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Subcutaneous versus intravenous administration of human recombinant erythropoietin in patients on chronic hemodialysis

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TRATAMIENTO CON ERITROPOYETINA HUMANA RECOMBINANTE EN PACIENTES EN HEMODIALISIS: ADMINISTRACION SUBCUTANEA FRENTE A INTRAVENOSA

RESUMEN

En teoría se considera que un estímulo medular más constante como el conseguido con la administración subcutánea aumentaría la eficacia de la EPO.

En un estudio prospectivo se trataron dos grupos de pacientes en diálisis (n = 21 en cada grupo) con EPO bien por vía s.c. o i.v. Uno de los grupos recibió inicialmente 50 U/kg por vía intravenosa, los pacientes del otro grupo recibieron 50 U/kg (n = 10) o 25 U/kg (n = 11) administradas por vía subcutánea después de cada diálisis. Se realizaron ajustes a intervalos de cuatro semanas según el aumento de los niveles de Hb. Se monitorizaron las pendientes de las curvas de Hb, las dosis requeridas para aumentar o mantener un nivel de Hb predeterminado y los efectos colaterales del tratamiento.

En el grupo con 25 U/kg no se observaron aumentos significativos de los niveles de Hb durante las primeras cuatro semanas, las dosis de todos los pacientes debieron aumentarse. Los pacientes tratados por vía i.v. requirieron también de un aumento de la dosis de EPO para mantener una elevación constante de la Hb. Durante el período de mantenimiento pudieron reducirse las dosis en ambos grupos. A lo largo de todo el estudio la dosis media de EPO administrada al grupo s.c. fue significativamente menor que la del grupo i.v., mientras que los niveles de Hb en ambos grupos fueron prácticamente idénticos. La hipertensión, como efecto secundario general de la EPO, se produjo en ambos grupos con una frecuencia similar; sin embargo, los efectos secundarios inespecíficos, como el dolor óseo o los síndromes «flu like», sólo se observaron en el grupo i.v.

Se concluye que la administración s.c. de EPO reduce ligeramente los requerimientos del fármaco, pero su mayor ventaja reside en la completa ausencia de los efectos secundarios inespecíficos que se observan con el tratamiento por vía i.v.

Palabras clave: ***EPO. Subcutánea. Intravenosa.***

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SUMMARY

Theoretical considerations suggest that a more constant marrow stimulation as with s.c. administration could enhance r-EPO effectiveness.

In a prospective study 2 groups of dialysis pts (n = 21 in each group) were treated either s.c. or i.v. with r-HuEPO. One group received initially 50 U/kg b.w. intravenously, the patients of the other group received either 50 U/kg (n = 10) or 25 U/kg b.w. (n = 11) administered subcutaneously after each hemodialysis. Adjustments were done in 4 weeks intervals according to the increase of Hb levels. The slope of the Hb curves, the dosage required to increase or maintain a target Hb level and the side effects of therapy were monitored.

In the group with the 25 U/kg b.w. no significant increase of Hb-level was noticed in the first 4 weeks; the dose of all patients had to be increased. I. v. treated patients required an increase of the r-HuEPO dose too to maintain a constant Hb raise. In the maintenance period the dosage could be reduced in both groups. Throughout the whole study the mean r-HuEPO dose in the sc-group was significantly lower than in the i.v. group whereas the Hb-levels in both groups were almost identical. As general side effect of r-EPO increases of blood pressure occurred with similar frequency in both groups, however, unspecific side effects as bone pain or flu-like syndromes occurred only in the i.v. group.

It is concluded that s.c. administration of r-HuEPO reduces dose requirements slightly, but that the major advantage lies in the complete absence of unspecific side effects which occur with i.v. treatment.

Key words: ***r-HuEPO. Subcutaneous. Intravenous.***

Introduction

Inappropriatety low serum erythropoietin levels are the major cause of anemia in the chronic renal failure [1, 2]. Recombinant human erythropoietin is now generally available for therapy of renal anemia. Randomized studies tried to delineate optimal dose and frequency of application [3-5]. As most of these patients are on chronic hemodialysis, i.v. application after each dialysis was the logical route of administration.

As the half life of i.v. administrated hormone is rather short [6], other application forms providing a more constant stimulation of the bone marrow seemed of interest: s.c.-application with a maintained plateau level was supposed to increase the effectiveness of r-HuEPO, thus probably reducing the amount of the substance required to achieve a desired hemoglobin level.

