PGE_1$-CD was dissolved and diluted by, 200 ml of 5% glucose, they were then infused intravenously for 90–120 min. The room temperature and humidity were kept constant at 25 °C and 60% respectively.

The effects of $PGE_1$ were evaluated objectively as well as subjectively. Changes in sensation of warmness and relief of numbness were reported. Digital plethysmograms (pulse waves) were taken before and after the $PGE_1$ infusion as an objective assessment. A Photo Plethysmograph, Model PT-300, Fukuda Denshi, Tokyo, was employed for measuring plethysmograms.

Although the subjective data were not reliable because of an open labelled study, all patients with scleroderma treated by 3 μg of lipo-$PGE_1$ showed a relief in Raynaud's phenomenon and experienced a sensation of warmth in their extremities. All 4 diabetic patients treated with lipo-$PGE_1$ showed a remarkable

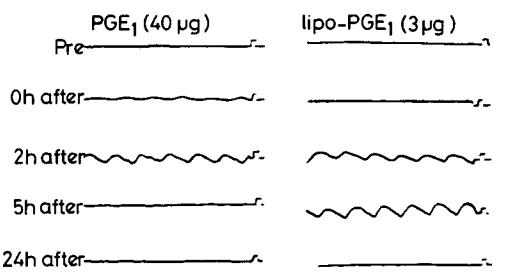


FIG. 1. Changes in plethysmogram (pulse wave) induced by infusion of $PGE_1$ ($PGE_1$-CD) and lipo-$PGE_1$ ($PGE_1$ incorporated in lipid microspheres) in a patient with scleroderma. Amplitude is mV/V (mV is an amplitude produced by 1 mV, and V is a thickness of finger, 10 mm = 1).

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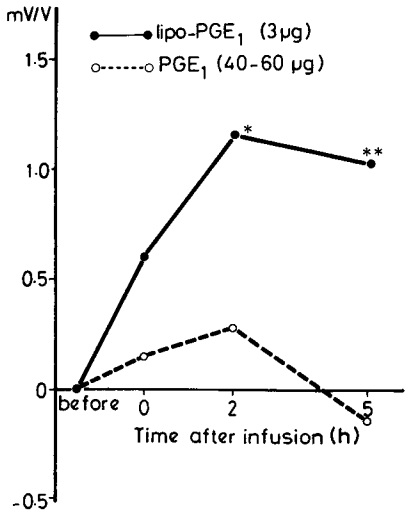


FIG. 2. Changes in amplitude of a digital plethysmogram induced by $PGE_1$ and lipo-$PGE_1$ (see legend of Fig. 1 and text for details) before and after the infusion in patients with peripheral vascular diseases. The values are averages in 9 patients, 5 with scleroderma and 4 with diabetes. mV/V (see legend of Fig. 1). $*P < 0{\cdot}01$, $**P < 0{\cdot}001$ ($t$-test) in relation to $PGE_1$.

improvement in numbness and cold sensation. The subjective improvement in the patients treated with 40–60 μg of $PGE_1$-CD was not so marked. Plethysmograms on a right middle finger of a patient with scleroderma are shown in Fig. 1. It shows a long-lasting vasodilating effect of lipo-$PGE_1$. The summarized plethysmograms in 9 cases of scleroderma and diabetes are shown in Fig. 2. An average amplitude of the pulse wave (mV/V) in plethysmograms on right index fingers with scleroderma and on right big toes in diabetes are given in Fig. 2. This shows that 3 μg of lipo-$PGE_1$ was significantly more effective than 40–60 μg of $PGE_1$-CD when the effects were compared at 2 and 5 h after the infusions. An average amplitude at 2 h in patients with diabetes treated with lipo-$PGE_1$ and $PGE_1$-CD was 1·7 and 0·25 mV/V, respectively, and that in scleroderma was 0·49 and 0·3 mV/V. Therefore, it seems that the difference in effectiveness between lipo-$PGE_1$ and $PGE_1$-CD groups was more distinct in the diabetic peripheral vascular disease. Some diabetic patients felt warmth and showed a high amplitude in the plethysmogram even 24 h after the infusion. No side effects were observed in this study except vascular pains near the site of injection in 3 cases of $PGE_1$-CD group.

Intravenous infusion of $PGE_1$ is one of the most useful treatments of peripheral vascular diseases such as scleroderma, Buerger's disease and diabetic angiopathy. However, $PGE_1$-CD preparations have some problems as described above. $PGE_1$-CD is a stable and water soluble preparation of $PGE_1$ and has the same pharmacological effects as that of $PGE_1$ (Kawasaki et al 1979). Since $PGE_1$ in the form of lipo-$PGE_1$ is incorporated in a lipid microsphere, it is speculated that lipo-$PGE_1$ is more stable than free $PGE_1$ against enzymatic inactivation in the body and causes less irritation. The less irritation caused by lipo-$PGE_1$ than $PGE_1$-CD to the upper respiratory tract in man was proved by Mizushima et al (1983). Moreover it was found that the lipid microspheres (intralipid, Green Cross Co., Ltd, Osaka) were highly accumulated in the inflamed tissues (Mizushima et al 1982). It is suggested, therefore, that lipo-$PGE_1$ is also accumulated in lesions in peripheral vascular diseases. Probably by virtue of these properties, lipo-$PGE_1$ ($PGE_1$ incorporated in lipid microsphere) showed a much more beneficial effect than $PGE_1$-CD for peripheral vascular diseases.

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