JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY, 1991, 42, 3, 327—331

B. A. PESKAR [1], W. CAWELLO [2], W. ROGATTI [2], G. RUDOFSKY [3]

ON THE METABOLISM OF PROSTAGLANDIN E_1 ADMINISTERED INTERAVENOUSLY TO HUMAN VOLUNTEERS

[1]Department of Pharmacology and Toxicology, Ruhr-University of Bochum, D-4630 Bochum, [2]Schwarz Pharma AG, D-4019 Monheim and [3]Department of Internal Medicine, University of Essen, D-4300 Essen, Germany

We have demonstrated recently the formation of a biologically active metabolite of prostaglandin (PG) E_1, 13,14-dihydro-PGE_1, during intravenous infusions of PGE_1 in patients with peripheral arterial occlusive disease. We have now investigated the levels of the immediate precursor of 13,14-dihydro-PGE_1, the biologically inactive 15-keto-13,14-dihydro-PGE_1, during intravenous administration of 20 μg, 40μg or 80 μg PGE_1 over a period of 60 min to human volunteers. It was found that levels of 15-keto-13,14-dihydro-PGE_1, but not those of PGE_1 itself, increased in a dose-dependent manner. Thus, increased formation of 13,14-dihydro-PGE_1 from 15-keto-13,14-dihydro-PGE_1 with increasing doses of PGE_1 can be expected to occur. It remains to be investigated, to which extent formation of small amounts of 13,14-dihydro-PGE_1 during intravenous infusion of PGE_1 could contribute to the therapeutic effects of PGE_1 in patients with peripheral arterial occlusive disease.

Key words: *intravenous prostaglandin E_1 infusion — prostaglandin E_1 metabolism — 15-keto-13,14-dihydro-prostaglandin E_1 — 13,14-dihydro-prostaglandin E_1 — arterial occlusive disease*

INTRODUCTION

It has been demonstrated repeatedly (1, 2) that not only intraarterial, but also intravenous infusion of PGE_1 is an effective treatment of peripheral arterial occlusive disease. The results with intravenous drug administration are surprising, since a major portion of circulating PGE_1 is rapidly metabolized during passage through the human lung (3). The initial metabolites formed, 15-keto-PGE_1 and 15-keto-13,14-dihydro-PGE_1 (KH_2PGE_2), have only negligible biological activity (4, 5). We have found recently (6), however, formation of 13,14-dihydro-PGE_1 (H_2PGE_1), a biologically active metabolite (4,5), during intravenous infusions of PGE_1. Since KH_2PGE_1 is the immediate precursor of H_2PGE_1, we have now investigated the dose-dependent formation of KH_2PGE_1 during intravenous infusions of PGE_1.

MATERIALS AND METHODS

PGE_1 (prostavasin^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 PGE_1 and KH_2PGE_1 radioimmunologically as described previously (7). KH_2PGE_1 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 PGE_2 and KH_2PGE_2, respectively, while increases during the infusions of PGE_1 should be due to PGE_1 and its circulating metabolite KH_2PHE_1, respectively.

The time course of plasma levels of PGE_1 and KH_2PGE_1 from 0 min to 120 min (60 min after the end of PGE_1 infusions) achieved with the 3 different doses of PGE_1 were evaluated by calculation of the „area under the curve" (AUC_{0-120}). The AUC_{0-120} values for PGE_1 and the metabolite KH_2PGE_1 were then related to the doses of PGE_1 administered by linear regression analysis.

