ON THE METABOLISM OF PROSTAGLANDIN E₁ ADMINISTERED INTERAVENOUSLY TO HUMAN VOLUNTEERS

We have demonstrated recently the formation of a biologically active metabolite of prostaglandin (PG) E₁, 13,14-dihydro-PGE₁, during intravenous infusions of PGE₁ in patients with peripheral arterial occlusive disease. We have now investigated the levels of the immediate precursor of 13,14-dihydro-PGE₁, the biologically inactive 15-keto-13,14-dihydro-PGE₁, during intravenous administration of 20 μg, 40 μg or 80 μg PGE₁ over a period of 60 min to human volunteers. It was found that levels of 15-keto-13,14-dihydro-PGE₁, but not those of PGE₁ itself, increased in a dose-dependent manner. Thus, increased formation of 13,14-dihydro-PGE₁ from 15-keto-13,14-dihydro-PGE₁, with increasing doses of PGE₁, can be expected to occur. It remains to be investigated, to which extent formation of small amounts of 13,14-dihydro-PGE₁ during intravenous infusion of PGE₁ could contribute to the therapeutic effects of PGE₁ in patients with peripheral arterial occlusive disease.

Key words: intravenous prostaglandin E₁ infusion — prostaglandin E₁ metabolism — 15-keto-13,14-dihydro-prostaglandin E₁ — 13,14-dihydro-prostaglandin E₁ — arterial occlusive disease

INTRODUCTION

It has been demonstrated repeatedly (1, 2) that not only intraarterial, but also intravenous infusion of PGE₁ is an effective treatment of peripheral arterial occlusive disease. The results with intravenous drug administration are surprising, since a major portion of circulating PGE₁ is rapidly metabolized during passage through the human lung (3). The initial metabolites formed, 15-keto-PGE₁ and 15-keto-13,14-dihydro-PGE₁ (KH₂PGE₂), have only negligible biological activity (4, 5). We have found recently (6), however, formation of 13,14-dihydro-PGE₁ (H₂PGE₁), a biologically active metabolite (4, 5), during intravenous infusions of PGE₁. Since KH₂PGE₁ is the immediate precursor of H₂PGE₁, we have now investigated the dose-dependent formation of KH₂PGE₁ during intravenous infusions of PGE₁.
MATERIALS AND METHODS

PGE₁ (prostavasin\textsuperscript{R}, Schwarz Pharma AG, Monheim, Germany) was infused into the cubital vein of 12 healthy male volunteers (21—33 years of age) at doses of 20 μg, 40 μg or 80 μg over a period of 60 min. Blood was taken from the contralateral cubital vein before and 5 and 30 min after the start of the infusions as well as at the end (60 min) and 5, 35 and 60 min after the end of the infusion periods. Blood was collected into syringes containing sodium-EDTA as anticoagulant and indomethacin as cyclooxygenase inhibitor (final concentrations 5.4 and 0.1 mM, respectively) and plasma was separated immediately. The unextracted plasma samples were analyzed for PGE₁ and KH₂PGE₁ radioimmunologically as described previously (7). KH₂PGE₁ was converted to a stable degradation product prior to assay (8). The antisera used recognize the monoenoic and dienoic compounds equally well. Thus, basal levels measured represent most probably the amounts of cross-reacting dienoic prostanoids, mainly PGE₁ and KH₂PGE₁, respectively, while increases during the infusions of PGE₁ should be due to PGE₁ and its circulating metabolite KH₂PHE₁, respectively.

The time course of plasma levels of PGE₁ and KH₂PGE₁ from 0 min to 120 min (60 min after the end of PGE₁ infusions) achieved with the 3 different doses of PGE₁ were evaluated by calculation of the "area under the curve" (AUC\textsubscript{0-120}). The AUC\textsubscript{0-120} values for PGE₁ and the metabolite KH₂PGE₁ were then related to the doses of PGE₁ administered by linear regression analysis.

RESULTS

As shown in Fig. 1 infusion of three different doses of PGE₁ did not result in dose-dependent increases in the venous plasma levels of PGE₁. On the other hand, circulating levels of the major initial metabolite of PGE₁, KH₂PGE₁, increased clearly with the dose of PGE₁ administered (Fig. 2). Consequently, while for PGE₁ there was no obvious correlation (r = 0.6454) between the AUC\textsubscript{0-120} values and the doses of PGE₁ infused (Fig. 3), a correlation coefficient of r = 0.9996 was observed for the metabolite (Fig. 4).

DISCUSSION

The present results show that venous plasma levels of KH₂PGE₁, but not of PGE₁, correlate with the dose of PGE₁ administered. The data on PGE₁ may be due to rapid and variable metabolism during passage through the lungs (3), while the half-life of KH₂PGE₁ in the circulation is several minutes and thus considerably longer than that of PGE₁ (9, 10). Since KH₂PHE₁ is the immediate precursor of the biologically active H₂PHE₁, continuous and dose-dependent formation of H₂PHE₁ during infusion of PGE₁ can be expected to occur. We have, in fact, observed formation of this metabolite in patients suffering from peripheral arterial occlusive
Fig. 1. Plasma levels of PGE₁ before, during and after a 60 min intravenous infusion of 20 μg (○), 40 μg (◇) or 80 μg (△) PGE₁. Results represent means ± S.E.M. of n = 12.

Fig. 2: Plasma levels of 15-keto-13,14-dihydro-PGE₁ before, during and after a 60 min intravenous infusion of 20 μg (○), 40 μg (◇) or 80 μg (△) PGE₁. Results represent means ± S.E.M. of n = 12.
Fig. 3: Relationship between $AUC_{0-150}$ for PGE$_1$ and dose of PGE$_1$ administered by intravenous infusion over a time period of 60 min.

Fig. 4: Relationship between $AUC_{9-150}$ for 15-keto-13,14-dihydro-PGE$_1$ and dose of PGE$_1$ administered by intravenous infusion over a time period of 60 min.

disease treated with intravenous infusions of PGE$_1$ (6). The concentrations of the metabolite found were, however, rather low with $16\pm5$ pg/ml at the end of a 60 min infusion of 80 $\mu$g PGE$_1$/patient (6). These levels are more than 30 times lower than those found for $\text{KH}_2\text{PGE}_1$ under identical infusion conditions in human volunteers (Fig. 2). It remains to be investigated, to which extent formation of small amounts of $\text{H}_2\text{PGE}_1$ from the
major initial metabolite KH$_2$PGE$_1$ could contribute to the therapeutic effects of PGE$_1$ administered intravenously to patients with peripheral arterial occlusive disease.

Acknowledgements. This work was in part supported by the Deutsche Forschungsgemeinschaft (Pe 256/4-1).

REFERENCES


Received: January 25, 1991
Accepted: February 6, 1991
Author's address: Department of Pharmacology and Toxicology Ruhr — University of Bochum, D—4630 Bochum