Brief Communication

Diabetic Microangiopathic Hemolytic Anemia: Beneficial Effect of an Antiplatelet Agent?

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A 66-yr-old man with non-insulin-dependent diabetes mellitus complicated by retinopathy and nephropathy presented with shortened red cell survival associated with prominent fragmentation of erythrocytes and leading to severe hemolytic anemia. Neither abnormal carbohydrate tolerance per se nor renal failure was related to the red cell fragmentation syndrome. Also, a marked platelet hyperaggregability, which disappeared under treatment with ticlopidine, was demonstrated. Furthermore, during treatment with this potent platelet inhibitor, red cell survival normalized and all signs of hemolysis, as well as the schistocytes present in the peripheral blood smears, disappeared. Two weeks after stopping ticlopidine administration, microangiopathic hemolytic anemia relapsed. We suggest that the fragmentation hemolysis in this patient was related to diabetic microangiopathy, and that the beneficial effects of ticlopidine are related to its platelet-inhibiting activities. This case further reaffirms that antiplatelet agents may have a beneficial effect on the vascular disease of diabetes mellitus. DIABETES CARE 1985; 8:169–71.

Microangiopathic hemolytic anemia has been described in a variety of diseases and is characterized by the presence of fragmented erythrocytes.[1] In 1976, Brunning et al.[2] described red cell fragmentation in seven patients with long-standing diabetes mellitus related to the diabetic microangiopathy. We report on another patient with diabetic microangiopathic hemolytic anemia, in whom the red cell survival improved during treatment with ticlopidine, a potent platelet inhibitor.[3]

MATERIALS AND METHODS

Standard methods were used for routine laboratory tests. The red cell life span was measured by labeling the red cells with chromium-51 and reinjecting them. The rate of disappearance of the isotope from the blood was assessed over a period of 15 days. The Cr survival data were plotted on a semilogarithmic scale, from which the disappearance half-time ($t^{1/2}$ Cr) was derived. At the same time, sequestration of the red cells in the spleen was assessed by counting the radioactivity over that organ and comparing it with that of other parts of the body.

Platelet aggregation was studied in a platelet aggregation profiler PAP-3, BIO DATA Corporation, Willow Grove, Pennsylvania. For the preparation of platelet-rich plasma (PRP), venous blood was mixed with 3.8% sodium citrate in the proportion 9:1. Platelet counts of PRP before and during ticlopidine treatment were 253.0/mm^3 and 360.0/mm^3, respectively. Aggregating agents were obtained from STAGO diagnostica, Asnieres, France. Aggregation was induced by adding 1 vol aggregating agent to 4 vol PRP; final concentration was 5 μM for ADP and adrenaline and 40 μg/ml for collagen.

CASE REPORT

A 66-yr-old man presented with anemia, renal failure, edema, and arterial hypertension. His medical history was unremarkable, except for non-insulin-dependent diabetes mellitus of 12 yr duration. He had been treated with oral hypoglycemic agents during the first 6 mo after diagnosis, but since that time he had required daily injections of insulin. On admission, his treatment consisted of insulin (8 U Actrapid and 32 U Lente in the morning, and 10 U Lente in the evening), clonidine (0.15 mg t.i.d.) and furosemide (40 mg o.d.). Blood pressure was 180/90 mm Hg. Physical abnormalities included generalized edema, pallor, diminished arterial pulses in the lower extremities, and signs of polyneuropathy. Funduscopy showed nonproliferative diabetic retinopathy. Fasting blood glucose was 217 mg/dl; plasma creatinine, 3.1 mg/dl; urea,

118 mg/dl; and creatinine clearance, 25 ml/min. Serum albumin was low (2.3 g/dl) and there was severe proteinuria (5 g/24 h). The urinary sediment showed microscopic hematuria and hyaline urinary casts. A severe normochromic normocytic anemia was documented (hemoglobin concentration 7.5 g/dl, hematocrit 22%). The white cell count was normal; the platelet count was 179.0/mm^3. Features of hemolysis—including increased LDH, increased reticulocyte count (2.8% of erythrocytes), and decreased haptoglobine—and hemoglobinuria were present (Table 1). Marked fragmentation of red cells was seen in peripheral blood smears. Ham test and sucrose test were negative. Hemoglobin electrophoresis and osmotic resistance were normal. There were no enzyme deficiencies. A moderate marrow hyperplasia was found. The Cr^{51} disappearance half-time was decreased to 16 days (normal $t^{1/2}$ Cr, 25–35 days). Erythrocyte sequestration in the spleen was not observed (Table 1).