RESULTS

As shown in *Fig. 1* infusion of three different doses of PGE_1 did not result in dose-dependent increases in the venous plasma levels of PGE_1. On the other hand, circulating levels of the major initial metabolite of PGE_1, KH_2PGE_1, increased clearly with the dose of PGE_1 administered (*Fig. 2*). Consequently, while for PGE_1 there was no obvious correlation ($r = 0.6454$) between the AUC_{0-120} values and the doses of PGE_1 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 KH_2PGE_1, but not of PGE_1, correlate with the dose of PGE_1 administered. The data on PGE_1 may be due to rapid and variable metabolism during passage through the lungs (3), while the half-life of KH_2PGE_1 in the circulation is several minutes and thus considerably longer than that of PGE_1 (9, 10). Since KH_2PHE_1 is the immediate precursor of the biologically active H_2PHE_1, continuous and dose-dependent formation of H_2PHE_1 during infusion of PGE_1 can be expected to occur. We have, in fact, observed formation of this metabolite in patients suffering from peripheral arterial occlusive

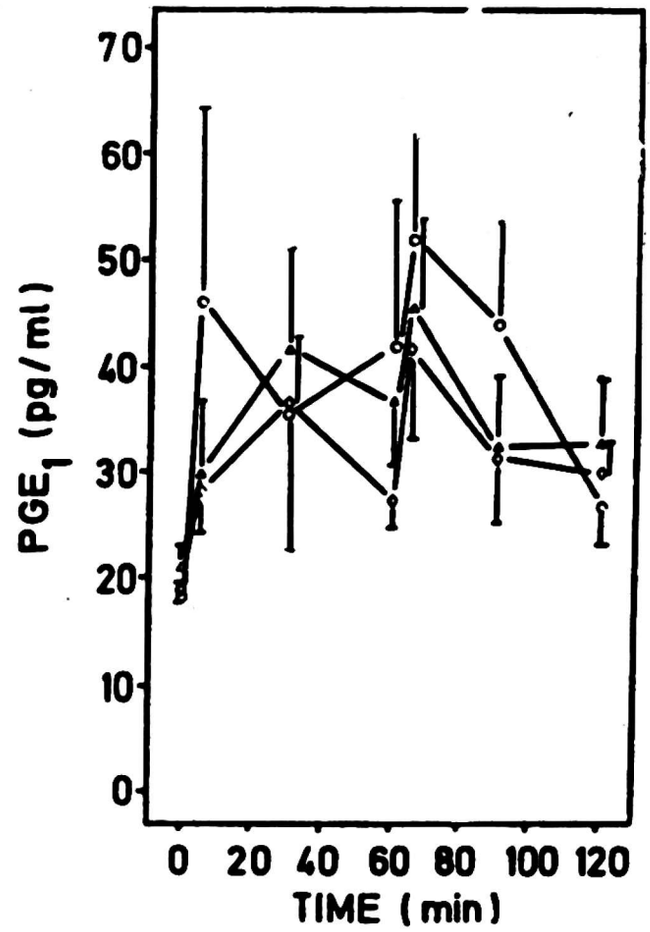

Fig. 1. Plasma levels of PGE_1 before, during and after a 60 min intravenous infusion of 20 μg (○), 40 μg, (◇) or 80 μg (△) PGE_1. Results represent means±S.E.M. of n = 12.

