Extremely Prolonged Half-Life of Prostacyclin in Plasma Causative for Bleeding in an Uremic Patient?

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Dear Sir,

In uremia, an imbalance in the prostaglandin (PG) system, and altered platelet function are well known. A number of disturbances in the PG system related to PGL₂, such as increased plasma factor activity [1], and prolonged [2] as well as increased [3] formation of PGL₂ by the vessel wall have been described.

In vivo, PGL₂ is bound to proteins and thereby stabilized. So far, a shortened PGL₂ half-life ($t_{1/2}$) has been described in thrombotic thrombocytopenic purpura [4], indicating impaired stabilization due to decreased protein binding, as well as after myocardial infarction [5, 6] and – with an extremely low prevalence – in healthy adults [7].

We report for the first time an extreme prolongation in the degradation half-life of the biologically active PGL₂ in vitro due to unknown reason. It is assumed that this defect leading to the prolonged local availability of PGL₂ at higher amounts might have contributed to the clinically manifest bleeding observed in our patient.

A 65-year-old male patient on long-term hemodialysis for 13 years was hospitalized due to severe epistaxis, occult blood loss in stool, and chest pains. At hospital admission, blood pressure (115/50), heart rate (80/min), and plasmatic coagulation parameters (PTT, fibrinogen) were normal. The platelet count was extremely decreased (2,000/ μ l), normochromic anemia was present; the semi-quantitative evaluation of bone marrow aspiration showed a normal ratio of granulo- to erythropoiesis beside a significantly decreased megakaryopoiesis. In serum, neither antibodies against rhesus factor nor HR antibodies were found; the platelet immune fluorescence antibody test was negative. Due to the extremely low platelet count, further extensive platelet function testing was not possible.

Table 1. PGI₂ degradation ($t_{1/2}$) and PF in the patient compared to a healthy control

During hospitalization, the patient received transfusions as well as platelet concentrates and fresh frozen plasma. Beside his standard therapy, he underwent treatment with 7S immunoglobulins, corticosteroids, danazole, and vincristine.

PGL₂ $t_{1/2}$ was measured with a bioassay, and measurements of PGL₂ synthesis stimulating plasma factor (PF) were performed using a bioassay compared to a radioimmunoassay (RIA).

Our patient showed an extreme prolongation in the in vitro degradation half-life of the biologically active PGL₂ to 108 min (table 1), the normal values under the same assay conditions

being 10.34 ± 2.36 min ($n = 196$). This value tended to normalize within time due to unknown reasons. However, even the best value was still almost threefold increased (36 min). PF activity, measured via 6-oxo-PGF α RIA, was increased to an extent ($\pm 57\%$) which is normally seen in uremic patients. The value measured via bioassay, in contrast, was extremely increased (191%). Throughout the follow-up period, no apparent changes occurred in PF activity.

PGL $\cdot$ is an important coregulator of hemostatic balance. The prolonged stabilization of this potent anti-platelet component to the extent seen in this patient could have caused the bleeding. It is not clear whether this prolongation was due to an increased stabilization of PGL $\cdot$. Bleeding in an Uremic Patient due to Prolonged PG Half-Life?

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Sinzinger H, Rauscha F, Fitscha P, et al: Prevalence of a shortened prostacyclin half-life in plasma in healthy adults – Results of a screening investigation. *Am J Hematol* 1990;33:139–141. PGL $\cdot$ on proteins or to a lack in degrading compounds. All drugs the patient was treated with were shown in vitro to be of no influence on these findings. Furthermore, it should be mentioned that during partial clinical remission a concurrent improvement in PGL $\cdot$ $t_{1/2}$ was seen. The discrepancy between moderately increased PF measured by RIA and extremely increased PF by bioassay is due to the fact that the biologically active PGL $\cdot$ formed by the vessel wall shows a comparably delayed decay to the biologically inactive and more stable 6-oxo-PGF α in platelet-poor plasma and later in platelet-rich plasma.

In conclusion it cannot be answered whether this phenomenon communicated is a primary or a secondary event, as this test was not applied before in this patient. However, it would have been of interest to see whether the prolonged PGL $\cdot$ $t_{1/2}$ may have influenced the PGL $\cdot$ -6 binding sites on various cells. It seems likely that the disturbance in the PG system described contributed to the severe bleeding complications our patient was suffering from.

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