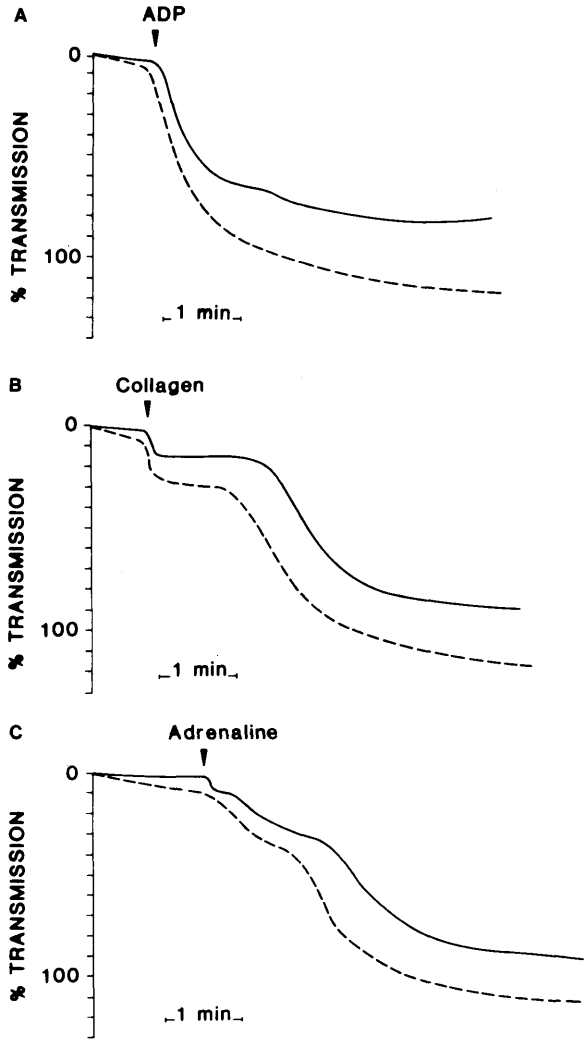

FIG. 1. Platelet aggregation profiles before (---) and during (—) ticlopidine treatment. (A) ADP (5 μM), (B) collagen (40 μg/ml), and (C) adrenaline (5 μM).

TABLE 1
Effects of ticlopidine (T) treatment

	Before T	During T	2 Wk after stopping T
Hemoglobin concentration (g/dl)	7.5	10.9	7.9
Schistocytes	+	/ − /	+
LDH (IU/L)	480	254	456
Haptoglobin (g/L)	<0.3	1.25	<0.3
$t^{1/2}$ Cr (days)	16	29	18

After transfusion hemoglobin rose to 10.4 g/dl but fell again to 8.4 g/dl within 6 days. After a second transfusion, hemoglobin was 11.0 g/dl and ticlopidine 250 mg b.i.d. was added to the treatment. Two months later hemoglobin was 10.9 g/dl and hematocrit 37%. Haptoglobin was normal and there were no signs of hemolysis. Schistocytes were no longer observed. The $t^{1/2}$ Cr was normal (Table 1).

Figure 1 illustrates the platelet aggregation profiles before and during ticlopidine treatment. Before ticlopidine treatment, spontaneous aggregation was observed in the absence of aggregating agents; this phenomenon disappeared during ticlopidine treatment. A significant inhibition of 5 μM ADP-induced platelet aggregation and of the reaction time of collagen-induced (40 μg/ml) aggregation was seen during ticlopidine treatment; the inhibitory effect of ticlopidine on 5 μM adrenaline-induced platelet aggregation was only mild.

Two weeks after stopping ticlopidine administration, the hemolytic anemia relapsed, with reappearance of schistocytes in the peripheral blood smears (Table 1). The Cr^{51} half-life, measured 4 wk after stopping ticlopidine, was 18 days. During the whole observation period renal function, blood pressure control, and control of the glucose-insulin homeostasis remained stable.

COMMENTS

In this patient, a marked platelet hyperaggregability as well as a shortened red cell survival associated with prominent fragmentation of erythrocytes and leading to severe hemolytic anemia were demonstrated. The patient had moderate hypertension, but he did not have malignant hypertension and there was no evidence of other conditions classically known to be associated with fragmentation hemolysis.[1] However, he had severe diabetic microangiopathy, as reflected by retinopathy and nephropathy. Microvascular obliteration is a characteristic endstage of this disorder in certain capillary beds, including the retina, kidneys, and toes.[4,5] There is much evidence that disease of the small vessel, through which there is a rapid and continuous flow of blood, may be responsible for microangiopathic hemolytic anemia, irrespective of its initial etiology.[1] We therefore assume that in this patient the fragmentation hemolysis was related to his prominent diabetic microangiopathy.