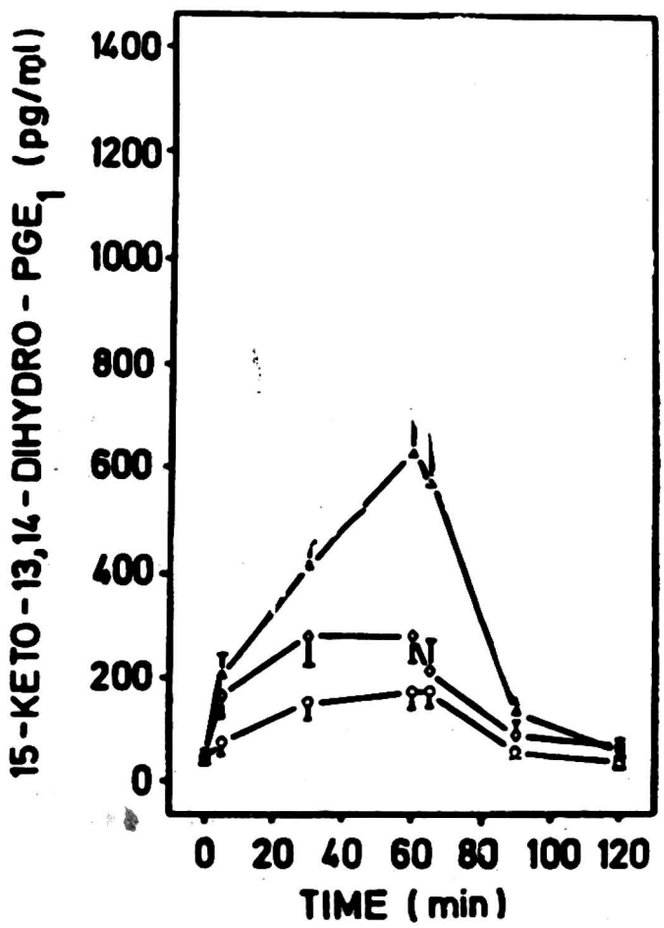

Fig. 2: Plasma levels of 15-keto-13,14-dihydro-PGE_1 before, during and after a 60 min intravenous infusion of 20 μg (⊙), 40 μg (◇) or 80 μg (△) PGE_1. Results represent means±S.E.M. of n = 12.

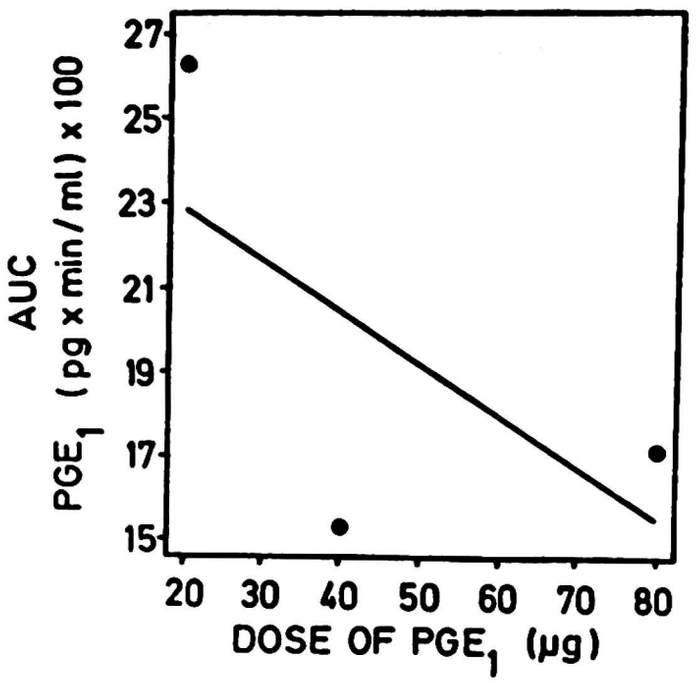

Fig. 3: Relationship between AUC_{0-120} for PGE_1 and dose of PGE_1 administered by intravenous infusion over a time period of 60 min.

