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Some unanswered questions in the pathogenesis of hypertension in patients treated with erythropoietin

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ALGUNAS CUESTIONES SIN RESOLVER EN LA PATOGENIA DE LA HIPERTENSION DE LOS PACIENTES TRATADOS CON ERITROPOYETINA

RESUMEN

La hipertensión constituye uno de los más prominentes efectos colaterales del tratamiento con eritripoyetina humana recombinante (EPO) en los pacientes en hemodiálisis crónica. Su patogénesis se explica básicamente como una reversión de la vasodilatación hipóxica secundaria a la corrección del estatus anémico. Sin embargo, existen unos pocos factores que no pueden explicarse basándose en mediciones hemodinámicas. Se presentan tres casos típicos de pacientes con episodios hipertensivos, en los que se contradicen las ideas actuales que explican la fisiopatología de la hipertensión relacionada a EPO. Según estas observaciones, parece existir una relación entre el desarrollo de hipertensión y la velocidad a la que aumenta el nivel de hemoglobina. Por lo tanto, las dosis de EPO deben mantenerse bajas para evitar ascensos rápidos de los niveles de hemoglobina.

Palabras clave: ***EPO. Hipertensión.***

SUMMARY

Hypertension is one of the most prominent side effects of treatment with recombinant human erythropoietin (r-HuEPO) in patients on chronic dialysis. The pathogenesis is basically understood as a reversal of hypoxic vasodilation due to the correction of the anemic state. There are a few features, however, which cannot be explained on the basis of hemodynamic measurements. Three typical cases of patients with hypertensive episodes are presented, in whom the current understanding of the pathophysiology of r-HuEPO related hypertension is contradicted. It appears from these observations that there is a relationship between the development of hypertension and the velocity of the hemoglobin increase. The r-HuEPO dose therefore should be kept low to avoid rapid increases of hemoglobin values.

Key words: ***r-HuEPO. Hypertension.***

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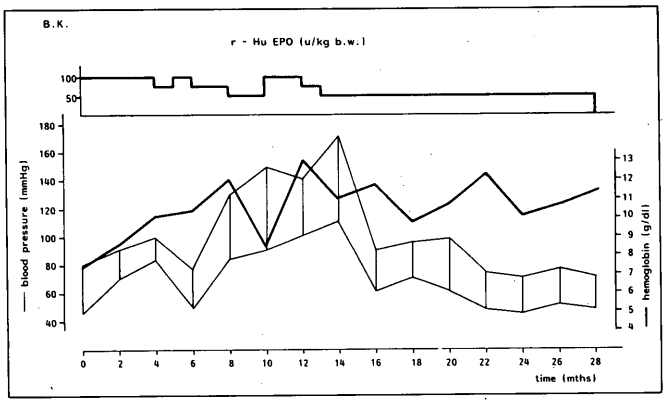

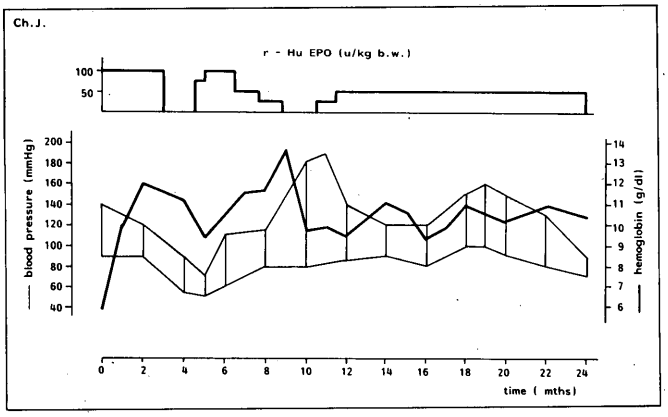

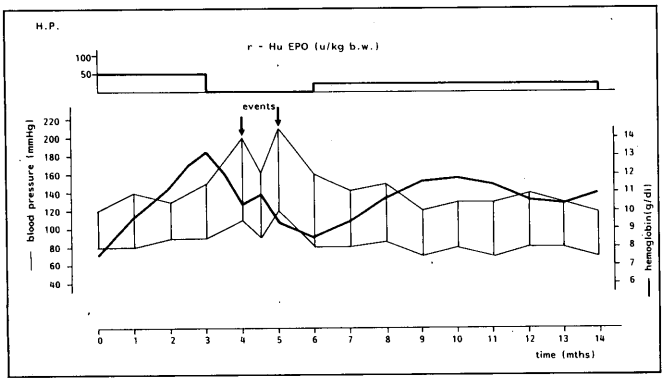

Figs. 1, 2 and 3.—Individual courses of blood pressure, hemoglobin levels and r-HuEPO dose over time.

