Recombinant Human Erythropoietin Therapy and Autonomic Nervous System

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Dear Sir,

Arterial hypertension is a most important complication for hemodialysis patients treated with recombinant human erythropoietin (rHuEPO), that may develop hypertensive encephalopathy with seizures. It is generally thought that the autonomic nervous system has correlation to such hypertension. However, the pathophysiological change of its system during rHuEPO therapy is unclear. Recently, Jandeleit et al. [1] reported that the autonomic nervous system activity was increased in rHuEPO therapy by measurement of plasma noradrenaline levels and stimulation of angiotensin II in hemodialysis patients. In this study, we measured plasma noradrenaline levels and dopamine- β -hydroxylase (DBH) activity to investigate a reaction of the sympathetic nervous system on hemodynamic changes during rHuEPO therapy.

Eleven patients (mean age 55 ± 4 years; 4 male and 7 female) received regular hemodialysis 3 times a week, with the diagnosis of chronic glomerulonephritis in 9 patients and nephritis due to toxemia of pregnancy in 2. They had all normal arterial blood pressure according to WHO criteria before rHuEPO therapy. rHuEPO was administered at a dose of 48 U/kg body weight 3 times a week for 8 weeks. Plasma noradrenaline levels and DBH activity were determined before therapy and at 4 and 8 weeks after the therapy. Anemia was corrected by

rHuEPO therapy. Mean hematocrit value significantly increased from $20.4 \pm 0.8\%$ (before therapy) to $26.8 \pm 0.8\%$ (at 8 weeks). Mean values for mean arterial blood pressure remained unchanged throughout the 8 weeks, i.e., 89.6 ± 2.8 mm Hg before therapy, 88.7 ± 4.1 mm Hg at 4 weeks and 89.2 ± 3.2 mm Hg at 8 weeks. Plasma noradrenaline levels and DBH activity before therapy and 4 and 8 weeks after the therapy were as follows: noradrenaline 0.384 ± 0.049 , 0.328 ± 0.042 and 0.364 ± 0.045 ng/ml; DBH 26.4 ± 4.5 , 38.9 ± 8.2 (p < 0.05) and 43.4 ± 8.6

($p < 0.05$) IU, respectively. An increase in plasma DBH activity was observed in all 11 patients after 8 weeks of therapy (fig. 1).

DBH, which converts dopamine to noradrenaline and is located in the noradrenaline vesicles at the sympathetic nerve endings, is proportionally released along with noradrenaline from the noradrenaline vesicles when the sympathetic nervous system is activated [2]. Measurement of both plasma noradrenaline levels and DBH activity has thus been described to be useful as an index of the sympathetic nervous system. Many investigators have reported that plasma DBH activity was lowered in hemodialysis patients [3,4]. A recent study has shown that plasma DBH activity was diminished in correlation with the autonomic neuropathy in these patients [5]. Our series showed that

$p < 0.05$

$\Gamma p < 0.05$ -i

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Before therapy

Time, weeks

Fig. 1. Changes in serum dopamine- β -hydroxylase activity during 8 weeks of rHuEPO therapy (individual data).

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while plasma noradrenaline levels and DBH activity before therapy were similar to the findings in the before-mentioned studies, after 4 and 8 weeks of therapy, however, a significant increase in plasma DBH activity was observed in spite of plasma noradrenaline levels remaining unchanged. This impaired changes between plasma noradrenaline levels and DBH activity could show that noradrenaline kinetics presumably increased at the sympathetic nerve endings, indicating that the sympathetic nervous function was normalized following rHuEPO therapy in the remaining patients with unchanged normal arterial blood pressure. We concluded that this change in the autonomic nervous system might play some role in arterial antihypertensive mechanisms in rHuEPO therapy.

References

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116

Suwata/Maeda/Ohmori/Ohwa/Ohtsuka/ rHuEPO and Autonomic Nervous System
Shimoyama