Does Intravenous Erythropoietin Lead to an Immediate, Transient Increase in Arterial Blood Pressure in Dialysis Patients?

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12 3 4 5 min PLACEBO

Dear Sir,

The development of hypertension in 20-30% of hemodialysis patients receiving recombinant human erythropoietin (rHuEPO) remains an important side effect often requiring antihypertensive treatment [1-5]. The factors involved in the occurrence or aggravation of high blood pressure with rHuEPO are still matter of controversy. A first explanation is provided by the constant increase in total peripheral resistance secondary to both the rise in hematocrit (and hence blood viscosity) and to the correction of tissue hypoxia. However, our recent findings in rats show that rHuEPO-generated blood pressure elevation cannot be attributed solely to increases in blood viscosity and hemoglobin concentration [6]. It has also been suggested that the pressor effect of rHuEPO may be explained by action of the hormone on vascular smooth muscle, either directly [7] or via an activation of the tissue renin-angiotensin system [8]. Finally, rHuEPO could also induce hypertension by acting on the vascular endo-thelium [9-12]. Because, in a recent preliminary report, a direct blood pressure-raising effect of rHuEPO has been claimed [11], we decided to reexamine this question in 10 chronic hemodialysis patients in our dialysis facility (4 females, 6 males; mean age 47 years, range 20-81 years). The duration of their intermittent hemodialysis treatment was 28.2 months (range 3-120 months). Patients had the usual distribution of nephropathies, with 1 patient having non-insulin-dependent diabetes. Six of the ten patients received antihypertensive therapy (ACE inhibitors in 3 patients, calcium channel-blocking agents in 4, and β -

12 3 4 5 min rHuEPO

Mean $\pm$ SEM i SBP i DBP i MAP i Heart Rate

Fig. 1. Minute-to-minute variations in mean $\pm$ SEM values of systolic (SBP), diastolic (DBP), mean arterial (MAP) blood pressure and heart rate (beats per minute, bpm) during the 5-min period after the intravenous injection of placebo and thereafter during the 5-min period after the intravenous injection of rHuEPO into 10 hemodialysis patients. No difference was seen between placebo and rHuEPO periods at any time point of the study, using Student's paired t test or ANOVA.

min of baseline monitoring, patients received first a placebo injection (5% dextrose solution) at time point 5 min and thereafter a rHuEPO injection at time point 10 min. The injected volume of either placebo or rHuEPO was identical for each patient.

Figure 1 shows variations in the mean values of systolic and diastolic blood pressure as well as the pulse rate for the 10 patients

adrenergic-blocking agents in 1). The patients had been on intravenous rHuEPO treatment, administered 3 times a week (on average 142 IU/kg body weight/week), for an average of 15 months (range 3-36 months).

Blood pressure and pulse rate were continuously monitored for 15 min, starting at the end of a hemodialysis session, and registering each minute using a Dynamap device. After 5

during the 5-min placebo study period and then during the 5-min rHuEPO study period. The results indicate that no immediate blood pressure rise could be observed after the intravenous administration of rHuEPO, compared with the administration of placebo. Similarly, no difference in pulse rate was found between the two study periods.

The absence of any acute blood pressure-elevating effect of rHuEPO appears to be at variance with recent in vitro studies suggesting a direct vasoactive action of the hormone when added in pharmacological concentrations to isolated mesenteric or renal arterioles [7]. It also contrasts with the other recent in vitro studies demonstrating a direct enhancing effect of rHuEPO on endothelin-1 release by vascular endothelium [10-12] and on vasoconstrictor prostanoids [10]. It is possible that extremely high concentrations of rHuEPO at the target tissue level must be achieved to induce a direct and immediate action, and that such high concentrations are not obtained even after the intravenous injection of pharmacological doses of rHuEPO. Another possibility is that the hormone exerts growth factor effects at the level of the vascular smooth muscle. We are presently investigating such a possibility in our laboratory.

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