Early studies of Bommer [7] suggested that s.c. administration of r-HuEPO in fact allows a dose reduction by almost 50 %. Other pharmacokinetic data, however, casted some doubts on the advantages of s.c. administration, as area under the curve and calculated bioavailability always were less for s.c. versus i.v. [8, 9]

The present study wants to examine on clinical grounds whether s.c. versus i.v. administration of r-HuEPO is advantageous with regards to effectiveness, safety and side effects.

Patients and methods

42 patients, 29 men and 13 women were enrolled in the study. The patients background is shown in Table 1.

The patients entered the study consecutively and were divided up in 3 groups: 21 received initially 50 U/kg b.w. i.v., 11 received 50 U/kg b.w. s.c. and 10 were started with 25 U/kg b.w. s.c. after each hemodialysis.

Hematologic parameters were measured before each HD. After a starting period of 4 weeks, dose adjustments were done in steps of 25 U/kg b.w. in 2 weeks intervals in order to keep the rise of hemoglobin below 1 g/dl every 2 weeks. Target hemoglobin for the correction period was 10 g/dl, which was maintained throughout the study.

As parameter for iron stores, ferritin levels were controlled every four weeks. Serum ferritin of at least 100 ng/ml was assumed as adequate.

Table I. Patients background and baseline data

Baseline Data

	n	Men/ women	Mean age (years)	HD (months)
I.v. 50	21	15/6	41 (18-63)	39.6
S.c. 50	10	5/5	50 (20-74)	38.6
S.c. 25	11	0/2	57 (29-72)	10

Underlying disease

Glomerulonephritis	21
Tubulo-interst.	8
Hypertensive nephropathy	7
Polycystic kidneys	1
Unknown origin	5

Hematologic parameters

	RBC	Hb	Hkt	WBC	MCV
I.v.	2.31 ± 0.36	7.34 ± 0.99	21.6 ± 2.9	5.58 ± 1.6	92 ± 6.02
S.c.	2.58 ± 0.46	7.80 ± 0.85	23.3 ± 2.64	6.66 ± 2.0	93 ± 4.19

All patients, who achieved at least three months of EPO therapy were taken in consideration. Withdrawal before the end of the study occurred in 2 i.v. treated patients because of unspecific side effects (severe bone pain and unwellbeing).

Results

Following earlier studies of safety and efficacy studies of EPO the i.v. was started with 50 U/kg b.w. For comparative reasons and for dose finding, the s.c. group was divided in two groups: one receiving the same dose s.c. than the i.v. group and the other starting with only 25 U/kg b.w.

In the patients starting with 25 U/kg b.w., no significant increase of hematocrit levels was achieved in the first 4 weeks. The increase of the hematologic parameters (hemoglobin, hematocrit) in the s.c. and i.v. group was parallel reaching the target-hemoglobin of 10 mg/dl after approximately 10 weeks (Figures 1 & 2). For this purpose the dosage had to be increased in both groups: the mean dose for the i.v. treated patients in this period was around 70 U/kg b.w. whereas with s.c. administration around 50 U/kg b.w.

In the maintenance phase a dose reduction in both groups was possible although further increases of hemoglobin occured. The difference between the two groups remained significant. No significant differences between the two groups were found concerning other hematologic parameters (i.e. leucocytes, mcv). For more comprehensive analysis, the doses of every individual patient were compared (Table 2). In the i.v. group half of the patients needed 75 U/kg b.w. or more thrice weekly whereas 2/3 of the s.c. treated patients had only 50 U/kg b.w. or less to maintain a hemoglobin > 10 g/dl.

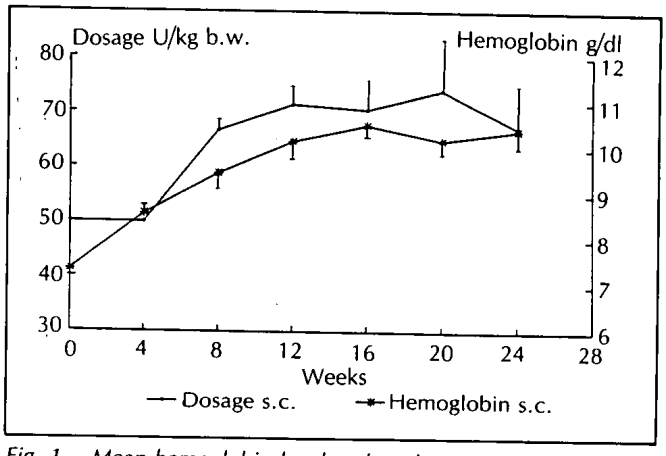

Fig. 1.—Mean hemoglobin level and erythropoietin dose of i.v. treated patients (± SEM).

