Increased Activity of the Autonomic Nervous System and Increased Sensitivity to Angiotensin II Infusion after Therapy with Recombinant Human Erythropoietin

K.		Jandeleit ^a
B.		Heintz ^a
E.		Gross-Heitfeld ^a
J.		Kindler ^a
H.G.		Sieberth ^a
R.		Kirsten ^b
K.		Nelson ^b

^aDepartment of Internal Medicine II, RWTH Aachen, FRG; ^bClinical Pharmacology, University of Frankfurt, FRG

Bernhard Heintz, MD, Department of Internal Medicine II, RWTH Aachen, Pauwelsstreet 30, D-5100 Aachen (FRG)

Dear Sir,

The pathophysiological role of the autonomic nervous system in the development of arterial hypertension during regular therapy with recombinant human erythropoietin (rh-EPO) is unclear [1]. Recently, Fritschka et al. [2] reported elevated plasma norepinephrine concentrations and a decrease of $< \frac{3}{4}$ -adrenoreceptors in dialysis patients treated with rh-EPO. Blood samples were drawn from 11 haemodialysis patients at rest and at the peak of physical exercise (initially 25 W, increased by 25 W every 2 min) to determine epinephrine (E), norepinephrine (NE), aldosterone (ALD) concentrations and plasma renin activity (PRA) before and after 6 weeks and 3 months of rh-EPO treatment. An initial dose of 40 IU/kg body weight 3 times per week intravenously was administered. If a haematocrit of 35% was not reached after 4 weeks the dose was increased by 40 IU/kg body weight. If the haematocrit exceeded 35% the dose was reduced by 40 IU/kg body weight or the infusion was completely stopped. Before, after 6 weeks and 3 months after rh-EPO administration an angiotensin II infusion test was performed (initial dose 0.5 µg/min with stepwise increase of 0.5 µg/min until the mean arterial pressure showed an increase of 20 mm Hg). Cardiac output (technetium ven-triculography) was measured and total peripheral resistance (TPR) calculated from mean arterial blood pressure as well (table 1).

Resting blood pressure values did not change during the course of rh-EPO therapy. Aldosterone and renin activity also remained unchanged, but epinephrine and particularly norepinephrine increased during rh-EPO therapy, with a peak at 6 weeks of treatment. Exercise caused the systolic blood pressure to increase before and

after rh-EPO therapy, whereas exercise had no influence on the diastolic blood pressure before rh-EPO treatment, but increased with exercise after treatment. Neither exercise nor rh-EPO therapy caused significant differences in ALD or PRA. Both resting and exercise NE and E values were above normal, with values increasing after exercise. A large increase in resting NE

occurred after 6 weeks of rh-EPO therapy but had returned to pretreatment levels after 3 months. The TPR increased and less angiotensin II was required to increase the mean arterial blood pressure by 20 mm Hg after rh-EPO therapy. Erythropoietin and catecholamines activate adenylate cyclase independently, via different receptors [3]. The down-regulation of Therapy with Recombinant Human Erythropoietin
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NE receptors reported by Fritschka et al. [2] may account for normal resting blood pressure values in dialysis patients, despite large increase in NE concentrations, during the course of rh-EPO treatment. These high NE concentrations may allow mild stimuli, such as exercise or low doses of angiotensin II, which normally increase blood pressure moderately, to be the cause of hypertensive crises in patients treated with rh-EPO.

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Setschenkska MS; Bonanou-Tzedaki SA, Arnstein HRV: Independent activation of adenylate cyclase by erythropoietin and Isoprenaline. Mol Cell Endocrinol 1988;56:199–204.

References