The association of diabetic microangiopathy and fragmentation hemolysis was reported in 1976 by Brunning et al.,[2]

who found a shortened red cell survival and fragmentation of erythrocytes in 7 of 120 diabetic patients. All seven had severe retinopathy and nephropathy and were terminally ill, and all but one had insulin-dependent, juvenile-onset diabetes. As in the present case, abnormal carbohydrate metabolism per se or renal failure did not appear to be related to the red cell fragmentation syndrome. The increased platelet adhesiveness and increased in vitro sensitivity to platelet-aggregating agents present in insulin-dependent and non-insulin-dependent diabetes mellitus may play a role in the pathogenesis of diabetic microangiopathy.[4] Abnormalities of the physical properties of the erythrocytes, including increased whole blood and plasma viscosity, reduced erythrocyte deformability and increased adhesion to endothelial cells, have been related to the vascular complications of diabetes.[6] Alteration of the erythrocytes by passage through the diseased vascular bed may explain the red cell abnormalities[6] and may finally lead to fragmentation hemolysis.

Ticlopidine, 5-[2-chlorophenyl(methyl)]-4, 5, 6, 7-tetrahydrothieno [3, 2-C]pyridine hydrochloride, a new, long-lasting, oral antiplatelet drug, is already available to physicians as an antithrombotic agent in human beings in some European countries and in Japan.[3] It has been shown to reduce platelet aggregation and release reaction, prolong the bleeding time, and decrease platelet adhesiveness in animals and man.[3] Furthermore, several authors have claimed that ticlopidine increases the compliance of red cells and diminishes the blood viscosity in patients suffering from vascular disease.[3] The drug has been shown to protect against hypotonic hemolysis[7] and to increase the fluidity of the membrane phospholipidic core, which could be beneficial from a rhealogic point of view. In diabetes, ticlopidine corrects the thrombotic tendency as well as the hypercoagulable state.[8] The above-mentioned properties are presumably relevant to the reported clinical efficacy of ticlopidine in the following situations: extracorporeal circulation in cardiac surgery and in hemodialysis, trophic leg ulcers, aortocoronary bypass, postsurgical complications after rupture of intracranial aneurysm, thrombosis of the central retinal vein, and sickle cell disease.[3]

In the present case also, the beneficial effects of ticlopidine on fragmentation hemolysis is probably related to its platelet-inhibiting activity and to its effect on the erythrocyte membrane. This case further suggests that antiplatelet agents such as ticlopidine may be useful in the treatment of diabetic vascular disease and appears to justify the prospective clinical trials in progress to assess the value of that drug in the prevention of retinal damage in diabetic patients.[3]

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REFERENCES

[1] Brain, M. C.: Microangiopathic hemolytic anemia. N. Engl. J. Med. 1969; 281:833–35.

[2] Brunning, R. D., Jacobs, H. S., Brenckman, W. D., Jimenez-Pasquau, F., and Goetz, F. C.: Fragmentation hemolysis in patients with severe diabetic angiopathy. Br. J. Haematol. 1976; 34:283–89.

[3] Panak, E., Maffrand, J. P., Picard-Fraire, C., Vallee, E., Blanchard, J., and Roncucci, R.: Ticlopidine: a promise for the prevention and treatment of thrombosis and its complications. Haemostasis 1983; 13 (Suppl. 1):1–54.

[4] Colwell, J. A., Halushka, P. V., Sarji, K., and Sagel, K.: Platelet function and diabetes mellitus. Med. Clin. North Am. 1978; 62:753–66.

[5] McMillan, D.: Deterioration of the microcirculation in diabetes. Diabetes 1975; 24:949–57.

[6] Wautier, J. L., Paton, R. C., Wautier, M. P., Pintigny, D., Abadie, E., Passa, P., and Caen, J. P.: Increased adhesion of erythrocytes to endothelial cells in diabetes mellitus and its relation to vascular complications. N. Engl. J. Med. 1981; 305:237–42.

[7] Daveloose, D., Sablayrolles, M., Molle, D., and Leterrier, F.: Interaction of ticlopidine with the erythrocyte membrane. Biochem. Pharmacol. 1982; 31:3949–54.

[8] Hirayama, T., and Uehara, S.: Antiplatelet action of ticlopidine: clinical trial on the diabetes. Jpn. J. Clin. Exp. Med. 1979; 56:653–60.