Another unsolved problem is the situation of the iron status. Polytransfused patients seem to respond better to EPO therapy with their rise in hematocrit values because of their higher iron stores [10]. As an exact analysis of the iron status is not available (neither ferritin nor transferrin levels as markers are uncontested) differences in response to EPO therapy can be due to differences in iron availability.

All side effects were monitored. The most frequent problem of hypertension [11, 12] was registered in both

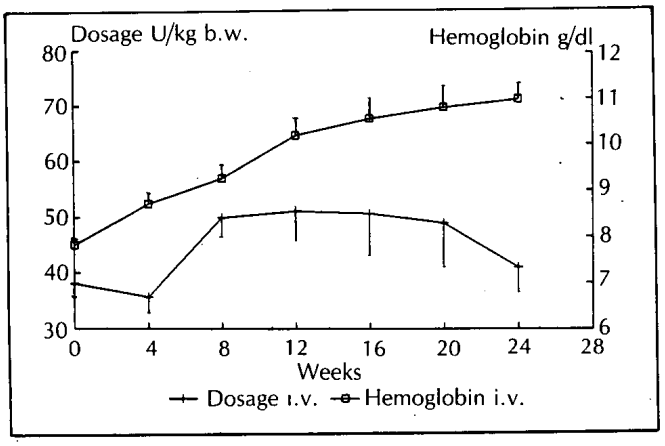

Fig. 2.—Mean hemoglobin level and erythropoietin dose of s.c. treated patients (± SEM).

groups with similar frequency. In 14 of 21 from the i.v. group and 15 of 21 from the s.c. group (i.e. around 60 % of patients in each group) an increase or an initiation of antihypertensive therapy had to be performed.

Only patients from the i.v. group complained about unspecific side effects: bone pain or head ache was a common problem in this group and in 2 cases even withdrawal of therapy was necessary. On the other hand, patients from the s.c. group complained of pain at the injection site during s.c. administration.

Discussion

Our results suggest that s.c. administration in fact is more effective in the treatment of renal anemia in patients on chronic hemodialysis then a repeated i.v. bolus regimen. Early optimism on savings up to 50 % could not be confirmed in our study. The differences between our results and those of Bommer[7] predominantly can be explained by the different study design. Whereas our study covers the whole area of r-HuEPO treatment from the initial phase to the maintenance phase the Bommer data were shown only for the maintenance phase. Additionally, for studying patients in the maintenance phase only, a control group of patients on a reduced i.v. dose would have given valuable information. There is definitely the chance that at least some of our patients maintained on r-HuEPO are receiving amounts which are actually too high and that more r-HuEPO is administered then is required.

The more carefully performed study of Granolleras[13] with daily s.c. doses of r-HuEPO suggests that substantial savings of r-HuEPO indeed are possible. From a pharmacokinetic point of view naturally the more then twice as frequent administrations certainly are favourable, for the patients, however, this is an additional hassle and the number of patients complying to this kind of treatment will be limited.

The real advantage of s.c. administration of r-HuEPO appears to be the complete absence of so called unspecific side effects. For instance bone pain, as sometimes seen with i.v. administration, can reach a subjective magnitude that patients decide to discontinue treatment. Our personal experience shows that especially these patients do exceptionally well with s.c. therapy. The major drawback of s.c.

Table II. Individual EPO dose during therapy

	EPO dose (U/kg b.w.)										
Weeks	**0**	**25**	**40**	**50**	**66**	**75**	**80**	**100**	**125**	**150**	**175**
0				21							
4				21							
8				7		14					
12				7		10		4			
16		2		6		7	1	4	1		
20		3		6		4	1	1	2	2	
24		3		5		5		1	1	1	
					I.v.-group						
0		10		11							
4		13		7		1					
8		4		14		2		1			
12	2	1		14	1	1		1	1		
16	2	4		12	1			1			1
20	2	4	1	10	1	1		1			
24	3	1	5	7	1	1		1			
					S.c.-group						

administration of r-HuEPO at the moment is pain at the injection site reported by most of the patients. This is most likely due to the rather large volumes which have to be administered because of the formulations currently available. Future preparations containing more units per ml possibly will avoid this problem completely.

In conclusion our study suggests that s.c. administration of r-HuEPO has some advantages when compared to i.v. therapy but that these advantages are limited. The savings are certainly not sufficiently convincing to call for an universal switch of i.v. treated patients to the s.c. route. Rather, patients with problems of unspecific side effects treated i.v. are likely to benefit from a switch and should be the candidates of choice.

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