Introduction

The development or aggravation of hypertension in some patients treated with r-HuEPO for renal anemia has been noted already in the very first reports on the effectiveness of this new treatment [1, 2]. Among the side effects of r-HuEPO therapy hypertension certainly is the one of major relevance [3]. Studies on the hemodynamic consequencs of anemia in dialysis patients have shown that with a rising degree of anemia there is a compensatory increase of cardiac output and apparently due to peripheral hypoxia peripheral resistance values are found in a rather low range [4, 5]. Strikingly, there is a linear relationship between peripheral resistance and hemoglobin values in the sense that the lower the hemoglobin the lower the peripheral resistance is found [4]. From the pathophysiological point of view increasing hemoglobin values then will result in cessation of peripheral hypoxia with a concomitant increase of peripheral resistance, and blood pressure [6]. Similarily, breathing of oxygen in anemic children results in increases in peripheral resistance [7]. Another potential contribution to rises in blood pressure could come from increases in blood viscosity. Indeed, whole blood viscosity in patients treated with r-HuEPO increases, a fact which is merely due to increases in hematocrit, but not in plasma viscosity [8-11]. Taken together the mentioned effects seemed to give ample explanations to the underlying mechanisms of hypertensive problems of r-HuEPO therapy in dialysis patients with anemia.

In the following we present the case histories of three patients as an example that things are not as easy as one might think and that the final chapter of r-HuEPO associated hypertension still has to be written.

Case 1: A 1964 born female which entered chronic dialysis therapy because of chronic glomerular nephritis. She received kidney transplants in 1976 and 1978, but in both cases rejections lead to a rapid loss of the transplants. Since 1978 she is on chronic hemodialysis again. The patient was severely anemic all the time of her dialysis therapy with a transfusion dependency of two units of blood to maintain hemoglobin values of less than 6 g/dl. She was hypertensive till 1982, but became progressively hypotensive thereafter. In June 1987 r-HuEPO treatment was started. At this time hemoglobin was 6 g/dl, blood pressure was 80/50 mmHg. Initially 100 U/kg b.w. erythropoietin were administered three times a week. Within five months under treatment with r-HuEPO the patients' blood pressure returned to normal values (RR = 120/80 mmHg), when the patients' hemoglobin rose to 10 g/dl. According to the study protocol at this time the erythropoietin dose was reduced to 75 U/kg b.w. and subsequently to 50 U/kg b.w. three times a week. Although the patients' hemoglobin dropped down (Hg = 9,0 g/dl), the rise of blood pressure continued (RR = 150/110 mmHg). Antihypertensive medication was started with 100 mg Labetalol two times a day and finally with 100 mg three times a day blood pressure was controlled at values of 140/90 mmHg. Since the hemoglobin value dropped to 8 g/dl an erythropoietin dose adaptation was necessary (100 U/kg b.w. three times a week). This time the rise in hemoglobin was not followed by a further rise in blood pressure. For 6 months the patients' blood pressure was stabilized with this regimen and with slight adaptations of the erythropoietin dosage her hemoglobin was maintained at about 11 g/dl. Without any changes in medication or changes in hemoglobin levels the patients' blood pressure suddenly dropped in November 1988 (RR = 70/50 mmHg). Immediatly antihypertensive medication was discontinued, but the blood pressure did not regain normal levels despite an hemoglobin of 11.8 g/dl. Until now the patients' blood pressure is at about 80/50 mmHg.