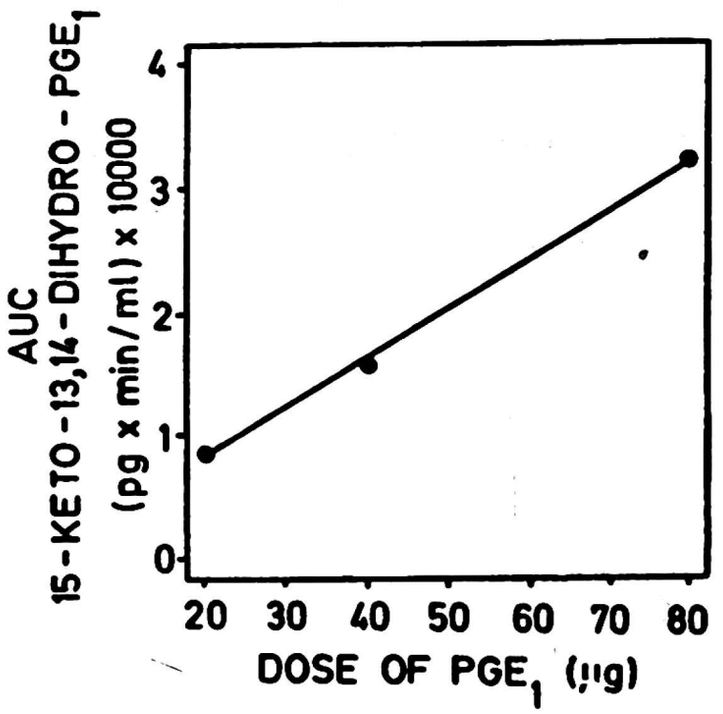

Fig. 4: Relationship between AUC_{0-120} for 15-keto-13,14-dihydro-PGE_1 and dose of PGE_1 administered by intravenous infusion over a time period of 60 min.

disease treated with intravenous infusions of PGE_1 (6). The concentrations of the metabolite found were, however, rather low with 16 ± 5 pg/ml at the end of a 60 min infusion of 80 µg PGE_1/patient (6). These levels are more than 30 times lower than those found for KH_2PGE_1 under identical infusion conditions in human volunteers (*Fig. 2*). It remains to be investigated, to which extent formation of small amounts of H_2PGE_1 from the

major initial metabolite KH_2PGE_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

1. Carlson LA, Olsson AG. Intravenous prostaglandin E_1 in severe peripheral vascular disease. *Lancet* 1976; ii: 810.
2. Sinzinger H, Virgolini I, O'Grady J. Clinical trials of PGE_1, PGI_2 and mimetics in patients with peripheral vascular disease. In: Prostaglandins in Clinical Research, (Schrör K and Sinzinger H, eds.) *Alan Liss Inc*, New York, 1989: 85—96.
3. Golub M, Zia P, Matsuno M, Horton R. Metabolism of prostaglandins A_1 and E_1 in man. *J Clin Invest* 1975; 56: 1404—1410.
4. Änggård E. The biological activity of three metabolites of prostaglandin E_1. *Acta physiol scand* 1966; 66: 509—510.
5. Westwick, J. The effect of pulmonary metabolites of prostaglandins E_1, E_2 and $F_{1\alpha}$ on ADP-induced aggregation of human and rabbit platelets. Br *J Pharmacol* 1976; 58: 297P—298P.
6. Hesse WH, Matamoros R, Horsch S, Peskar BA. On the metabolism of prostaglandin E_1 in porcine lung homogenates and human circulation. In: Thrombosis and Haemorrhagic Disorders. Proc 6th Int Meeting Danubian League against Thrombosis and Haemorrhagic Disorders (Sinzinger H and Vinazzer H, eds.) 1989: 437—440.
7. Fitscha P, Simmet T, Peskar BA, Reuter H, Sinzinger H, Rogatti W, Tilsner V. Untersuchungen zur fibrinolytischen Aktivitat, Thrombozytenfunktion und Pharmakokinetik während intraarterieller oder intravenöser Prostaglandin-E_1-Infusion bei Patienten mit chronisch arterieller Verschlußkrankheit. Wien Klin Wochenschr 1988; 100: 477—481.
8. Bothwell W, Verburg M, Wynalda M, Daniels EG, Fitzpatrick FA. A radioimmunoassay for the unstable pulmonary metabolites of prostaglandin E_1 and E_2: An indirect index of their in vivo disposition and pharmacokinetics. *J Pharmacol Exp Ther* 1982; 220: 229—235.
9. Hamberg M, Samuelsson B: On the metabolism of prostaglandin E_1 and E_2 in man. *J Biol Chem* 1971; 246: 6713—6721.
10. Simmet Th, Peskar BA, Wolf HRD. On the metabolism of prostaglandin E_1 in patients suffering from arterial occlusive disease. In: Prostaglandin E_1 in Atherosclerosis (Sinzinger H, Rogatti W, eds.) Springer-Verlag, Heidelberg 1986: 8—12.

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