Case 2: A 1954 born male suffered from chronic glomerular nephritis since the age of three years. Kidney function progressively deteriorated and because of end stage renal failure hemodialysis was in 1978. After 4 unsuccessful kidney transplantations because of rejections the patient is continously on chronic hemodialysis since 1984. In February 1988 treatment with r-HuEPO (50 U/kg b.w. three times a week) was initiated at a hemoglobin of 7.0 g/dl. At this time the patients' blood pressure was 120/80 mmHg as it has been throughout the last two years. Within 4 months under EPO therapy hemoglobin rose from 7.0 to about 12.0 g/dl, but blood pressure remained normal. Because of the relative high hemoglobin level EPO dosage was reduced to 75 U/kg b.w. three times a week. On the 29th of May the patient complained about severe head ache and blurred vision, the blood pressure was 210/110 mmHg. Immediatly treatment with dihydralazin together with labetalol was initiated. Blood pressure returned to normal range and the patients' well being was restored. Treatment with r-HuEPO was discontinued and with the final antihypertensive medication of 150 mg dihydralazin, 75 mg captopril and 15 mg minoxidil daily blood pressure was well controlled. Treatment with r-HuEPO was initiated again at a hemoglobin level of 8 g/dl at an escalating dose regimen starting with 25 U/kg b.w. He now is stabilized at a hemoglobin round 11 g/dl and continues to be normotensive without any antihypertensive therapy.

Case 3: Another male patient, born in 1961, on chronic hemodialysis since 1980 because of chronic glomerular nephritis with transfusion dependant severe renal anemia was started with r-HuEPO therapy in June 1987. At this time the patients' hemoglobin was 5.8 g/dl, blood pressure 140/90 mmHg. Initial EPO dose was 100 U/kg b.w. three times a week. Although the patients' hemoglobin rose from 5.8 to 14.3 g/dl

within two months of r-HuEPO therapy initially the patients' blood pressure dropped to hypotensive values (RR ≒ 90/50 mmHg) but returned to normal when hemoglobin was 14.3 g/dl. At this hemoglobin level EPO therapy was discontinued immediatly. R-HuEPO treatment was started again when hemoglobin dropped below 10 g/dl. Thereafter the hemoglobin levels were maintained at about 11 g/dl with various EPO-dose adaptations. In March 88 hemoglobin suddenly increased above 13 g/dl without a preceding r-HuEPO dose increase. Concomitantly the blood pressure rose to 200/105 mmHg and the patient complained of severe headaches. R-HuEPO was discontinued and an antihypertensive regimen (dihydralazine 75 mg daily) instituted. After regaining hemoglobin values of below 10 g/dl the blood pressure returned to normal, antihypertensive therapy could be discontinued and r-HuEPO was started again. Since then the patient is constantly at hemoglobin values about 11 g/dl and normotensive without antihypertensive therapy.

Discussion

The initial phase of patient #1 represents the typical situation to confirm the current belief of mechanisms involved in rising blood pressure by reliefing peripheral hypoxia. The patient had longstanding and severe anemia and was extremely hypotensive. With rising hemoglobin peripheral hypoxia and thus hypoxic vasodilation disappeared and the patient entered happily a normotensive phase. There is, however, a complete lack of an explanation to what happened afterwards. True believers in todays thoughts of the pathophysiological background will argue that even the following hypertensive phase can be explained by the hemoglobin-resistance relationship, but the reappearance of hypotension with unchanged values of hemoglobin and an unchanged dose of r-HuEPO make this interpretation rather unlikely.

Patients #2 and #3 have something intriguing in common. Both develop an equivalent or true hypertensive crisis in a phase where hemoglobin values show a rather rapid increase. In patient #2 this occured in an early phase of r-HuEPO treatment and might be explained sufficiently by current pathophysiological understanding, patient #3, however, was on chronic r-HuEPO therapy for more then 12 months already when the problem occured. Although it is difficult to find a satisfactory explanation it appears that there is a relation between the rapidity of increases in hemoglobin and the incidence of hypertensive episodes. In contrast to dialysis patients treatment with r-HuEPO in healthy subjects is never complicated by hypertension [12]. In these studies the changes of hemoglobin values are actually very rapid, as repeated phlebotomies of more than 400 ml are performed and the aim is to regenerate normal erythrocyte counts as fast as possible, which questions the time —hemoglobin rise— hypertension theory. Additionally, a pressory effect of r-HuEPO by itself or by some unknown compound in the preparation is ruled out by these data.

In conclusion our case reports demonstrate that there is still no definite explanation for the development of hypertension in patients treated with r-HuEPO for renal anemia. Although the currently pathophysiological understanding allows an interpretation of the problem in many patients there are still quite a few patients which do not fit into the scheme. What emerges, however, is that it is very reasonable to aim for a slow and constant rise of hemoglobin values by starting the treatment with rather low doses, as at least in some patients hypertensive problems occur with exceptionally rapid increases of hemoglobin.

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